

Clinical Neurology Update

from NEJM Group

■ Roundtable on
Aducanumab &
Alzheimer's

■ Practical
Approaches
to Managing
Concussion

■ Modern
Migraine
Treatments

■ Link
Between Gut,
Microbiota &
Brain



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FROM the Editor

This is a time of new treatment development and advances in knowledge for common neurologic disorders. This issue of *Clinical Neurology Update* includes many of the advancements from the past year. The articles in this issue help us understand these developments while providing practical considerations for clinical practice.

One of the larger news items in neurologic therapeutics was the release of the first agent directed at disease modification in Alzheimer's disease. The data and process used for approval of this medication resulted in both hope and controversy. Our Roundtable Discussion includes three distinguished experts who help us understand the variety of considerations surrounding the approval of aducanumab and future implications. Our Roundtable discussants include Dr. Paul Aisen of the University of Southern California, Dr. Samuel Gandy of Mount Sinai, and Dr. Lon Schneider of the University of Southern California.

More information continues to emerge to further advance our understanding of concussion. Two national experts in concussion, Dr. Shae Datta, Co-Director of the NYU Langone Concussion Center, and Dr. Christopher Giza, Director of the UCLA Steve Tisch BrainSPORT program, synthesize the latest knowledge and help present an organized approach for these patients.

Many new treatments have been added to the possible toolbox of options for migraine headaches. The Topic Update by two experienced headache experts, Dr. Yulia Orlova of the University of Florida and Dr. Andrea Harriott of Massachusetts General Hospital, summarizes these newer treatments and provides understanding of the clinical contexts for which they are used and how these newer treatments relate to one another.

There is increasing interest in the role of the microbiota in neurologic disease. Dr. Robin Voigt and Dr. Ali Keshavarzian, Operations Director and Director of the Rush University Center for Integrated Microbiome and Chronobiology Research, respectively, bring us up to date on current understanding as knowledge continues to rapidly advance toward translation as we evolve from understanding the microbiota as a biomarker to a potential target of therapeutics.

It is an exciting time for neurology therapeutics as new developments raise new questions on how best to apply and utilize these treatments. We hope that these articles are both informative and practical.

Michael S. Jaffee, MD, FAAN

Dr. Jaffee is Vice Chair of the Department of Neurology at the University of Florida College of Medicine, Gainesville, and Director of the UF Brain Injury, Rehabilitation, and Neuroresilience (BRAIN) Center. He has received grants from the National Institutes of Health, Florida Department of Elder Affairs, and U.S. Department of Veterans Affairs; served as a consultant to McDermott, Will, and Emery on behalf of NCAA; served as chair of congressionally directed medical research program for peer-reviewed Alzheimer's research program; and served as a member of Novo Nordisk advisory board.

Roundtable Discussion

Aducanumab: A New Treatment for Alzheimer's Disease

In June 2021, the FDA granted accelerated approval to aducanumab (Aduhelm), the first approved treatment for Alzheimer's disease (AD) since 2003.

The approval has not come without controversy. Editor-in-Chief **Michael S. Jaffee, MD, FAAN**, asked three national experts to review the current situation to help clinicians better understand the context of this emerging important issue as there are several other amyloid immunotherapy agents currently in phase 3 trials, and in January, the Centers for Medicare and Medicaid Services (CMS) released a draft position statement on whether to cover anti-amyloid monoclonal antibodies.

Our three distinguished experts include **Paul Aisen, MD**, Professor of Neurology and Director of the Alzheimer's Therapeutic Research Institute at the Keck School of Medicine of the University of Southern California; **Samuel Gandy, MD, PhD**, Professor of Neurology and Psychiatry, Associate Director of the Mount Sinai Alzheimer's Disease Research Center in New York City, and Chairman Emeritus of the National Medical and Scientific Advisory Council of the Alzheimer's Association; and **Lon S. Schneider, MD, MS**, Professor of Psychiatry, Neurology, and Gerontology at the Keck School of Medicine of the University of Southern California and Co-Director of the clinical core of the University of Southern California Alzheimer's Disease Research Center (NIH). Their responses have been edited for space and clarity.

Jaffee: What's different about aducanumab compared with prior FDA-approved treatments?

Aisen: All prior approved medications for Alzheimer's are symptomatic treatments. They act on neurotransmission to provide a modest boost to cognitive function. But they have no significant

impact on AD neuropathology — the plaques, tangles, and synaptic loss. The benefits of the cholinesterase inhibitors and memantine can be measured relatively quickly, over the course of 12 weeks, and persist with continued treatment. But progression of the underlying disease is unchanged; after the initial boost, the rate of decline in cognitive function and clinical status

is the same as in untreated individuals. This is similar to using an analgesic to treat a progressive, destructive condition such as rheumatoid arthritis.

In contrast, aducanumab and similar drugs are dramatically effective in removing fibrillar amyloid plaques from brain. If, as many experts agree, amyloid accumulation in brain is an inciting and driving feature of AD, removal of amyloid at the right stage of disease should favorably

influence the course of the illness.

Schneider: At an advisory committee meeting in 2020, the FDA presented a favorable briefing recommending aducanumab's approval based on a nominally statistically significant clinical outcome in one of two phase 3 trials that were stopped early for futility after only 50% of participants had had a chance to complete. Nevertheless, the FDA considered that trial along with biomarker evidence from a phase 2, multiple-dose, cohort trial to be enough to recommend regular approval. The FDA's Office of Biostatistics strongly disagreed, as did the advisory committee by unanimous vote (with one abstention).

In June 2021, the FDA granted aducanumab *accelerated* approval after having failed the

The reasonable and useful outcome used to evaluate the efficacy of medications for Alzheimer's should be demonstration of meaningful clinical benefit as traditionally defined through randomized, placebo-controlled trials.
— Dr. Samuel Gandy



Left to right:

Michael S. Jaffee, MD, FAAN; Paul Aisen, MD; Samuel Gandy, MD, PhD; Lon S. Schneider, MD, MS

minimal FDA standard for regular approval, i.e., substantial evidence of effectiveness based on an adequate, well-controlled trial plus confirmatory evidence. Criteria for accelerated approval require that the drug be for a serious condition with an unmet medical need, the drug affects a surrogate biomarker reflecting the illness pathology, and FDA believes it is *reasonably likely* that the biomarker effect will predict clinical benefit.

Thus, the basis for aducanumab's approval was reduction in amyloid plaque that was considered predictive of clinical benefit and not FDA's standard low bar of actual demonstration of clinical benefit. In brief, FDA approved aducanumab because it reduces plaques.

Gandy: In its approval of aducanumab, the FDA (and the sponsor, Biogen) have made no claims that the drug offers meaningful clinical benefit. A meta-analysis earlier in 2021 (prior to the drug's approval) showed that reducing brain amyloid plaque burden, according to amyloid PET scan, fails to reliably predict meaningful clinical benefit. This result was anticipated by many neuropathological reports as far back as 1988.

Jaffee: FDA approval was based on evidence that showed a reduction of cortical amyloid on PET scans. There has been controversy because the medications can be associated with development of amyloid-related imaging abnormalities (ARIA) and the clinical effects haven't been as robust. With misalignment between demonstrated amyloid reduction and clinical effects, does this mean the amyloid cascade hypothesis may not be correct?

Aisen: The evidence supporting the amyloid hypothesis is compelling. There is an enormous body of evidence showing the toxic effects of amyloid species on synaptic function. More convincing still is the genetic support for the hypothesis. Every mutation that causes autosomal dominant AD involves beta or gamma secretase or APP cleavage sites to directly increase the generation of toxic amyloid species. The near universal occurrence of early-onset AD in Down syndrome, trisomy 21, is linked to APP overexpression since the APP gene resides in chromosome 21. The rare protective genetic variant, the Icelandic APP mutation, reduces toxic A β 42 generation.

Amyloid accumulation is the inciting and driving mechanism leading to AD. But AD follows a decades-long course, beginning with a presymptomatic phase during which amyloid accumulates and triggers tau pathology and neurodegeneration. By the time symptoms appear in 15 years or so, neurodegeneration is advanced and irreversible and complicated by additional pathologies, such as synucleinopathy and vascular disease. Beneficial anti-amyloid interventions must begin very early, before significant cognitive impairment, to lead to major clinical benefit. Even "early AD," spanning mild cognitive impairment and mild dementia, may be too late in the course for optimal benefit. This is the rationale for recent trials of anti-amyloid immunotherapy that are being conducted at the presymptomatic stage.

Schneider: It's important to consider that amyloid deposition is a seminal event in the pathogenesis of Alzheimer's dementia. The fact that

none of these drugs targeting particular points in the amyloid cascade has demonstrated unconflicted clinical benefit has little bearing on the amyloid cascade hypothesis, *per se*. The latter can be true even if no drug targeting it produces clinical benefit as it is possible that amyloid may not be an effective target or targeted too late. Additionally, various timings, doses, and durations of interventions haven't been systematically studied. With five treatments and six late-phase trials still underway, it's premature to pronounce amyloid antibodies as ineffective and the amyloid hypothesis as dead. These antibodies may not be effective in the prodromal and mild AD populations being tested but might be in earlier preclinical or at-risk populations and with longer treatment.

Gandy: The “amyloid cascade hypothesis” is an imprecise term that fails to account for the as-yet unknown complexity of non-fibrillar conformers (or oligomers) of the A β peptide. To deal with aducanumab, restricting the surrogate endpoint to amyloid plaque PET scans dooms that drug to failure, as presaged by decades of neuropathology. About 15% of patients with clinical AD have negative amyloid plaque scans. About 34% of patients with clinical mild cognitive impairment have negative amyloid plaque scans. Thus, plaque burden is not reliably linked to cognition in any consistent way.

The “amyloid cascade hypothesis” has come to be equated with the “amyloid plaque hypothesis” or the “amyloid fibril hypothesis,” neither of which accurately represents what's known about A β structural polymorphism. One example worth citing involves the action of A β oligomers (and NOT A β fibrils) to cause Golgi fragmentation through activation of cyclin-dependent protein kinase 5 (cdk5) and cdk5-related phosphorylation of the structural Golgi substrate phosphoprotein, GRASP65. This reaction has

the effect of stimulating A β release. Given the importance of processing newly synthesized proteins through Golgi compartments, it's no surprise that Golgi fragmentation can cause devastating damage to any cell type. While this scenario links A β oligomers to Golgi fragmentation and abnormal tau phosphorylation, the fragmented Golgi and/or the dysregulated cdk5 might well exert toxicity through mechanisms other than those that involve phospho-tau. If this chain of events plays a role in some patients with Alzheimer's, then the prediction will be that they accumulate A β oligomers that cannot be cleared by anti-A β -fibril antibodies while also accumulating damage due to Golgi fragmentation *per se* or due to dysregulated cdk5.

Jaffee: In your opinion, how significant of a concern is ARIA?

Aisen: Clinicians prescribing amyloid-lowering immunotherapy must be familiar with ARIA; they must understand risk factors such as prior episodes and *APOE* genotype, necessary monitoring with multiple MRI scans, and management. Most cases of ARIA are asymptomatic and incon-

sequential, but severe cases can occur, particularly in individuals homozygous for *APOE4*.

Schneider: Rates of edema or ARIA-E are high with aducanumab, 41% in *APOE4* carriers and 35% in noncarriers. Most cases are identified early with frequently performed MRIs generally showing small areas of edema that resolve after temporarily stopping infusions, or even while maintaining the dose in many instances. It is argued that with the specified MRI surveillance carefully timed for after dosing increases, safety can be ensured. Despite this level of surveillance, there are cases of edema and hemorrhage requiring hospitalization, corticosteroids, and intensive care, and recovery may take months. At least one death has been reported, possibly

Safety ... is a relative consideration to efficacy. In the absence of clinical benefit, there is no upside to aducanumab, and ARIA is of great concern.

— Dr. Lon S. Schneider

due to edema not being recognized early enough and infusions not stopped.

Safety, however, is a relative consideration to efficacy. In the absence of clinical benefit, there is no upside to aducanumab, and ARIA is of great concern. ARIA rates probably differ by antibody and the extent to which it binds to vascular amyloid. Other amyloid antibodies may be associated with less or more ARIA.

Gandy: If randomized, placebo-controlled trials of aducanumab show evidence for meaningful clinical benefit, then the decision to accept the risk for such a side effect would be up to patients and their advocates via the usual principles of informed consent. The fact that an antibody is intended to perturb amyloid fibrils deposited within the walls of amyloid-laden cerebral vessels says to me that there will be some inherent risk that cerebral vessel damage, leakage, and/or rupture will be associated with all anti-amyloid antibodies.

Jaffee: **What reasonable and useful outcomes should be used to evaluate efficacy of Alzheimer's medications?**

Schneider: Depending on the trial design and the stage of illness of study participants, there are several useful clinical outcomes for Alzheimer's trials. They can be divided into measures of cognition, function, or a combination of both; general global ratings; and clinical staging and events, such as onset of mild cognitive impairment.

Perhaps most unexpectedly, the most used cognitive composite is the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-cog), and the most used functional scale is the Alzheimer's Disease Cooperative Study ADL Scale (ADCS-ADLs). They have been used for over 25 years across the range of disease severity. Combined with a functional scale, these should be good enough to detect meaningful treatment effects. The Clinical Dementia Rating (CDR) is a composite scale commonly used as a primary outcome. It involves a history, mental status exam, and assessment of social and domestic activities and self-care.

Any of these would be useful and would have distinguished drug effects in the past. An issue in interpretation is whether there is a sufficiently large enough difference to be minimally clinically important.

Gandy: The reasonable and useful outcome used to evaluate the efficacy of medications for Alzheimer's should be demonstration of meaningful clinical benefit as traditionally defined through randomized, placebo-controlled trials.

Aisen: Presently, there's no assessment that can accurately evaluate the efficacy of treatments targeting AD neurobiology. Drugs such as aducanumab are expected to slow disease progression with long-term therapy; no short-term improvement is anticipated. Since individual trajectories of decline vary greatly, tracking cognitive decline isn't very useful in this regard. Decisions regarding treatment continuation should therefore consider adverse effects, cost, and the expectation of slowing of decline. There is some hope that in the future, downstream plasma biomarkers such as ptau217 may provide an indication of expected clinical benefit.

Jaffee: **The recent CMS proposed decision, developed due to FDA approval of aducanumab, will likely affect all future medications targeting amyloid. What are your thoughts on this proposed CMS guidance?**

Aisen: The FDA accelerated approval adopts the position that substantial reduction in brain amyloid is reasonably likely to lead to clinical benefit; this conclusion is supported by multiple randomized, controlled trials of aducanumab, lecanemab, and donanemab. The CMS decision that proposes noncoverage for aducanumab outside of approved randomized, controlled trials appears to reject this view, apparently concluding that evidence of benefit doesn't outweigh the risk. The extension of this judgment to future FDA approvals is difficult to understand; the anti-amyloid antibodies differ significantly in safety. One anti-amyloid antibody, solanezumab, carries no risk of ARIA. The coming phase 3 trial data of solanezumab, lecanemab, gantenerumab,

and donanemab must be evaluated to inform CMS decisions.

Schneider: When you strip away the verbiage and the apparent emphasis on the details and performance of a Coverage with Evidence Development trial (CED), the CMS decision is simply not to reimburse for aducanumab because it's not a "reasonable and necessary" treatment under CMS's guidance. ("Reasonable and necessary" means safe and effective, not experimental, and appropriate for Medicare patients.) Safe and effective is about the same criteria that FDA uses for regular approval of a drug. Having recognized the lack of demonstrated benefit for aducanumab, CMS is saying they will reconsider coverage if aducanumab can show benefit in a future trial that will be designed similarly to their phase 3 trials, and CMS will pay for it under the CED program.

As a practical matter, the CMS's CED coverage decision will be applied only to aducanumab and will have no practical effect on other amyloid-fibril antibodies. The lecanemab and gantenerumab phase 3 trial results are expected in 2022 and will make CMS's CED program decision moot: One or both antibodies will meet the FDA's "substantial evidence for effectiveness" standard, or both won't. If the former, then that treatment will get regular approval, and CMS will provide coverage because the trials comply with CMS's CED trials criteria.

Jaffee: If you could develop an ideal AD medicine, what would your drug's proposed mechanism be?

Schneider: The pathogenesis of late-life cognitive decline including Alzheimer's is multidetermined and complex, more than just plaques and tangles. There are far too many potential drug targets, and all — except for cholinesterase inhibitors — are unvalidated in that so far drugs

that engage any of the hypothesized targets have not demonstrated clinical benefit. So, thinking about any future drug or proposed mechanism is more of a guess, albeit based on preclinical molecular and epidemiologic models, that requires empirical testing and proof.

Gandy: Based on our own team's investigation, one model medicine that might treat Alzheimer's disease would sustain synaptic integrity even in the face of proteinopathy and neuroinflammation, perhaps via promotion of neurogenesis. A proneurogenic mGluR2/3 antagonist is one example of such a compound that's shown promise in our hands in transgenic mouse models. Immunoproteostasis mechanisms are of increasing interest as targets for AD clinical trials. However, much remains to be clarified regarding target selection, which disease stage(s) would be ideal for a particular intervention, and the valence of that intervention. One of the first immunoproteostasis agents to reach clinical trials, an anti-TREM2 antibody, is under development but has recently been placed on clinical hold.

Aisen: Based on compelling genetic and basic laboratory evidence supporting the pivotal role of amyloid peptides in AD initiation and propagation, primary prevention and very early intervention studies should target amyloid. Secretase inhibitors or modulators, carefully dosed toward 50% or less inhibition of A β 42 generation, make the most sense for primary prevention. For pre-symptomatic AD, targeting the accumulation of amyloid with passive or active immunotherapy is appropriate. But as the disease progresses, multiple pathologies — involving tau, synuclein, TDP-43 and vascular disease — complicate the illness, likely requiring a combination of therapies to significantly slow progression. Cognitive enhancers and behavioral interventions should be tailored to disease stage and symptoms.

The likelihood of widespread use of effective disease-modifying AD treatment soon is high.
— Dr. Paul Aisen

Jaffe: Any additional thoughts on emerging Alzheimer's treatments?

Schneider: The three amyloid-beta antibodies targeting plaque in phase 3 trials will soon have results. It's likely that one or two will be associated with less edema and hemorrhage. These outcomes, whether suggesting clinical benefit or not, will help to better frame the overall usefulness and future of this treatment mode.

In any event, the outcomes of the lecanemab and gantenerumab trials toward the end of 2022 are likely to reduce much of the aducanumab controversy.

Gandy: The National Institute on Aging's Accelerating Medicines Partnership for Alzheimer's Disease (AMP-AD) appears to hold promise for revising how we think about AD. Multi-omic approaches have led to the formulation that late-onset sporadic Alzheimer's may be driven by pathological networks and "hubs" or "drivers." Using this approach, the existence of several subtypes of Alzheimer's has been proposed, each driven by hubs and drivers. Notably, molecular targeting of these hubs and drivers can be demonstrated to modulate mouse models of Alzheimer's pathology, but in a far more desirable way than one might have guessed. When the gene for a molecule discovered by the AMP-AD approach is deleted from a mouse model of amyloidosis or tauopathy, either proteinopathy occurs with the usual time course and severity, but when the hub or driver is deleted from the amyloidosis mouse or the tauopathy mouse, rather than neurodegeneration, there is instead maintenance of synaptic integrity, electrophysiological function, and learning behavior. The

AMP-AD approach is based on human post-mortem multi-omic analysis, and, given the validation by the mouse models, this would appear to be more reason to either refocus Alzheimer's drug discovery or at least include measures of synaptic integrity in drug discovery and development. The lessons of AMP-AD and aducanumab may be that targeting proteinopathy alone doesn't get at the underlying network pathology that is truly driving Alzheimer's pathogenesis.

Moreover, during 2021, while aducanumab has received most of the attention, new data have emerged indicating that galantamine, methylphenidate, candesartan, sildenafil, bumetanide, and atomoxetine hold promise for producing meaningful clinical benefits in Alzheimer's disease. All of these have well-known safety profiles. Efforts at matching AD subtypes with polygenic risk scores and biomarker profiles might move us closer to personalized diagnosis and intervention for Alzheimer's and related diseases.

Aisen: Overall, the outlook is bright. Beyond amyloid-lowering antibodies, many exciting therapeutic programs are moving forward, targeting amyloid monomers and oligomers, tau species, neurotrophic mechanisms, endocrine pathways, and inflammation. Trial methodology has seen major advances, particularly in blood-based biomarkers. Plasma assays now provide accurate indicators of fibrillar amyloid load, tau pathology, and neurodegeneration, facilitating AD diagnosis and staging and providing an indication of drug effects. The likelihood of widespread use of effective disease-modifying AD treatment soon is high.

DISCLOSURES

Paul Aisen, MD, reports personal fees from Biogen, Roche, Merck, Abbvie, Shionogi, and Immunobrain Checkpoint and grants from Janssen, Lilly, Eisai, NIA, Alzheimer's Association, and FNHI.

Samuel Gandy, MD, PhD, receives research support from the NIH, the ADDF, and the VA MERIT review; serves as a consultant for Ritrova Therapeutics and as founder of Recuerdo Pharmaceuticals (inactive); has received compensation for chart review in connection with medical litigation in the area of cognitive function; has a patent for induced pluripotent stem cell protocol for generation of basal forebrain cholinergic neurons; serves on the Medical Safety and Advisory Board of Alzheimer's Disease International; and holds stock or stock options in Recuerdo Therapeutics (inactive).

Lon S. Schneider, MD, MS, reports grants and personal fees from Eli Lilly; personal fees from Neurim, Ltd., Cognition Therapeutics, Immunobrain Checkpoint, Cortexyme, AC Immune, Otsuka, GW Research, and Novo Nordisk; and grants from Biogen, Biohaven, and Washington University/NIA DIAN-TU.

Topic Update

Practical Approach to Management of Concussion

Shae Datta, MD, and Christopher C. Giza, MD

Concussion or mild traumatic brain injury (mTBI) is a serious public health concern, with estimates of over 3 million cases annually in the United States. Concussion is a clinical syndrome of neurologic dysfunction following a biomechanical force to the brain, in the absence of overt structural injury (*Continuum [Minneapolis]* 2021; 27:1646). Concussion is thus a form of TBI, with underlying pathophysiology that evolves over time. Neurologists can play a central role in concussion management, from accurate diagnosis to facilitating recovery (see Table). In this update, we discuss advances in evidence-based care of concussion, from initial recognition of injury to treatment of persistent post-concussion symptoms (PPCS).

Protecting Patients from Repeat Injury

Strong evidence supports removal from contact-risk activity when a concussion is suspected. Although the window for vulnerability to repeat concussion is not absolute, sports studies show that the interval between in-season repeat concussions has increased with implementation of more-gradual return to play (RTP) protocols (*Br J Sports Med* 2020; 54:102).

In addition, delayed removal from sports activity is associated with longer recovery compared with immediate removal (*Am J Sports Med* 2018; 46:1465). This is also reported in high school athletes (*Pediatrics* 2016; 138:e20160910). In other words, “playing through a concussion” can result in prolongation of recovery.

Anticipating and Facilitating Recovery

Reassurance, education, and cognitive restructuring can facilitate recovery in both pediatric and adult patients (*Pediatrics* 2001; 108:1297; *J Clin Exp Neuropsych* 2001; 23:829). It is also essential to identify patients at risk for developing PPCS, defined as ongoing symptoms at 1 to 3 months. PPCS carry a significant burden and may be associated with

depressed mood, lower quality of life, and school/work absenteeism.

Validated PPCS prognostic tools allow for earlier tailoring of management by risk level — i.e., provision of education and reassurance to low-risk individuals and psychological intervention and referrals as needed to higher-risk patients. For pediatric patients, a validated clinical risk score includes age, sex, prior concussion, prior migraine, answering questions slowly, imbalance, and current symptoms of headache, fatigue, and/or phonophobia (*JAMA* 2016; 315:1014). In adults, premorbid psychiatric conditions, preinjury health system usage, and older age were associated with PPCS risk and used to develop a risk score (*PLoS Med* 2021; 18:e1003652).

Promoting Early Reintroduction to Physical and Cognitive Activity

Previous recommendations for removing athletes from contact risk after concussion have expanded into “cocoon therapy” or “complete brain rest.” However, such forced inactivity isn’t supported by evidence, and prolonged inactivity may impede recovery. In one randomized, controlled trial, patients assigned to 5 days of strict rest reported more daily symptoms than those assigned to 1 to 2 days of rest followed by a stepwise return to activity (*Pediatrics* 2015; 135:213), supporting the role of early activity in concussion management.

Aerobic exercise has shown to have positive effects on the autonomic nervous system, brain neuroplasticity, and cerebral blood flow regulation. In another randomized trial, adolescent concussion patients assigned to aerobic exercise recovered faster (in 13 days) than those assigned to a placebo routine of stretching (17 days; *JAMA Pediatr* 2019; 173:319). Together, these studies suggest that returning to cognitive and physical activity sooner may promote more rapid concussion recovery.

Table: Persistent Postconcussion Symptoms (PPCS)

Acuity	Management Goal	Clinical Considerations	Action
Acute (minutes to hours)	Diagnose	<ul style="list-style-type: none"> Was there a mechanism? Was there a temporal onset of symptoms? Were the symptoms typical? Was there a lack of alternative diagnosis for acute symptoms? 	<ul style="list-style-type: none"> Properly diagnose concussion
	Protect from repeat injury	<ul style="list-style-type: none"> Avoid increased concussion risk Avoid risk of extremity injury Avoid prolonged concussion recovery 	<ul style="list-style-type: none"> Remove suspected concussion patient from contact risk (don't play through injury)
	Anticipate and facilitate recovery	<ul style="list-style-type: none"> Most concussions show improvement Impairments may be diverse: symptoms, cognition, balance, vestibular, ocular Identify those at risk for PPCS 	<ul style="list-style-type: none"> Educate, reassure, provide cognitive restructuring Use multimodal assessment Use validated tools to assess PPCS risk
Subacute (hours to days)	Promote activity	<ul style="list-style-type: none"> Symptoms may initially limit activities Nonrisky activities (cognitive, gentle physical) don't cause damage or prolong recovery Aerobic exercise may facilitate recovery Prolonged inactivity associated with longer recovery 	<ul style="list-style-type: none"> Avoid "cocoon" therapy Encourage early "safe" activities (cognitive, gentle physical) Prescribe gradual return to activity including aerobic exercise
	Manage headaches	<ul style="list-style-type: none"> What is the headache phenotype? What are the comorbidities? 	<ul style="list-style-type: none"> Conduct additional exam/diagnostic testing Treat the headache phenotype Consider comorbidities when choosing medications
	Manage dizziness	<ul style="list-style-type: none"> What is the differential diagnosis? 	<ul style="list-style-type: none"> Conduct additional exam/diagnostic testing Treat the diagnosis/diagnoses
	Manage sleep	<ul style="list-style-type: none"> What type of sleep problem is there? What are the comorbidities? 	<ul style="list-style-type: none"> Provide general sleep hygiene recommendations Conduct additional exam/diagnostic testing
Chronic (days to weeks)	Manage mental health	<ul style="list-style-type: none"> Consider behavioral responses to PPCS Identify mental health comorbidities 	<ul style="list-style-type: none"> Obtain neuropsychological assessment Treat identified mental health issues/diagnoses

Addressing Persistent Postconcussion Symptoms

HEADACHES

Headaches, often with migrainous features, are reported in over 50%–80% of concussion patients and can persist for months (*Continuum [Minneapolis]* 2021; 27:1646). The phenotype of post-traumatic migraine headache has implications for treatment and has been associated with prolonged recovery in a pediatric cohort (*JAMA Netw Open* 2021; 4:e211312).

A consensus approach to treatment of post-traumatic headache is to target the headache phenotype; however, evidence is lacking. Randomized, controlled pharmacotherapy trials for post-traumatic headache (PTH) or migraine (PTM) have been inconclusive. The choice of preventative medication for PTM may be guided by synergy for comorbidities and avoidance of undesirable adverse effects.

TBI/concussion may release nociceptive neuropeptides such as calcitonin gene–related peptide (CGRP) and others. Therefore, anti-CGRP medications may have a role in treating patients with post-traumatic

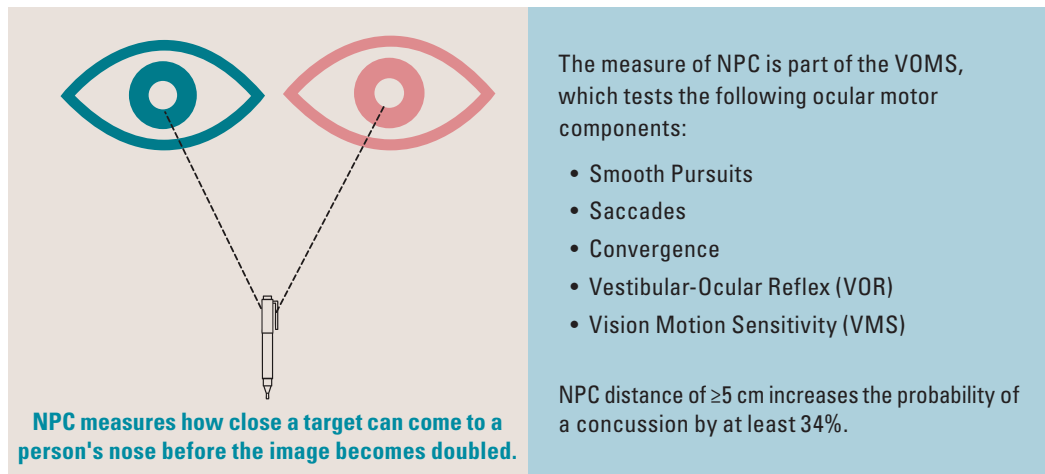
migraine (*J Headache Pain* 2020; 21:55). Triptans have also been shown to decrease CGRP-related inflammation. (For more information on these migraine medications, see the Topic Update on p. 15.)

DIZZINESS

Vestibular and ocular impairment occur frequently after concussion. Determining the etiology of post-traumatic dizziness requires careful history, examination, and differential diagnosis. Treatment may then be directed toward the underlying diagnosis, which may include migraine, benign paroxysmal positional vertigo (BPPV), syncope/presyncope, dysautonomia, and/or vestibular concussion.

It is important to screen the vestibular system in symptomatic patients. To evaluate the vestibulo-spinal system, we employ the Balance Error Scoring System (BESS). The Vestibular/Ocular Motor Screening (VOMS) tool is a good tool to assess vestibulo-ocular symptom provocation (*Am J Sports Med* 2014; 42:2479). While not intended to serve as a comprehensive measure of vestibular and ocular motor impairments, VOMS may aid in prompting referrals to rehabilitation.

FIGURE: Near Point Convergence (NPC)



Ocular motor impairments and symptoms in concussion may manifest as blurred vision, diplopia, impaired eye movements, difficulty in reading, dizziness, headaches, ocular pain, and poor visual-based concentration. The Vestibular/Ocular Motor Screening (VOMS) was developed to assess vestibular and ocular motor impairments via patient-reported symptom provocation after each assessment. The findings indicate that the VOR, VMS, and NPC distance components of the VOMS in combination are clinically useful in identifying concussions.

For a pictorial guide (appendix 2) on how to test each component of the VOMS test (appendix 1), refer to:

Mucha A et al. A Brief Vestibular/Ocular Motor Screening (VOMS) assessment to evaluate concussions: Preliminary findings. *Am J Sports Med* 2014; 42:2479. (<https://doi.org/10.1177/0363546514543775>)

Vestibular rehabilitation can treat vestibular hypofunction, BPPV, migraine-related dizziness, and central vestibular disorders. Vision therapy may treat oculomotor problems, accommodative deficits, impaired version movements, and minor ocular misalignments. For near point convergence insufficiency (>5 cm), targeted vision therapy has been shown effective (see Figure).

SLEEP DISTURBANCES

Sleep disturbances are reported in approximately 50% of concussion patients and, if left untreated, can amplify other symptoms (*Continuum [Minneapolis Minn]* 2021; 27:1646). Specific post-TBI sleep disturbances include insomnia, circadian rhythm disturbance, and excessive daytime sleepiness.

Providers should target sleep cycle regulation, beginning with environmental and behavior modifications including setting a nighttime sleep schedule, reducing daytime naps, and avoiding stimulants. Therapies such as melatonin, amitriptyline, and trazodone are recommended while benzodiazepines are contraindicated (*Arch Phys Med Rehabil* 2020; 101:382). Using medications to treat underlying pain syndromes and mood disturbances may also help insomnia. Persistent sleep issues may warrant a formal sleep evaluation.

COORDINATING MULTIDISCIPLINARY CARE

Non-evidence-based management of acute concussion (e.g., prolonged inactivity), preexisting or current comorbidities (e.g., cervical pain, sleep problems), and psychosocial factors (e.g., fear avoidance as a coping strategy) may prolong concussion recovery (*Continuum [Minneapolis Minn]* 2021; 27:1646). The

needs of concussion patients, particularly those with PPCS, benefit from a comprehensive approach to care. Neurologists can play a critical role in proper diagnosis and coordination of multidisciplinary care for PPCS. Clinicians in neuro-rehabilitation, sleep medicine, sports medicine, orthopedics, neuropsychology, and psychiatry all may contribute to optimal concussion care. Recognition and treatment of a concussion is best accomplished by a team that adopts an integrated focus on alleviating symptoms and encouraging a return to functional capacity (*Continuum [Minneapolis Minn]* 2021; 27:1646; *JAMA Netw Open* 2021; 4:e210207).

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DISCLOSURES

Shae Datta, MD, reports no disclosures.

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Topic Update

Modern Migraine Treatment — A Practical Approach

Yulia Orlova, MD, PhD, and Andrea M. Harriott, MD, PhD

The armamentarium for acute and preventive treatment of migraine has grown from a limited number of options repurposed from other indications to more-selective drugs and devices. The American Headache Society has issued a consensus on integrating new migraine treatments into clinical practice (*Headache* 2021; 61:1021). In this update, we will discuss three axes of migraine management in adults — lifestyle modifications, acute treatment, and preventive treatment — within the scope of therapies currently available in the United States.

Lifestyle Modifications

Lifestyle modifications should center around improving wellness and self-care. Traditionally, patients are advised to avoid external triggers, but this advice can lead to maladaptive coping. Some patient-reported triggers may represent premonitory symptoms like

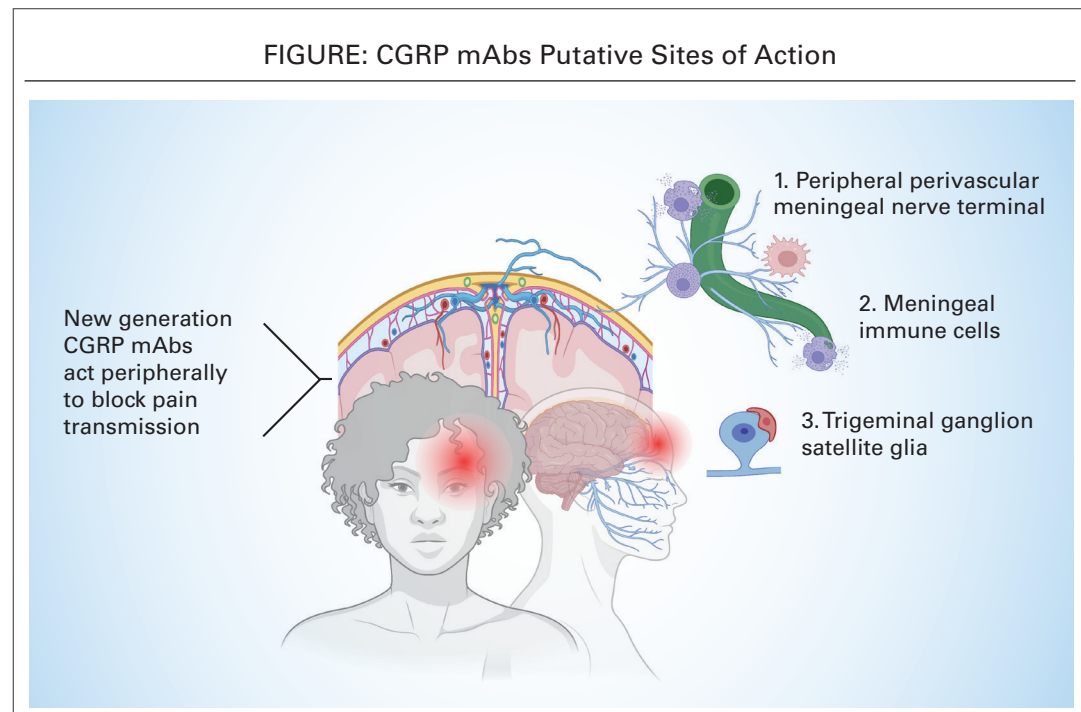
food craving and mood changes that may involve the hypothalamic, midbrain, and limbic areas (*Front Neurol* 2020; 11:140).

Acute Pharmacological Therapy

Acute treatment of migraine attacks should be initiated early. Acute medication use should be limited to 2 days/week to prevent medication overuse headache (MOH). Opioids and butalbital-containing medications should be avoided.

Nonsteroidal anti-inflammatory drugs (NSAIDs) and combined analgesics are effective for mild-to-moderate attacks. Migraine-specific treatments like triptans and newer drugs (ditans and gepants) are recommended for those with moderate-to-severe attacks.

FIGURE: CGRP mAbs Putative Sites of Action



CGRP mAbs — calcitonin gene-related peptide monoclonal antibodies

Created with BioRender.com

Triptans are selective serotonin (5HT) 1B/1D/1F receptor agonists. Lack of response to one triptan does not mean that other triptans will not be effective. Most payers require that at least two different triptans be tried before gepants or ditans are offered. Lasmiditan (Reyvow) is a ditan, a new 5HT 1F receptor agonist (Table). It is a controlled substance due to its central effect and may cause MOH (*J Headache Pain* 2019; 20:54). Unlike triptans, ditans do not act on 5HT 1B receptor and lack vasoconstrictive effect.

Gepants are small-molecule calcitonin gene–related peptide (CGRP) receptor antagonists. These include ubrogepant (Ubrovelvy) and rimegepant (Nurtec). Gepants have no direct vasoactive effect and can be used when there are contraindications to triptans. However, endogenous CGRP is a potent vasodilator, so there remains doubt if CGRP antagonists should be used in patients with poorly controlled vascular disorders (*Ann Neurol* 2020; 88:771).

Chest tightness, neck pain, and paresthesia are common side effects of triptans and can be misinterpreted as a coronary event or anaphylactic reaction. These are less common with almotriptan and frovatriptan. In a recent comparative study of triptans and newer migraine medications, ditans (Lasmiditan) were associated with the highest rate of side effects, but chest symptoms with ditans were rare (*JAMA Netw Open* 2021; 4:e2128544). Overall, triptans were more effective than gepants and ditans, but gepants had fewer side effects.

Ergotamine and dihydroergotamine (DHE) are probably effective. A new form of DHE nasal spray (Trudhesa) is now available that uses a precision olfactory delivery system to improve drug absorption and tolerability (*Headache* 2020; 60:40).

Nonpharmacological Treatment

Nonpharmacological therapy should be offered to patients who prefer not to take medications and in those with polypharmacy, adverse side effects, or medication contraindications. Cognitive behavioral therapy, biofeedback, and relaxation therapies are proven for migraine prevention, but there is limited evidence of their effectiveness for acute treatment. Mindfulness-based stress reduction may also improve quality of life and disability (*JAMA Intern Med* 2021; 181:317).

There are also devices approved by the FDA for acute and preventive treatment. These include a trigeminal nerve stimulator (Cefaly), a noninvasive vagus nerve stimulator (gammaCore), a single-pulse transcranial magnetic stimulator (sTMS mini), and a new remote electrical neuromodulation device for acute treatment (Nerivio).

Unfortunately, behavioral therapies and devices are often only considered when patients do not respond to multiple drug trials. Lack of access to care and cost are additional barriers to their use.

Preventive Pharmacological Therapy

Consider prevention in patients with disabling migraine or >4 migraine days per month. In selecting a medication, account for comorbidities, medication interactions, age, pregnancy planning, and frequency (i.e., episodic vs. chronic migraine, the latter defined as ≥15 headache days per month, 8 of which are migraine days).

OLDER-GENERATION THERAPIES: Beta-blockers (propranolol, metoprolol, timolol), anticonvulsants (divalproex, topiramate), and candesartan have established efficacy for migraine prophylaxis. Other classes and agents that are probably effective include antidepressants (amitriptyline, venlafaxine), other beta-blockers (atenolol, nadolol), lisinopril, and memantine. Tricyclic antidepressants like amitriptyline and beta-blockers tend to be tried first because of their low side-effect profiles. Both topiramate and divalproex carry risks for the developing fetus (cleft lip/palate and neural tube defects, respectively) and should not be used during pregnancy.

Most third-party payers require patients to try older drugs before starting newer ones because the older drugs are most cost-effective. Older-generation drugs require *slow* titration until: a) the target dose is reached; b) optimal benefit of at least 50% reduction in attacks occurs; or c) side effects appear. If patients do not respond after 2 to 3 months, consider switching therapy. Other medications, including zonisamide, may be helpful in those who do not respond to first-line agents. Medications like gabapentin and verapamil that have conflicting or inadequate evidence for efficacy *should not* be used as first-line drugs.

(continued on page 19)

Table: New Migraine Treatments

	Indication	Dose, Form	Mechanism of Action	Most Common Side Effects	Contraindications, Warning/Precautions
Devices					
Nerivio Wearable device connected to smartphone for remote nonpainful electrical upper arm skin stimulation	Acute treatment of episodic migraine	45-minute treatment	Conditioned pain modulation by stimulation of C and Aδ noxious sensory fibers of the upper arm	Local paresthesia, momentary pain increase	Contraindicated in those with implanted medical electronic device, uncontrolled epilepsy, congestive heart failure, severe cardiac or cerebrovascular disease
Ergot Derivatives					
Dihydroergotamine (Trudhesa) Nasal spray containing a single-dose DHE vial and precision olfactory delivery system	Acute treatment	1.45 mg administered as two metered nasal sprays 0.725 mg each into both nostrils	5HT _{1A} , 1B, 1D, 1F, 2A receptor, dopamine and norepinephrine α ₁ /α ₂ -adrenoceptor agonist	Rhinitis, nausea, dysgeusia, dizziness, vomiting, somnolence, pharyngitis, diarrhea	Contraindicated in pregnancy and in patients with coronary, cerebral, or peripheral vascular disease, uncontrolled hypertension, or arteriosclerosis
Ditans					
Lasmiditan (Reyvow)	Acute treatment	50 mg, 100 mg oral tablet, no more than one dose in 24 hours	5HT _{1F} receptor agonist	Dizziness, paresthesia, sedation	Controlled substance; avoid driving for at least 8 hours after taking; avoid in pregnancy; avoid in severe hepatic impairment
Gepants					
Rimegepant (Nurtec)	Acute treatment Prevention of episodic migraine	75 mg ODT as needed, limit to one dose in 24 hours 75 mg ODT every 48 hours	Small-molecule CGRP receptor antagonist	Nausea, abdominal pain, dyspepsia	Significant drug interactions; may require dose adjustment with CYP3A4 inhibitors and inducers and P-gp and BCRP inhibitors; avoid in pregnancy, severe hepatic impairment, and end-stage renal disease
Ubrogepant (Ubrolevy)	Acute treatment	50 mg, 100 mg oral tablet as needed	Small-molecule CGRP receptor antagonist	Nausea, somnolence	Significant drug interactions; may require dose adjustment with CYP3A4 inhibitors and inducers, P-gp and BCRP inhibitors; avoid in pregnancy and end-stage renal disease; reduce dose in severe liver disease

(continued on next page)

Gepants (continued)	
Atogepant (Qulipta)	<p>Prevention of episodic migraine</p> <p>60 mg daily, available in 10 mg, 30 mg oral tablet daily</p> <p>Small-molecule CGRP receptor antagonist</p> <p>Nausea, constipation, fatigue</p> <p>Significant drug interactions; may require dose adjustment with CYP3A4 inhibitors and inducers and OATP inhibitors; avoid in pregnancy and severe hepatic impairment; reduce dose in end-stage renal disease</p>
CGRP Monoclonal Antibodies	
Erenumab (Aimovig)	<p>Prevention of migraine</p> <p>70 mg or 140 mg sc every 28–30 days</p> <p>Fully human CGRP monoclonal Ab that binds CGRP receptor</p> <p>Injection site reaction, constipation, cramps, muscle spasm</p> <p>Serious hypersensitivity; avoid in pregnancy, constipation, hypertension</p>
Galcanezumab (Emgality)	<p>Prevention of migraine</p> <p>Loading dose 240 mg once, then 120 mg monthly sc</p> <p>Humanized monoclonal Ab that binds to CGRP ligand</p> <p>Injection site reactions</p> <p>Serious hypersensitivity; avoid in pregnancy</p>
Fremanezumab (Ajovy)	<p>Prevention of migraine</p> <p>225 mg monthly or 675 mg quarterly sc</p> <p>Humanized monoclonal Ab that binds to CGRP ligand</p> <p>Injection site reactions</p> <p>Serious hypersensitivity; avoid in pregnancy</p>
Eptinezumab (Vyapti)	<p>Prevention of migraine</p> <p>100 mg or 300 mg IV every 3 months</p> <p>Humanized monoclonal Ab that binds to CGRP ligand</p> <p>Hypersensitivity reactions, including angioedema, urticaria, facial flushing, and rash</p> <p>Serious hypersensitivity; avoid in pregnancy</p>

DHE — dihydroergotamine; ODT — orally disintegrating form; CGRP — calcitonin gene-related peptide; CYP3A4 — cytochrome P450 3A4 enzyme; P-gp — P-glycoprotein efflux transporter; BCRP — breast cancer resistance protein; OATP — organic anion-transporting polypeptide; sc — subcutaneous; Ab — antibody; IV — intravenous

(continued from page 16)

For chronic migraine, 155 units of onabotulinum toxin A can be administered as a series of 31 injections in the head and neck every 3 months if three oral preventives have been tried without benefit for at least 2 to 3 months.

NEWER-GENERATION THERAPIES: Headache involves activation of CGRP-containing peripheral nociceptors that innervate the meninges (*Lancet Neurol* 2019; 18:795). When released from the peripheral nerve terminal, CGRP may act on peripheral nerves, meningeal immune cells, or specialized satellite glial cells (Figure). Newer migraine-specific medications target CGRP to block pain transmission. CGRP monoclonal antibodies (CGRP mAbs: erenumab [Aimovig], fremanezumab [Ajovy], galcanezumab [Emgality], eptinezumab [Vypti]) have similar efficacy and a good tolerability profile (Table). These drugs do not require slow titration and are given as monthly or quarterly self-injection or infusion (*Nat Rev Neurol* 2018; 14:338).

Oral rimegepant (Nurtec) is indicated not only for acute treatment but also for prevention when it is taken every other day (*Lancet* 2021; 397:51). Atogepant (Qulipta) is an oral gepant approved for prevention only and is taken daily (*N Engl J Med* 2021; 385:695). Most payers only cover CGRP mAbs or gepants if a patient has tried at least two older-generation medications without benefit for 2 to 3 months. While injectable CGRP mAbs do not have meaningful drug–drug interactions, oral gepants are subject to drug interactions when coadministered with cytochrome P450 3A4 enzyme (CYP3A4) or P-glycoprotein efflux transporter (P-gp) inhibitors/inducers. Some interactions can lead to toxicity or loss of clinical effect and may require dose reduction or complete avoidance. We encourage clinicians to check possible interactions when prescribing gepants.

Combination therapies (gepant with mAb or Botox with mAb) can be effective and require further study.

Challenges and Future Direction

The CGRP blockers brought with them the sense of a new era in migraine treatment. However, the limitations in prescribing them have raised concern about whether the focus of future drug development should take into account drug delivery systems and how to make these systems less cost-prohibitive. The need for prior authorization for migraine-specific drugs imposes enormous administrative burdens that affect patient care. Future studies should not only address these quality-of-care needs but also compare efficacies of newer versus older pharmacological and nonpharmacological approaches with acute and preventive migraine treatments.

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DISCLOSURES

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Topic Update

The Microbiota-Gut-Brain Axis: A Highway of Communication Between Lifestyle and Brain Health

Robin M. Voigt, PhD, and Ali Keshavarzian, MD, FRCP, FACP, AGAF, MACG

Organs and tissues in the body are in bidirectional communication in healthy and disease states. The brain influences the function of many organs and concurrently brain function is impacted by organs including the kidneys, lungs, heart, and the gastrointestinal tract (GIT), as well as the microorganisms within the GIT (called the microbiota). The microbiota-gut-brain axis has emerged as an important communication axis and could be a mechanism by which lifestyle impacts brain health and disease.

Microbiota-Gut-Brain Communication

The microbiota-gut-brain axis is a term that describes the bidirectional communication that occurs between the microbiota that inhabit the GIT and the brain (*Physiol Rev* 2019; 99:1877). This communication can be categorized as top-down or bottom-up. Top-down communication occurs when insults (e.g., stroke), trauma (e.g., traumatic brain injury), psychological stress, and even brain disease induce proinflammatory changes in the intestinal microbiota (called dysbiosis). Bottom-up communication has been elegantly elucidated in studies demonstrating that the intestinal microbiota influences brain development, neuroinflammation, structure, function, behavior (affect, social behavior, cognition), and pathology/disease.

The Microbiota: A Canary in a Coal Mine?

Lifestyle is important in the development of many neurologic disorders, but precisely how it impacts the brain remains unclear. Numerous lifestyle factors that influence risk of neurologic disease also impact the microbiota, including consumption of a Western diet and alcohol, stress, disrupted sleep/circadian rhythms, and lack of physical activity. While there is no “normal” microbiota, suboptimal lifestyles are associated with dysbiotic microbiota communities characterized by a high abundance of putative proinflammatory bacteria and pathobionts (microorganisms that can cause harm under certain circumstances) and low abundance of putative

beneficial bacteria. Dysbiotic microbiota are also observed in many neurologic diseases, which has led to the microbiota being considered a proverbial “canary in the coal mine.” However, compelling data indicate that the microbiota are not just a passive bystander and may influence brain disease (*Nat Rev Microbiol* 2021; 19:241).

Mechanisms of Communication

Mechanisms of communication between the microbiota and the brain include changes in intestinal and blood brain barriers, the peripheral/brain immune system, production of neurotransmitters and metabolites, modification of diet and host-produced substances, enteroendocrine signaling, autonomic and enteric nervous system, hypothalamic-pituitary-axis, and other mechanisms that are only just beginning to be understood, such as extracellular vesicles (*Physiol Rev* 2019; 99:1877). It is likely that many mechanisms contribute in tandem to mediate communication between the intestinal microbiota and the brain.

Neurologic Conditions with Evidence of Microbiota-Gut-Brain Communication

Compelling data suggest an association between the microbiota and the development/progression and treatment of numerous brain diseases and disorders. We do not aim to comprehensively cover all neurologic conditions; instead, we will focus on Alzheimer’s disease (AD) and Parkinson’s disease (PD).

Evidence indicates that the microbiota are clinically important in AD and PD. Individuals with AD (*Front Aging Neurosci* 2021; 13:650047) and PD (*Neurosci Res* 2021; 168:100) have microbiota dysbiosis, but no studies have conclusively demonstrated that dysbiosis precedes diagnosis, which is needed to establish causality. However, diet (which robustly impacts the microbiota) is a well-established risk factor for AD (*Front Neurosci* 2021; 15:736814) and PD (*Front Neurol* 2019; 10:1245). Dietary components can impact the brain directly, independent of the microbiota; however,

studies that directly manipulate the microbiota are useful in demonstrating the microbiota-brain connection. Microbiota-modifying interventions (e.g., prebiotics, probiotics) demonstrate beneficial effects on cognition and memory, which lends strength to the premise that microbiota are key in mediating the effects of diet on the brain in AD (*Front Aging Neurosci* 2021; 13:650047). Similarly, modifying the microbiota improves PD symptoms (*Neurosci Res* 2021; 168:100). However, it should be noted that not all studies report positive outcomes of microbiota modifications; this may be related to study-specific issues such as dose, duration, or patient population.

The microbiota also influence response to pharmacologic treatment. For example, the intestinal microbiota can metabolize levodopa and consequently influence levodopa-induced dyskinesia (*Nat Commun* 2019; 10:310). Therefore, treatment of diseases with levodopa (e.g., PD, multiple system atrophy) may be impacted by the microbiota, and similar effects are likely true for other pharmacotherapies.

Other microbiota niches in the GIT may be important. For example, convincing data link the oral microbiota to AD, with reports demonstrating increased risk of AD associated with poor oral hygiene (*Int J Environ Res Public Health* 2021; 18:11157).

Finally, compelling data exist implicating the microbiota-gut-brain axis in other neurologic conditions, including multiple sclerosis, multiple system atrophy, amyotrophic lateral sclerosis, epilepsy, stroke, migraine, traumatic brain injury, and spinal cord injury and psychiatric conditions including addiction, post-traumatic stress disorder, depression, anxiety, schizophrenia, attention deficit-hyperactivity disorder, and autism (*Lancet Neurol* 2020; 19:179).

Clinical Usefulness of the Microbiota

A tremendous body of research demonstrates that the microbiota are altered in neurologic conditions. However, the notion that the microbiota is sufficient to cause brain disease is highly controversial. It is possible that the microbiota are only a biomarker of disease, and yet compelling data suggest that the microbiota impact the brain. We contend that even if lifestyle-induced changes in the microbiota are not an initiating cause of a disease (and are instead a consequence of the disease, i.e., top-down communication), the microbiota can influence disease progression and treatment via neuroinflammation and drug

metabolism. Therefore, modifying or “remodeling” the microbiota is an opportunity to improve brain function, influence disease development/progression, and improve treatment.

Multiple approaches can be used to remodel the microbiota: antibiotics (depleting bacteria), probiotics (live bacteria), prebiotics (promoting growth of beneficial bacteria), and symbiotics (combination prebiotic/probiotic) can be used to selectively promote or disfavor groups of bacteria. Lifestyle interventions can also beneficially influence the microbiota, including regular physical activity, sleep/circadian hygiene, stress reduction, and consumption of a high-fiber, low-sugar diet. Approaches such as administration of beneficial postbiotics (products of the microbiota) can be administered to mimic beneficial modifications in the microbiota, and to alter the microbiota community. Finally, fecal microbiota transplantation (FMT) is being used in certain GI diseases.

Additional studies are required to determine if lifestyle modification-induced changes in the microbiota improve disease course and quality of life in patients with neurologic conditions. Microbiota modification may be a low-risk, potentially high-reward approach to enhance existing treatment approaches for neurologic conditions.

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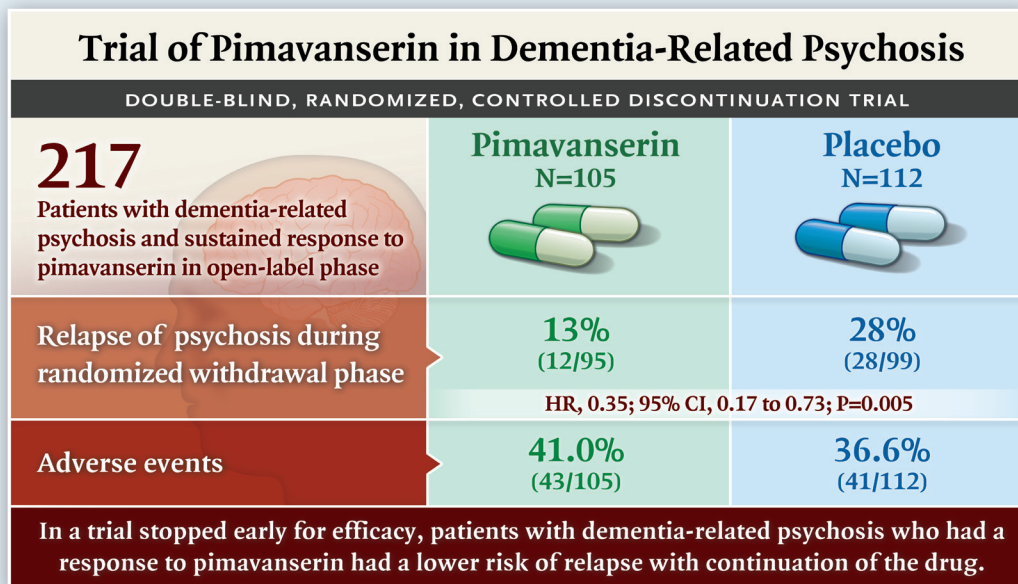
DISCLOSURES

Robin M. Voigt, PhD, reports no disclosures.

Ali Keshavarzian, MD, FRCP, FACP, AGAF, MACG, reports no disclosures.

NEJM Visual Abstract

Trial of Pimavanserin in Dementia-Related Psychosis



Background

Patients with dementia due to neurodegenerative disease can have dementia-related psychosis. The effects of the oral 5-HT_{2A} inverse agonist and antagonist pimavanserin on psychosis related to various causes of dementia are not clear.

Conclusions

In a trial that was stopped early for efficacy, patients with dementia-related psychosis who had a response to pimavanserin had a lower risk of relapse with continuation of the drug than with discontinuation. Longer and larger trials are required to determine the effects of pimavanserin in dementia-related psychosis. (Funded by Acadia Pharmaceuticals; HARMONY ClinicalTrials.gov number, NCT03325556.)

Pierre N. Tariot, MD, et al.

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 DOI: 10.1056/NEJMoa2034634

Guideline Watch

2021 Guidelines on MRI Use for Multiple Sclerosis

A consensus report from three MS organizations.



SPONSORING ORGANIZATION

Magnetic Resonance Imaging in MS (MAGNIMS), Consortium of MS Centers (CMSC), and North American Imaging in MS Cooperative (NAIMS)

BACKGROUND AND OBJECTIVE

Experts from the sponsoring organizations recently met to update international consensus recommendations on how and when to use magnetic resonance imaging (MRI) for multiple sclerosis (MS) diagnosis, prognosis, and treatment monitoring.

KEY RECOMMENDATIONS

Highlights from the report include:

- Recommended standardized brain, spinal cord, and optic nerve protocols are defined for field strength, thickness, resolution, and coverage. Optional sequences are listed.
- Gadolinium should include at least a 5-minute time delay, and more optimally a 10-minute delay. Gadolinium is recommended for the initial, diagnostic scan and for a variety of scenarios for monitoring, if the presence of a gadolinium lesion would change management.
- For radiologically and clinically isolated syndromes not fulfilling MS criteria, follow-up imaging should include brain MRI every 6 to 12 months with identical imaging parameters, without gadolinium.
- Standardized imaging interpretation and reporting should include T2 lesion counts, gadolinium lesion counts, the types of lesions, and interval changes.
- Spinal cord and optic nerve imaging should be included for select circumstances. For example, spinal cord imaging is important for diagnosis and prognosis, optic nerve imaging for differential diagnosis and for new visual symptoms.
- MRI should be repeated 3 to 6 months after treatment onset. MRI should be considered annually, with longer intervals for clinically stable patients after the first few years of treatment.
- MRI should be used for drug safety monitoring, such as for progressive multifocal leukoencephalopathy (PML) and cryptococcal meningitis. For medications that confer high risk for PML, a brain MRI should be performed before switching to the next agent.

WHAT'S CHANGED

These guidelines represent a consolidation of those made in the 2015 MAGNIMS and 2016 CMSC guidelines on MRI use in MS diagnosis and monitoring.

Comment

These recommendations are based on a comprehensive review of the literature to date and provide good details on the key issues and variables with MRI in MS care and treatment decisions. In addition, they can aid neuroradiologists in updating their protocols and reports.

Robert T. Naismith, MD

Robert T. Naismith, MD, serves as Neurology Clerkship Director at Washington University in St. Louis. His disclosure information is available at www.jwatch.org/NA53783.

Wattjes MP et al. MAGNIMS–CMSC–NAIMS consensus recommendations on the use of MRI in patients with multiple sclerosis. *Lancet Neurol* 2021 Aug; 20:653. ([https://doi.org/10.1016/S1474-4422\(21\)00095-8](https://doi.org/10.1016/S1474-4422(21)00095-8))

Refining Treatment Decisions for Patent Foramen Ovale Associated with Stroke

Patient and PFO characteristics affect likelihood of benefiting from PFO closure.

Trials evaluating patent foramen ovale (PFO) closure for patients with stroke or transient ischemic attack have had varied results. Recent studies show a modest benefit for closure. Since PFO prevalence in the general population is estimated to be 20% to 25%, PFO is not considered causally linked to stroke in some patients. Refining which patients are more likely to have a link between PFO and stroke would be useful. These investigators pooled data from six trials that included 3740 patients (median age, 46 years; 55% men). They compared the stroke rate between patients assigned to medical treatment versus closure. In addition, they calculated treatment implications of a high versus low RoPE score, which assigns points according to stroke characteristics and risk factors. Using the PASCAL classification system, which adds PFO shunt size and atrial septal aneurysm to the RoPE score, they estimated treatment effects.

A large shunt was present in 45% of patients, and an atrial septal aneurysm was present in 33%. The annual stroke risk was 1.09% with medical treatment and 0.47% with PFO closure. The treatment benefit was increased with a higher RoPE score (implying greater

likelihood that the PFO was causal). In the PASCAL categories of unlikely, possible, or probable relation of the PFO to stroke, the hazard ratios were 1.14, 0.38, and 0.10, respectively. The 2-year absolute risk reduction was -0.7% , 2.1% , and 2.1% in the unlikely, possible, and probable categories. Atrial fibrillation present beyond 45 days was higher in the closure group (2.4% vs 0.8%), as was venous thromboembolism (1.4% vs 0.5%).

Comment

This study provides useful estimates of which patients are likely to benefit from PFO closure and which patients are unlikely to benefit. The overall recurrent-stroke rate is low in this population, reinforcing that PFO is not a “ticking time bomb.” Shared decision making among patients, stroke specialists, and cardiologists is strongly recommended.

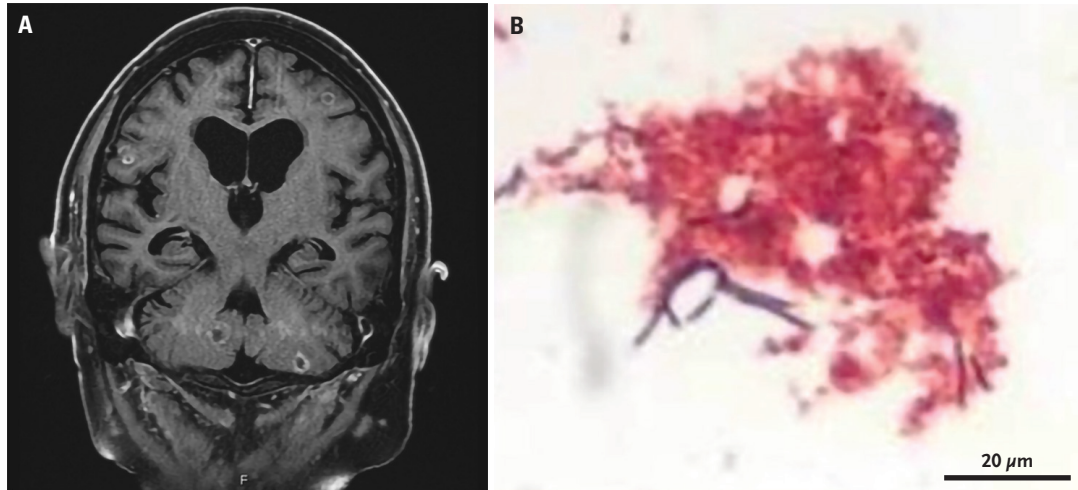
Seemant Chaturvedi, MD

Seemant Chaturvedi, MD, is the Stewart J. Greenebaum Endowed Professor of Stroke Neurology and Stroke Program Director at the University of Maryland Medical System. His disclosure information is available at www.jwatch.org/na54425.

Kent DM et al. Heterogeneity of treatment effects in an analysis of pooled individual patient data from randomized trials of device closure of patent foramen ovale after stroke. *JAMA* 2021 Dec 14; 326:2277. (<https://doi.org/10.1001/jama.2021.20956>)

Images In Clinical Medicine

Nocardial Brain Abscesses



An 80-year-old man undergoing treatment for multiple myeloma presented to the emergency department with a 2-week history of low-grade fevers and confusion. On examination, he had slurred speech and was not oriented to place or time. A computed tomographic image of the head and a radiograph of the chest were normal. Despite empirical treatment with broad-spectrum antibiotic agents while further evaluation was ongoing, the patient became obtunded. Magnetic resonance imaging of the head revealed multiple ring-enhancing lesions (Panel A). A lumbar puncture was performed. Cerebrospinal fluid (CSF) analysis showed 923 nucleated cells per microliter (reference range, 0 to 5), of which 91% were neutrophils; the glucose level was 36 mg per deciliter (2.0 mmol per liter; reference range, 40 to 80 mg per deciliter [2.2 to 4.4 mmol per liter]), and the total protein level was 147 mg per deciliter (reference range, 15 to 45). A CSF culture grew *Nocardia farcinica* (Panel B). *Nocardia* are aerobic gram-positive bacilli that can invade the lung, skin, or central nervous system, especially in immunocompromised persons. The patient was treated with a prolonged course of antibiotics. His hospital course was complicated by a subarachnoid hemorrhage, a mycotic aneurysm, and hemiplegia. He was ultimately discharged home.

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