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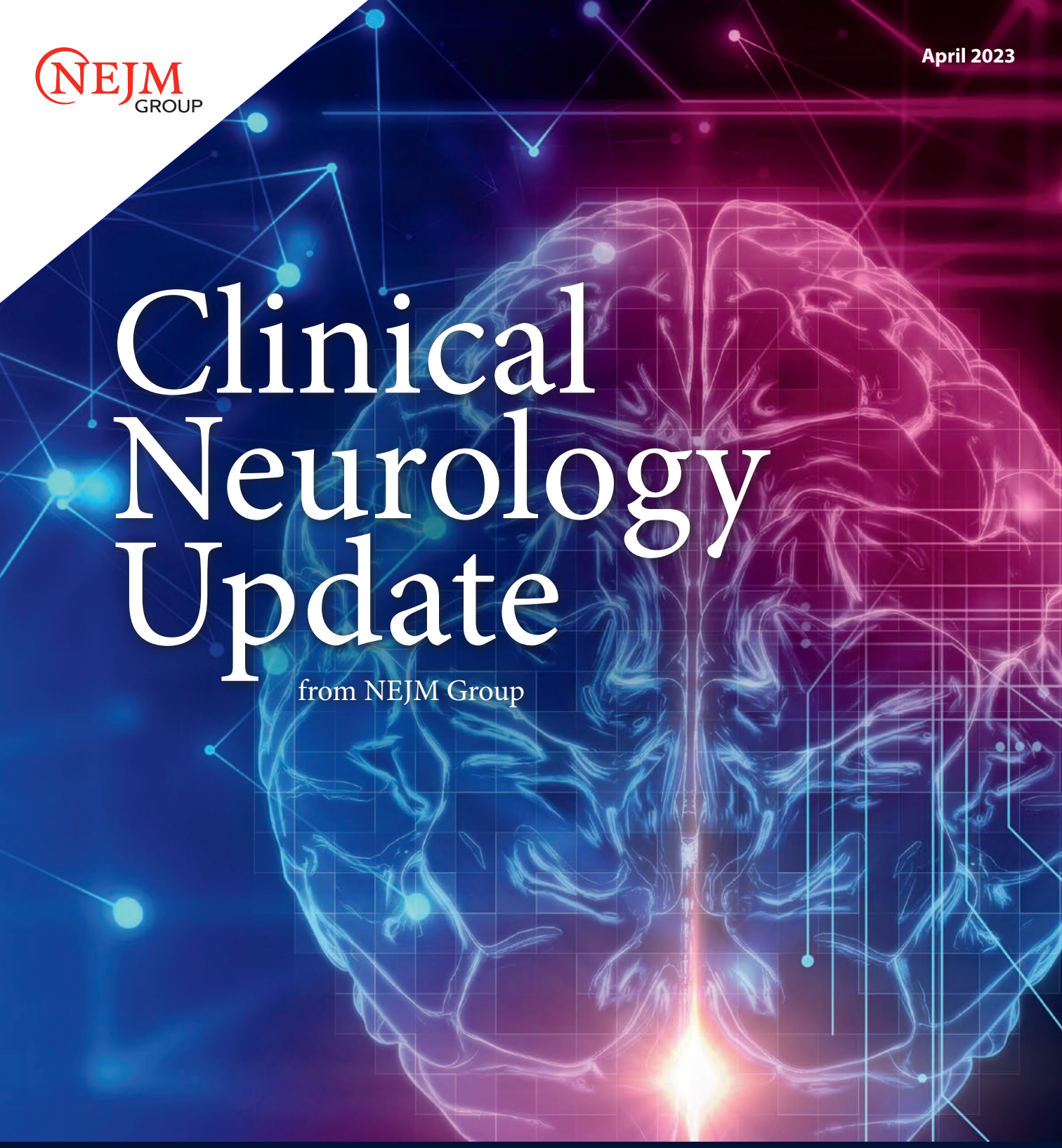

- What's New in Epilepsy Treatment?
- Treating Hypersomnia
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FROM the Editor

The past year has shown continued advances in our understanding of neurological disease. In addition, we now have more treatment options than ever before. This issue of NEJM Group's *Clinical Neurology Update* features these innovations across the breadth of neurology and our subspecialties.

Our first Topic Update from Dr. Baibing Cheng and Dr. Joseph Sirven features the latest developments in epilepsy management and allows us to contextualize the variety of available medications and modalities of therapy with some useful clinical pearls.

The second Topic Update from Dr. Jennifer Grom and Dr. Karin Johnson summarizes the emerging and expanding treatments for management of hypersomnia. After years of limited options, there are newer treatments and mechanisms available for both primary disorders of hypersomnolence as well as hypersomnolence due to medical or neurological disorders.

Our third Topic Update from Dr. James Wymer features updated guidelines for the diagnosis of amyotrophic lateral sclerosis (ALS) and includes a practical summary of newer ALS treatments. This is another example of a disease that now has expanded treatment options due to our more nuanced understanding of its mechanism.

Our Research Summary features the study that led to FDA approval of lecanemab, the second anti-amyloid medication for Alzheimer's disease. The Guideline Watch is a summary of updated practice guidance for hemorrhagic stroke. Our Visual Summary illustrates efficacy of subcutaneous treatment for advanced Parkinson's disease. NEJM Journal Watch Summaries include a selection of important articles from the past year in ischemic stroke, multiple sclerosis, brain health, and autoimmune disease. Finally, Images in Clinical Medicine illustrates spinal cord involvement from nitrous oxide.

It is an exciting time for neurology, as advances in our mechanistic understanding of disease are leading to further innovations with expanding and increasing therapeutic options across all aspects of our field. We hope that these articles help you enhance and update your patient care.

Michael S. Jaffee, MD, FAAN

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Topic Update

Approaches to Managing Epilepsy

Baibing Chen, MD, MPH, and Joseph I. Sirven, MD

An estimated 3.5 million people in the United States live with epilepsy. The burden of epilepsy extends beyond the effects of seizures themselves to encompass significant negative impacts on mental health, social and financial well-being, and overall quality of life. Here we will discuss the current options for treatment of epilepsy, focusing on practical approaches for neurologists.

Epilepsy is defined as the occurrence of two seizures more than 24 hours apart, or one seizure with supportive evidence (e.g., magnetic resonance imaging or electroencephalogram abnormalities) that indicates increased risk of a recurrent seizure. Current management options include antiseizure medications (ASMs), dietary therapies, neuromodulation devices, and surgical management. The main goal of antiseizure therapy is to achieve seizure freedom, ideally with the lowest effective dosing of appropriate ASM(s) and/or the least invasive method. Should one fail to achieve seizure freedom with ASM alone, other therapeutic options are available.

Antiseizure Medications

There are currently more than 25 FDA-approved ASMs available in the United States for the management of epilepsy (see Table on following pages), each with its own unique advantages and disadvantages. To individually tailor ASM selection to each patient, the prescribing physician must consider efficacy against specific seizure types or epilepsy syndromes, side effect profiles, patient comorbidities, available formulations, and pharmacokinetic properties. Should a patient require multiple ASMs, considerations should be taken to minimize drug–drug interactions. Most ASMs are metabolized by the liver and carry risks of interactions when taken together.

Special consideration should be given to prescribing ASMs for women who are pregnant or plan to become pregnant and for elderly patients. All women of pregnancy age should be counseled on ASM side effects on the fetus. The risk of teratogenicity varies between agents. Valproate, carbamazepine, ethosuximide, phenobarbital, phenytoin, and topiramate carry the highest risk of fetal malformation. Additionally, many ASMs can decrease in concentration during pregnancy and therefore increase the risk of breakthrough seizure. It is beneficial to check ASM levels early in pregnancy and every trimester (*JAMA Neurol* 2022; 79:370). Free ASM levels may be more advantageous compared with total ASM levels, particularly for ASMs that are less protein-bound and as total plasma protein decreases throughout the course of a pregnancy. In the elderly population, comorbid illnesses, reduced protein binding, decreased renal clearance, and slower metabolism also increase risk of ASM toxicity. Due to high prevalence of comorbidity in this population, special attention should be paid to drug interactions and adverse effects.

For those who continue to have seizures on an appropriate monotherapy at a therapeutic dose, the next step is to try an alternative monotherapy or a dual therapy with synergistic effects (e.g., lamotrigine and valproate) while minimizing synergistic toxicity (e.g., combining two sodium-channel blockers). Approximately 30% of people with epilepsy do not achieve seizure freedom with one to two ASMs (*Epilepsia* 2018; 59:2179). Those who fail to achieve sustained seizure freedom after adequately trying two appropriately chosen ASMs, either as monotherapy or in combination, have drug-resistant epilepsy. These patients should be considered for alternative methods of seizure control, including dietary therapy, epilepsy surgery, and/or neuromodulation.

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Joseph I. Sirven, MD, is Professor of Neurology and Chair Emeritus at the Department of Neurology at Mayo Clinic in Jacksonville, Florida. He is Chair of Education for the American Academy of Neurology and Editor-in-Chief of *Brain & Life en Español*. **Disclosures:** Dr. Sirven reports equity ownership or stock options in Doximity and serves on the data-monitoring safety boards of Medtronic and Neurona.

Table. Current Antiseizure Medications and Their FDA-Approved Indications in Epilepsy

Seizure Type/ Epilepsy Syndrome	FDA-Approved Antiseizure Medication	Mechanism of Action							Pearls/Comments
		Ca^{2+} channel	Na^{+} channel	GABA	NMDA receptor	SV2A	AMPA receptor	Serotonin	
Generalized seizure	Ethosuximide (absence seizure)	Block T-type							Long half-life of 30–60 hours; risk of headache in children
	Felbamate			Enhance	Antagonize				Risk of lethal aplastic anemia and/or hepatic failure
	Lacosamide		Block						Enhance slow inactivation of Na^{+} channel; dose-dependent PR interval prolongation
	Lamotrigine		Block						Risk of SJS; levels increase with valproate, decrease with pregnancy
	Levetiracetam					Bind			Risk of psychiatric side effects including suicidal ideations
	Perampanel						Antagonize		Risk of psychiatric side effects including suicidal and homicidal ideations
	Phenobarbital			Enhance					Potent P450 inducer; risk of osteoporosis; contraindicated in AIP
	Phenytoin/ Fosphenytoin		Block						Risk of ataxia, incoordination, nystagmus, osteoporosis
	Primidone			Enhance					Risk of osteoporosis; contraindicated in AIP
	Topiramate		Block	Enhance	Antagonize				Risk of cognitive impairment, kidney stones, weight loss
	Valproate	Block T-type	Block	Enhance					Risk of teratogenicity, hepatotoxicity, pancreatitis

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Table. Current Antiseizure Medications and Their FDA-Approved Indications in Epilepsy (continued)									
Seizure Type/ Epilepsy Syndrome	**FDA-Approved Antiseizure Medication**	**Mechanism of Action**							**Pearls/Comments**
		Ca^{2+} channel	Na^{+} channel	GABA	NMDA receptor	SV2A	AMPA receptor	Serotonin	
Focal seizure	Brivaracetam					Bind			Higher affinity and selectivity for SV2A compared with levetiracetam
	Carbamazepine		Block						Risk of SJS in Asian patients with *HLA-B*1502* allele
	Cenobamate		Block						Long half-life of 50–60 hours; rare risk of DRESS
	Eslicarbazepine		Block						Enhance slow inactivation of Na^{+} channel
	Felbamate			Enhance	Antagonize				Risk of lethal aplastic anemia and hepatic failure
	Gabapentin	Bind α2δ subunit							May cause myoclonus; adjunct therapy only
	Lacosamide		Block						Enhance slow inactivation of Na^{+} channel; dose-dependent PR interval prolongation
	Lamotrigine		Block						Risk of SJS; levels increase with valproate, decrease with pregnancy.
	Levetiracetam					Bind			Risk of psychiatric side effects including suicidal ideations
	Oxcarbazepine		Block						Risk of hyponatremia; exacerbate absence and myoclonic seizures
	Perampanel						Antagonize		Risk of psychiatric side effects including suicidal and homicidal ideations

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Table. Current Antiseizure Medications and Their FDA-Approved Indications in Epilepsy (continued)

Seizure Type/ Epilepsy Syndrome	FDA-Approved Antiseizure Medication	Mechanism of Action							Pearls/Comments
		Ca^{2+} channel	Na^{+} channel	GABA	NMDA receptor	SV2A	AMPA receptor	Serotonin	
Focal seizure	Phenobarbital			Enhance					Potent P450 inducer; risk of osteoporosis; contraindicated in AIP
	Phenytoin/ Fosphenytoin		Block						Risk of ataxia, incoordination, nystagmus, osteoporosis
	Pregabalin	Bind α2δ subunit							May cause myoclonus at high doses; adjunct therapy only
	Primidone			Enhance					Risk of osteoporosis; contraindicated in AIP
	Tiagabine			Enhance					Risk of psychiatric side effects; exacerbate absence and myoclonic seizures
	Topiramate		Block	Enhance	Antagonize				Risk of cognitive impairment, kidney stones, weight loss
	Valproate	Block T-type	Block	Enhance					Risk of teratogenicity, hepatotoxicity, pancreatitis
	Vigabatrin			Enhance					Risk of permanent visual field impairment
	Zonisamide	Block T-type	Block						Long half-life of around 60 hours; not an enzyme inducer or inhibitor
Lennox–Gastaut syndrome (LGS)/ Dravet syndrome (DS)/Epileptic spasms (ES)	Cannabidiol (DS, LGS)			Enhance					May modulate intracellular Ca^{2+}; increase concentration of clobazam metabolite
	Clobazam (LGS)			Enhance					Adjunct therapy only; rare risk of SJS

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Table. Current Antiseizure Medications and Their FDA-Approved Indications in Epilepsy (continued)

Seizure Type/ Epilepsy Syndrome	FDA-Approved Antiseizure Medication	Mechanism of Action							Pearls/Comments
		Ca^{2+} channel	Na^{+} channel	GABA	NMDA receptor	SV2A	AMPA receptor	Serotonin	
Lennox–Gastaut syndrome (LGS)/ Dravet syndrome (DS) /Epileptic spasms (ES)	Clonazepam (LGS)			Enhance					Approved use in absence seizures in patients that fail ethosuximide
	Felbamate (LGS)			Enhance	Antagonize				Risk of lethal aplastic anemia and hepatic failure
	Fenfluramine (DS, LGS)							Enhance	Risk of decreased appetite, valvular heart disease
	Lamotrigine (LGS)		Block						Risk of SJS; levels increase with valproate, decrease with pregnancy
	Rufinamide (LGS)		Block						Risk of shortening QT interval
	Stiripentol (LGS)			Enhance					Adjunct therapy to patients also taking clobazam
	Topiramate (LGS)		Block	Enhance	Antagonize				Risk of cognitive impairment, kidney stones, weight loss
	Vigabatrin (ES)			Enhance					Risk of permanent visual field impairment

AIP — acute intermittent porphyria; AMPA — alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; DRESS — drug reaction with eosinophilia and systemic symptoms; GABA — gamma-aminobutyric acid; GTC — generalized tonic-clonic; NMDA — N-methyl-D-aspartate; SJS — Stevens–Johnson syndrome; SV2A — synaptic vesicle glycoprotein 2A

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Newer ASMs

In the United States, several new ASMs, including stiripentol, fenfluramine, and cenobamate, received FDA approval over the past few years for the management of seizures.

Stiripentol is approved as an adjunct therapy for patients with Dravet syndrome who are aged ≥6 months, weigh ≥15 pounds, and take clobazam. Its main mechanism of action (MOA) is likely through enhancing γ-aminobutyric acid neurotransmission and/or indirectly increasing clobazam concentration via cytochrome P450 inhibition (*Epilepsia* 2006; 47:704; *Drug Metab Dispos* 2006; 34:608).

Fenfluramine is approved for patients aged ≥2 years with Dravet syndrome or Lennox–Gastaut syndrome. Originally recognized as an appetite suppressant, fenfluramine has a unique MOA via serotoninergic pathways. Currently, the antiseizure effect from increased serotonin concentration in the central nervous system in the case of fenfluramine remains unclear (*CNS Drugs* 2020; 34:1001).

Cenobamate is approved for patients aged ≥18 years with focal onset epilepsy. It acts as a sodium-channel blocker with preference for the persistent sodium current, as well as a GABAergic agent. Studies have shown excellent efficacy in patients with refractory focal seizures, with monthly seizure reduction in up to 56% and seizure freedom rate of up to 28% (*Neurology* 2020; 94:e2311).

Dietary Therapy

Ketogenic diet, median chain triglyceride diet, modified Atkins diet, and low glycemic index diet are therapeutic options for patients with epilepsy, though the current evidence is stronger in the pediatric compared with the adult population (*Epilepsy Behav* 2011; 21:115).

Surgical Management

In patients with drug-resistant epilepsy who have a single seizure focus that can be safely resected, surgery provides the best option for seizure freedom, achieved in an estimated 65% to 73% of patients with temporal lobe seizures and in 27% to 60% of those with extratemporal lobe seizures (*Neurology* 2022; 98:e1902).

Anterior temporal lobectomy (ATL) can help achieve seizure freedom in most patients with mesial temporal onset epilepsy. Removal of symptomatic lesions such as cavernomas, indolent tumors, and focal cortical dysplasia is associated with a high rate of seizure freedom. Seizure outcomes are typically less successful in nontemporal lobe epilepsies and may carry more risk in terms of permanent deficits due to eloquent cortex (areas of the brain that if removed, may lead to significant linguistic, sensory, or motor deficits) at risk.

There is increasing interest in the use of minimally invasive surgical techniques. One such technique is laser interstitial thermal therapy (LiTT), which has become widely adopted for mesial temporal sclerosis (MTS), hypothalamic hamartomas, and small cortical dysplasias. A small series has shown LiTT amygdalohippocampotomy outcomes in MTS to be similar to those from open ATL, with less neurocognitive risk (*Ann Neurol* 2018; 83:575).

Neuromodulation

In patients who have seizure onset foci that are not amenable to surgical resection or disconnection, neuromodulation is a viable option. Three devices are approved for the management of refractory focal epilepsies: vagus nerve stimulation (VNS), deep brain stimulation of the anterior nucleus of the thalamus (ANT-DBS), and responsive neurostimulation (RNS). These devices do not eliminate the seizure focus but have been shown to significantly reduce seizure frequency in long-term treatment (*Neurosurgery* 2011; 69:957).

The RNS is a "closed-loop" device that can deliver electrical stimulation in response to detecting seizure activity. Although VNS and DBS "closed-loop" models are being developed and studied, the traditional VNS and DBS devices use open-loop systems where electrical stimulation is delivered based on a preset schedule irrespective of ongoing electrophysiological activity in the brain.

Future Directions

Looking ahead, with so many available therapeutic options, the goals and challenges of antiseizure therapy will be to customize and tailor to the individual patient based on genetics and early classification of a patient's electroclinical syndrome, as well as assessing who is likely to be drug-resistant so surgical options can be presented earlier to the patient.

Topic Update

Current Options for Treatment of Hypersomnia

Jennifer Grom, MD, MPH, and Karin G. Johnson, MD

Hypersomnia, or excessive daytime sleepiness (EDS), is a serious public health concern affecting the lives of our patients, the productivity of our economies, and the safety of our communities. New breakthroughs in pharmacologic treatment options have transformed achievable outcomes for patients with central disorders of hypersomnia — including narcolepsy, idiopathic hypersomnia, and Kleine–Levin syndrome — and for those with secondary causes of hypersomnia, including sleepiness despite treated sleep-disordered breathing (SDB) and shift-work disorder. Neurologists can play a central role in hypersomnia management, from prompt, accurate diagnosis to facilitating optimal medical management. In this update, we discuss recent advances in the treatment of hypersomnia disorders.

Assessment and Diagnostic Reasoning

Management of hypersomnia is dictated by the underlying cause. Therefore, optimal management depends on thorough assessment. A detailed history can ensure that the patient has true hypersomnia, rather than fatigue. While patients with hypersomnia suffer from unintended lapses into sleep, patients with fatigue suffer from a subjective lack of physical or mental energy. Scales to assess degree of sleepiness, such as the Epworth Sleepiness Scale, can be useful for initial screening but may be less useful for assessing treatment response (*J Sleep Res* 2020; 29:e13019).

HISTORY

The history should include assessment for insufficient sleep time, disrupted nocturnal sleep, disturbed circadian rhythm, sleep-related breathing disorders, and symptoms of central disorders of hypersomnia. It should also include assessment for depression, gastroesophageal reflux disease, pain, nocturnal symptoms of allergies and asthma, medications (including over-the-counter and supplements), alcohol use, caffeine intake, and recreational drug use, including stimulants (which can induce sleepiness during withdrawal). Prospectively gathered data such as patient sleep logs and actigraphy (wearable motion-sensing devices), collected over at least a 2-week period, are often helpful. A thorough neurologic exam is essential to assess for disorders affecting brainstem, thalamus, or hypothalamus. If exam findings prompt suspicion for an underlying disorder, magnetic resonance imaging is warranted.

TESTING

A polysomnogram (PSG) should be performed to rule out underlying sleep disorders. The Multiple Sleep Latency Test (MSLT) assesses mean sleep latency (<8 minutes consistent with hypersomnia) and the presence of sleep onset rapid eye movement (SOREM) periods. MSLT should be done the morning after a PSG to confirm at least 6 hours of sleep and either no significant SDB or SDB controlled by therapy. Sleep logs or actigraphy are recommended to confirm adequate sleep in the 2 weeks prior to testing and, if possible, medications that affect sleep, wakefulness, and SOREMs (e.g., most antidepressants and stimulants) should be discontinued for at least 5 half-lives. Cerebrospinal fluid orexin testing via lumbar puncture is now available when narcolepsy type I (with cataplexy) is suspected and should be considered, especially when PSG/MSLT is a challenge due to medication dependence.

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Disclosures: Dr. Grom reports no disclosures.

Karin G. Johnson, MD, is Professor of Neurology and Healthcare Delivery and Population Science at UMass Chan Medical School-Baystate, Director of the Baystate Health Regional Sleep Medicine Program, and Chair of the Sleep Section of the American Academy of Neurology.
Disclosures: Dr. Johnson reports external grant support from Avadel.

Nonpharmacologic Management

Most patients suffering from hypersomnia will not require pharmacologic therapy with wake-promoting agents. Nonpharmacologic treatments should be considered first for management of hypersomnia. The most important nonpharmacologic intervention is helping patients obtain sufficient sleep. Possible approaches include behavioral counseling, which is first-line treatment for patients with EDS secondary to insufficient sleep, poor sleep hygiene, or a circadian rhythm sleep-wake disorder (which also may be treated with light therapy).

Neurologists can play a central role in hypersomnia management, from prompt, accurate diagnosis to facilitating optimal medical management.

POSITIVE AIRWAY PRESSURE

In patients with EDS secondary to SDB, positive airway pressure (PAP) therapy is first-line treatment. Optimization of SDB treatment may require ensuring PAP adherence in patients with obstructive sleep apnea (OSA) for more than 6 hours per night (*Sleep* 2007; 30:711) or considering bilevel PAP or adaptive PAP therapy if suboptimal response with continuous PAP. In patients with medical or psychiatric problems, optimal management focuses on treating the underlying condition and limiting sedative medications. Additional evidence-based measures include scheduled naps, distraction (e.g., chewing gum), exercise, sleep hygiene measures, and behavioral therapy (*Mayo Clin Proc* 2021; 96:1288).

Pharmacologic Management

Pharmacologic agents — including wake-promoting agents and gamma-hydroxybutyric acid (GHB) salts — can have tremendous impact on functional outcomes and quality of life for patients suffering from hypersomnia disorders. While drugs are considered first-line, gold-standard therapy for patients with narcolepsy and idiopathic hypersomnia, they are otherwise considered second-line therapy and are usually only appropriate for refractory hypersomnia cases. Prior to treatment initiation, work with your patient to establish clearly defined, attainable, functional goals of pharmacologic treatment.

SELECTION CONSIDERATIONS

In selecting a medication (Table 1), consider patient factors including age, pregnancy and reproductive planning, goals of care, and comorbidities including cardiovascular disease, allergies, anxiety, and potential for drug misuse or dependency. In 2021, the American Academy of Sleep Medicine (AASM) released recommendations for pharmacologic therapies of hypersomnia disorders based on an updated meta-analysis of available literature (*J Clin Sleep Med* 2021; 17:1881).

Other considerations in selecting pharmacologic treatment include drug accessibility and affordability. Treatment of hypersomnia is often restricted by insurance prior authorizations. Treatments without FDA-approved indications for hypersomnia (e.g., methylphenidate and mixed amphetamine salts) are often used due to lower cost. Available treatment options have recently expanded with the generic availability of modafinil and armodafinil, as well as FDA approval of lower-sodium GHB (Xywav) for idiopathic hypersomnia (*Lancet Neurol* 2022; 21:53). Once-nightly GHB (Lumryz) has tentative FDA approval for the treatment of narcolepsy; final approval is expected in the latter half of 2023.

Secondary and Refractory Hypersomnia

Patients with secondary hypersomnia due to OSA (despite optimized PAP therapy), shift work, and medications or other medical disorders (including neurological disorders like multiple sclerosis and brain trauma) can benefit from modafinil, armodafinil, or solriamfetol, especially if sleepiness is impacting safety or work (*J Clin Sleep Med* 2021; 17:1881).

In patients with refractory hypersomnia, consider utilizing GHB salts or pitolisant, which often leads to life-changing responses that are unobtainable with stimulants or wake-promoting medications alone. However, keep in mind their limitations, which include high cost, several weeks for onset, and lack of response and/or adverse reactions in some patients.

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Table 1. Pharmacological Treatments for Hypersomnia				
Drug(s)	**Mechanism of Action**	**FDA Indications***	**Typical Adult Dose**	**Most Common Adverse Reactions** (Adults Only)**
Modafinil (Provigil)/Armodafinil (Nuvigil)	Increases extracellular concentration of dopamine by blocking reuptake	• EDS in narcolepsy • EDS in OSA • EDS in shift work disorder	Modafinil: 200 mg in AM or 1 hour before shift work‡ Armodafinil: 150–250 mg in AM (for shift work disorder: 150 mg taken 1 hour prior to shift)	Headache Modafinil only: Nausea
Sodium oxybate (high-sodium: Xyrem; low-sodium: Xywav)	Salts of GHB act as inhibitory neurotransmitter at $GABA_B$ receptors	• EDS in narcolepsy • Cataplexy in narcolepsy • Xywav only: EDS in idiopathic hypersomnia	Start 2.25 g at bedtime with 2.25 g 2.5–4 hours later Titrated weekly by 0.75/0.75 g to 4.5 g 2 times per night • Recommended range: 6–9 g total nightly • Allow at least 2 hours after eating • Take doses while in bed • Allow 6 hours before driving	High-sodium: Nausea, vomiting, confusion, dizziness Low-sodium: Nausea, headache
Pitolisant (Wakix)	Histamine-3 (H3) receptor antagonist/inverse agonist	• EDS in narcolepsy • Cataplexy in narcolepsy	8.9 mg once daily in AM for 1 week, then 17.8 mg for 1 week, then may increase to 35.6 mg daily • Dose decrease (maximum 17.8 mg once daily) with strong CYP2D6 inhibitors or CYP2D6 poor metabolizers • Dose increase with CYP3A4 inducers	Headache
Solriamfetol (Sunosi)	Inhibits dopamine and norepinephrine reuptake	• EDS in narcolepsy • EDS in OSA	Narcolepsy: 75 mg in AM x 3 days, then 150 mg in AM OSA: Starting dose 37.5 mg in AM	Headache

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Table 1. Pharmacological Treatments for Hypersomnia (continued)

Drug(s)	Mechanism of Action	FDA Indications*	Typical Adult Dose	Most Common Adverse Reactions** (Adults Only)
Dextroamphetamine (Dexedrine)/ Amphetamine/mixed amphetamine salts (Adderall)/ lisdexamfetamine (Vyvanse)	Promotes release of dopamine and norepinephrine from their storage sites in presynaptic nerve terminals	• EDS in narcolepsy (note: Vyvanse is used off label)	Start at 5 mg (short-acting formulation) or 5–10 mg (long-acting) in AM. Increase short-acting weekly up to 3 times/day every 3–6 hours and long-acting up to 2 times/day. Typical dose 5–60 mg/day‡‡	Anorexia, decreased appetite, xerostomia, headache, insomnia
Methylphenidate (Ritalin/Concerta)/ Dexmethylphenidate (Focalin)	Blocks the reuptake of norepinephrine and dopamine into the presynaptic neuron	• EDS in narcolepsy (note: Concerta and Focalin formulations are used off label)	Start 5 mg (short-acting formulation) or 5–10 mg (long-acting) in AM. Increase short-acting formulation weekly up to 3 times/day every 3–6 hours and long-acting up to 2 times/day. Typical dose 5–60 mg /day‡‡	Decreased appetite, nausea, xerostomia, headache, insomnia, irritability

FDA — Food and Drug Administration; EDS — excessive daytime sleepiness; OSA — obstructive sleep apnea; $GABA_B$ — γ-aminobutyric acid type B; GHB — gamma hydroxybutyrate

*Limited to indications for hypersomnia disorders in adults

**Includes adverse reactions occurring in at least 10% of adults

‡ In our experience, some patients with narcolepsy require 100–400 mg per dose and may require divided doses in AM and midday (up to max of 600 mg/day).

‡‡Total stimulant doses should be limited to 100–120 mg/day to minimize serious side effects (*Sleep* 2005; 28:667).

Table 2. Special Considerations in Prescribing Hypersomnia Treatment	
Issue	**Consideration**
Objective testing	• Formal diagnosis is often necessary for insurance prior authorization. • Test prior to starting medications. The Multiple Sleep Latency Test often requires that patients be off pharmacologic treatments for reliable results; getting patients to discontinue pharmacological treatments can be very difficult.
Safety counseling	• Patients should be counseled to avoid driving or caring for small infants while drowsy and to avoid operating heavy machinery. • Discuss ways to prevent driving drowsy by switching drivers and utilizing caffeine or napping before driving.
Medication storage	• Counsel patients about appropriate storage of medications in secure location.
Stimulant contracts	• Stimulant contracts should be considered, as well as random drug testing.

Table 3. Special Considerations in Managing Hypersomnia Treatment	
Issue	**Consideration**
Sleep inertia (difficulty waking in the AM)	• Consider setting alarm to take first dose prior to desired wake time. • Consider GHB salts to manage sleep inertia.
Disrupted nocturnal sleep	• Early timing and lower dosage of stimulants and wake-promoting medications should be used to avoid disrupting nocturnal sleep. • People with narcolepsy often have sleep instability that may require traditional sleeping aids or GHB salts at night.
Insufficient alertness and crashes	• Consider combinations of long- and short-acting agents, as-needed dosing, or more frequent dosing of small amounts. • For avoiding an afternoon crash, if there is suboptimal response with the maximum FDA-approved doses of armodafinil and solriamfetol, a second midday dose can be considered. Monitor blood pressure closely.
GHB salt	• Some patients do best with uneven GHB salt dosing of up to 6 g/dose and 9 g total. • Nausea typically is most severe when GHB salt is first started and improves within days. Taking with crackers and/or temporarily lowering dose and slowing titration can help. • Avoid combining with sedative medications and/or alcohol. • High salt content, especially of Xyrem, may affect hypertension, heart failure, or renal impairment. • Lumryz has similar salt content to Xyrem, requires shaking for 1 full minute before use (which improves tolerability), and may be useful for patients bothered by twice-nightly dosing. • Only available through Risk Evaluation and Mitigation Strategy (REMS) program
Pitolisant	• Pitolisant typically results in disappearance of daytime sleepiness rather than stimulating effect. • Pitolisant often has little or no effect for at least 3 weeks; patients should be encouraged to undertake at least a 2-month trial to evaluate for effectiveness. • If suboptimal response occurs with 17.8 mg when taking with CYP2D6 inhibitors, higher dosing may be tried. • Some patients experience initial weight loss that typically levels off to a new plateau. • Monitor renal function at baseline and as clinically indicated if impairment is found. • Only available through specialty pharmacy

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Additionally, some patients are wary of the deep sedation of GHB, especially if they live alone or care for young children. Special considerations based on our clinical experience in prescribing and managing medications for hypersomnia are summarized in Tables 2 and 3.

Cataplexy

Often, treatment of hypersomnia improves cataplexy (muscle weakness in the setting of emotions), which is experienced by about half of patients with narcolepsy. Again, consider GHB salts or pitolisant, which have FDA approval for this indication. Also, while tricyclics like imipramine have classically been used to control cataplexy, many patients respond well to small doses of selective serotonin reuptake inhibitors such as fluoxetine and serotonin–norepinephrine reuptake inhibitors such as venlafaxine and duloxetine.

Conclusion

Advances in hypersomnia treatments have improved many patients' lives, but lack of response or side effects still occur. Future agents, including orexin agonists and selective norepinephrine reuptake inhibitors (reboxetine), are in the pipeline.

Table 3. Special Considerations in Managing Hypersomnia Treatment (continued)

Issue	Consideration
Stimulants	• Short- and long-acting combinations are often necessary. Insurance will often cover up to 90 short-acting and 60 long-acting pills per month. • In our experience, methylphenidate often causes more anxiety and jitteriness and is less effective than mixed amphetamine salts. • Changing stimulant formulations (e.g., from a long- to short-acting formulation) or switching to a different drug within the same class (e.g., from mixed amphetamine salts to lisdexamfetamine or methylphenidate to dexmethylphenidate) may improve tolerance or effectiveness. • In the course of management, avoid progressive escalation of doses for small improvements in sleepiness without additional function or clear quality-of-life improvements. Reduce to lowest dose with significant improvement, or discontinue and try an alternative stimulant. • Due to withdrawal, patients may initially feel more tired when tapering down. • Assess for signs of misuse, abuse, or addiction throughout treatment. • Use during pregnancy and breastfeeding is not recommended.
Birth control	• Modafinil, armodafinil, and pitolisant can reduce effectiveness of hormonal contraceptives. • Solriamfetol does not affect birth control like modafinil or armodafinil, but otherwise has similar side effects.
Pregnancy	• While most hypersomnia treatments are not recommended during pregnancy, high-sodium GHB or low-sodium GHB (both FDA pregnancy category B*) may be safe. Most other hypersomnia medications — including modafinil, armodafinil, methylphenidate, and mixed amphetamine salts — are FDA pregnancy category C.* Solriamfetol's pregnancy category is currently unassigned. • The US Provigil/Nuvigil Pregnancy Registry showed a potential increased risk for major congenital malformations.** • The risks of discontinuing medications — especially regarding the ability to drive, work, and care for self and family — should be considered when discussing whether or not to continue or discontinue medications during pregnancy.

GHB — gamma-hydroxybutyrate; FDA — Food and Drug Administration

*FDA pregnancy categories — Category B: No well-controlled studies have been conducted in humans; animal studies show no risk to the fetus. Category C: No well-controlled studies have been conducted in humans; animal studies have demonstrated an adverse effect on the fetus.

**JAMA Intern Med 2021; 181:275

Topic Update

Treatment of Amyotrophic Lateral Sclerosis — A Practical Approach

James Wymer, MD, PhD

In the last few years, the diagnosis and treatment of amyotrophic lateral sclerosis (ALS) has transformed from reactive and supportive management to a new treatment paradigm that is proactive, featuring comprehensive multidisciplinary care and multiple new treatment options that can impact disease progression and quality of life. This update examines diagnosis, the role of genetics, establishing a treatment regimen, and deciding on pharmacologic therapy, focusing on therapies currently available in the United States.

Making the Diagnosis

ALS is a progressive motor neuron disease of upper and lower motor neurons. Patients present with a history of progressive generalized fasciculations, weakness, atrophy, and spasticity. ALS has a life expectancy of 2 to 5 years and no known cure.

Identification of ALS is typically based on clinical exam and electromyography testing. Neuroimaging of the head and neck and blood work are used to exclude other mimic causes. With this background, the El Escorial diagnostic criteria were developed in 1994 and modified in 1998 and 2006 (*Amyotroph Lateral Scler Other Motor Neuron Disord* 2000; 1:293; *Arch Neurol* 2012; 69:1410). These criteria required the presence of upper and lower motor neuron changes in multiple areas of the body to make a diagnosis of ALS and included three tiers of certainty: possible, probable, and definite. Electromyography could substitute for examination to identify lower motor neuron changes.

Using those criteria, it can take patients as long as 18 months to receive the diagnosis, thereby delaying treatment. Such delay has been attributed to misdiagnosis because of initial similarity to other diseases and the requirement of specialists to make the diagnosis (*J Neurol Sci* 2020; 417:117054). We know that in its early phases, ALS can mimic other diseases and involve a range of symptoms — from a predominance of spasticity/upper motor neuron disease to one of atrophy and fasciculations/lower motor neuron disease. To address these challenges, in 2020 the Gold Coast criteria were developed, which require the following for a diagnosis of ALS: (1) progressive motor impairment preceded by normal function; (2) upper and lower motor neuron changes in at least one area with progressive decline; and (3) exclusion of other possible causes (*Neurophysiol* 2020; 131:1975). This change reduced the diagnostic categories to two — yes or no — and should allow patients to receive a diagnosis earlier and thus begin therapy earlier.

The Role of Genetics

Only 5% to 10% of patients with ALS have a family history of disease; the rest are sporadic cases. However, testing has found that close to 10% of this sporadic group can have genetic mutations associated with ALS (*Genet Med* 2017; 19:267). Currently, despite its low cost and wide availability, genetic testing will not improve care and could raise anxiety about the future. Clinical trials of medications specific to the familial forms of ALS are currently underway. If successful, genetic testing will become a routine part of diagnosis, and these medications will be added where appropriate to a personalized care plan. The role of a genetics counselor is critical for such discussions and frequently provided by testing companies (*Genet Med* 2017; 19:267).

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Disclosures: Dr. Wymer reports external grant support from Mitsubishi Tanabe and Amylyx Pharma and publication responsibilities with Mitsubishi Tanabe.

Multidisciplinary Care

Once the diagnosis is made, the first step in managing the patient is the development of a multidisciplinary care program. This is a care plan that will focus on personalized interventions to identify disabilities, strengthen and maintain function, and hopefully slow the decline. This care can involve specialists in pulmonary care, physical therapy, occupational therapy, speech and language pathology, and nutrition (*Muscle Nerve* 2017; 56:848). Standards for multidisciplinary care are established (*Neurology* 2009; 73:1227).

Medications

Riluzole was approved in the mid-1990s after being shown to prolong survival by approximately 3 months (*Cochrane Database Syst Rev* 2012, Issue 3:CD001447). It appears to work through a glutamate pathway. In 2015, intravenous edaravone was approved based on evidence that it slowed disease progression in patients with early disease by 2.49 points on the 48-point ALSFRS-R scale after 6 months. Edaravone is thought to act by reducing oxidative stress. In the last year, the oral formulation of edaravone, and a third medication, sodium phenylbutyrate–taurursodiol (PB-TURSO), were approved. PB-TURSO is thought to reduce endoplasmic reticulum stress and mitochondrial dysfunction. In a clinical trial (for which I am an investigator), PB-TURSO slowed decline over 6 months by 2.32 points on the ALSFRS-R and prolonged ventilation-free survival and long-term survival by 6.5 months during the open-label phase in those patients originally on treatment, compared with those originally on placebo (*Muscle Nerve* 2021; 63:31). With this most recent addition, we now have a total of three oral medications with the potential to slow the decline associated with ALS (Table).

COMBINATION THERAPY

At this time, no statement can be made about the efficacy of combination therapy, despite its investigation in several clinical trials. In a phase 3 trial of edaravone, over 90% of the patients were on riluzole, and no new safety signals emerged (*Lancet Neurol* 2017; 16:505). In the PB-TURSO study, 71% of participants were on riluzole, 34% on intravenous edaravone, and 28% on both — again, without evidence of worsening safety (*N Engl J Med* 2020; 383:919). Although neither study was designed to test combination efficacy, the unique mechanism of each agent offers hope that they might have an additive effect with regard to functional and survival benefits Currently, I will start patients newly diagnosed with ALS on riluzole. After 1 month on riluzole, I will discuss the addition of one or both of the other two medications. Both have efficacy to slow disease and are available in oral formulation. The choice of which to start with is based on tolerability, availability, and insurance coverage. After a patient is stable on the second medication, I will consider the third.

Moving Forward

For many years, the treatment of ALS has been limited to supportive care with one medication that provides modest effect on disease. Over the last several years, we have learned that care for the ALS patients can be proactive with incorporation of multidisciplinary care to personalize therapy and enhance function. We now have three FDA-approved oral medications and a very active clinical trial network. Looking ahead, care of the ALS patient will be a personalized program that has the potential to improve quality of life and function throughout the course of this devasating disease.

Table. Pharmacologic Therapies Currently Approved in the United States

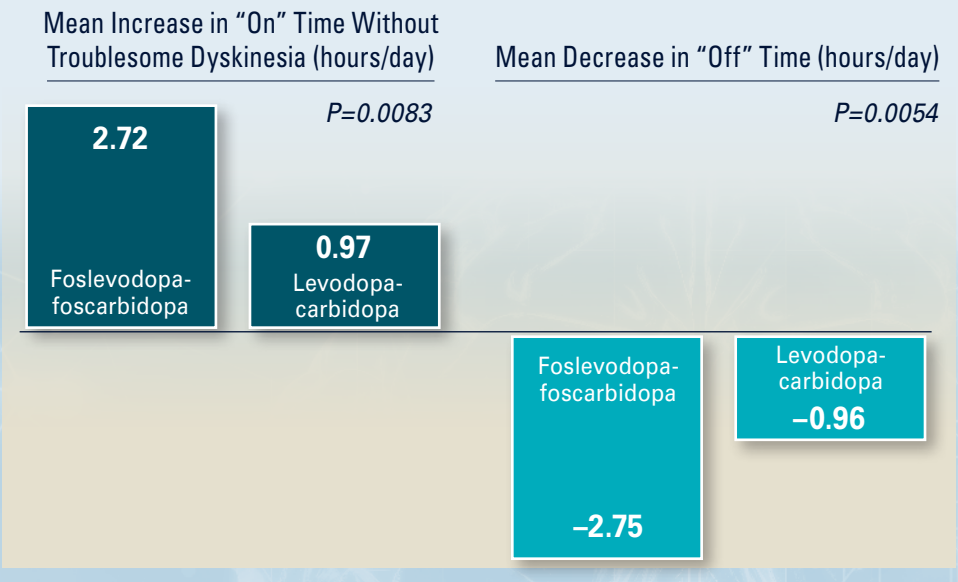
Medication (formulation)	Brand Name	Mechanism of Action	Published Efficacy
Riluzole (oral)	Rilutek (generic also available)	Antiglutamatergic	Extended survival[1]
Edaravone (oral or intravenous)	Radicava	Free radical scavenger	Slowed loss of function[2]
Sodium phenylbutyrate–taurursodiol (PB-TURSO; oral)	Relyvrio	Reduce endoplasmic reticulum stress and mitochondrial dysfunction	Slowed loss of function, prolonged survival[3]

1. Riluzole was found to extend survival by 2–3 months.
2. Edaravone was found to slow disease progression on the ALSFRS-R scale by 2.49 points over 6 months.
3. PB-TURSO was found to slow disease progression on the ALSFRS-R scale by 2.32 points after 6 months and in the open-label phase extended survival in those in the treatment arm of the trial by 6.5 months, compared with those in the placebo arm.

Visual Summary

Subcutaneous Foslevodopa-Foscarbidopa for Advanced Parkinson Disease (PD)

In a phase 3 study, 141 advanced PD patients (with an average daily "off" time of ≥2.5 hours) were randomized to receive 12 weeks of continuous subcutaneous infusion of foslevodopa-foscarbidopa plus oral placebo or continuous subcutaneous infusion of placebo plus oral levodopa-carbidopa.



Comment

The field has long awaited the arrival of subcutaneous levodopa and carbidopa prodrugs that may be infused subcutaneously. This approach, if FDA-approved, will add to a growing list of options that can be considered prior to the use of more-invasive procedures, such as duodenal pumps, deep-brain stimulation, or ablative brain therapies.

Michael S. Okun, MD, reviewing Soileau MJ et al. *Lancet Neurol* 2022 Dec

Dr. Okun is Adelaide Lackner Professor and Chair of Neurology and Executive Director of the Fixel Institute for Neurological Diseases at the University of Florida McKnight Brain Institute, Gainesville. **Disclosures:** Dr. Okun reports consultant or advisory board roles with the Parkinson's Foundation and Tourette Association of America; speaker's bureau roles with Medscape/WebMD, MedEdicus, Movement Disorders Society, and the American Academy of Neurology; royalties from Books4Patients, Demos, Cambridge, Taylor and Francis, Henry Stewart Talks, Robert Rose, and Public Affairs; grants and research support from the National Institutes of Health, Parkinson's Foundation, Tourette Association of America, and University of Florida Foundation; and editorial board positions with the Parkinson's Foundation, *Tremor and Other Hyperkinetic Movements*, and *JAMA Neurology*.

NEJM Research Summary

Lecanemab in Early Alzheimer's Disease

van Dyck CH et al. DOI: 10.1056/NEJMoa2212948

CLINICAL PROBLEM

Some evidence suggests that amyloid removal slows the progression of Alzheimer's disease. Lecanemab, an anti-amyloid monoclonal antibody with high affinity for soluble amyloid protofibrils, is being tested in early Alzheimer's disease.

CLINICAL TRIAL

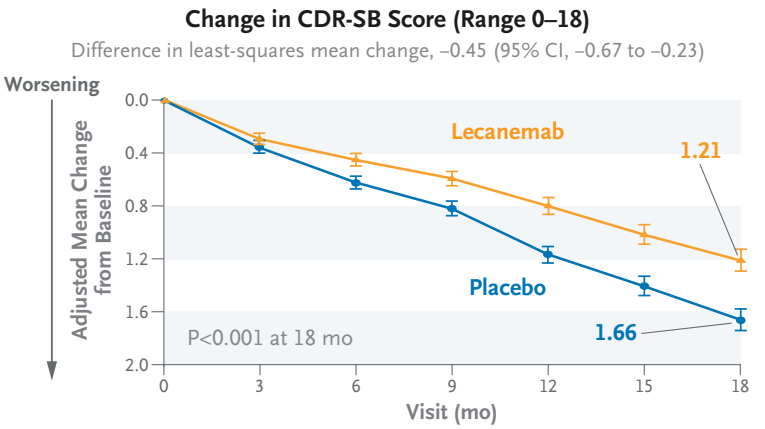
Design: A phase 3, multicenter, double-blind, randomized, placebo-controlled trial assessed the efficacy and safety of lecanemab in patients 50 to 90 years of age with early Alzheimer's disease.

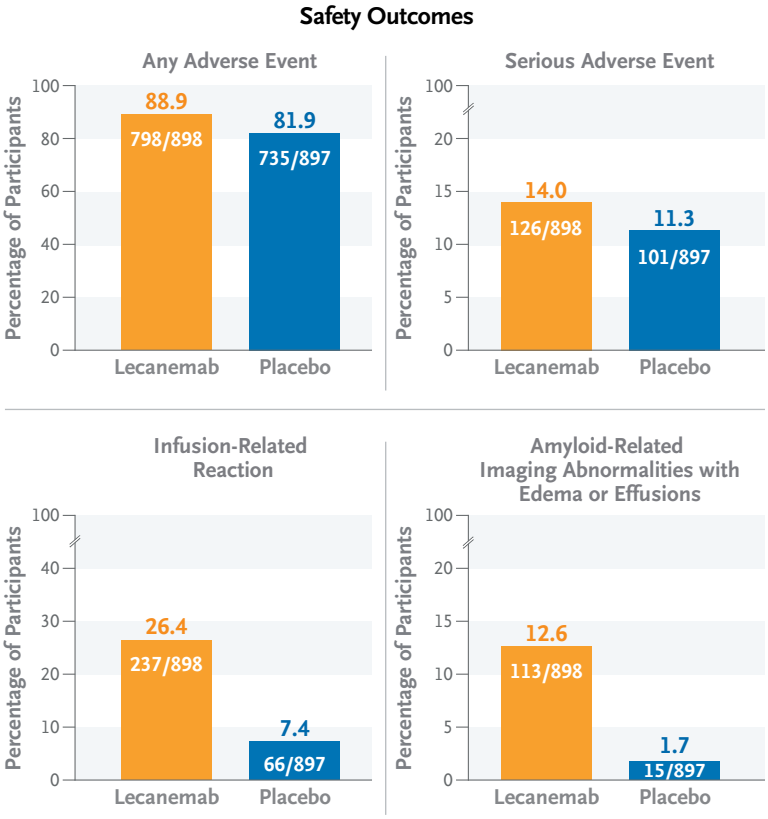
Intervention: 1795 participants in North America, Europe, and Asia were assigned to receive intravenous lecanemab (10 mg per kilogram of body weight every 2 weeks) or placebo. The primary efficacy end point was the change in the score on the Clinical Dementia Rating–Sum of Boxes (CDR-SB) from baseline, with higher scores indicating greater impairment.

RESULTS

Efficacy: At 18 months, mean CDR-SB scores had worsened in both groups. The mean change in CDR-SB score was smaller (indicating less cognitive and functional decline) in the lecanemab group.

Safety: Overall incidences of adverse events were similar in the two groups. The most common adverse events in the lecanemab group included infusion-related reactions and amyloid-related imaging abnormalities with edema or effusions.





LIMITATIONS AND REMAINING QUESTIONS

- Longer-term follow-up is needed; an open-label extension study is ongoing.
- The trial was conducted during the Covid-19 pandemic and, as a result, faced challenges including missing data, missed doses, delayed assessments, and intercurrent illnesses.
- Occurrences of amyloid-related imaging abnormalities may have led to unblinding of participants and investigators.

CONCLUSIONS

In patients with early Alzheimer's disease, lecanemab was associated with moderately less decline on measures of cognition and function than placebo over a period of 18 months.

Guideline Watch

Intracerebral Hemorrhage Guidelines 2022: Key New Aspects

Updated guidelines are based on findings from several recent clinical trials.

SPONSORING ORGANIZATION

American Heart Association/American Stroke Association (AHA/ASA)

BACKGROUND AND OBJECTIVE

Intracerebral hemorrhage (ICH) continues to be a deadly form of stroke; 90-day mortality ranges from 15% to 40%. Because of increasing population age and use of anticoagulants and greater effects in poor and minority communities, the AHA/ASA compiled these evidence-based recommendations, updated from 2015 (*Stroke* 2015; 46:2032).

KEY RECOMMENDATIONS

- Use acute computed tomography angiography (CTA) and consider venography to exclude macrovascular causes or cerebral venous thrombosis in the following cases: Patients with lobar spontaneous ICH and age <70 years, deep/posterior fossa spontaneous ICH and age <45 years, or deep/posterior fossa and age 45 to 70 years without history of hypertension. (Class I)
- In patients with spontaneous intraventricular hemorrhage and no detectable parenchymal hemorrhage, use catheter intra-arterial digital subtraction angiography (to exclude a macrovascular cause). (Class I)
- MRI and magnetic resonance angiography can be considered in patients with spontaneous ICH and negative CTA/venography, to establish a nonmacrovascular cause of ICH. (Class IIa)
- When administering treatment to lower blood pressure acutely in patients with spontaneous ICH, titrate carefully to ensure continuous smooth and sustained blood pressure control. (Class IIa)
- In patients with spontaneous ICH of mild-to-moderate severity and systolic blood pressure (SBP) between 150 and 220 mm Hg at presentation, aiming to maintain SBP between 130 and 150 mm Hg (target, 140 mm Hg) is safe and may improve functional outcomes. (Class IIb)
- In patients with vitamin K antagonist–associated spontaneous ICH and international normalized ratio (INR) ≥2.0, four-factor prothrombin complex concentrate is preferable to fresh-frozen plasma for quick INR correction and limiting of hematoma expansion. (Class I)
- Do not provide platelet transfusions to patients with spontaneous ICH being treated with aspirin unless emergency surgery is planned. (Class III)
- In patients with spontaneous ICH, provide care in a specialized inpatient (e.g., stroke) unit with a multidisciplinary team to improve outcomes. (Class I)
- In patients with spontaneous ICH who are not ambulatory, low-dose unfractionated heparin or low-molecular-weight heparin may reduce the risk for pulmonary embolism. (Class IIa)
- In individual patients with spontaneous ICH, baseline severity score should not be the only predictor used for prognosis or to consider limiting life-sustaining treatment. (Class III)

Comment

These guidelines provide new information based on several recent clinical trials and offer a useful approach to management of anticoagulant-related hemorrhage. The uncertainties regarding surgical treatment of ICH are highlighted, as are several other areas where the evidence is conflicting. Clinicians involved with ICH care should review the guidelines to identify current best approaches for diagnosis and treatment.

Seemant Chaturvedi, MD

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Greenberg SM et al. 2022 guideline for the management of patients with spontaneous intracerebral hemorrhage: A guideline from the American Heart Association/American Stroke Association. **Stroke** 2022; 53:e282. (https://doi.org/10.1161/STR.0000000000000407)

NEJM Journal Watch Summary

Is Tenecteplase a Viable Thrombolytic Medication for Acute Ischemic Stroke?

A Canadian trial provides strong support.

Tissue plasminogen activator (TPA, alteplase) has been approved for more than 25 years as a medication for select patients with acute ischemic stroke who meet treatment criteria. In recent years, increased interest has focused on tenecteplase (TNK) as an alternative to alteplase. Tenecteplase is administered as an intravenous bolus without the need for a 1-hour infusion, making it appealing for rapid treatment. Comparative trials thus far have been fairly modest in size. These authors conducted a pragmatic trial at 22 centers in Canada, in which patients who could be treated within 4.5 hours after symptom onset were randomized to alteplase or tenecteplase. Patients received either a tenecteplase bolus (0.25 mg/kg; 25 mg maximum) or an alteplase infusion (0.9 mg/kg; 90 mg maximum). The primary outcome was modified Rankin Scale (mRS) score of 0 to 1 (excellent outcome) at 90 to 120 days. Treatment was open-label, but outcome was determined in blinded fashion.

Of 1600 patients enrolled, 1577 (median age, 74 years; 48% female) were available for final analysis. On average, stroke severity was moderate (median NIH Stroke Scale score, 9.5). Endovascular thrombectomy was performed in about one third of patients, and symptom onset–to-thrombolysis time was 129 minutes. Excellent outcome was seen in 37% of TNK patients and 35% of TPA patients. A priori criteria for noninferiority of tenecteplase were met. The treatment groups did not differ significantly in rates of symptomatic intracerebral hemorrhage (TNK, 3.4%; TPA, 3.2%) or 90-day mortality (TNK, 15.4%; TPA, 15.3%).

Comment

This trial is likely to be a "game changer" in that it provides strong evidence that tenecteplase is noninferior to alteplase. Despite not being FDA approved for acute stroke treatment, some stroke centers have already switched to tenecteplase as the thrombolytic of choice, and other hospitals are likely to switch after reviewing these trial data. For hospitals that decide to switch to tenecteplase for acute stroke treatment, this trial provides a strong rationale.

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Menon BK et al. Intravenous tenecteplase compared with alteplase for acute ischaemic stroke in Canada (AcT): A pragmatic, multicentre, open-label, registry-linked, randomised, controlled, non-inferiority trial. **Lancet** 2022 Jul 16; 400:161. (https://doi.org/10.1016/S0140-6736(22)01054-6)

NEJM Journal Watch Summary

Neurofilament and Predicting Disease Activity in Multiple Sclerosis

An international collaboration confirms the role of serum neurofilament as a marker of disease activity.

Serum neurofilament light chain (sNfL) is a biomarker in multiple sclerosis (MS) previously shown to correlate with disease and MRI activity (*Neurology* 2020; 94:e2457). In this multicenter, international study, investigators sought to create a clinical tool to predict worsening MS and to model treatment effects. They collected 10,133 blood samples from 5390 healthy controls and evaluated 7769 samples from 1313 patients with relapsing forms of MS over a median follow-up of 5.6 years. Evidence of disease activity (EDA)–3 was defined as relapses, Expanded Disability Status Scale (EDSS) score worsening, or new MRI activity.

Using Z scores derived from sNfL values adjusted for age and body-mass index, patients with scores >1.5 were more likely to have recent disease activity than those with lower Z scores. Higher sNfL Z scores were associated with a greater probability, in the following year, of relapses, EDSS worsening, and EDA-3. Patients treated with higher-efficacy therapies had lower sNfL Z scores than those treated with oral therapies, and oral-therapy patients had lower sNfL than platform-therapy patients. Upon starting each of these categories of therapies, higher-efficacy therapies had the greatest decline in sNfL Z scores over the first year, followed by orals, followed by interferons and glatiramer acetate. A validation cohort of 4341 patients confirmed the results. The authors created an internet-based app based on sNfL values from the reference database to determine individual Z scores in clinical practice.

Comment

This significant effort sets the stage for the possibility of using sNfL values to aid treatment decisions. Among patients receiving MS treatment, those with a higher sNfL Z score were more likely to worsen. Perhaps untreated patients can be segmented for risk based on sNfL as well. Future studies should evaluate the effect of escalating therapy in response to an elevated sNfL level.

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Benkert P et al. Serum neurofilament light chain for individual prognostication of disease activity in people with multiple sclerosis: A retrospective modelling and validation study. **Lancet Neurol** 2022 Mar; 21:246. (https://doi.org/10.1016/S1474-4422(22)00009-6)

NEJM Journal Watch Summary

Ultraprocessed Foods and Cognition

Consumption of ultraprocessed foods is associated with cognitive decline.

The consumption of ultraprocessed foods (UPF) may be a risk factor for dementia. In this multicenter study, researchers assessed whether UPF consumption affected cognition in 10,775 Brazilian participants (mean age, 52 years; 55% female; 53% white; 57% with a college degree). Daily UPF consumption was extracted by data from a validated food frequency questionnaire and calculated as a percentage of total energy. Cognitive outcomes were based on tests of global cognition, memory, and executive function. Covariates included sociodemographic, clinical, and lifestyle variables.

At baseline, the mean body-mass index was 26.9 kg/m^2 and the mean total daily caloric intake was 2856 kcal. After a median follow-up of 8 years, those with >19.9% UPF consumption had a 28% faster rate of global cognitive decline and a 25% faster rate of executive function decline but no significant changes in memory scores compared with those with <19.9% UPF consumption (*P* for trend 0.004 for global cognition, 0.04 for executive function, and 0.86 for memory). A faster rate of global cognitive decline was apparent with UPF consumption >19.9%, compared with lower consumption, in those younger than 60 years but not in older participants. Additional sensitivity analyses showed similar results.

Comment

The results of this study support following a healthy diet as a way to promote brain health. The addition of biomarkers in future studies may provide additional insight into how UPF consumption contributes to cognitive decline.

Jennifer Rose V. Molano, MD

Dr. Molano is Associate Professor at the University of Cincinnati. She serves on the editorial board of *Brain & Life* and is a member of the engagement committee of the American Academy of Neurology.

Gonçalves NG et al. Association between consumption of ultraprocessed foods and cognitive decline. **JAMA Neurol** 2023; 80:142. (https://doi.org/10.1001/jamaneurol.2022.4397)

NEJM Journal Watch Summary

Newly Described Central Nervous System Syndromes with Septin Antibodies

Septin-5 was associated with cerebellar disease, and septin-7 with encephalitis.

Autoimmune neurologic disease associated with septin-5 and septin-7 antibodies was described recently. Septins have diverse roles in biology, including regulating microtubules, actin, and diffusion. Investigators now describe 23 patients, of whom 17 of 18 with sera samples and all 12 with cerebrospinal fluid (CSF) samples had septin-specific immunoglobulin G (IgG) antibodies. By a cell-based assay, 15 patients were positive for septin-7, 6 for septin-5, and 2 for both.

The patients' median age was 63 (range, 40–85), and 61% were male. All patients with septin-5 antibodies had ataxia with prominent eye movement disorders. None had identifiable neoplasms. Two patients with septin-5 antibodies had cerebellar atrophy on MRI. Most patients with septin-7 antibodies had encephalopathy, but some had myelopathy, radiculopathy, and psychiatric syndromes; 4 had a neoplasm, and 2 developed symptoms after HSV-1 encephalitis. In the septin-7 group, MRI findings included nonspecific changes, bilateral T2 abnormalities in the hippocampus, and atrophy in the frontal or temporal lobes. CSF often showed inflammatory changes. Outcomes were available in 6 with septin-5, and 5 with septin-7 antibodies. Immunotherapy typically led to improvements.

Comment

Septin-associated autoimmunity is another condition to consider testing for in clinically appropriate patients.

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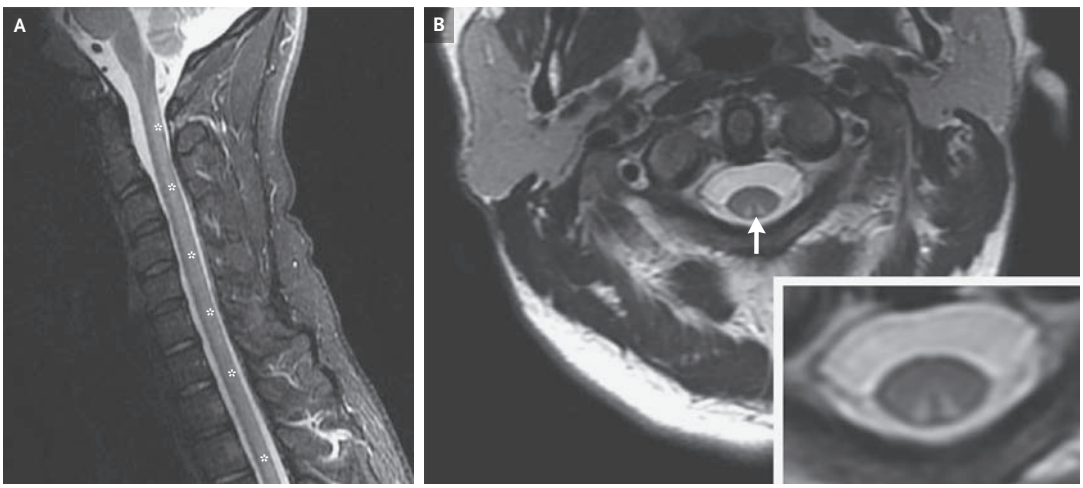
Hinson SR et al. Septin-5 and -7-IgGs: Neurologic, serologic, and pathophysiologic characteristics. **Ann Neurol** 2022; 92:1090. (https://doi.org/10.1002/ana.26482)

Images in Clinical Medicine

Subacute Combined Degeneration from Nitrous Oxide Use



A 32-year-old man presented to the emergency department with a 6-week history of tingling in his arms and legs and a 2-week history of inability to walk. Two months before presentation, he had begun inhaling nitrous oxide — also known as "whippets" or "laughing gas" — daily. On physical examination, the Romberg test was positive, and sensory ataxia, impaired proprioception and vibratory sensation, and preserved nociception were noted. Magnetic resonance imaging of the whole spine showed hyperintensity in the posterior spinal cord from C1 to T12 on T2-weighted images (Panel A, asterisks). Axial images revealed a lesion in the dorsal column that was hyperintense on both T2-weighted images and fluid-attenuated inversion recovery (FLAIR) sequence, a finding known as the "inverted-V sign" that is seen in subacute combined degeneration (Panel B, arrow and inset). The patient's vitamin B_{12} level was 107 pg per milliliter (reference value, >231). There was no macrocytic anemia. Antibody testing for autoimmune gastritis was negative. A diagnosis of subacute combined degeneration associated with nitrous oxide use was made. Long-term use of nitrous oxide causes the inactivation of vitamin B_{12}, which then interrupts methionine synthase activity. After the patient ceased nitrous oxide use and received treatment with cyanocobalamin injections for 2 weeks, his vitamin B_{12} level normalized. At the 4-week follow-up, he was able to walk independently.

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September 1, 2022; **N Engl J Med** 2022; 387:9
www.nejm.org/doi/full/10.1056/NEJMicm2119871