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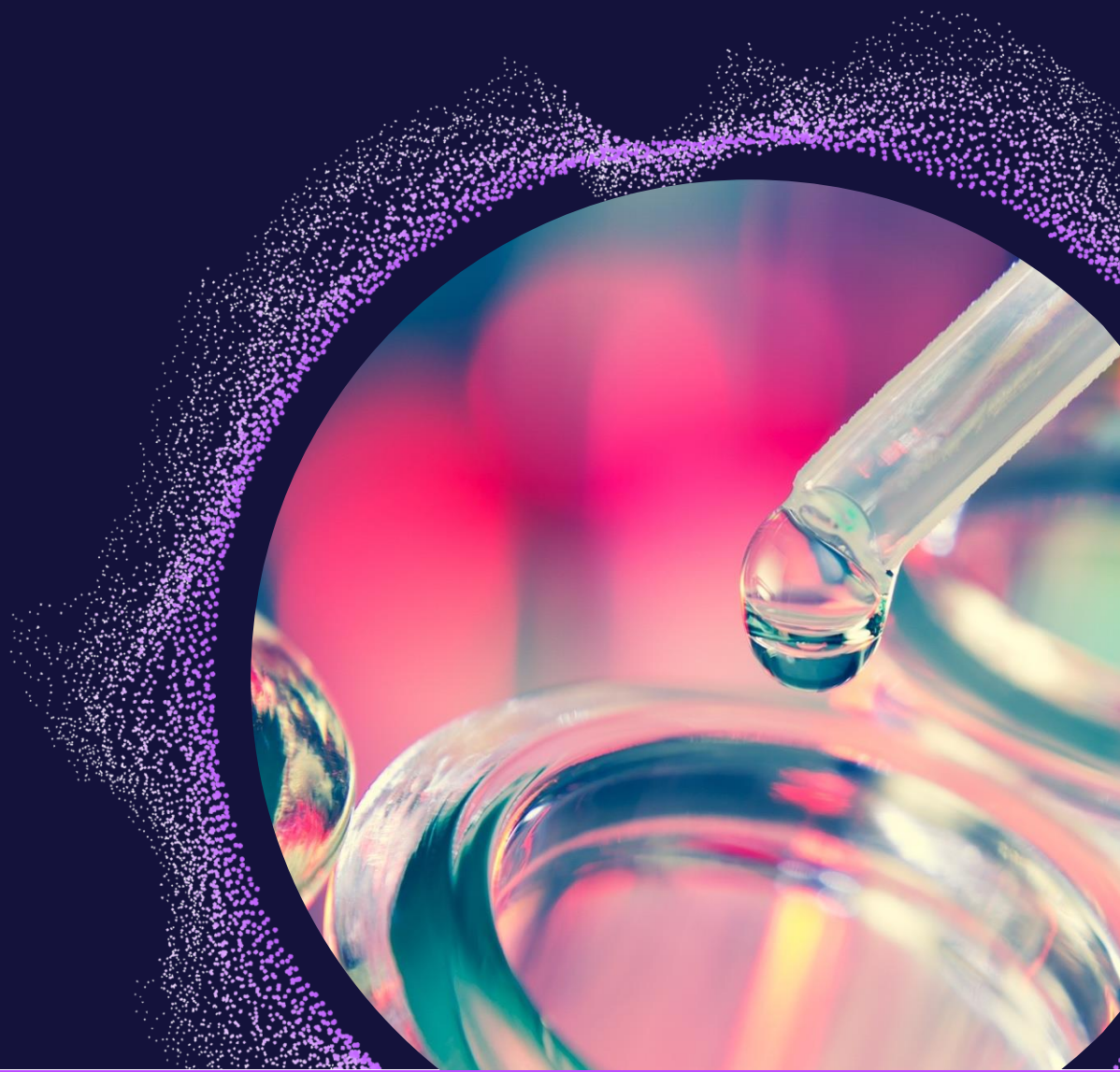
# AAN Post-Conference Report



June 2024

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## Executive Summary

The 76th American Academy of Neurology (AAN) Annual Meeting was held on 13–18 April in Denver, Colorado. AAN is considered the largest association of neurologists in the world. This year, information was presented on Alzheimer's disease, amyotrophic lateral sclerosis, epilepsy, myasthenia gravis, headache and migraine, Huntington's disease, multiple sclerosis, narcolepsy, Parkinson's disease, tics and Tourette syndrome, and more.


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# Alzheimer's Disease

## Lecanemab for the Treatment of Early Alzheimer's Disease: The Extension of Efficacy Results from Clarity AD

Michael Irizarry, MD (Eisai)

*Dr. Michael Irizarry presented results from the tau PET substudy from lecanemab's Phase III Clarity AD trial, as well as results from the open-label extension through two years.*

Tau PET was measured at baseline and followed up in 342 subjects. Lecanemab slowed the spread of tau tangles in several cortical regions, but especially in the early Braak regions, particularly the medial temporal lobe, meta temporal lobe, and temporal lobe.

**Tau PET SUVR**

| Brain region | Adjusted mean difference | p-value |
|---|---|---|
| Medial temporal | -0.068 | <0.01 |
| Meta temporal | -0.071 | 0.01 |
| Temporal | -0.065 | 0.02 |
| Frontal | -0.023 | 0.22 |
| Cingulate | -0.034 | 0.13 |
| Parietal | -0.029 | 0.25 |
| Occipital | -0.003 | 0.91 |
| Whole cortical gray matter | -0.035 | 0.10 |

40% of participants in the tau PET substudy were classified as having low tau, with tau restricted to the entorhinal and transentorhinal cortex. Although this low tau subgroup is associated with slower progression, separation is nonetheless seen from placebo on cognitive outcomes, like CDR-SB.


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**Tau PET substudy**

| Outcome | % Less decline | Change | p-value |
|---|---|---|---|
| CDR-SB | 37.9% | -0.53 | 0.03 |
| ADAS-Cog14 | 16.0% | -1.01 | 0.34 |
| ADCS MCI-ADL | 39.2% | 1.92 | 0.04 |

**Low baseline Tau (<1.05)**

| Outcome | % Less decline | Change | p-value |
|---|---|---|---|
| CDR-SB | 54.9% | -0.59 | 0.02 |
| ADAS-Cog14 | 52.4% | -1.74 | 0.20 |
| ADCS MCI-ADL | 88.2% | 3.26 | 0.009 |

**Intermediate-high baseline Tau (>1.05)**

| Outcome | % Less decline | Change |
|---|---|---|
| CDR-SB | 27% | -0.49 |
| ADAS-Cog14 | 9% | -0.77 |
| ADCS MCI-ADL | 13% | 0.67 |

From 18 to 24 months, separation is maintained between the early-start arm that initiated lecanemab at the beginning of the study and the delayed-start arm that started treatment at 18 months, suggesting a benefit to starting treatment earlier. Additionally, in comparison to a natural history cohort, as the extension period was open label, the delayed-start group separated from matched controls.


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## Clinical Relevance of Donanemab Treatment

Alireza Atri, MD, PhD (Banner Sun Health Research Institute)

*In a post-hoc exploratory analysis, Dr. Atri from the Banner Sun Health Research Institute showed data demonstrating a significant beneficial effect of donanemab on more interpretable individual item measures from iADRS and CDR-SB domains. Specifically, donanemab improved specific memory items, like keeping appointments or talking about something the patient saw on TV, or items related to executive function like making a meal, using household appliances, and personal care, thus enabling greater independence for a longer period of time.*

Donanemab treatment delivers outcomes that are valued by patients and their care partners, including benefits seen across several individual cognitive ADAS-Cog and functional ADCS-iADL items and across all six domains of the CDR.

**CDR-SB domains**

| Domain | % Slowing | p-value |
|---|---|---|
| Cognition | | |
| Memory | 32.9 | <0.001 |
| Orientation | 23.3 | 0.002 |
| Judgment and problem solving | 26.3 | 0.001 |
| Function | | |
| Community affairs | 21.2 | 0.002 |
| Home and hobbies | 31.4 | <0.001 |
| Personal care | 31.0 | 0.002 |


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**ADAS-Cog individual item scores**

| Domain | % Slowing | p-value |
|---|---|---|
| Episodic memory | | |
| Word recall | 31.94 | <0.001 |
| Delayed word recall | 14.76 | 0.121 |
| Word recognition | 23.14 | 0.017 |
| Orientation | 25.24 | <0.001 |
| Remembering test instructions | 36.33 | 0.010 |
| Executive functioning | | |
| Number cancelation | 32.54 | 0.004 |
| Language | | |
| Word finding difficulty | 16.04 | 0.152 |
| Commands | 16.69 | 0.336 |
| Naming objects and fingers | 3.45 | 0.833 |
| Spoken language ability | 20.36 | 0.170 |
| Comprehension | 12.26 | 0.500 |
| Praxis | | |
| Constructional praxis | 4.15 | 0.769 |
| Ideational praxis | 10.44 | 0.375 |


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**ADCS-iADL individual item scores**

| Domain | % Slowing | p-value |
|---|---|---|
| Communications | | |
| Write things down | 28.59 | 0.043 |
| Perform pastime | 34.75 | 0.010 |
| Talking about reading | 40.14 | <0.001 |
| Talking about television | 64.32 | <0.001 |
| Keep appointments | 32.53 | 0.008 |
| Pay attention to conversation | 18.15 | 0.379 |
| Talking about events | 29.35 | 0.020 |
| Household | | |
| Use a telephone | 19.47 | 0.098 |
| Obtain beverage | 13.65 | 0.376 |
| Clear dishes | 33.68 | 0.318 |
| Make a meal | 32.25 | 0.010 |
| Use household appliance | 39.90 | 0.001 |
| Dispose of garbage | 23.48 | 0.278 |
| Find belongings | 36.31 | 0.065 |
| Usual dressing performance | 17.98 | 0.207 |
| Outdoor activities | | |
| Shopping | -1.12 | 0.921 |
| Get around outside the home | -0.49 | 0.964 |
| Being left alone | 33.91 | 0.031 |


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Dr. Atri showed a Venn diagram outlining outcomes valued by different stakeholders in the Alzheimer's landscape, including patients, their care partners, and healthcare professionals. Inside were results from surveys that endorse the value of slowing disease progression to remain at earlier stages of disease longer, maintaining their level of independence and ability to participate in activities that matter most to them. Specifically, outcomes identified in eight or more studies that intersected with all three stakeholders were:

- memory/slowing of forgetfulness
- mental health
- independence and patient autonomy
- caregiver burden
- health services and disease information
- activities of daily living
- maintaining identity or personality.

Items that only fell under patients were length of life and executive function, caregivers cared about eating behaviors, while caregivers and healthcare professionals valued items like family participation in care, apathy, and caregiver social support. Among those items valued by both patients and their caregivers were language and communication, stigma, and quality of their relationship.

Finally, Dr. Atri showed data on the risk of progression to the next stage of dementia as defined by the CDR Global score. Donanemab showed a 37.4% lower risk of progression to the next stage of disease over 76 weeks.


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## Efficacy and Safety of AXS-05 in Agitation Associated with Alzheimer's Disease: Results from ACCORD, a Phase III, Double-Blind, Placebo-Controlled, Relapse Prevention Trial

Anton Porsteinsson, MD (University of Rochester)

*During a plenary session, Dr. Porsteinsson reported topline results from the Phase III randomized withdrawal ACCORD study evaluating AXS-05 (Auvelity) in the treatment of Alzheimer's disease agitation.*

A total of 178 patients entered the study, which started with an open-label period where patients were treated with AXS-05 for up to nine weeks (until they had a 30% or greater improvement on the CMAI score that was also associated with improvement on the patient global impression scale that was sustained for four weeks). During this time, patients showed about a 27-point drop in the CMAI score for those who were considered persistent responders and entered the double-blind phase.

Six weeks into treatment, about 80% of patients were considered responders, with safety results consistent with Auvelity's depression label (mild dizziness and a brief period of a looser stools or diarrhea). At the end of the open-label period, 53 patients were randomized to continue treatment, while 55 were randomized to placebo.

About a quarter of participants randomized to placebo relapsed, defined as at least a 10-point increase in CMAI score from randomization or a CMAI score greater than at study entry for two consecutive weeks. This was significantly worse than the 8% of patients who continued treatment. AXS-05 statistically increased the time to relapse, with relapses mostly occurring in the first 12 weeks and many patients in both groups making it to the full 26-week study period with no relapse.

During the double-blind treatment period, AXS-05 was not associated with cognitive impairment or sedation and was generally considered safe and well tolerated.


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## A Phase I Study, INTERCEPT-AD, of ACU193: Safety, Target Engagement, and Biomarker Changes

Eric Siemers, MD (Acumen Pharmaceuticals)

*Dr. Siemers presented total data from the Phase I INTERCEPT-AD study evaluating sabirnetug (ACU193) in early Alzheimer's disease patients. Notably, the fluid biomarker data were being newly presented.*

Although this was a first-in-man study, Acumen demonstrated that safety information could be collected in patients, as opposed to the standard enrollment of healthy volunteers. After confirming safety in single ascending dose cohorts, three multiple doses were evaluated:

- 10mg/kg monthly
- 60mg/kg monthly
- 25mg/kg biweekly.

Sabirnetug is a recombinant antibody designed to target beta amyloid oligomers over monomers (500-fold) and over fibrils/plaques (80-fold). As such, ARIA was monitored closely, with one symptomatic case occurring in a APOE4 heterozygote on the highest 60mg/kg dose, and asymptomatic cases occurring in each of the multiple dose arms. The symptomatic case was mild and transient, resolving along with the scan.

The ARIA-E rates were relatively low and no APOE4 homozygotes developed ARIA-E, though the study was small, enrolling just 65 patients. INTERCEPT-AD showed target engagement of sabirnetug and enabled dose selection of 35mg/kg and 50mg/kg for the Phase II study.

On fluid biomarkers, trends were consistent with plaque lowering for the highest dose groups on CSF beta amyloid 42/40 ratio, ptau181 (nominally statistically significant), ptau217, and presynaptic biomarker VAMP2, as well as post-synaptic biomarker neurogranin.


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## Positive Disease-Modifying Effects of Oral ALZ-801 on Plasma Biomarkers, Volumetric MRI and Cognition at 104 Weeks: Results of a Phase II Study in APOE4 Carriers with Early

James Kesslak, PhD (Alzheon)

*In a brief presentation, Dr. Kesslak provided an overview of an open-label, single-arm Phase II biomarker trial, conducted in the Czech Republic and Netherlands, evaluating ALZ-801 (valiltramiprosate) in patients with early Alzheimer's disease.*

A 104-week, open-label study evaluated valiltramiprosate. The study enrolled 31 APOE 4/4 homozygotes and 53 heterozygotes (APOE 3/4). Reductions in plasma p-tau181 over the course of two years were described as a range, when previously it was reported that there was a 43% reduction at one year and a 31% reduction noted at two years.

A question was posed about the efficacy of tramiprosate, which is available as a nutritional supplement, to which Dr. Kesslak pointed out that ALZ-801 is a prodrug with higher brain penetration, fewer side effects, and better stability.

Results from a Phase III study are expected in Q3 2024.


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## Alzheimer's Disease: Is Amyloid Enough?

Eric McDade, DO (Washington University)

David Jones, MD (Mayo Clinic)

*In the plenary session covering controversies in neurology, one talk debated whether amyloid was enough in Alzheimer's. Dr. McDade from Washington University framed the question in the context of the revised ATN criteria, accepted for publication, for diagnosis and staging AD, including solely on an abnormal amyloid PET or CSF beta amyloid 42/40 ratio regardless of symptoms. However, the audience concluded that amyloid alone is not sufficient, agreeing with a rebuttal from Dr. Jones of the Mayo Clinic.*

The 2018 NIA-AA criteria provided a biological definition for Alzheimer's disease, based on amyloid and tau pathology, versus defining the disease solely on clinical symptoms. If amyloid is not present, then you do not have Alzheimer's disease, even though symptoms may be thought of as Alzheimer's dementia. The 2018 NIA-AA criteria depicted different biomarker profiles based on the presence of amyloid (A), tau (T), and neurodegeneration (N).

**2018 NIA-AA criteria**

| AT(N) profiles | Biomarker category |
|---|---|
| A- T- (N)- | Normal |
| A+ T- (N)- | Alzheimer's disease pathological change |
| A+ T+ (N)- | Alzheimer's disease |
| A+ T+ (N)+ | Alzheimer's disease |
| A+ T- (N)+ | Alzheimer's disease pathological change and non-Alzheimer's disease pathological change |
| A- T+ (N)- | Non-Alzheimer's disease pathological change |
| A- T- (N)+ | Non-Alzheimer's disease pathological change |
| A- T+ (N)+ | Non-Alzheimer's disease pathological change |

More recently, the criteria have been revised because:

- new research differentiates stages of tau pathology
- there are therapies now approved that specifically target amyloid pathology, and
- blood-based biomarkers are becoming increasingly sensitive at identifying pathology.

The 2024 AA guidelines have been accepted for publication and reflect the ability to diagnose Alzheimer's disease using a core 1 biomarker alone, which can be amyloid alone, with or without symptoms. Compared to the 2018 ATN criteria, in which an individual being just amyloid positive (tau biomarker negative) was


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considered an Alzheimer's pathological change, but they had to be amyloid positive and tau positive to be considered to have Alzheimer's disease.

**2024 AA guidelines**

| Biomarker category | CSF or plasma analytes | Imaging |
|---|---|---|
| Core 1 | | |
| A | Abeta42 | Amyloid PET |
| $T_1$ | p-tau 217<br>p-tau181<br>p-tau231 | |
| Core 2 | | |
| $T_2$ | C-terminal tau fragments (ex. MTBR-tau243)<br>Other phosphorylated tau forms (ex. p-tau205)<br>Non-phosphorylated tau fragments | Tau PET |
| Non-specific process involved in AD | | |
| N | NfL | Anatomic MR<br>FDG PET |
| I | GFAP | |
| Non-AD co-pathology | | |
| V | | Infarction on MR or CT |
| S | Alpha-synuclein SAA | |

A = beta amyloid proteinopathy; I = inflammation, astrocytic activation; N = injury, dysfunction, or degeneration of neuropil; S = alpha-synuclein; $T_1$ = phosphorylated and secreted AD tau; $T_2$ = AD tau proteinopathy; V = vascular brain injury.


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Dr. McDade outlined several controversies surrounding the updated criteria, with rebuttals to each:

- **Making a diagnosis of AD on amyloid biomarkers alone negates the definition of Alzheimer's as being characterized by amyloid plaques and tau tangles.**
    - Amyloid PET is very sensitive in symptomatic individuals and in identifying moderate-to-frequent neuritic plaques that meet a moderate-to-high pathological criteria for AD that typically includes tau pathology. Amyloid PET scans are used to qualify plasma biomarkers. The thresholds for these biomarkers are established by sensitivity and specificity in predicting amyloid plaques, so clearly exceeding a cut-off for plasma beta amyloid or plasma p-tau means there is not just amyloid pathology, but underlying tau pathology as well.
- **The use of biomarkers is usurping clinical diagnosis.**
    - The use of biomarkers does not negate clinical judgment. For example, if a neurologist sees an individual who has severe clinical symptoms but has only a mild amyloid pathology, it is probably not the amyloid that is driving the disease. Likewise, if a patient has very mild cognitive impairment but an advanced biomarker profile, this is an individual who can be counseled that they have a high probability within a relatively short period of time of advancing.
- **The argument that amyloid plaques are just a normal process of aging.**
    - There are a substantial number of 80-year-olds who have no clinical symptoms and no amyloid plaques, so this is not a normal part of aging. A similar example is hypertension, which increases as people age, but is not a normal part of aging.
- **How to tell someone who is asymptomatic that they have Alzheimer's disease.**
    - The lifetime risk of someone in their 60s or 70s risk developing Alzheimer's dementia is probably somewhere between 25% to 55%. But if that person has higher levels of pathology, the four- to five-year risk is substantially higher, getting to the point of 60–70%.

In a rebuttal presentation, Dr. David Jones of the Mayo Clinic answered no, separately, to each question as to whether amyloid was enough to cause neurodegeneration, to know that clinical symptoms are caused by AD, to medically diagnose and manage AD, or to know that no other factors needed to be treated. He first outlined several points that they likely agreed on:

- Alzheimer's is a disease
- amyloid and tau are always present when the disease is present
- isolated tau is not AD
- isolated beta amyloid does not cause neurodegeneration
- it is possible to have asymptomatic disease states
- genetic data are consistent
- many individuals will be amyloid positive and never develop brain degeneration from AD
- testing results require clinical context for proper interpretation.

Then, Dr. Jones called out a major point of disagreement being that AD is the same entity in every way as amyloid plaques in the brain. He went over three points to support this view:


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- **Protein biology is not the only form of biology.**
    - A third of older individuals will be amyloid positive without brain degeneration or symptoms related to AD. He commented that almost everyone has more than one abnormal protein later in life, stating that isolated protein biology is a confused foundation to build a medical ontology that is useful in neurologic practice.
- **AD is a degenerative disease of brain function.**
    - The NIH definition of a disease is an abnormal condition that affects the structure or function of part or all of the body and is usually associated with specific signs and symptoms. This means that an abnormal physiological element is required for a disease to be defined and that symptoms must be present.
- **Amyloid positivity does not meaningfully capture the neurodegenerative landscape.**
    - Dr. Jones showed examples of patients who have amyloid in the brain, which included patients who had Lewy body dementia, progressive supranuclear palsy, and normal controls.

The audience agreed with Dr. Jones, voting that amyloid alone is not sufficient.


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## Autosomal Dominant Alzheimer's Disease in Colombia

Francisco Lopera Restrepo, MD, PhD (Universidad de Antioquia)

*Dr. Lopera Restrepo of the Universidad de Antioquia described the natural evolution of Alzheimer's disease in Colombian families with the presenilin 1 E280A mutation that leads to early-onset disease. Clinical deterioration can be detected over a decade before dementia onset in carriers of the pathogenic autosomal dominant Alzheimer's disease mutation PSEN1 E280A.*

Dr. Lopera Restrepo outlined the median time to progress through each stage of Alzheimer's disease for the autosomal dominant cohort.

| Disease stage | Median time of progression |
|---|---|
| Asymptomatic to symptomatic pre-MCI | 4 years |
| Symptomatic pre-MCI to MCI | 6 years |
| MCI to dementia | 5 years |
| Dementia to death | 10 years |

Dr. Lopera Restrepo showed preclinical and clinical phases of familial Alzheimer's disease.

| Stage | Phase | Age | Characterization |
|---|---|---|---|
| Preclinical | F0 | 0 years | NfL, pTau217 |
| Preclinical | F1 | 24 years | CSF beta amyloid 42 |
| Preclinical | F2 | 28 years | Amyloid PET |
| Preclinical | F3 | 32 years | Word list recall |
| Preclinical | F4 | 38 years | Tau PET |
| Clinical | MCI | 44 years | MCI |
| Clinical | Dementia | 49 years | Dementia |
| Clinical | Death | 59 years | Death |

Dr. Lopera Restrepo also presented two cases of individuals who were protected from autosomal dominant Alzheimer's disease: one was an APOE3 Christchurch gene homozygote, and the other was heterozygous for H3447R Reelin, dubbed the COLBOS mutation.


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## Diagnosing and Treating Cognitive Decline in Neurodiverse Patients

Jessica Solomon Sanders, MD (University of Colorado)

Tara Carlisle, MD, PhD (University of Colorado)

Seth Keller, MD (Neurology Associates of South Jersey)

*People with intellectual and developmental disabilities (IDD) may often be overlooked when it comes to diagnosing and treating cognitive decline, as the mental and behavioral changes are sometimes attributed to their IDD. However, there are extra considerations involved since it can be challenging to figure out which symptoms are related to IDD, which are part of normal aging, and which are indicative of something else.*

In all, 7.4 million people in the US have IDD and, while it can be difficult to determine whether symptoms are part of their disability, normal aging, or potentially cognitive decline, in the interest of equitable care, it is vital to learn how to adapt methods of diagnosis and treatment to these populations.

IDD encompasses many different disorders and syndromes, including but not limited to Down's syndrome, cerebral palsy, and autism spectrum disorder. The heterogeneity of many of these populations may require physicians to get creative in their efforts to diagnose and treat cognitive decline.

A show of hands in the meeting room revealed that while most of the neurologists attending the lecture treat patients with IDD and most of them also assess patients for cognitive decline, only a fraction assess their IDD patients for cognitive decline.

Because many patients may come in with caregivers who might not know much about their past, it is imperative that physicians take the time to speak with any family members, previous caregivers, or anyone who could provide more information on the patient's past abilities in order to properly assess the type and degree of decline.

Both diagnostic overshadowing, where a physician attributes any decline to the patient's IDD, and the opposite, where behavioral changes that may be part of normal aging are pathologized, are diagnostic patterns that can be difficult to avoid when treating IDD populations.

While many of the tests typically used for cognitive decline may not be appropriate or useful for some patients with IDD, there are a number of tests that have been developed for these populations. The Dementia Screening Questionnaire for Individuals with Intellectual Disabilities (DSQIID) works well for patients with Down's syndrome, although it is labor-intensive and often used in research rather than regular clinical practice. The Early Detection and Screen for Dementia (EDSD) is similar to the DSQIID but can be performed by a caregiver and is helpful in identifying initial cognitive decline.

The incidence of different dementias, including Alzheimer's disease, is higher in patients with Down's syndrome than in the neurotypical population, and often results in quite rapid decline. However, the availability of biomarker tests and anti-amyloid drugs may make it easier to identify Alzheimer's earlier, although these anti-amyloids have not been trialed in people with Down's syndrome, so it is unknown whether these patients are at a higher risk for some of the safety and tolerability concerns such as ARIA.


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## Validation of Icobrain Aria - An AI-Based Software Tool for Automated Detection and Quantification of Amyloid-Related Imaging Abnormalities

Annemie Ribbens, PhD (icometrix)

Belgium-based icometrix has developed an automated tool, icobrain aria, to quantify ARIA using deep learning technology using data from Biogen's aducanumab. Using icobrain aria to assist radiological readings of MRI for ARIA improved the sensitivity of ARIA detection, though this was at the cost of lowering specificity. Regardless, specificity remained above 80% for assisted reads. FDA approval is pending for this software.

## Conversational Coherence in Alzheimer's Disease and Mild Cognitive Impairment: A Decision Tree Classifier Analysis

Peter Pressman, MD (University of Colorado)

Dr. Peter Pressman of the University of Colorado presented a strategy to screen for Alzheimer's disease by using two-minute recorded conversations and applying machine learning to analyze the logical flow and consistency of conversation. The commonly used technique, called leave-one-out cross-validation, for this decision tree classifier showed promising performance, with over 95% precision and accuracy, though validation in broader populations is needed.

## Machine Learning-Enhanced Dementia Testing: Reliability and Accuracy of the Autonomous Cognitive Examination

Calvin Howard, MD

Dr. Howard presented a cognitive assessment test that is designed to enable use even in low-resource environments via a single link. The tool was validated in a randomized controlled trial with 46 patients, who received the standard paper-based test or the new digital cognitive test. Individuals who score below 76% are likely impaired, based on 100% specificity, and individuals who score about 87% are likely cognitively normal, based on a sensitivity of 100%, and those who score in between these values should be referred to a clinician for further testing.


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# Amyotrophic Lateral Sclerosis

## The Future of Amyotrophic Lateral Sclerosis (ALS)

Jinsy A. Andrews, MD (Columbia University Irving Medical Center)

*Dr. Andrews discussed the latest research and developments in the field of neurodegenerative diseases, with a focus on ALS. She provided insights into clinical trials, biomarker analyses, genetic advancements, and potential therapies. She also highlighted the importance of early detection, multidisciplinary care, and the impact of environmental factors.*

The approved treatments for ALS include riluzole, edaravone, sodium phenylbutyrate/TURSO, and tofersen. Riluzole has demonstrated improved survival regardless of treatment onset, although further real-world evidence is needed to fully assess its benefits. The FDA has approved an oral formulation of edaravone, but another oral formulation tested in the Phase III ADORE study did not show any survival or ALS function advantages. However, since the formulation, dose, and dosing schedule of this alternative formulation differed from the FDA-approved product, more information regarding its efficacy is pending until June 2024. Sodium phenylbutyrate/TURSO (Relyvrio) unfortunately did not pass its confirmatory trial, leading to the manufacturer's decision to withdraw the drug from the market. Tofersen (Qalsody), an antisense drug that reduces SOD1 gene expression in ALS patients, received accelerated approval from the FDA in 2023 and has also had a positive opinion from the CHMP in Europe.

Currently, numerous pipeline drugs are undergoing early-phase clinical trials. One example is QRL201, currently in a Phase I study, which targets the Stathmin-2 protein. Pridopidine is being evaluated in the HEALEY ALS Platform trial and has demonstrated some positive impact on speech and disease progression in a subgroup of patients with a disease onset of ≤18 months. PrimeC is a small molecule that aims to address microRNA synthesis, neuroinflammation, glutamate excitotoxicity, and oxidative stress. Its Phase IIb study has shown promising safety and tolerability profiles. The manufacturer plans to meet with the FDA and EMA and initiate a Phase III study based on the results of biomarker analysis, including TDP43 and prostaglandin J2, expected to be available during 2024. CAR-T cell therapy, both autologous and allogeneic, is in the early stages of clinical development, specifically targeting neuroinflammation. Another ongoing study is implementing neural progenitor stem cells in the motor cortex, currently enrolling patients in a Phase I trial. BrainStorm is advancing its autologous bone marrow-derived stem cell therapy through intrathecal injection in a Phase IIIb study. Furthermore, its Phase II study using intrathecal autologous adipose-derived mesenchymal stem cells has shown positive safety and tolerability profiles, with efficacy and biomarker analyses pending.

Early diagnosis plays a crucial role in enhancing the quality of life and survival rates for individuals with ALS, given the advancements in current treatment options. To facilitate early diagnosis, the thinkALS program has been designed to assist general neurologists in identifying ALS patients at an early stage. Additionally, research is now exploring the evaluation of asymptomatic individuals and gene carriers. A study by Benatar et al. (2018) indicated that neurofilament light (NfL) could serve as a potential biomarker for presymptomatic ALS. Building on this finding, the Phase III ATLAS study has been initiated for presymptomatic SOD1 variant carriers. These individuals will undergo monthly monitoring of their NfL levels, and when NfL levels surpass a certain threshold, they will receive treatment with tofersen to prevent the onset of ALS. This study is actively enrolling participants.

The HEALEY ALS Platform trial aims to expedite the screening process for potential ALS treatments in a fast and efficient manner. Through the utilization of a shared placebo and established infrastructure, this platform has successfully evaluated five drugs within 3.5 years. Among these, two drugs, namely CNM-Au8 and pridopidine, have demonstrated promising signs of efficacy, leading them to progress into Phase III trials.


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Various theories regarding disease development and novel treatments have been explored in the field.

- In a paper published by Goutman et al. (2023), the role of gene-environment interactions in ALS was proposed. Characterization of the ALS exposome, which encompasses the lifetime accumulation of environmental exposures that increase disease risk and impact progression, may inform the contributing factors of ALS. This hypothesis suggests that individuals with SOD1 variants may require fewer steps to initiate disease onset compared to those with sporadic ALS.
- Additionally, the presence of cryptic exons, abnormal mRNA sequences that include incorrect intronic exons due to TDP43 loss-of-function, has been identified as a potential biomarker and therapeutic target for TDP43 proteinopathies like ALS and frontotemporal dementia (FTD).
- Another significant finding by the research group at UCSF (Sachdev et al., 2024) demonstrated that CRISPR-mediated allele-specific excision can reverse the pathology induced by C9orf72 mutations, suggesting a potential therapeutic strategy for ALS through the excision of the mutant C9orf72 allele using CRISPR gene editing.

Multiple data repositories are currently in progress, including cell-based studies, longitudinal clinical data integrating multi-omics approaches, whole-genomic sequencing facilitated by Neuromine, whole-genomic sequencing data available through AnVIL under NIH funding, and a clinical trial database managed by PRO-ACT.

In late 2021, the Accelerating Access to Critical Therapies for ALS Act was signed, establishing public-private partnerships as the basis. This act consists of two components: an FDA action plan designed to accelerate the development of treatments for neurodegenerative disorders, and an NIH strategic planning working group that provides guidance and prioritization for NIH-funded initiatives aimed at understanding ALS and developing effective therapies. The ALL ALS program, supported by NIH funding, aims to coordinate longitudinal observational data collection in both symptomatic and asymptomatic individuals with ALS.

## ALS Epidemiology, Presentation, Diagnosis, and Treatment

Stephen Goutman, MD (University of Michigan)

*There is overlap in the symptoms of ALS and FTD, but the most common diagnostic criteria are focused solely on motor symptoms.*

ALS is caused by the deterioration of motor neurons in the brain, but it is also related to FTD; up to 50% of ALS patients will meet some of the criteria for FTD, indicating that it is not a purely motor disease.

The Gold Coast diagnostic criteria, however, are solely focused on motor symptoms, defining the disease by progressive motor impairment and presence of both upper and lower motor neuron dysfunction in at least one body region, among other diagnostic processes.

There are three FDA-approved drugs to slow disease: riluzole, edaravone, and tofersen, with the latter relegated to only SOD1 mutation-related ALS. These drugs offer a modest at best survival benefit, and in the recent Phase III ADORE study in Europe, edaravone failed both primary and key secondary endpoints.

A number of studies show that there is benefit both to multidisciplinary care and to maintaining body weight in ALS patients.


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## The Emergence of Expanded Access Protocols in ALS

Suma Babu, MD (Harvard Medical School)

*Expanded Access Protocols (EAPs) have allowed patients who may not meet trial inclusion criteria to still access experimental therapeutics, which is particularly important in diseases like ALS where there are not many approved drugs.*

EAPs, also known as compassionate use programs, offer a pathway for patients with immediately life-threatening or serious diseases to access investigational therapies outside of clinical trials. This can be on the scale of a single patient all the way up to large populations across multiple sites.

On the clinical side, EAPs allow for the gathering of real-world data on long-term safety and efficacy, which is particularly important given that long-term data are often unknown at the time of approval, and the trial populations for drugs are often not representative of the post-FDA approval consumers. Some EAPs specifically target individuals who do not qualify for the clinical trial itself.

In ALS, 90% of the population in the US does not have access to experimental therapeutics. EAPs in ALS are relatively new, with the first program initiating in 2018, and the FDA released encouraging guidance in 2019 suggesting that companies making investigational ALS drugs strongly consider incorporating EAPs into their development programs. It is important to note that EAPs should not interfere with or otherwise compromise clinical trials that could support marketing approval, although the safety data from these protocols can be submitted as part of the registrational package.

The first multicenter EAP was a companion to the Healey ALS Platform trial in July 2021. This program boasted centralized operations and site training along with standardized data capture and was funded mostly through philanthropic foundations. In late 2021, an act was signed into law that created NIH grants for research via intermediate-sized EAPs in ALS, making launching these programs more feasible.

## Disentangling the Relationship Between Social Cognition, Executive Functions, and Behavior Changes in Amyotrophic Lateral Sclerosis

Francesca Palumbo (University of Turin)

*While social cognition impairment is quite common in ALS patients, there were no significant associations with behavior changes and an executive function deficit cannot reliably predict social cognition deficits.*

Social cognition (SC) impairment is often observed in ALS patients, but only recently have some revised diagnostic criteria been released that include SC deficits.

In a study of 121 ALS patients at the Turin ALS Centre and 56 matched healthy controls, 39.3% showed a deficit in at least one executive function test. A total of 14.8% showed behavior changes, and 13.1%, the majority of whom were male, had SC deficits that were subclinical and not combined with any other cognitive impairment or behavioral change.

The study also found that executive function deficits cannot reliably predict SC impairment and, furthermore, there was no significant association between SC impairment and behavior changes.


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# Epilepsy

## Efficacy and Safety of ES-481, a Novel TARP Inhibitor, in Drug-Resistant Epilepsy: A Double-Blind Randomized Placebo Controlled Phase IIa Trial

Terence O'Brien, MD (Monash University)

*In this proof-of-concept study, ES-481 reduced seizures in patients with a broad range of drug-resistant epilepsy syndromes.*

ES-481 selectively targets hippocampal excitatory transmission by blocking TARP-dependent glutamatergic receptors.

This Phase IIa trial had a crossover design, where patients either started in the active treatment arm and then moved to placebo halfway through, or vice versa. Dosing was increased on a weekly basis and then there was a seven-day stepdown and washout period before switching treatments. This study enrolled 22 adults with a history of drug-resistant epilepsy (DRE), 17 of whom completed the double-blind phase and 16 entered the open-label extension.

In the modified intent-to-treat population of 22 participants, there was a 68–80% improvement in weekly seizure frequency while taking ES-481 compared to a 38–69% improvement for placebo. The highest dose did produce a statistically significant reduction in seizures over placebo with a p-value of 0.047.

EEG findings were no different between ES-481 and placebo, although many of the patients lacked EEG seizures at baseline.

The safety profile was reasonable, with dizziness, insomnia, and somnolence being the most common adverse events in the ES-481 group compared to placebo.


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## First-in-Human Trial of NRTX-1001 GABAergic Interneuron Cell Therapy for Treatment of Focal Epilepsy - Emerging Clinical Trial Results

Cory Nicholas, PhD (Neurona Therapeutics)

*Cell therapy with NRTX-1001 resulted in notable seizure reduction in this small, early-phase trial.*

During development, most GABAergic interneurons that provide inhibition originate in the medial ganglionic eminence (MGE) and then migrate into the cortex before birth. These MGE stem cells have been successfully transplanted into adult brains where they similarly migrate, integrate, and increase local inhibition in multiple different animal models.

NRTX-1001 is comprised of human MGE-type GABAergic interneurons derived from pluripotent stem cells administered as an intracerebral single dose to the hippocampus.

The ongoing Phase I/II First-in-Human trial is an open-label study in 10 adults with chronic unilateral mesial temporal lobe epilepsy and mesial temporal scarring, who would normally be lobectomy candidates.

In the first five patients who received the low dose, four experienced a greater than 50% reduction in seizures at month six, and three of those had >75% seizure reduction. These results appear to be durable as three of the five participants have been completely free of disabling seizures for up to 20 months.

None of the adverse events were attributed to the cell therapy, most were related to the delivery procedure and resolved in the first month, or to the immunosuppression regimen that patients were on starting one year prior to administration.


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## The Impact of Disease Severity on Responder Rates in a Phase 2b Study of XEN1101, a Potent, Selective Potassium Channel Opener, in Adults with Focal Epilepsy (X-TOLE)

Roger Porter, MD (University of Pennsylvania)

*XEN1101 performed admirably in X-TOLE, exhibiting a clear dose response as well as statistically significant improvements over placebo at all three dosages. Interestingly, however, XEN1101 was more effective in the study population that had indicators of less severe disease.*

| | Change from baseline in seizure frequency | Patients with 50% or greater reduction in seizure |
|---|---|---|
| Placebo | -18.2% | 14.9% |
| 10mg | -33.2% (p<0.05) | 28.3% (p<0.05) |
| 20mg | -46.4% (p<0.001) | 43.1% (p<0.001) |
| 25mg | -52.8% (p<0.001) | 54.5% (p<0.001) |

XEN1101 is a novel Kv7 potassium channel opener in development by Xenon Pharmaceuticals for focal onset and tonic-clonic seizures, as well as major depressive disorder.

The results from the Phase IIb X-TOLE study showed a predictable dose response, as well as statistically significant improvements over placebo for all three doses, both on the primary endpoint of median percent change in seizure frequency from baseline and the secondary endpoint of the percent of patients experiencing a 50% or greater reduction in seizures.

Safety-wise, XEN1101 was generally well tolerated, with a discontinuation rate due to treatment-emergent adverse events of 12.3%, which is within a similar range to other modern anti-seizure medications (ASMs).

The patient population was quite severe, almost half of the placebo and 25mg patients were on three concomitant ASMs, and almost three quarters had failed more than three ASMs prior to the study. These patients began with roughly 13 seizures per month at baseline. However, XEN1101 was relatively more effective in the study population that had indicators of less severe disease, such as failing fewer medications prior to the trial.


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## Bexicaserin (LP352) Phase Ib/2a PACIFIC Study in Participants with Developmental and Epileptic Encephalopathies

Randall Kaye, MD (Longboard Pharmaceuticals)

*Bexicaserin's safety profile appeared to be good in this small study and there was evidence of potential efficacy, but larger studies will need to be conducted to better characterize the prospects of this drug.*

Bexicaserin is a highly selective 5-HT2c receptor agonist that offers the potential for fewer off-target effects and a smoother safety profile. This study did find that the most common adverse event leading to discontinuation was somnolence, occurring in 12 patients in the bexicaserin group and one patient in the placebo group.

The PACIFIC study enrolled 52 patients between the ages of 12 and 65 years, inclusive, with developmental and epileptic encephalopathies (DEEs). DEEs include patients with Lennox-Gastaut syndrome (LGS), Dravet syndrome (DS), SCN2A-related epilepsies, and CDKL5 deficiency disorder.

There was a 59.8% reduction in observed countable motor seizures in the bexicaserin group compared to a 17.4% reduction in the placebo group (p=0.0538). A post-hoc exploratory analysis reported a 51.9% placebo-adjusted mean seizure reduction (p=0.0206), but while both of these efficacy results trended positively, it is important to remember that this study was not powered for efficacy.

Within the LGS and DEE-other subgroups, there was roughly a one third reduction in median observed countable motor seizures over placebo, and while the DS subgroup experienced a numerically larger reduction, there were no placebo DS patients to compare with.

## Characterization of BHV-7000: A Novel Kv7.2/7.3 Activator for the Treatment of Seizures

Kelly Picchione, PhD (Biohaven Pharmaceuticals)

*BHV-7000 is a Kv7.2/7.3 voltage-gated potassium channel activator that regulates the hyperexcitability seen in epilepsy. The specificity of the mechanism results in fewer off-target effects, such as somnolence and cognitive or mood disturbances, which are common with other ASMs.*

BHV-7000 is a Kv7.2/7.3 voltage-gated potassium channel activator that regulates the hyperexcitability seen in epilepsy.

The drug was well tolerated in the Phase I SAD/MAD trial, without the dose-limiting central nervous system side effects seen with other ASMs, like somnolence and cognitive or mood disturbances.

BHV-7000 is currently in clinical development for both focal and generalized epilepsy, as well as bipolar disorder and major depressive disorder. The RISE 2 Phase II/III study in partial/focal seizures was initiated in March 2024.


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## Long-Term Effectiveness of Cannabidiol (CBD) Against Focal-Onset Seizures in Treatment-Resistant Epilepsies (TRE): Experience from the Expanded Access Program (EAP)

Karthik Rajasekaran, MD (Jazz Pharmaceuticals)

*CBD is currently approved in the US for Lennox-Gastaut syndrome, Dravet syndrome, and tuberous sclerosis complex, but other patients with treatment-resistant epilepsy who received compassionate access to the drug through an expanded access program also had a moderate reduction in focal seizure.*

| | Median percent reduction in focal seizures | Patients with 50% or greater reduction in focal seizures | Patients with 75% or greater reduction in focal seizures | Patients with 100% reduction in focal seizures |
|---|---|---|---|---|
| Week 12 | 63% | 55% | 41% | 20% |
| Week 144 | 76% | 69% | 51% | 22% |

Epidiolex, or cannabidiol (CBD), is currently approved in the US for Lennox-Gastaut syndrome, Dravet syndrome, and tuberous sclerosis complex, but patients with treatment-resistant epilepsy received compassionate access to the drug through an expanded access program (EAP) during 2014–19.

A total of 351 patients in the EAP had focal seizures at baseline, and over the course of the 144 weeks of treatment, 113 patients withdrew, primarily due to lack of efficacy. However, trends in seizure reduction indicate that CBD may be effective against focal seizure regardless of epilepsy diagnosis.

Safety was consistent with the rest of the EAP participants and with Epidiolex clinical trials, including some abnormal liver function tests.


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## Mood Disorders in Epilepsy – Identification, Causes, and Treatment

Cornelia Drees, MD (Mayo Clinic)

*There is quite a high prevalence of psychiatric conditions like anxiety and depression in people with epilepsy, which negatively impact their ability to handle seizures and tolerate ASMs, as well as decreasing their quality of life.*

Psychiatric co-morbidity in epilepsy is common, but not necessarily more so than in other chronic neurological conditions. However, co-morbid anxiety and depression are associated with poorer seizure control, greater side effects of ASMs, and poorer quality of life.

Suicide accounts for 11.5% of deaths in people with epilepsy vs. 1.6% of the general population. There is a bidirectional effect for mood disorders, suicidality, and epilepsy, with the strongest association with suicide attempts in people with co-morbid bipolar or panic disorders, although the suicide rate in epilepsy has been gradually falling as more physicians start treating these psychiatric co-morbidities. Interestingly, suicidality is much lower in patients with both epilepsy and a developmental disability, potentially due to the increased presence and support of caregivers.

Some ASMs may increase or decrease depressive symptoms and on the flip side, some antidepressants and anxiolytics can also affect seizure frequency, but the main takeaway is the emphasis on partnering with psychiatrists to determine which ASMs and depression or anxiety treatments may work best for a particular patient. While clinicians are good at evaluating for depression, anxiety and bipolar disorders can be more difficult to identify.

## What's New for Kids with Epilepsy?

Courtney Wusthoff, MD (Stanford University)

*There have been a number of changes to the classifications of seizure in children, as well as the recommended treatment guidelines, over the last five to 10 years. There is clear evidence for the use of phenobarbital over levetiracetam in neonates, and there are now rescue medications available for children over the age of six months with a variety of routes of administration.*

The field of neonatal epilepsy has matured immensely over the last five to 10 years. There is now a new classification system, removing the need to try to fit neonatal seizures into one of the categories for older children and adults. This new system is based on EEG, so now babies cannot be diagnosed with seizure without quantifiable evidence from continuous EEG. Observational evidence or amplitude EEG can be at most classified as a probable seizure.

80% of the time, neonatal seizures are symptomatic of acute brain injury such as cerebral hypoxia-ischemia or stroke. The remaining 20% are due to early-onset epilepsy, most commonly KCNQ2 mutations, but also other brain malformations or syndromes.

A new study, NEOLEV2, found that levetiracetam is much less effective than phenobarbital in neonatal seizure. This drug should be first line in neonates, regardless of seizure etiology. Additionally, ASM can be discontinued much earlier than previously thought to avoid sending babies home with phenobarbital, since prolonged ASM use has been shown by the Neonatal Seizure Registry to not prevent epilepsy.

In infantile epileptic spasms syndrome, there is clear evidence that regardless of etiology or pre-existing neurological diagnoses, adrenocorticotropic hormone, high-dose prednisolone, and/or vigabatrin should be the first-line treatment.

There are now rescue medications available for children aged six months and older with refractory epilepsy or prior status epilepsy, including intranasal and buccal midazolam as well as rectal and intranasal diazepam.


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## Hormones and Epilepsy: Principles and Management

Courtney Schusse, MD (Barrow Neurological Institute)

*The interaction between hormones, ASMs, and seizures is complex, highlighting the importance of carefully choosing a treatment that works with a particular individual's age, fertility plans, sex, gender identity, and sexual behavior.*

Estrogens potentiate glutamate responses primarily via NMDA receptor activity, but also by affecting GABAergic transmission. Estradiol in particular can also increase clearance of some ASMs. Progesterone, on the other hand, can enhance postsynaptic GABAergic activity, often through allopregnanolone.

Testosterone is less consistent and has both inhibitory and excitatory action with regards to seizure.

Given this significant interplay between hormones, ASMs, and seizure, steroid hormones have a significant role in the management of epilepsy. Both seizures themselves and many ASMs impact hypothalamic-pituitary function in both men and women and can cause reproductive dysfunction.

Catamenial seizures, or menstrual-related seizures, impact about half of women with epilepsy. Nonhormonal treatment options include acetazolamide and off-label benzodiazepines like clobazam and clonazepam. Hormonal treatments like medroxyprogesterone acetate can lead to seizure reduction over time but come with significant unwanted side effects like weight gain and hair loss. Ganaxolone, which is synthetic allopregnanolone, is in trials for catamenial epilepsy, with promising early results.

Women with epilepsy are more prone to premature ovarian failure, with symptoms worsening during perimenopause and improving after confirmed menopause. Hormone replacement therapy is not recommended for women with hormonal-sensitive epilepsies.

In transgender individuals who are on gender-affirming hormone therapy, trans men may experience a decrease in seizures since testosterone can be protective. ASMs like valproic acid and levetiracetam may increase testosterone levels, while estrogen presence can increase the metabolism of lamotrigine, leading to lower levels of the drug.


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## Epilepsy in the Elderly Population

Amy Crepeau, MD (Mayo Clinic)

*Like neonates, the elderly are more at risk for seizures. Other aging-related diseases such as Alzheimer's disease and dementia may heighten this risk, although the medications used to treat these disorders can also lower the seizure threshold.*

The incidence of epilepsy across the lifespan is a U-shaped curve, with the highest risk at the beginning and end of life.

Auras are less common in older adults, potentially due to co-existing dementia. Symptoms are more nonspecific, such as brief periods of confusion, lightheadedness, or other vague symptoms.

Although the etiology of late-onset epilepsy is most often cerebral infarction, many antidepressants may increase the risk of seizures, including bupropion, citalopram and escitalopram, fluoxetine, sertraline, and fluvoxamine.

While seizures are more common in patients with early-onset Alzheimer's, many of the drugs used to treat Alzheimer's, such as antidepressants, first-generation antipsychotics, and acetyl-cholinesterase inhibitors, may increase seizure risk as well. NMDA receptor agonists have a potentially more favorable seizure profile. Anti-amyloids like lecanemab carry a risk for ARIA with either brain edema or hemorrhage, which may be associated with new-onset seizure.

Elderly patients with well-defined epilepsy can safely undergo epilepsy surgery and often have favorable outcomes and notable improvements in quality of life.


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## Status Epilepticus (SE) Update

Dr. Luis Caboclo, MD, PhD (Israelita Albert Einstein Hospital)

Dr. Clio Rubinos, MD (University of North Carolina)

*In SE, there is not much data to suggest that one benzodiazepine is notably more efficacious than another. The timing of treatment within the first hour of SE holds far more weight than which drug is used. Ketamine is underutilized in refractory SE and can be quite effective, particularly when administered early on alongside midazolam.*

Dr. Caboclo gave an overview of the recommended treatments for the Golden Hour, which refers to the first hour of SE when medication will be most effective.

While there are a number of drugs used for SE, lorazepam is the most common since it has a fast onset, a short to intermediate duration of action, and can have a prolonged clinical effect after a single dose. However, in the evidence-based guidelines from the American Epilepsy Society, for both children and adults, intravenous lorazepam is equivalent to intravenous diazepam, despite diazepam having up to a 50% seizure reoccurrence rate.

In children, non-intravenous midazolam, such as intramuscular, intranasal, or buccal, is likely to be more effective than either intravenous or rectal diazepam.

A systematic review of the use of lacosamide for SE shows that it works far better in focal motor SE (92% of the 522 SE episodes evaluated) than nonconvulsive (57%) or generalized-convulsive (61%).

Overall, the speed with which medication is administered has proved far more important than the particular benzodiazepine used.

Dr. Rubinos' lecture focused mostly on approaches to refractory and super-refractory SE. First-line anesthetics for refractory SE include propofol or midazolam, and pentobarbital tends to be used for super-refractory SE. A recent review study shows that there is no difference in withdrawal seizures or breakthrough seizures between these three drugs, although an older study found that midazolam was associated with statistically higher rates of the latter.

While pentobarbital has a higher rate of success in controlling refractory SE compared to midazolam, the safety and tolerability profile can make it a less attractive option.

One of the most important takeaways, however, is the use of ketamine. While this drug is typically used later on, if at all, in refractory SE, there are a number of advantages to administering it early, ideally with GABAergic drugs like midazolam. Ketamine has not been shown to increase intracranial pressure and does modulate some cytokines that may reduce inflammation. It also does not lead to cardiovascular depression but can cause hypertension, which can be an advantage when co-administered with midazolam, since this drug can cause hypotension.


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# General Myasthenic Gravis

## AChR-Positive Myasthenia Gravis

Srikanth Muppidi, MD (Stanford Health Care)

*Dr. Muppidi provided a concise overview of the pathogenesis, diagnosis, and current as well as future treatment options for myasthenia gravis (MG).*

MG is a neuromuscular junction disease characterized by immune cells attacking protein molecules, leading to impaired signal transmissions between neurons and muscles. Diagnosis of MG relies on autoantibody testing against acetylcholine receptor (AChR), muscle-specific kinase (MuSK), or lipoprotein-related protein 4 (LRP4). Studies have indicated that AChR antibodies may trigger the formation of the complement membrane attack complex, suggesting that detecting complement activation in patients could help inform personalized drug prescriptions.

Conventional treatments for MG include azathioprine and mycophenolate mofetil, both of which have been shown to improve quality of life in over 50% of patients according to the PROMISE-MG study. Thymectomy, a surgical procedure, has demonstrated the ability to make patients independent of or require lower doses of prednisone in the MTGX study. Post-hoc analysis of the MTGX study also revealed that more patients who underwent thymectomy achieved complete withdrawal of prednisone and faster minimal manifestations. However, thymectomy is not widely practiced and requires further study to determine its underlying causes. Newer therapies for MG encompass complement inhibitors, FcRn inhibitors, B cell and plasma cell-directed therapies, and T cell-directed therapies.


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Three clinical studies examined the use of rituximab in MG patients, and their key results are shown below. Early-onset MG patients may benefit more from rituximab compared to those with refractory disease. In addition to rituximab, the anti-CD19 antibody inebilizumab is being tested in the MINT study.

| Study | Trial design | Primary endpoint | Result | Conclusion |
|---|---|---|---|---|
| BEAT-MG, Phase II | Rituximab vs. placebo | Steroid sparing | 60% rituximab vs. 56% placebo (p=0.03) | Improvement by rituximab is unlikely to be achieved in a Phase III trial. No safety issues. |
| Swedish retrospective study | Rituximab in refractory and new-onset gMG | Median time to remission | 7 months (new onset) vs. 16 months (refractory disease) | Rituximab is more favorable in new-onset patients and over conventional treatment |
| | Rituximab vs. conventional immunotherapy in new-onset disease | | 7 months (rituximab) vs. 11 months (conventional therapy) | |
| RINOMAX study, RCT | Rituximab vs. placebo in early-onset gMG | Minimal disease manifestations | 71% (rituximab) vs. 29% (placebo) | A single dose of 500mg of rituximab was associated with greater probability of minimal MG manifestations |

Small-scale studies targeting CD19 or BCMA with CAR-T cell therapy have shown promising potential for the treatment of generalized myasthenia gravis (gMG) in the future.


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## Myasthenia Gravis: Ocular and MuSK

Neelam Goyal, MD (Stanford Health Care)

*Dr. Goyal presented an introduction to the less prevalent subpopulation of MG, specifically highlighting the underserved patients with ocular myasthenia gravis (OMG) in clinical trials.*

Ocular Myasthenia Gravis (OMG)

- Patients with OMG experience symptoms such as ptosis (droopy eyelids), double vision, eye closure weakness, and variable manifestations. Approximately 85% of all MG patients exhibit ocular symptoms. While, initially, 50% of MG patients present with only ocular symptoms, the majority eventually develop gMG, leaving only 15% with OMG as the sole manifestation of the disease.
- Diagnosing OMG can be challenging. In addition to clinical bedside symptoms, laboratory tests involving autoantibody analysis and electrophysiological analysis through single fiber EMG are recommended. It is noteworthy that while 60% of OMG patients test positive for AChR antibody (50%) or MuSK and LRP4 antibody (10% combined), 40% of OMG patients test negative in ocular seropositivity analysis.
- OMG disease severity tends to peak within the first one to three years. A retrospective review of 78 patients observed over an eight-year period showed that 54% achieved remission, 33% experienced clinical improvement with ongoing symptoms, and 13% had stable disease without improvement.
- Although OMG is not life-threatening, patients with this condition often face challenges in their daily lives and work. They are frequently excluded from clinical trials, highlighting a significant unmet need for drug development in this population.

Muscle-Specific Kinase (MuSK) myasthenia gravis

- MuSK MG patients exhibit distinct clinical features compared to AChR MG. The onset of MuSK MG typically occurs in female patients in their 30s. It is characterized by an acute onset with rapid progression, primarily affecting muscles in the neck, shoulder, face, and those innervated by the bulbar region, observed in 80% of MuSK MG patients. Muscle atrophy and wasting, particularly in the tongue muscle, are frequently observed, without any thymic abnormalities. Diagnosis relies on serology testing for MuSK IgG positivity, as well as electrophysiology and electromyography analysis.
- The effectiveness of thymectomy, acetylcholinesterase inhibitors, and intravenous immunoglobulin for MuSK MG patients remains uncertain due to a lack of clear evidence. However, B cell-depleting therapy with rituximab has demonstrated superior efficacy in treating these patients. In 2023, rozanolixizumab was approved for the treatment of MuSK MG patients.


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## Complement inhibition in MG

Srikanth Muppidi, MD (Stanford Health Care)

*Dr. Muppidi provided an in-depth overview of the clinical trial data for complement inhibitors, namely eculizumab, ravulizumab, and zilucoplan.*

Three complement inhibitors have been approved by the FDA for treating gMG.

| Therapy | Mode | Type | Frequency of administration | Dosing |
|---|---|---|---|---|
| Eculizumab | IV | mAb | Every two weeks | Standard |
| Ravulizumab | IV | mAb | Every two months | Weight-based |
| Zilucoplan | SC | Peptide | Daily, self administered | Weight-based |

Several outcome measures for MG were introduced, with notable consideration given to the presence of placebo effects in all clinical trials involving MG, posing a significant challenge.

| | |
|---|---|
| **Quantitative MG (QMG)** | QMG takes 30 minutes to complete, so is not a popular method in clinical practice. |
| **MG-Activities of Daily Living (MG-ADL)** | This popular measure assesses MG's impact on patient activity levels. It includes eight expanded QMG questions and uses a linear scoring system ranging from 0 (no symptoms) to 3 (severe symptoms). It takes less than five minutes to complete. |
| **MG-QOL15r** | A patient-reported measure scoring quality of life. |
| **MG Composite** | A mixed-outcome measure reported by both physicians and patients. The score ranges from 0 (no symptoms) to 50 (severe symptoms). |

Eculizumab functions by inhibiting the cleavage of C5, thereby decreasing the formation of the complement membrane attack complex (MAC). While its Phase III REGAIN study did not demonstrate significant improvement in the primary outcome measure compared to placebo in the treatment of gMG, several secondary measures showed significance, including MG-ADL, QMG, and MG-QOL15. A higher proportion of patients treated with eculizumab experienced improved MG-ADL and QMG over the 26-week treatment period. The long-term open-label study also provided support for eculizumab treatment, indicating a reduction in MG exacerbations, hospitalizations, and MG-related hospitalizations, with favorable safety outcomes. It is important to note that patients with thymoma were included in the clinical trials.

The FDA has granted approval for ravulizumab, a long-acting next-generation version of eculizumab, for the treatment of MG. Ravulizumab has demonstrated a safety profile similar to that of eculizumab. A post-hoc analysis has revealed that ravulizumab treatment leads to improved clinical outcomes for patients with AChR+ gMG, irrespective of time since diagnosis. Additionally, a numerical trend suggests a more favorable treatment effect when ravulizumab is administered earlier rather than later following diagnosis.

Zilucoplan is a synthetic peptide that specifically binds to C5 and C5b, effectively inhibiting the cleavage of C5. In the Phase III RAISE study conducted in patients with gMG, zilucoplan demonstrated a rapid clinical


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response within just one week of treatment initiation. As a result of the positive findings, in 2023 the FDA granted approval for zilucoplan as a treatment option for gMG patients.

As the complement system plays a crucial role in combating encapsulated bacteria, patients who are prescribed complement inhibitors are strongly advised to receive meningococcal vaccinations to protect against Neisseria meningitidis infection.

Unfortunately, there are currently no identifiable prognostic factors that can indicate the most appropriate candidates for complement inhibitor treatment. Moreover, in patients with AChR+ MG, complement activity does not correlate with clinical status or autoantibody titer.


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## Myasthenia Gravis: FcRn Therapeutics

Neelam Goyal, MD (Stanford Health Care)

*Dr. Goyal gave an overview of FcRn inhibitors efgartigimod and rozanolixizumab, while sharing her treatment algorithm for patients with MG*.

The Neonatal Fc receptor (FcRn) plays a crucial role in binding IgG and preventing its degradation in lysosomes. Consequently, inhibiting FcRn leads to an accelerated clearance of IgG, including pathogenic autoantibodies. At present, there are two FcRn inhibitors that have received approval for the treatment of generalized gMG.

| Agent | Molecule | Disease state | Mode | Trial status |
|---|---|---|---|---|
| Efgartigimod<br>Vyvgart, Vyvgart Hytrulo (Argenx) | Fc fragment | AChR-positive, generalized, nonrefractory | IV, SC | FDA approved in December 2021<br>SC formulation approved in June 2023<br>Indications: AChR+ gMG |
| Rozanolixizumab<br>Rystiggo (UCB) | IgG4 | AChR-positive, generalized, moderate to severe | Weekly SC | FDA approved in June 2023<br>Indications: AChR+ and MuSK+ gMG |

Efgartigimod obtained approval based on the favorable outcomes of the Phase III ADAPT study. Participants received an initial cycle of either efgartigimod or placebo treatment, followed by a five-week follow-up to assess clinical response. Non-responding or partially responding patients underwent an additional cycle. This trial design, post-approval, enables physicians to gradually reduce treatment when patients' symptoms improve and efgartigimod is no longer necessary. Common side effects included mild-to-moderate headache, nasopharyngitis, and injection site reactions observed in subcutaneous formulations, which tended to improve with repeated dosing. The open-label extension ADAPT+ study provided long-term efficacy and safety profiles, demonstrating that three years of efgartigimod use did increase frequency of adverse effects.

Rozanolixizumab, a monoclonal antibody formulated for subcutaneous injection, received approval based on the favorable results obtained from the Phase III MycarinG study. It is worth noting that the MycarinG study included a larger cohort of MuSK MG patients compared to the ADAPT study. This pivotal study serves as the basis for the approval and prescription of rozanolixizumab not only for AChR MG patients but also for MuSK MG patients.


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Pipeline FcRn therapies in the gMG treatment landscape are shown below.

| Agent | Molecule | Disease state | Mode | Trial status |
|---|---|---|---|---|
| Nipocalimab, M281 (Janssen) | IgG1 | AChR-positive, generalized | IV | Phase III complete<br>Topline results positive (February 2024) |
| IMVT-140, RVT-1401 (Batoclimab, Immunovant) | IgG4 | AChR-positive, generalized, nonrefractory | Weekly SC | Phase III ongoing (started June 2022) |

Dr. Goyal shared her insight of MG therapeutics as shown below.

| Initiation | Fast (oral) | Fast (oral) | Slow (infusion, insurance, port, +/- vaccination) | Fast (oral) | Slow (infusion, insurance, +/- vaccination) | Slow (surgical) |
|---|---|---|---|---|---|---|
| **Time to/ Level of efficacy** | **Fast (hours)/ Low** | **Fast (weeks)/ High** | **Fast (days to weeks)/ High** | **Slow (months)/ Moderate** | **Slow (weeks/months)/ High** | **Slow (years)/ Moderate** |
| **Cost/SE** | **Low/Low** | **Low/High** | **High/~SE** | **Low/~SE** | **High/~SE** | **High/~SE** |
| **MOA** | **Downstream** | **Upstream** | **Downstream** | **Upstream** | **Upstream/ Downstream** | **Upstream** |
| | **A** | **B** | **C** | **D** | **E** | **F** |
| | Pyridostigmine | Steroids | IVIG | Mycophenolate mofetil | Rituximab | Thymectomy |
| | | | PLEX | Azathioprine | Eculizumab | |
| | | | Efgartigimod IV, SC | Tacrolimus | Ravulizumab | |
| | | | Rozanolixizumab | Methotrexate | Zilucoplan | |
| | | | +/- Eculizumab | | | |
| | | | +/- Ravulizumab | | | |
| | | | +/- Zilucoplan | | | |


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The decision-making process takes into account several factors, including the speed of treatment initiation, time required to observe efficacy, drug side-effect profiles, cost considerations, and potentially the mechanism of action. The ultimate goal is to achieve control over the patient's condition using drugs classified under Column D. However, for patients who do not respond adequately, treatment options from Columns A, B, C, D, and E may be considered concurrently to manage their progressive disease.

- Pyridostigmine, while cost effective, exhibits limited efficacy.
- Steroids are known for their efficacy, but they also carry a high risk of toxicity.
- Drugs classified under Column D may require some time to take effect.
- Treatments in Column C demonstrate rapid efficacy but may have a delayed initiation period. Both approved FcRn inhibitors are administered based on symptoms, allowing physicians to gradually reduce the dosage when appropriate.
- Drugs in Column E are predominantly administered via infusion. Once initiated, it can be challenging to determine the appropriate tapering protocol for these treatments.
- The option presented in Column F involves a surgical procedure and may take years before its effects become noticeable.

Dr. Goyal foresees the potential benefits of initiating targeted therapy at an early stage and omitting steroid treatments for patients with gMG. Additionally, she expressed anticipation for the emergence of novel therapies in the field, such as IL-6 inhibitors, alternative B cell-targeted therapies, and CAR-T cell therapy.


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## Industry Therapeutic Update from UCB: Harnessing New Potential in Generalized Myasthenia Gravis (gMG): When Individuality Meets Optionality

Neelam Goyal, MD (Stanford Health Care)

*This presentation, sponsored by UCB, reinforced the clinical data published by the company regarding two of its drugs: rozanolixizumab (an FcRn inhibitor) and zilucoplan (a complement inhibitor).*

Rozanolixizumab

- The MycarinG study was a Phase III placebo-controlled trial that evaluated rozanolixizumab in patients with anti-AChR or anti-MuSK-positive gMG. Patients received one treatment cycle (one weekly injection for six weeks) of low (7mg/kg) or high (10mg/kg) doses of rozanolixizumab or placebo, followed by an eight-week observation. Key efficacy data are shown below.

| Day 43 | Placebo | 7mg/kg | 10mg/kg |
|---|---|---|---|
| ***Generalized MG*** | | | |
| MG-ADL (primary endpoint) | -0.78 | -3.37 | -3.40 |
| MGC | -2.03 | -5.93 | -7.55 |
| QMG | -1.92 | -5.40 | -6.67 |
| ***MuSK gMG*** | | | |
| MG-ADL | 2.28 | -7.28 | -4.16 |
| Responder rates (≥2-point improvement) | 14% | 100% | 100% |

- The most commonly reported adverse events associated with rozanolixizumab included headache, diarrhea, pyrexia, and nausea. In clinical trials, patients receiving rozanolixizumab reported a higher incidence of infections compared to the placebo group, including upper respiratory tract infections (17%), COVID-19 (14%), urinary tract infections (9%), and herpes simplex (6%). Serious infections were reported in 4% of patients receiving treatment. Hypersensitivity reactions were observed in 11% of patients treated with rozanolixizumab, emphasizing the need for close monitoring for 15 minutes following administration.
- The MG0004 and MG0007 studies investigated the long-term efficacy and safety profiles of rozanolixizumab. Throughout the treatment cycles, the occurrence of treatment-emergent adverse effects remained consistent, regardless of the cycle number, meaning that the incidence of adverse effects did not increase with repeated cycles of treatment when compared to Cycle 1. In MuSK MG patients, the incidence of adverse effects was in line with that observed in the overall population.
- The table presented below displays the changes in MG-ADL scores from baseline following rozanolixizumab treatment in both MuSK MG patients and the overall population across multiple treatment cycles. Notably, both populations exhibited clinically significant improvements throughout repeated cycles of treatment.


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| Cycle | Dose | Anti-MuSK Ab+ | Overall population |
|---|---|---|---|
| **Cycle 1** | 7mg/kg | -8.1 | -3.7 |
| | 10mg/kg | -3.7 | -3.8 |
| **Cycle 2** | 7mg/kg | -5.0 | -3.7 |
| | 10mg/kg | -7.0 | -4.0 |
| **Cycle 3** | 7mg/kg | -5.0 | -3.4 |
| | 10mg/kg | N/A | -3.3 |
| **Cycle 4** | 7mg/kg | -4.2 | -3.5 |
| | 10mg/kg | N/A | -4.0 |

- When considering an MG-ADL score of 0 or 1 at any point during the treatment and observation periods, more than 25% of patients in the overall population achieved minimal symptom expression (MSE) across Cycles 1–6. In the MuSK MG population, MSE was achieved in over 25% of patients treated with rozanolixizumab 7mg/kg, and in over 33% of patients treated with 10mg/kg, specifically during Cycles 1 and 2.

| | Cycle 1 | Cycle 2 | Cycle 3 | Cycle 4 | Cycle 5 | Cycle 6 |
|---|---|---|---|---|---|---|
| Overall patients with MSE at Day 43 | 27.6% | 26.8% | 25.5% | 32% | 33.3% | 40.6% |

- In the MG0007 study, the majority of patients experienced treatment-free intervals ranging from four to eight weeks, regardless of the specific treatment cycle.
- In summary, the MycarinG study provided evidence of the effectiveness and safety of rozanolixizumab, an FcRn inhibitor, in patients with both AChR or MuSK MG. The study demonstrated statistically significant and clinically meaningful improvements in MG-ADL scores with rozanolixizumab treatment. Notably, the efficacy of rozanolixizumab in MuSK MG patients remained consistent across multiple treatment cycles and various endpoints, aligning with the findings observed in the overall population.

Zilucoplan

- The Phase III RAISE study was a 12-week randomized, double-blind, placebo-controlled trial that assessed the efficacy and safety of zilucoplan in patients with anti-AChR antibody-positive gMG. Following the completion of the initial treatment period, eligible patients were given the opportunity to participate in the RAISE-XT extension study.
- The effectiveness of zilucoplan was noticeable as early as Week 1, and by Week 12 it demonstrated a statistically significant reduction from baseline in MG-ADL score (-4.39) compared to the placebo group (-2.30).


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- The use of zilucoplan was associated with a higher occurrence of treatment-related adverse events. Specifically, patients treated with zilucoplan reported increased lipase and amylase levels (6.9% and 4.7%, respectively) compared to the placebo group (0% and 1.1%, respectively). Additionally, the zilucoplan group experienced a higher incidence of infections (27% vs. 18%), primarily driven by upper respiratory tract infections (14% vs. 7%). It is important to note that all patients in the RAISE study received meningococcal vaccinations prior to enrollment, thus no Neisseria infections were observed. The most commonly reported adverse effects included injection site reactions (16%), as well as upper respiratory infections and diarrhea (10%).
- In the open-label RAISE-XT study, adverse events were generally consistent with those reported in the RAISE study. However, pancreatic events were observed in 3.3% of patients, and morphea was reported in 5% of patients. The following key endpoints demonstrate the sustained efficacy of zilucoplan in reducing MG disease severity from baseline over a 60-week treatment period.

| | MG-ADL | | QMG | | MGC | | MG-QoL15r | | Neuro-QoL Fatigue | |
|---|---|---|---|---|---|---|---|---|---|---|
| Week | PBO/ZLP | ZLP/ZLP | PBO/ZLP | ZLP/ZLP | PBO/ZLP | ZLP/ZLP | PBO/ZLP | ZLP/ZLP | PBO/ZLP | ZLP/ZLP |
| 24 | -6.46 | -6.06 | -8.72 | -9.13 | -13.49 | -12.28 | -8.44 | -8.94 | N/A | N/A |
| 60 | -6.85 | -5.95 | -8.92 | -8.28 | -13.51 | -11.42 | -9.62 | -9.07 | -8.8 | -8.46 |

- The table presented below demonstrates the higher responder rates, as measured by MG-ADL, QMG, and MSE, observed in the zilucoplan group up to Week 24, which were maintained through Week 60. Additionally, the group that switched from placebo to zilucoplan experienced an increase in responder rates within one week after the switch.

| | MG-ADL (≥3-point reduction from baseline) | | | QMG (≥5-point reduction from baseline) | | | MSE (MG-ADL score of 0 or 1) | | |
|---|---|---|---|---|---|---|---|---|---|
| Week | PBO | PBO/ZLP | ZLP/ZLP | PBO | PBO/ZLP | ZLP/ZLP | PBO | PBO/ZLP | ZLP/ZLP |
| 12 | 52% | - | 74% | 37% | - | 60% | 8% | - | 19% |
| 13 | - | 76% | 71% | - | 63% | 71% | - | 22% | 25% |
| 24 | - | 82% | 85% | - | 72% | 81% | - | 33% | 31% |
| 60 | - | 86% | 87% | - | 77% | 85% | - | 39% | 35% |

In conclusion, the RAISE study showed that zilucoplan treatment maintained its effectiveness for up to 12 weeks, with noticeable improvements starting as early as Week 1 and resulting in clinically significant enhancements in MG-ADL scores. The drug exhibited a favorable safety profile with no major safety concerns, although mild injection site bruising was the most commonly reported adverse effect. The interim analysis of the RAISE-XT study revealed that approximately 87% and 85% of patients were MG-ADL and QMG responders respectively, while more than 35% of patients achieved MSE after 60 weeks of zilucoplan treatment.


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# Huntington's Disease

## Pridopidine for the Treatment of Huntington's Disease: PROOF-HD Phase III Results

Micheal R. Hayden, PhD (Prilenia Therapeutics)

*PROOF-HD and an integrated analysis show consistent beneficial effect in patients off antidopaminergics.*

Only limited symptomatic treatments for chorea are available. There is a high unmet need for new disease-modifying therapies impacting progression, cognition, function, and motor abilities. Natural history, as well as interventional studies, show predictable longitudinal decline in global disease progression (cUHDRS), function (TFC), cognition (Stroop Word Reading Test; SWR) and motor (Q-Motor) functions. Improvements in any of these measures are not normally observed, and no drug to date has shown any sustained benefit in these clinical measures.

Activation of the sigma-1 receptor by pridopidine positively influences protective pathways including synaptic function, autophagy, mitochondrial function, calcium homeostasis, and mitochondrial-ER contact. In the Phase III PROOF-HD study, 499 patients were randomized to receive either placebo or pridopidine 45mg for 78 weeks. The primary endpoint was the change from baseline in Total Functional Capacity (TFC).

In the whole population, pridopidine did not reach a significant benefit on the primary endpoint and key secondary endpoints.

Previous studies have suggested that antidopaminergic medications (ADMs) are associated with more rapidly progressive HD. Patients in PROOF-HD were allowed to take ADMs alongside the investigational treatment if necessary.

In this presentation, the speaker focused on a new analysis in a subset of patients, namely those not taking ADMs:

- In this population, there was a significant improvement in slowing of decline on cUHDRS and SWR up to Week 52 compared to placebo. This improvement continued up to 78 weeks, although this was no longer significant. Each of the four components of the cUHDRS (TFC, SWR, SDMT [Symbol Digit Modalities Test], and TMS [Total Motor Score]) contributed to the overall benefit at all visits in patients off ADMs, demonstrating that the impact is not driven by one domain and not by chance.
- Pridopidine significantly improved Q-Motor finger tapping inter-onset interval compared to placebo in patients off ADMs up to 78 weeks.
- Quality of life (HD-QoL) scores were improved with pridopidine compared to placebo through Week 78; however, this was not statistically significant at any time point.
- An integrated analysis from four placebo-controlled studies confirms a consistent impact on patients off ADMs. In total, 435 patients out of the 762 patients in these trials (both treatment and placebo arms) were evaluated. Pridopidine showed a robust improvement versus placebo in TFC up to 78 weeks (statistically significant at weeks 26, 39, 52, and 78), a statistically significant improvement in cUHDRS at weeks 26, 39, and 52, and a statistically significant improvement in Q-Motor scores at all time points except week 65.
- Pridopidine also has placebo-like safety.


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## Sustained Improvements with Once-daily Valbenazine in Chorea Associated with Huntington's Disease: Interim Results from a Long-Term Open-Label Study

Erin Furr-Stimming, MD (University of Texas)

*In these interim analyses of KINECT-HD2, long-term treatment with once-daily valbenazine was well tolerated and provided a clinically meaningful improvement in chorea severity, regardless of concomitant antipsychotic therapy.*

Valbenazine (Ingrezza) is a highly selective VMAT2 inhibitor that is approved for the treatment of adults with tardive dyskinesia and to treat chorea associated with HD. The approval in HD was primarily based on data from Neurocrine's Phase III KINECT-HD study. In this 12-week trial, once-daily valbenazine significantly improved chorea versus placebo, as assessed on the UHDRS TMC score, CGI-C, and PGI-C. Individuals who completed KINECT-HD, along with de novo participants, have been enrolled in KINECT-HD2, the first long-term open-label study of valbenazine in this population.

In KINECT-HD2, patients received valbenazine for up to 156 weeks, which included an eight-week dose-adjustment period. At the time of the interim analysis, 127 participants were enrolled (98 had participated in KINECT-HD and 29 were de novo), and 115 had completed the dose-adjustment period. Concomitant antipsychotics were allowed in KINECT-HD2, unlike in KINECT-HD.

- Interim analysis results from KINECT-HD2 support the findings from the KINECT-HD study and show sustained chorea improvements in adults with HD after up to 50 weeks of treatment.
- Improvement in Total Maximal Chorea (TMC) score was observed as early as week two. More than half of participants (60.9%) and investigators (58.9%) rated symptoms as "much improved" or "very much improved" at week six, and about three-quarters of participants (74.2%) and investigators (76.9%) rated symptoms as "much improved" or "very much improved" by week 50.
- Additional preliminary analyses indicate the clinical profile of valbenazine is similar irrespective of background antipsychotic therapy.
- Valbenazine was generally well tolerated; however, 24 participants discontinued treatment, with 15 patients discontinuing due to adverse events. Additionally, 95.2% of patients (119) experienced treatment-emergent adverse events (TEAEs), including 13.6% of patients (17) who experienced serious TEAEs.


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## Motor Manifestations in HD: Recognition and Treatment

Emily Forbes, DO (University of Colorado)

Motor manifestations of HD include chorea (brief, abrupt, irregular, flowing movements), dystonia (abnormal posture, frequently associated with rigidity), rigidity (increased muscle tone), and bradykinesia (slow, diminutive movements). A multidisciplinary approach is normally used to treat these symptoms. Chorea only needs to be treated if it is causing issues for the patient. Treatments for chorea, which mostly target dopamine regulation, consist of VMAT2 inhibitors (the only FDA-approved treatments for HD) and neuroleptics (off-label; normally D1 receptor antagonists). Risperidone tends to be the first neuroleptic of choice for chorea, followed by olanzapine and tiapride. Neuroleptics are normally chosen over VMAT2 inhibitors if co-morbid depression, agitation, and/or psychosis are present.

Focal dystonia can be treated with botulinum toxin injection. Tetrabenazine and deutetrabenazine have also been suggested, and anticholinergics can be used (with caution, however, due to the cognitive co-morbidities in this population). Bradykinesia and rigidity, which is prominent in juvenile HD, can be side effects of VMAT2 inhibitors or neuroleptics. Levodopa may provide relief but normally increases chorea, and amantadine or dopamine agonists are recommended.

## Ribbon of Highway: Cognition and Behavior in HD

Karen E. Anderson, MD (Georgetown University)

Suicidality in HD can present differently to suicidality in depression. It is not always tied to a depressed mood, and is instead linked to impulsivity and suicide attempts with no warning. The risk of suicidal ideation normally peaks in Stage 2 HD. There is potential for VMAT2 inhibitors to cause or worsen suicidal ideation, so doses must be lowered if suicidal symptoms emerge.

Delusions are the most common psychotic symptoms of HD. All antipsychotics can be used for psychotic symptoms, but the speaker stated that she likes to use olanzapine, as weight gain and sedation can be helpful, as well as quetiapine.

Other psychotic symptoms of HD include irritability and depression. Many medications that help irritability are sedating and some can worsen fall risk and cognitive issues. Antidepressants are often used as the first-line treatment for depression, followed by antipsychotics, mood stabilizers, and benzodiazepines.

For apathy, antidepressants and stimulants are the most commonly used medications, although these may worsen irritability. While bupropion works well as an antidepressant, it has minimal efficacy against apathy.

There are no FDA-approved treatments for the cognitive symptoms of HD.


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## Western Roundup: In the Ring and Coming Down the Chute – A Research Update in Huntington's Disease

Dr. Andrew Feigin, MD (NYU Langone Health)

*Many drugs in the pipeline are focusing on disease modification via RNA/DNA-based therapies, which seek to lower or alter mutant Huntingtin (mHTT) or disease-modifying genes (e.g. DNA damage repair pathways). Some therapies are also aimed at the downstream effects of mHTT, largely involving anti-inflammatory mechanisms (including the SIGNAL and PROOF-HD trials).*

Unmet needs in HD include treatments for:

- gait/balance/falls
- dysarthria/dysphagia
- eye movements
- coordination
- dementia
- apathy, irritability, aggression
- disease modification.

Therapies aimed at lowering DNA damage repair proteins may reduce somatic expansion (when individual neurons develop CAG expansions beyond the inherited repeat length) to delay or slow the disease without lowering the mHTT. Zinc finger therapies may lower mHTT and reduce somatic expansion.

RNA/DNA-based therapies currently in the pipeline that focus on mHTT lowering include:

- antisense oligonucleotides, which are either non-allele-specific (Roche/Ionis [tominersen]) or allele-specific (Wave [WVE-003], Vico [VO659]),
- RNA interference (uniQure [AMT-130]),
- and small molecule RNA splicing modulators (PTC [PTC518], Skyhawk [SKY-0515]).

Non-allele-specific therapies knock down both mHTT and non-mutant HTT. Development of Novartis's small molecule RNA splicing modulator branaplam was suspended in 2022 due to peripheral neuropathy.

There are also some approaches targeting inflammation, including Annexon's ANX-005, which blocks C1q in HD patients, reducing inflammation and improving clinical function. Inhibition of C1q protects against synapse loss in animal models of HD.

In Roche/Ionis's Phase I/IIa trial, four monthly doses of tominersen were well tolerated, and high doses achieved 40% mean CSF mHTT lowering. Interestingly, there was an increase in neurofilament light chain observed in this study, which is a biomarker of neurodegeneration. Nonetheless, tominersen was advanced into the Phase III GENERATION HD1 trial. In this trial, there were poorer outcomes in the higher-dose group compared to placebo, and the study was stopped by an independent data monitoring committee. The cause of the trial failure remains uncertain, although it has been speculated that it could have been from the lowering of the normal HTT allele or due to a CNS inflammatory response. Following a post-hoc subgroup analysis which showed that there was benefit for those aged below 48 years with a CAP (disease severity) score below 500, the Phase II GENERATION HD2 study, which is now enrolling, was designed for this patient population.


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The rationale for lowering mHTT still remains compelling, although investigators may need to titrate the effects to achieve acceptable lowering of the normal allele in cases where approaches are not allele-specific.


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# Migraine and Headaches

## Long-Term Safety, Tolerability, and Efficacy of Atogepant for the Preventive Treatment of Migraine: Interim Analysis of a Phase 3, Multicenter, Open-Label, 156-Week Long-Term Safety Extension Study

Sait Ashina, MD

*This open-label extension (OLE) of two Phase III migraine trials, ELEVATE and PROGRESS, combined participants with episodic and chronic migraine. The safety profile was consistent with previous assessments and the efficacy persisted through Week 48 of the OLE.*

Atogepant, also known as Qulipta, is already approved for the prevention of both episodic and chronic migraine. This OLE safety analysis population consisted of 595 patients, combined from the ELEVATE episodic migraine trial and the PROGRESS chronic migraine trial; however, some patients did have a gap between their lead-in study and the OLE during which they were not on the drug.

A common side effect of anti-calcitonin gene-related peptide (CGRP) drugs is constipation, which, at the point of this interim analysis, did occur in 8.2% of patients in the OLE. 5.9% of patients discontinued use of atogepant due to TEAEs. Overall safety results were consistent with the known profile for atogepant.

In the modified intent-to-treat population of 524 participants, 73.5% of the episodic group and 67.0% of the chronic group achieved a 50% or greater reduction in monthly migraine days from the lead-in study baseline at Weeks 13–16 and this was consistent over 48 weeks.


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## Vaporized Cannabis versus Placebo for Acute Migraine: A Randomized Controlled Trial

Nathaniel Schuster, MD (University of California San Diego)

*Four puffs of vaporized THC+CBD flower was efficacious in the acute treatment of migraine and was well tolerated with no serious adverse events.*

This was a single-center study conducted at the University of California San Diego, where over the course of one year, each patient could treat up to four distinct migraine attacks with one of four treatments: THC 6%, THC 6% + CBD 11%, CBD 11%, or placebo cannabis. A minimum of a one-week washout period was maintained between treated migraine attacks.

73 patients treated at least one migraine attack, 52 of whom used all four treatments. It should also be noted that more than a third of the participants had never used cannabis before.

Blinding analysis showed that these results are unlikely explainable through unmasking, as most patients who got THC or THC+CBD did not think they got a THC treatment. Additionally, there were no serious adverse events, and the THC+CBD mix was better tolerated than either THC or CBD alone, with lower rates of euphoria, cognitive impairment, and subjective “highness.”

| | THC | THC+CBD | CBD | Placebo |
|---|---|---|---|---|
| 2h pain relief | 68.9% (p=0.016) | 67.2% (p=0.008) | 52.6% | 46.6% |
| 2h pain freedom | 27.9% | 34.5% (p=0.017) | 22.8% | 15.5% |
| 2h freedom from most bothersome symptom | 47.5% | 60.3% (p=0.005) | 42.1% | 34.5% |


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## Safety and Tolerability of Ubrogepant for the Acute Treatment of Migraine in Participants Taking Atogepant for the Preventive Treatment of Episodic Migraine: Results from the TANDEM Trial

Jessica Ailani, MD (Georgetown University)

*The combination of atogepant with as-needed ubrogepant did not result in any hepatic issues or incidence of fatigue, nausea, or constipation inconsistent with atogepant alone.*

TANDEM is a Phase IV open-label study that enrolled 263 patients with fewer than 15 headache days per month, evaluating the safety and tolerability of ubrogepant (Ubrelvy) as a rescue treatment with concomitant atogepant (Qulipta) as a preventive.

For the first 12 weeks, patients took only 60mg of atogepant, and for the following 12 weeks they took ubrogepant as needed.

8.8% of participants in the atogepant-only phase discontinued the trial due to adverse events. A further 1.4% of participants in the ubrogepant use period discontinued due to adverse events.

Constipation rates were slightly lower in this trial, at 5.3%, than in the original atogepant studies, and only an additional 0.9% reported this side effect when ubrogepant was added in. Additionally, no hepatic issues related to the combination of ubrogepant and atogepant were identified, and none of the discontinuations were due to elevated liver enzyme levels.


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## New Therapies for Migraine and Other Headache Disorders

Jessica Ailani, MD (Georgetown University)

Rebecca Burch, MD (University of Vermont)

Zubair Ahmed, MD (Apex Medical)

*CGRP-targeting therapies are not only the newest entrants to the migraine field, but also boast the best efficacy and safety profiles. Real-world evidence suggests that layering these with onabotulinumtoxinA or gepants create a safe, complementary, and effective treatment paradigm.*

Jessica Ailani, MD:

- For pediatric migraine, acute treatments are typically ibuprofen and triptans. If the triptans are ineffective, it is suggested that the patient try a different NSAID and triptan combination. On the prevention side, evidence suggests that amitriptyline and CBT, topiramate, or propranolol are effective; however, more recent research has found that the latter two drugs may not be as effective as simply counseling the patient on lifestyle changes.
- Migraine freedom does not necessarily mean zero migraine attacks, it just means that the patient has access to effective acute treatment that allows them to return to normal functioning quickly.
- There have been quite a few real-world data studies indicating that layering onabotulinumtoxinA and an anti-CGRP monoclonal antibody can be quite effective. Similarly, gepants combined with an anti-CGRP monoclonal antibody also work in a complementary way.

Rebecca Burch, MD:

- Anti-CGRP monoclonal antibodies changed the entire landscape of migraine treatment. These drugs work well, even in refractory patients and those with chronic migraine with medication overuse. This class not only has long-term efficacy, but also boasts a better safety and tolerability profile than the majority of older treatments.
- A 12-month open-label randomized clinical trial evaluating the benefit of erenumab compared to older oral prophylactics found that 56% of the erenumab group and 17% of the oral preventive group experienced a 50% reduction in headache frequency. This trial enrolled 621 participants across 17 countries, assigned in a 2:1 ratio to erenumab or a nonspecific oral preventive.
- A meta-analysis of data from New Drug Applications for gepants found that small molecule anti-CGRPs are effective in women but are much less so in men, with almost half of the endpoints in men favoring placebo over treatment, although it should be noted that the sample size of men was only 17% of that of women. However, the anti-CGRP monoclonal antibodies were similarly effective regardless of sex.
- The American Headache Society published a statement arguing that since anti-CGRPs are migraine-specific and show significantly better efficacy and tolerability profiles than past therapies, these drugs should be a first-line option for prevention and should not require the failure of nonspecific medication trials. Unfortunately, many insurance companies do not recognize anti-CGRPs as first line, creating a barrier for patient access.
- Updated recommendations for management of migraine in pregnancy suggest acetaminophen, diphenhydramine, metoclopramide, or small amounts of caffeine. Gepants are not currently recommended as there is not enough data yet to determine safety. OnabotulinumtoxinA does not cross the placenta and therefore does not negatively affect pregnancies, even if the exposure is during the first trimester.


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Zubair Ahmed, MD:

- Monotherapy is always the priority, as it increases adherence and reduces the potential for drug interactions and side effects. However, less than half of patients have a 50% or greater reduction in headache frequency with preventive monotherapy, and 70% have moderate or severe disability even after rescue treatment.
- Combination therapies are often necessary for proper management of migraine. Preclinically, the rationale for the layering of gepants and onabotulinumtoxinA is thought to be complementary blockage of the activation and sensitization of certain types of trigeminal vascular neurons. In the COURAGE clinical trial, 70% of participants reported satisfaction with combination therapy of ubrogepant and onabotulinumtoxinA.
- Another study evaluated the safety and efficacy of combining ubrogepant with erenumab, and found that the pharmacokinetics of ubrogepant was not significantly altered when co-administered with erenumab or galcanezumab since the metabolic pathways are different. Additionally, ubrogepant may have access to CGRP receptors not available to the monoclonal antibody anti-CGRPs.


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## Comprehensive Migraine Update: Advances in Acute, Preventive, and Cognitive Behavioral Therapies

Melissa Rayhill, MD (University at Buffalo Jacobs School of Medicine)

Rebecca Burch, MD (University of Vermont)

Deena Kuruvilla, MD (Westport Headache Institute)

*The arrival of gepants has revolutionized migraine treatment, but most payers still require patients to fail two triptans before covering this drug class. Additionally, many of the older drugs put patients at risk of medication-overuse headache, and neuromodulation or gepants can be a good option if this is a concern, although the latter may pose a fetal risk in pregnant individuals.*

Most insurance companies require that patients fail two triptans before trying any next-generation treatments for migraine such as gepants or ditans, although many headache specialists will prescribe these drugs earlier if the patient can get coverage, due to their superior efficacy and side-effect profiles.

One of the advantages to gepants is that they are not believed to cause medication-overuse headaches. However, there is not enough information available regarding safety during pregnancy, so this class is currently contraindicated.

Lasmiditan is the only ditan available and targets a number of serotonin receptor subtypes, but the tolerability profile is much wider than gepants, and patients are not allowed to drive for eight hours post administration.

When it comes to rescue therapies, it is important to have backup options if the primary acute treatment does not work. These specialists recommended non-oral formulas, and there is some evidence that even anti-nausea suppositories like phenothiazine and indomethacin also help relieve migraine pain. There is less compelling evidence for the use of butalbital combination medications and opiates due to high risk of overuse headache and withdrawal symptoms, but on rare occasions they may be used as a rescue. For status migrainosus, or prolonged refractory migraines, steroids or valproate may be a good option.

It is not uncommon for patients to respond inconsistently to medications or for a drug to stop working. Some approaches to prolong the usefulness of regimens include treating the migraine early, changing the formulation or route of administration, moving between drugs within a class, and adding preventive therapy on top of acute options.

Nonpharmacological treatments include lifestyle modifications such as regular exercise, healthy sleep practices, drinking enough water, and not skipping meals, as well as mindfulness practices, biofeedback, and cognitive-behavioral therapy. Nutraceuticals are also an option, including magnesium, butterbur, feverfew, coenzyme Q10, riboflavin, and others.

Neuromodulation approaches such as supraorbital transcutaneous nerve stimulation and single pulse transcranial magnetic stimulation, among others, are approved by the FDA for both acute and preventive use.

The MOTS trial on medication-overuse headache found that in chronic migraine patients, the efficacy of preventive therapy is not dependent on whether patients reduce use of their acute drug.

Many of the more effective and common approaches to migraine are associated with the potential for fetal adverse events in pregnant patients, but calcium channel blockers or antihistamines as a preventive, and triptans or low-dose aspirin for acute treatment, may not have these negative effects. With regard to gepants, CGRP is known to regulate utero-placental blood flow and uterine relaxation, so it is recommended that patients stop anti-CGRP monoclonal antibodies five to six months prior to conception since these have long half-lives. It is also known that IgG crosses the placenta through the neonatal Fc receptor, although animal studies have not identified reproductive toxicity.


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## Blocks, Botox, and Buzzers to Treat Headache in Children

Christina L. Szperka, MD (Children's Hospital of Philadelphia)

*Nerve blocks can be a good option for patients with refractory migraine, including children.*

In a study of 205 patients with chronic migraine, two-thirds benefitted from unilateral lidocaine-methylprednisolone injections, which lasted between five and nine weeks. A comparative study at the Headache Center in Saint Louis, Missouri assessed acute headache pain reduction and found that there was approximately a one-point improvement in pain score with nerve blocks over intravenous or intramuscular rescue medications.

Another trial of 58 adolescents with episodic or chronic migraine found a 1.2-point improvement in pain reduction over placebo for occipital lidocaine nerve blocks ($p=0.013$). Additionally, this study collected data on race, ethnicity, and gender, and included a diverse group of patients.

There are a number of ongoing trials for anti-CGRP drugs in children and adolescents, but real-world evidence from a retrospective study on rimegepant and ubrogepant in young patients found that half reported that headaches resolved at least some of the time, and more than half thought it was more effective than their past rescue medication.

While a randomized controlled trial of onabotulinumtoxinA showed no benefit over placebo in children, pediatric trials in general are often affected by high placebo response, which was also the case in this study. Other studies totaling 190 children eight years of age or older with chronic headache did find some benefit from onabotulinumtoxinA treatment, which was quite well tolerated, yet insurance coverage does remain an issue.

There are many medical devices approved for use in migraine, although these may be expensive. Most studies for these devices in adolescents are small but do report some benefit. However, Nerivio Migra, a remote electrical stimulation device approved for children aged 12 years and older, has real-world data from 1,629 children showing consistent improvement in symptoms. Most notably, these devices are all considered to be safe, and children may often prefer them over other later lines of therapy such as injectables.


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## Headache Special Populations – Individuals with Severe Cognitive, Mental, and/or Physical Impairments and the Caregiver

Susan Woolner, CPXP (Trinity Health West Michigan)

*Headaches and migraines may look different in IDD populations, leading to disparities in healthcare for adults and children with complex medical conditions and IDD.*

Susan Woolner discussed the issues with diagnosing headaches in IDD populations.

Children and adults with IDD can have multiple disadvantages when trying to treat headaches and migraines, such as anxiety, depression, OCD, tracking of symptoms, caregiver availability, awareness of headaches, communication challenges, etc.

Behavior changes that can indicate headaches or migraine include self-injury, aggression, biting, head banging, altered awareness, etc.

Recommendations on how to care for patients with IDD include use of contextualized interviewing, asking for accommodations to reduce anxiety, providing examples on how to track, asking if the caregiver needs anything, providing education on what migraine phases may look like, and development of common language to distinguish pain.

## Headache in Special Populations – the Rural Patient

David Watson, MD (WVU Rockefeller Neuroscience Institute)

*There are unique challenges when treating headaches and migraines in rural America that need to be noted and considered.*

Dr. Watson discussed the challenges of treating headaches and migraines in rural America. Most in rural America are of low socioeconomic status, resulting in dependency on OTC treatments and Medicaid/Medicare, as well as loss of work and travel expense.

- 19.3% of the US population lives in rural America, meaning about 60 million people living in 97% of the total land area of the US.
- Rural America tends to have higher emergency department use, opioid usage, and increased headache burden compared to urbanized areas.
- Rural America tends to lean towards low socioeconomic status, with higher poverty rates, heavy reliance on Medicaid/Medicare, higher travel expense, loss of work due to medical visits, and susceptibility to low-cost OTC treatments.
- Rural patients often suffer from lower health literacy, resulting in greater blind trust in local providers and a reduced ability to self-educate on health topics (22.3% of rural America lack broadband coverage, and 2.7 million rural households lack internet connectivity completely).

Dr. Watson advocated an increase in internet connectivity to allow more telemedicine access, setting up visiting bundling with other patients in the area, and simplifying medication schedules due to low literacy.


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## Forecasting Migraine Attacks: A Machine Learning Approach Based on Clinical Symptoms and King-Devick Test

Chia-Chun Chiang, MD (Mayo Clinic)

*Using an AI model to help predict migraine attacks more efficiently than current standard practice.*

Current migraine forecasting models are predicated on once-daily measurements of common migraine triggers, stress level, and headache diary symptoms to predict migraine attacks the next day.

Using the King-Devick test (KDT) as a basis, a trial was created in which 30 adults with episodic migraine completed a minimum of three daily entries for four months with a record of at least eight migraine attacks.

- KDT score was significantly slower during prodrome migraine attack, postdrome, and non-migraine headache attacks compared to the interictal baseline, suggesting KDT score itself is insufficient.
- The machine learning model used 4,951 data entries with 294 variables, with the outcome set at having a migraine attack at the next data entry, which was approximately six hours. The model was trained using a leave-one-out approach: 29 participants to train the model, one was a test, repeat 30 times, creating 30 models. The model used the H2OAutoML (3.44.0.3) package within Python 3.7.0.
- In the average of the 30 models, average training AUC was 0.92, while the test AUC was 0.66. Overall, the accuracy was 0.81, with the top four models having an accuracy above 90%.

To further individualize the AI model deployment, an embedding was created that represents each participant using long short-term memory (LSTM), including baseline features and time sequence data. The participants were then separated into two clusters, and the model was trained using demographics, symptoms, and KDT at the first recording to assign participants into one of the two clusters.

Important clinical features for the accuracy of the model prediction include current migraine phase, KDT scores, sleep state, fatigue, photophobia, and phonophobia.

The model was able to accurately forecast a migraine attack over the next six hours and displayed the feasibility of combining clinical symptoms and objective measures into AI models to forecast migraine attacks.


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## Brain Iron Accumulation in Participants with Acute Post-Traumatic Headache

Simona Nikolova, PhD (Mayo Clinic)

*Researchers try to determine the correlation between iron accumulation in the brain and treatment efficacy for post-traumatic headaches (PTH).*

Iron is essential in oxygen carrier proteins and metabolic enzymes, but also accumulates in neurodegenerative diseases. Iron deposits in areas involved in pain modulation are associated with poorer response to medication in migraine.

Iron deposits in pain processing regions can serve as neuroimaging predictors of treatment outcome in migraine.

- 60 participants with acute PTH and 60 age-matched healthy controls underwent 3T MRI using susceptibility weighted (T2) imaging sequence.
- PTH participants had higher iron accumulation in several areas of the brain, including occipital, cerebellar, and temporal regions.
- In PTH participants, headache frequency, number of lifetime traumatic brain injuries, and SCAT symptom severity scores correlated with iron accumulation.


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# Multiple Sclerosis

## Longer-Term (Up to 6 Years) Efficacy of Ofatumumab in People with Recently Diagnosed and Treatment-Naive Relapsing Multiple Sclerosis

Gabriel Pardo, MD (Oklahoma Medical Research Foundation)

Ofatumumab is a second-in-class anti-CD20 biologic delivered subcutaneously. Dr. Pardo discussed the six-year results from the OLE of the Phase III ALITHIOS trial. In recently diagnosed treatment-naïve patients receiving continuous ofatumumab, the OLE study showcased a 52% reduction in annualized relapse. In recently diagnosed patients, improvements across several efficacy outcomes were seen after switching to ofatumumab, including significant reductions in annualized relapse rate (ARR) (71.3%) and in MRI lesion activity (Gd+ T1: 98.5% reduction; neT2: 93% reduction), and an increase in rates of NEDA-3. However, rates of three- and six-month confirmed disability worsening (CDW) events remained higher than in patients receiving continuous ofatumumab, indicating that the efficacy benefit of first-line ofatumumab on delaying disability worsening was not fully achieved in the switch group.

In the overall ALITHIOS population, ofatumumab showed sustained efficacy up to six years, including low ARR (49.9% reduction between core Phase III trials and extension phase), suppression of MRI lesion activity (Gd+ T1: 56.7% reduction; neT2: 89.3% reduction), sustained reduction of six-month CDW events (14.1%, relative to the switch group), lower rates of six-month progression independent of relapse activity (PIRA), and sustained high rates of NEDA-3. The study also found that ofatumumab was well tolerated, and no unexpected safety signals were identified. Over six years, there was no rise in the frequencies of significant AEs, malignancies, serious infections, or AEs.

## Impact of Fenebrutinib Treatment on MRI Outcomes and Cerebrospinal Fluid Penetrance in Multiple Sclerosis: Results from the Phase II FENopta Study

Amit Bar-Or, MD (Penn Medicine)

Bruton’s tyrosine kinase (BTK) has been a molecular target for numerous oncology drugs approved over the past decade, and recently drug developers have been swarming over the utilization of this pathway in the treatment of MS. Fenebrutinib is a potent, highly selective, noncovalent, reversible BTK inhibitor. Dr. Bar-Or discussed brain penetration and early reduction of new lesion activity from the Phase II randomized, double-blind, placebo-controlled FENopta trial. Fenebrutinib, administered orally twice a day, met the primary endpoint with a 69% reduction in the total number of T1 Gd+ lesions, and rapid onset of lesion reduction was seen as early as week four. The drug was also found to be present in the CSF at sufficient levels to reduce B-cell activation and microglia *in vitro*, suggesting its impact on mechanisms underlying chronic progressive MS. The drug did not demonstrate any serious AEs; however, two cases of grade 3 asymptomatic liver transaminase level elevations were seen. Similar hepatic involvement was also seen with evobrutinib, and could potentially be a class-wide phenomenon.


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## 10 Years of Ocrelizumab Treatment in Multiple Sclerosis: Long-Term Efficacy and Safety Clinical Trial Data

Stephen L. Hauser, MD (University of California, San Francisco)

Ocrelizumab is the gold standard in MS therapy and is the only approved therapy for primary progressive MS (PPMS) patients. The drug, administered as an infusion every six months, acts by depleting B cells. In this session, Dr. Hauser discussed the long-term results from OPERA I and OPERA II in RRMS patients, as well as from the ORATORIO Phase III trials in PPMS patients. In all, 90% of patients opted to continue receiving ocrelizumab after Phase III trials ended and continued in the OLE trials. The long-term results, where patients were continuously treated with ocrelizumab for 10 years, showcased the drug's efficacy and safety parameters, with almost eight out of 10 patients with RRMS and one-third of patients with PPMS being found to be progression-free. The study results also revealed a stable and favorable safety profile with low rates of serious infections.

## OCARINA II, Phase III Study: Results of Subcutaneous Ocrelizumab Administration in Patients with Multiple Sclerosis

Scott Newsome, DO (Johns Hopkins)

With ocrelizumab already enjoying the top spot in MS treatment choice among neurologists, developing a subcutaneously administered version is expected to improve patient convenience greatly. Dr. Newsome discussed the results from the Phase III OCARINA trial that demonstrated the efficacy and safety of subcutaneously administered ocrelizumab in patients with MS. OCARINA II is a Phase III, global, multicenter, randomized study evaluating the pharmacokinetics, safety, and radiological and clinical effects of the subcutaneous formulation of Ocrevus compared with Ocrevus IV infusion in 236 patients with relapsing MS (RMS) or PPMS. The trial achieved the primary endpoint of non-inferiority of ocrelizumab IV 600mg with respect to area under the curve. Ocrelizumab showcased a near-complete suppression of relapse activity, as 97.2% of patients had no relapse during the treatment phase. In an exploratory patient-reported outcome measure, which included 52 patients, on level of satisfaction, 92.3% were satisfied or very satisfied, and 90.1% felt that subcutaneously administered ocrelizumab was convenient or very convenient. The new formulation was also well tolerated, and no treatment-related AEs were seen.

## Safety and Efficacy of Frexalimab in Relapsing Multiple Sclerosis: 48-Week Results from the Phase 2 Open-Label Extension

Patrick Vermersch, MD, PhD (University of Lille)

Frexalimab is the first of the second-generation anti-CD40L antibodies designed to avoid lymphocyte depletion to be studied in MS. The Phase II trial evaluated two doses of frexalimab, with both attaining statistically significant percentage reductions in new gadolinium-enhancing (GdE) lesions on T1-weighted MRI at week 12. The 24-week data were favorable for the higher dose. In this session, Dr. Vermersch spoke on the 48-week results from the Phase II OLE trial of frexalimab. The drug demonstrated sustained reduction in disease activity, with 96% of patients in the high-dose frexalimab arm and 87% of those who continued on low-dose frexalimab free of new Gd+T1 lesions at week 48. Patients who continued on high-dose frexalimab experienced a low ARR of 0.04 over the 48-week treatment period, with 96% being free of relapses. The drug was also well tolerated, and propels further development of the CD40L mechanism in MS treatment.


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## Treatment of PIRA with Nasal Foralumab Dampens Microglial Activation and Stabilizes Clinical Progression in Non-Active Secondary Progressive MS

Tarun Singhal, MD (Brigham and Women's Hospital)

PIRA is a significant unmet need in non-active secondary progressive MS (SPMS) patients. TSPO-PET imaging is a molecular imaging technique reporting glial density and has been shown to predict PIRA. Preclinical evaluation of nasal anti-CD3 (foralumab) showed a decrease in microglial and astrocyte activation, which are key components driving PIRA, while also being neuroprotective. Dr. Singhal discussed results from the Phase I study of foralumab in healthy human volunteers. The study enrolled six non-active SPMS patients with PIRA who were worsening despite B cell-depleting therapy. PET imaging was conducted at baseline and at three and six months following treatment. The study found a 36% median reduction in white matter compared to baseline at three months across all six subjects. In the expanded access program, where 10 patients were evaluated, the drug did not demonstrate any toxicities and showed good improvement in TSPO-PET imaging, fatigue, and Expanded Disability Status Scale (EDSS) score. Currently, a multicenter placebo-controlled Phase II trial of nasal foralumab is ongoing. The drug has also shown some potential in Alzheimer's disease, and a Phase II trial in mild Alzheimer's disease is expected to begin during 2024.

## Nine-Year Trends in Payments for Disease Modifying Therapies in Multiple Sclerosis and Autoimmune Neurological Related Disorders in Medicare Part D

Ka-Ho Wong (University of Utah)

Disease-modifying therapies (DMTs) account for over 40% of Medicare Part D drugs, and the actual costs have far exceeded the overall prescription drug and healthcare inflation rate for old and new drugs. With ever-increasing spending on Part D drugs, Congress authorized the Centers for Medicare & Medicaid Services to initiate the Medicare price negotiation program under the 2022 Inflation Reduction Act. This will come into force in 2026 for 10 pilot drugs. However, no DMTs are included in this list. Dr. Wong conducted a nine-year retrospective trend analysis of prescription claims from Medicare Part D Prescriber Public Use Files from 2013 to 2021, which included costs/claims rate and trend change. The study found that Medicare Part D drug spending for neurological drugs doubled from 2013 to 2021.

Interestingly, the study also found that the cost of DMTs increased by 20%, higher than the inflation rate over the study period. Although oral DMT claims decreased by half over the study period, the cost increased by 19%, which was higher than the amount after adjusting for inflation. Dr. Wong added that further analysis will be required to distinguish between DMTs and understand the drivers for cost increases.


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## Multiple Sclerosis Disease Modifying Treatment Overview

Veronica P. Cipriani, MD (University of Chicago)

MS is a chronic and progressive disease, and starting treatment at the earliest stage is essential to prevent irreversible damage and normalize life expectancy. In general, the goals of MS treatment include decreasing the number of relapses and decreasing MRI activity. These goals can be extended to include a decrease in clinical disability progression and a reduction in brain and spinal cord atrophy. Currently, over 20 approved therapies are available to treat MS. This session, headed by Dr. Cipriani, looked at the DMTs used in the treatment of MS.

Drug classification based on mechanism of action:

| Immune modulators | Reduce cell trafficking | Immune cell sequestration | Immune cell ablation | Immune cell ablation-reconstitution |
|---|---|---|---|---|
| Interferons | Natalizumab | Fingolimod | Mitoxantrone | Alemtuzumab |
| GA | | Siponimod | Teriflunomide | Cladribine |
| DMF | | Ozanimod | Ocrelizumab | |
| Diroximel Fumarate | | Ponesimod | Ofatumumab | |
| Monomethyl Fumarate | | | Ublituximab | |

From a healthcare practitioner standpoint, the safety of DMTs was considered the most crucial factor in choosing a DMT, while efficacy came in second. On the other hand, patients preferred drugs which improve symptoms and were willing to accept some level of serious risk. Additionally, patients preferred oral formulations over parenteral formulations. Dr. Cipriani asserts that this difference in opinion must be addressed by shared decision-making by clinicians and patients.

A study conducted by Spelman et al. looked at the proportion of patients who remained relapse-free concerning time since first-line DMTs. The study compared Sweden and Denmark, where the former initiated patients on high-efficacy treatment early on, while the latter relied on a treatment escalation strategy. This study pointed to a higher number of patients in the Swedish study group experiencing a longer relapse-free interval as compared to the Denmark group.

Another study, conducted by Brown et al., compared GA or interferon beta with fingolimod, alemtuzumab, or natalizumab in MS patients and found that the latter, higher-efficacy group had a lower proportion of patients converted to SPMS.

In a study conducted by Lizak et al., starting high-efficacy DMTs in disabled patients also led to a higher decrease in EDSS scores compared to lower-efficacy therapy. This suggests that initiating high-efficacy DMTs later in the disease course can also improve patient outcomes.

Dr. Cipriani also pointed out the need for more equity in clinical trials, and that the proportion of diverse populations was very low compared to whites.


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## Selection of Disease Modifying Treatments for MS

Marwa Kaisey, MD (Cedars-Sinai)

Dr. Kaisey spoke on the selection of DMTs. Over the last 30 years, over 20 DMTs have been introduced to treat MS. Many factors must be considered when choosing DMTs. Patient-related factors such as co-morbidities, pregnancy planning, lifestyle, and insurance play a major role in DMT selection.

One of the older studies in MS, conducted by Goodin et al., followed patients treated with interferon-beta 1b for over 20 years. The study showed that a significantly higher proportion of patients lived longer after being treated with interferon beta-1b than placebo. Even though interferon beta-1b is considered, among physicians, as a mild-efficacy agent in treating MS, these results warrant the use of DMTs in MS.

Dr. Kaisey believes that the first step in selecting DMTs involves the correct diagnosis. She believes that one in five patients who have been diagnosed with MS did not have MS. Currently, the 2017 McDonald criteria are used for diagnosing MS. However, research into disease pathology and diagnosis has rendered the 2017 McDonald criteria somewhat unreliable. This has led to the revision of the McDonald criteria, which is expected later in 2024.

After MS confirmation, it is equally important to diagnose the disease subtype. This is a remarkably complex step, as it is based on patient history, and there are no clinical markers to identify disease subtypes. Once this is confirmed, the patient's medical co-morbidities must be considered while also assessing reproductive status. Dr. Kaisey added that the last items on her checklist when selecting a DMT are drug formulation, patient scheduling, and insurance, which can also play a major role in shared decision-making. As DMTs are expensive, their choice for MS patients relies heavily on insurance coverage. Apart from coverage, drug-related factors such as side effects and lab monitoring, and patient factors such as compliance are also essential in DMT choice.

## Considerations for Switching, Monitoring and Discontinuation of DMTs

Daniel Kurz, MD (University of Chicago)

Dr. Kurz mentioned that the decision to switch therapy is an individualized decision between the patient and the clinician, and as several DMTs are available, switching is a common phenomenon in MS, especially as older, lower-efficacy agents are still prioritized by insurance. The most common causes of switching DMTs in MS are breakthrough disease activity, inadequate response, intolerability, adverse events, family planning, economic factors, psychosocial factors, and compliance factors. However, it is challenging to monitor inadequate response as ongoing disease activity cannot be accurately monitored, and none of the current therapies for MS are 100% effective.

Although switching and monitoring criteria vary with the options available in MS treatments, Dr. Kurz highlighted a few commonly seen monitoring considerations in treatment switches. While switching patients between DMTs, care should be taken to minimize the washout period and reduce the risk of disease activity. During these switches, it is also essential to watch out for potential compounding toxicities of overlapping therapies. As many patients are moved to ocrelizumab as the primary second-line choice, it is vital to keep in mind an increased risk of malignancy associated with the drug. In controlled trials, breast cancer occurred in six out of 781 patients compared to no patients treated with interferon beta-1a or placebo.


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## Industry Therapeutic Update from Sanofi: Navigating BTK Dynamics in Multiple Sclerosis

Jiwon Oh, MD, PhD (University of Toronto)

*This meeting, sponsored by Sanofi, focused on smoldering neuroinflammation characterized by progression independent of relapse activity, which is caused by activated microglia and can potentially be addressed with Bruton's tyrosine kinase inhibitors.*

The vsMS study conducted by Sanofi revealed that individuals with MS prioritize minimizing long-term disability and express concerns about disease progression and worsening physical functioning. While treatment approaches help, disability accumulation can persist without relapses, with PIRA being the main driver of disability.

- Minimizing long-term disability is a priority for people with multiple sclerosis (PwMS). In a global survey by Sanofi (the vsMS study), over 70% of PwMS expressed concerns about disease progression and future disability. More than 60% reported worsening physical functioning since diagnosis, 92% considered slow MS progression important in therapy choice, and 87% of care partners worried about increasing disability. While both escalating and early intensive approaches help, disability and brain atrophy persist without relapses. Relapse-associated worsening (RAW) contributes to disability primarily in early MS, but PIRA is the main driver of disability accumulation, with 90% not associated with relapses in treated patients.
- Smoldering neuroinflammation is considered a key factor in the accumulation of both physical and cognitive disability, as well as PIRA. This term encompasses chronic neuroinflammation in the CNS, which is associated with neurodegeneration and the gradual worsening of disability. It is believed to be driven by CNS resident cells such as astrocytes and microglia, and it can be present in the early stages of MS, even before clinical symptoms appear, persisting throughout the disease spectrum. This neuroinflammation contributes to the deterioration of the disease, including inflammation in the white matter and cortex, neurodegeneration, and loss of brain volume. PIRA is hypothesized to be the clinical manifestation of this ongoing smoldering neuroinflammation process.
- In summary, PwMS can experience disability progression even without relapse, despite receiving treatment. This progression is primarily attributed to smoldering neuroinflammation, which manifests as PIRA. The accumulation of disability in PwMS is often characterized by subtle motor symptoms and cognitive impairments. Making lifestyle and diet modifications can potentially enhance the quality of life for individuals with MS.


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## The Underlying Biology of Smoldering Neuroinflammation: A Closer Look at Microglia and BTK

Dr. Amit Bar-Or, MD (University of Pennsylvania School of Medicine)

*Dr. Bar-Or discussed various aspects of neuroinflammation, including the infiltration of B and T cells into the CNS during acute neuroinflammation, the role of activated microglia in smoldering neuroinflammation, the potential therapeutic targeting of Bruton's tyrosine kinase (BTK) to mitigate neuroinflammation, and the need for evolving clinical approaches to address both acute and smoldering neuroinflammation.*

During the acute phase of neuroinflammation, B and T cells infiltrate the CNS, resulting in clinical consequences such as RAW. In contrast, during smoldering neuroinflammation, activated microglia, derived from homeostatic microglia, contribute to widespread microglial inflammation, known as PIRA, which is associated with physical disability and cognitive decline. This molecular pathogenesis involves an immune network between T cells, B cells, microglia, macrophages, and astrocytes that drives smoldering neuroinflammation.

Communication occurs between the immune cells mentioned above through various mechanisms. For instance, microglia and astrocytes communicate via cytokines. Microglia release CXCL13, a chemokine that attracts both B cells and Th cells. B cells, in turn, act as antigen-presenting cells and provide co-stimulation to T follicular helper cells (Tfh), promoting the formation of lymphoid follicles. Additionally, B cells secrete proinflammatory cytokines that activate T cells, microglia, and astrocytes.

Microglia play a significant role in smoldering neuroinflammation, with their function being influenced by various states and the microenvironment. In their normal state, microglia contribute to the homeostasis of the CNS by promoting synaptic and myelin integrity, as well as clearing myelin debris. However, microglia can be activated by environmental signals, peripheral immune cells, and damage within the CNS. This activation is associated with various pathophysiological symptoms, including increased demyelination, the release of chemokines and cytokines, inhibition of remyelination, oxidative stress, iron neurotoxicity, excessive synaptic pruning, neuronal disruption, chronic smoldering neuroinflammation, and the accumulation of disability in MS. Studies have demonstrated that an activated microglia phenotype can be observed in the early stages of MS, with an altered proinflammatory profile found in brain autopsy tissue of individuals with SPMS. In summary, activated microglia contribute to neurodegeneration and perpetuate a neuroinflammatory immune microenvironment within the CNS.

BTK, a cytoplasmic non-receptor enzyme, plays a crucial role in regulating both adaptive (B cell) and innate immunity (microglia). Inhibiting BTK activity on B cells and microglia has been proposed as a strategy to mitigate smoldering neuroinflammation. However, for effective targeting of microglia and CNS-resident B cells involved in PIRA, factors such as brain penetrance, bioactivity within the CNS, reversibility, and selectivity of BTK inhibitors need to be carefully considered.

As clinical understanding advances, there is a growing need for evolving therapeutic approaches that can effectively address both acute and smoldering neuroinflammation. While existing treatment options focus on targeting acute focal neuroinflammation in peripheral areas, there is a demand for potential therapies that can adequately penetrate the brain and exhibit bioactivity within the CNS to address smoldering neuroinflammation.


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## Debunking Myths in MS

Anna Shah, MD (University of Colorado)

Leorah Freeman, MD, PhD (University of Texas at Austin)

Augusto Miravalle, MD (Rush University)

This session by Dr. Shah focused on neurologists and various myths associated with the treatment of MS and women's health. Dr. Shah elaborately debunked several myths in this session.

- Puberty does not affect MS.
    - Physiological puberty is attainted usually at age 8–12 years in girls and at age 9–14 years in boys. Several factors, including nutrition, genetic factors, and environment, impact this. A study by Harroud et al. found that for every year increase in the onset of puberty, there is an 8% decreased odds ratio for the development of MS. In another study looking at hundreds of adolescents, a consistent increase in onset of MS was seen after the age of eight years in females.
- MS is entirely hereditary.
    - Studies on the genetic component of MS have identified over 200 genetic loci associated with MS. The studies revealed that children have a 2–5% increased risk of developing MS if one parent has MS, and the risk increases to greater than 20% if both parents have MS. In identical twins, the risk of a twin developing MS if the other has MS is 25–30%. However, Dr. Shah mentioned that MS is not entirely hereditary.
- Family planning in MS should be addressed primarily by primary care or obstetrics.
    - Up to one-third of women with MS have a child after disease onset. As MS patients have regular visits with GPs and neurologists, it also becomes the responsibility of these specialists to educate and counsel patients on family planning. Additionally, physicians must also consider drug-drug interactions that can arise with the use of commonly used medications to treat MS along with contraceptives.
- All DMTs should be treated the same in pregnancy planning/during pregnancy.
    - Older DMTs, such as glatiramer acetate and interferons, have extensive safety data and no reports of fetotoxicity. The former can be used until conception and throughout pregnancy, while the latter may only be used until conception.
    - Among oral DMTs, although cladribine has no human evidence of fetotoxicity, a six-month or shorter washout period is advocated. Like fumarates, it should not be used during pregnancy. Teriflunomide and S1P receptor modulators are not compatible with pregnancy, supported by animal evidence of fetotoxicity in the former, while human evidence of fetotoxicity was established in the latter.
    - As a general rule, oral DMTs, which are smaller molecules, can easily pass through the placenta, could impact fetal development, and should be avoided.
    - Among infusible DMTs, anti-CD20 therapies, including off-label rituximab, ocrelizumab, ofatumumab, and ublituximab, have been found to transfer to infants with the presence of placental receptors that develop at weeks 16–22 of gestation.
    - Alemtuzumab should not be taken during pregnancy, while natalizumab may be a safe consideration during the first two trimesters, with discontinuation required in the third trimester.


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- Relapse during pregnancy cannot be treated.
    - MRI scanning without contrast is fine if needed, while contrast should be discussed and documented carefully. Treatment options include steroids, PLEX (plasmapheresis), and IVIG (intravenous immunoglobulins).
- Menopause has little effect on MS.
    - It is estimated that 30% of MS patients are perimenopausal or postmenopausal women, and MS does not affect the age of menopause. A slight increase in disability scores is seen in women after the final menstrual period; however, this was not seen across all trials.

Dr. Freeman continued debunking myths while discussing MS disease accumulation, the mechanisms underlying progression, and promising biomarkers of disease progression.

- Progression is a late phenomenon in MS.
    - MS disability accumulation occurs due to RAW and PIRA. In pediatric MS, RAW is the primary driver of progression, while this contribution is approximately 50% in adults. PIRA is the primary driver of disability accumulation in SPMS and PPMS patients and can also be seen in patients with successful suppression of inflammation with efficacious DMTs. Dr. Freeman pointed out that progression can occur at any time during the disease's duration and can also start early in the course of the disease.
- Neurologists are effective at detecting progression.
    - In the EPIC study conducted in 2019, 92 out of 138 patients who experienced insidious worsening of their clinical disability were still considered by their physicians as RRMS. These patients who remained classified as RRMS had similar rates of brain volume loss as those with SPMS, thus leading to the conclusion that progression is underestimated by neurologists.
      SPMS is a difficult disease to diagnose and treat, and this can lead to physicians being cautious in diagnosing patients with it. Additionally, medical insurance coverage as well as treatment options are also limited.
- Unchanged MRI is indicative of no disease progression.
    - Although MRI can detect white matter lesions, remyelination potential, diffuse inflammation, gray matter demyelination, and neurodegeneration are not visible on conventional MRI, and therefore neuropathological features of PMS are not readily assessed on routine MRI.
- NfL is specific for relapse-free progression.
    - NfL is strongly correlated with T2 gadolinium-enhancing lesions and relapses and EDSS increase in the next one to three years, which are measures of disease activity. Serum NfL elevation was detected approximately one year preceding disability worsening events associated with relapses, and one to two years before worsening events independent of clinical relapses. These point to NfL being associated with subsequent disease worsening with or without relapses. The rate of brain atrophy in healthy individuals is approximately 0.2–0.4% per year, whereas for an MS patient without DMT usage, the rate is 1.5–2% per year. MS patients have greater cortical activation than healthy subjects, and a higher number of lesions correlates with increased cortical activation.


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Dr. Miravalle spoke on the other side of the disease spectrum, regarding optimizing brain health in MS patients. He talked about incorporating lifestyle interventions and reviewing models of care aimed at incorporating brain health activities in MS care. Dr. Miravalle also explained the potential mechanisms underlying the beneficial effects of exercise. A study by Leavitt et al. found that aerobic exercise increased hippocampal volume and memory in MS patients. Another study by Stampanoni Bassi et al. found that preventive exercise and physical rehabilitation promoted neuronal plasticity in MS patients. These studies translate the role of exercise in MS in decreasing relapse rates, lesion volumes, and co-morbidities, and increasing muscle strength, balance, cognition, and walking performance. He also added the role of nutrition in MS patients. Studies have suggested that adherence to a Mediterranean diet could prevent brain atrophy in old age, and adherence to a MIND diet (which combines the DASH diet and the Mediterranean diet) was linked to larger thalamic volumes. Saturated fats and high salt intake were associated with pro-inflammatory cell activation via toll-like receptors.

An interesting point was also added on vitamin D, where MS prevalence was found to be highest in areas with low vitamin D. Although high vitamin D levels were associated with a lower risk of developing MS, case-control studies have found that sun exposure and not vitamin D was associated with MS risk. Dr. Miravalle added that the risk of MS in smokers is 50% higher than in non-smokers. While lifestyle interventions can influence the disease course, Dr. Miravalle concluded that optimizing brain health should be a targeted goal for MS care, and neurologists have a critical role in promoting and prescribing lifestyle interventions.


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## Unique Features of Pediatric MS and Updates in Treatment Approaches

Jennifer Graves, MD, PhD (University of California San Diego)

Lauren Krupp, MD (New York University)

MS is an autoimmune disorder triggered by genetic and environmental factors and is characterized by demyelination of the CNS. Genetic factors account for up to 25% of the risk of MS, among which HLA-DRB1*15:01 accounts for up to 10.5% of genetic variance underlying MS. In total, 48% of the genetic heritability has now been explained in MS, and more than 200 risk alleles have been identified, more than 100 of which have been confirmed in children. Pediatric MS represents approximately 5% of all MS cases worldwide.

Various factors have been investigated to understand the risk of the disease, as environmental factors also play a vital role. Maternal illness in pregnancy was found to have a 2.3-fold increase in the odds of having MS. Interestingly, among maternal factors associated with pediatric MS, C-section delivery was found to have a 60% lower odds ratio as compared to normal delivery while adjusting for race, ethnicity, age, and other factors. Dr. Graves hypothesized that the underlying mechanism could be the difference in the microbiome when delivered through C-section and vaginal delivery. Chemical exposure such as household pesticides or insecticide usage or the father of the child working in gardening work also increased the risk of pediatric MS. Low air quality with an increase in fine particulate matter, carbon monoxide, sulfur dioxide, and lead air emissions was also associated with increased odds for pediatric MS.

The role of Epstein-Barr virus (EBV) has long been debated in the pathogenesis of MS. Dr. Graves added that EBV alone is not sufficient to cause MS. Patients with early childhood EBV with no episodes of infectious mononucleosis were not at risk for MS. Still, there was a twofold risk if episodes of infectious mononucleosis occurred in adolescence or adulthood.

Cigarette smoking at 20 years of age had a 1.5-fold increase in the risk of MS, and the risk increases to 2.2-fold when parents are smokers, whereas second-hand smoke could interact with HLA-DRB1*15, further increasing the risk in children.

Causal support for obesity as a risk factor for MS has been established and may also reduce the efficacy of some treatments. Diet could be a key driver, as gut bacteria could influence the immune system. Studies in mice have demonstrated that mice kept in germ-free cages do not get MS.

Up to 99% of children diagnosed with MS typically have RRMS, and primary progressive cases are rare. Additionally, puberty is also associated with MS, as the incidence of MS increases, especially in females, after puberty. However, this is a characteristic of MS and not other demyelinating agents.

Considering the various factors in pediatric MS and its effect on patients at an early age, it is essential to approach DMT selection carefully. The treatment plan involves parental and child education and collaborative decision-making.

Early intervention with first-generation DMTs (interferons and glatiramer acetate) has been shown in observational studies to be efficacious in the pediatric population. Still, these studies were limited to a few enrolled patients and often were followed up for only a short period. Newer drugs have been tested in randomized controlled trials. Fingolimod was tested against interferon beta-1a and showcased an 81.9% relapse reduction, similar to DMF, which showed that 16% of patients were free of new lesions. In contrast, the active comparator, interferon-beta 1a, only showcased 5% of patients free of lesions. A study conducted by Abdel-Mannan (2021) in the UK pointed out that newer DMTs had a lower ARR compared to injectable DMTs.

Apart from efficacy, the safety of DMTs is a significant consideration in treating pediatric MS patients. Children are less likely to be JCV antibody positive, meaning that natalizumab can be a safe consideration.


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Additionally, as children have a developing immune system, B cell-depleting therapy should be used with caution. Dr. Graves also advocated more extended registry studies to explore this vulnerable population.

Dr. Krupp added that although high-efficacy treatment is available and, once treated promptly, does well on neuropsychological testing, subsets have shown slowed cognitive processing. This could be associated with behavioral problems, including anxiety, depression, fatigue, and memory problems. Dr. Krupp emphasized non-pharmacological interventions in these subsets, especially the impact of psychological support, counselling, and exercise, while some patients may also require psychiatric referrals.

## Emergent Biology and Social Determinants of MS Onset and Progression in Diverse Populations

Lilyana M. Amezcua, MD (University of Southern California)

The traditional belief was that MS was a “White disease,” but recent environmental and social changes have accounted for a more diverse population being diagnosed with MS. This increased incidence of MS in African American and Black individuals means MS is no longer predominantly a White-only disease. This perception had made it increasingly tricky for diverse populations to be diagnosed with MS, meaning that initiation of treatment had often been delayed.

Dr. Amezcua spoke on the social determinants of brain health, and added that during 2010–20 there was a 276% growth in MS prevalence in multiracial groups and a 12.1% increase in MS prevalence in the Black population. This increase in prevalence could be due to several factors that saw patients from these populations previously not diagnosed with MS. Structural racism, including the traditional belief of MS being a White-only disease, social determinants of health, environmental and social changes in the last 30–40 years, and genetic admixture could have played vital roles.

HLA-DRB1*15:01 and HLA-DQB1*06:02 have been linked to MS. The former allele is European, while the latter's ancestral origin is both European and African.

Dr. Amezcua demonstrated the social and environmental changes in Latin America in the last 50 years that could have led to an increase in MS diagnosis. She pointed to the introduction of soups and soda, which have increased rates of obesity and diabetes, both of which have links to MS. Early exposure to EBV was also seen in this region, where an analysis of 100 Mexicans younger than 20 years showed that they had a 90% rate of EBV infection. In contrast, with a similar cohort, the rate was 75% in the US. Interestingly, environmental risk factors were not shared across multiethnic populations. In a case-control study, cytomegalovirus seropositivity was associated with a lower risk of MS/clinically isolated syndrome (CIS) in Hispanics, but not in Black or White individuals. Similarly, another exciting case-control study found that sun exposure and not vitamin D was associated with MS risk in Black and Hispanic individuals.

Dr. Amezcua concluded the session by stating that although structural racism can explain the higher prevalence of MS in diverse populations, social determinants of health also have a crucial role to play.


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## Practical Considerations for MS Care in Diverse Population

Mitzi Joi Williams, MD (Joi Life Wellness Group)

Dr. Williams discussed the practical considerations for diverse MS care and research from patient perspectives and registries. She mainly focused on underserved communities, especially Black individuals and those from ethnic minorities. The underserved communities with MS, including patients from low-income communities, rural communities, immigrants, LGBTQ+ communities, people with disabilities, older patients, people with limited literacy and education, and those who are uninsured or underinsured, have higher mortality rates, higher rates of disease, higher medical costs, and a lack of access to treatments. Black and African American patients are more likely to experience greater severity of MS symptoms and faster disease progression, and non-Hispanic Black individuals have the highest rate of age-specific MS mortality under 55 years of age.

A study by Saadi et al. found that African Americans are 30% less likely to see a neurologist in the clinic and are more likely to seek care in an emergency room, while also being faced with higher hospital expenses.

In a study by Stuifbergen et al., African American women felt that healthcare providers were reluctant to consider an MS diagnosis.

Studies have also suggested that a lower percentage of Black (30%) and Hispanic (20%) individuals are initiated on high-efficacy DMTs in the two years post-diagnosis as compared to non-Hispanic White patients (39%). Additionally, 45% of patients with suboptimal therapy were Black, and they also had a higher rate of non-response and poor tolerability to first-line treatment with interferons. Dr. Williams emphasized the underrepresentation of Black individuals and those from ethnic minorities in clinical trials. A total of 37.8% of Phase III clinical trials investigating DMTs have no race or ethnicity reported, while 31.1% reported race and ethnicity as a percentage of patients with MS only. This underrepresentation could be due to racial stereotypes, lack of trial awareness, sociocultural factors, education, mistrust, and restrictive inclusion/exclusion criteria. Dr. Williams believes this problem can only be resolved by a multifaceted approach that includes clinicians and patients.

## Disease-Modifying Therapies and Real-World Strategies to Improve Care Throughout the Lifespan in Diverse Populations with MS

Jaime Imitola, MD (University of Connecticut)

Dr. Imitola discussed real-world strategies to improve care for diverse MS populations. The McDonald criteria, primarily based on data from adult White European and North American populations, can also be used in diverse populations. However, physicians must be vigilant to exclude alternative diagnoses, particularly neuromyelitis optica spectrum disorder (NMOSD), in African American, Asian, Latin American, and pediatric patients. Dr. Imitola also introduced a bilingual tool to increase awareness of MS, VISIBL-MS. It incorporates both English and Spanish to make patients quickly aware of the early symptoms of MS, particularly clinically isolated symptoms. Dr. Imitola concluded by advocating for increased awareness among healthcare providers and patients in identifying MS early and initiating early treatment. He also advocated for special consideration for patients in the LGBTQ+ community while focusing on equity in care.


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## Biomarkers in MS: Neurofilament Light

Bernd Kieseier, MD (Novartis)

Shane T. Arsenault, MD (Memorial University)

Thomas Leist, MD, PhD (Thomas Jefferson University)

*NfL is a promising prognostic marker of disease activity in MS. It has increasingly garnered attention among neurologists as NfL levels in CSF and plasma are well established.*

The McDonald criteria were revised and published in 2017 by the International Panel on the Diagnosis of MS. These revisions include specific guidelines for using MRI and CSF analysis to speed up the diagnostic process. They describe how MRI can be used to look for a second area of damage in a person who has experienced only one episode of CIS. Although widely recognized and used in MS diagnosis, new developments in understanding disease pathology and the role of biomarkers in diagnosing MS have yet to be included. An update on these criteria is expected later in 2024. This update could include adding optic nerve involvement, central vein sign, and paramagnetic lesions, as well as using NfL and kappa-free light chains as biomarkers. The following sessions provided further insight into these potential additions to the revised guidelines.

Due to the transient nature of the disease, it is imperative to find biomarkers that can help assess treatment outcomes and disease progression. Among the emerging imaging biomarkers, paramagnetic rim lesions, which characterize chronically active smoldering MS and iron accumulation in the microglia and central vein sign, are promising. These methods require MRI imaging, which is currently unavailable at all centers, and therefore biofluid biomarkers are expected to play an important role.

- Meta-Analysis for Neurofilament Light Chain as a Biomarker in Mouse Experimental Autoimmune Encephalomyelitis Studies
    - Dr. Kieseier discussed results from the meta-analysis for NfL as a biomarker in mouse experimental autoimmune encephalomyelitis (EAE). The study aimed to better understand the role of biomarkers as a helpful resource in setting up endpoints in clinical trials. This study revealed a significant correlation between plasma NfL levels and CSF NfL levels. Further analysis showed a significant correlation between EAE scores, CSF NfL scores, and plasma NfL scores. The data support the translational value of plasma NfL monitoring in mouse EAE studies for estimating the therapeutic potential of DMTs, as a significant correlation was established between EAE scores, CSF NfL scores, and plasma NfL scores.
- Cerebrospinal Fluid and Plasma Immune Cell Phenotyping Combined with Neurofilament Light Chain as Biomarkers of Inflammatory Activity and Disease Modifying Therapy Responsiveness in Multiple Sclerosis
    - Dr. Arsenault discussed the role of plasma biomarkers in MS and their role in high- versus low-efficacy DMTs. Dr. Arsenault evaluated three biomarkers in this study: pGFAP, pCXCL13, and pNfL. Although the use of DMTs (both high and moderate efficacy) did not alter pGFAP and pCXCL13 at one year, pNfL levels were significantly reduced in the high-efficacy DMT group at year one, while also showcasing a decrease in B cells, CD19 cells, and CXCR3 cells. The study also showed a positive correlation between CXCR3 and B cells and pNfL levels, as well as a negative correlation between T-helper cells and pNfL.
    - In another study by Dr. Arsenault on CSF immune cell phenotyping and NfL measurements as biomarkers of inflammation and DMT responsiveness in MS, CSF immune cells were found to be increased in treatment-naïve RRMS patients, which is expected as these infiltrating immune cells are associated with axonal damage. This increase in immune cells was also correlated with NfL and IgG index in treatment-naïve patients, while DMTs reduced


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lymphocyte and NfLs in RRMS CSF. Additionally, the immune cells, NfL, and IgG index in CSF decreased six months after a relapse in the treatment-naïve group. These findings introduce potential biomarkers of relapse activity and DMT responsiveness.

- Prognostic Value of On-Treatment Serum Neurofilament Light Chain for New or Enlarging T2 Lesions in People with Relapsing Multiple Sclerosis: Pooled Analysis of the ASCLEPIOS I/II Trials
    - Dr. Leist discussed results from the pooled analysis of the ASCLEPIOS I/II trials. The trials are Phase III trials comparing the efficacy of ofatumumab versus teriflunomide in patients with RMS. The studies also monitored sNfL levels in patients, who were divided into two groups (high sNfL ≥9.3pg/mL, and low sNfL ≤9.3pg/mL) based on median sNfL levels at baseline. A pre-planned analysis of baseline sNfL levels indicated that the biomarker was prognostic for on-study lesion formation and brain volume loss. Additionally, patients with high sNfL at month three had a 2.2-fold higher number of T2 lesions and a 3.6-fold higher number of T2 lesions at month 12 compared to the low sNfL group. While this study did have its limitations, as the patient population only included a younger cohort of patients (age 18–55 years), which is not a clear representation of the RMS population seen in everyday practice, and did not look at the treatment effects on sNfL, Dr. Leist concluded that the biomarker could still be used as a prognostic tool for future lesion formation.

## Stool GFAP Is Elevated in Progressive MS, Is Associated with Disability, and Predicts Disease Worsening

Luke Schwerdtfeger, PhD (Harvard)

In lieu of sNfL, other biomarkers were also discussed in the sessions. Dr. Schwerdtfeger addressed the role of stool GFAP in detecting disease progression. The study found stool GFAP to be a sensitive predictor for progressive MS as it showed correlations between stool GFAP and change in EDSS scores. As Parkinson's disease patients also have increased inflammatory biomarkers (fecal calprotectin and fecal zonulin), the study looked into understanding if these biomarkers were also increased in MS patients. This was not the case, as these biomarkers were not correlated with disease activity. Although these results point to GFAP being a potential tool in assessing progressive disease, Dr. Schwerdtfeger pointed out that further analysis is required to understand the source of GFAP and the specificity of progressive MS.

## Predictive Utility of Serum Protein Biomarkers from the Octave MSDA Panel for Optic Neuritis Events in People with Multiple Sclerosis

Ferhan Qureshi (Octave Bioscience)

Optic neuritis (ON) is commonly seen in MS due to inflammation of the optic nerve. Although several studies have been conducted to understand the effectiveness of biomarkers in MS, very few studies have explored the role of biomarkers in forecasting ON in MS. In this session, senior VP Qureshi dove into the predictive utility of serum protein biomarkers from the Octave MSDA panel for ON events in patients with MS. The study used machine learning models to assess the predictive power of serum protein biomarkers for predicting ON, which could, in turn, predict MS disease progression. The study pointed out that elevations in the concentration of CXCL13, CXCL9, OPN, and TNFSF13V were predictive of ON in the next five years. These protein biomarkers could potentially offer a window for early detection of ON and early intervention.


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# Myelin Oligodendrocyte Glycoprotein Antibody Disorders

## Clinical Features and Diagnosis of MOGAD

Brenda Banwell, MD (Children's Hospital of Philadelphia)

*Dr. Banwell gave an overview of myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) from aspects of clinical symptoms, diagnosis, and potential treatments.*

MOGAD is a rare inflammatory disease that affects the nervous system. Similar to MS and NMOSD, MOGAD begins with a clinical attack. Although closely associated with MS and aquaporin-4-positive (AQP4) NMOSD, it is unique and can manifest as monophasic or relapsing disease. Very little is known about the indication, its diagnosis, and treatment. This session, led by Dr. Banwell, shed light on MOGAD and the future of the disease.

Patients presenting with clinical demyelination symptoms such as optic neuritis, myelitis, acute disseminated encephalomyelitis (ADEM), cerebral monofocal or polyfocal deficits, brainstem or cerebellar deficits, or cerebral cortical encephalitis, often with seizures, should undergo a cell-based assay to detect the presence of anti-MOG antibodies.

Spinal cord involvement is common in patients with MOGAD, which is distinct from MS and AQP4 NMOSD disease. MOGAD is characterized by the recognition of immune responses against MOG. MOG IgG is detected in serum and spinal fluid, but other components, such as T effector cells, are also involved. This is particularly important as patients may have relapses even when MOG is no longer detectable.

However, if the clinical presentations and MRI scans of these patients indicate another disease, such as MS, then the MOG assay may not be necessary as the antibody results could potentially yield false positive results for MOGAD diagnosis.

The use of MOG-IgG testing is not recommended as a screening tool for all patients with CNS inflammatory demyelination. This is because the presence of MOG IgG is not specific to MOGAD, and elevated levels of MOG IgG can also be detected in patients with stroke or brain damage. The titers of MOG IgG, acute phenotypes, and inflammation levels are not indicative of the relapse risk in MOGAD.

MOGAD is an age-span disease. It is more prevalent in young children, but a small population beyond 50 years of age is also diagnosed with it. However, clinical features vary with age. ADEM is common in younger patients, while optic neuritis is typical across age groups and is the most prevalent clinical feature.

As the clinical features and antibody detection for a precise diagnosis of MOGAD are still lacking, a criterion was proposed for diagnosing MOGAD where an accurate diagnosis of the disease could only be deemed valid if different criteria were met.

These criteria include:

1. core clinical demyelinating event, which could involve optic neuritis, myelitis, ADEM, cerebral monofocal or polyfocal deficits, brainstem or cerebellar deficits, or cerebral cortical encephalitis, often with seizures
2. a positive MOG-IgG test; however, if titers are low, additional supporting clinical or MRI features, including optic neuritis, myelitis, or brain, brainstem, or cerebral syndrome, are considered
3. exclusion of better diagnoses, including MS.


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The speaker also emphasized that this was a continuously evolving field, where these criteria are expected to be constantly updated as the disease is further explored.

This diagnostic tool has limitations, as antibody testing is not universal, and cell-based assays are infrequently available. False favorable rates of up to 5% can be seen, especially if an older population is screened for MOGAD, as MS is a more likely diagnosis.

Relapse prediction in MOGAD is very poor, as age, antibody titer, IgG antibodies, disability scores, and MRI are not useful measures. However, patients who have relapses tend to be 18–40 years of age, and around 60% of patients with optic neuritis will relapse. The speaker also emphasized many uncertainties about MOGAD, where, unlike MS, there are not much data available. However, the disease is undoubtedly distinct from MS and AQP4 NMOSD, and further development in diagnosing and treating MOGAD is essential. Further research is necessary to identify biomarkers that can accurately predict the risk of relapse and determine whether relapsing MOGAD is a lifelong condition.

IL-6 has been identified in the CSF of certain MOGAD patients. Serum cytokines are less informative compared to CSF analysis. Anecdotal case reports suggest that the IL-6 inhibitor tocilizumab may have potential for treating the acute phase of MOGAD, but additional research is required to validate this treatment approach.

## Imaging Features of MOGAD and Key Flags

Giulia Fadda, MD (Children's Hospital of Philadelphia)

*Dr. Fadda gave insights into the imaging features of MOGAD and critical flags in the detection of the disease.*

As in the diagnostic criteria, if antibody tests are inconclusive, the diagnosis of MOGAD relies heavily on the use of MRI. MRI is then used to diagnose MOGAD based on spinal cord, brain, and optic nerve findings. Bilateral involvement of the optic nerve is often seen in MOGAD, which is not often seen in MS. Lesions involving the posterior parts of the optic nerves are suggestive of AQP4 NMOSD and are rarely seen in MOGAD.

Longitudinal extensive transverse myelitis is seen in 80% of cases, while 20% have short lesions in MOGAD. As a differential diagnosis, multiple short peripheral T2 lesions favor MS diagnosis, and bright spot signs favor NMOSD.

ADEM is among the most common brain presentations in children, with approximately 50% being MOG antibody positive. Dr. Fadda further added that based on advanced imaging techniques, persistent gray matter volume abnormalities despite clinical recovery and the absence of smoldering damage between clinical attacks are seen in MOGAD.


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## Pathological Insights into MOGAD Biology: Clues for Etiology and Treatment

Romana Höftberger, MD (Medical University of Vienna)

*Histological analysis of biopsies obtained from patients with MOGAD has yielded valuable molecular insights that can guide the development of potential therapeutic interventions.*

MOGAD is characterized by various clinical manifestations, such as optic neuritis, myelitis, ADEM, brainstem lesions, and cortical encephalitis. However, it is important to note that the diagnosis of MS should be considered before making a diagnosis of MOGAD.

Immunohistochemistry analysis of brain biopsies indicates that T helper cells are more prevalent in MOGAD, whereas CD8 T cells are more commonly observed in MS. Additionally, complement deposition on myelin sheets in the presence of active demyelination is frequently observed in MOGAD.

Dr. Höftberger proposed three factors that potentially impact the progression of MOGAD:

1. anti-MOG antibody characteristics (titer, affinity, and isoforms)
2. T cells (MOG-responsive T cells and their ability to activate macrophages)
3. host factors (age and genetic factors).

Animal studies have shown that high levels of T cells with low MOG antibodies tend to result in increased brain inflammation, while high levels of MOG antibodies with low T cells lead to more demyelination of brain neurons.

Dr. Höftberger gave updated insights into the disease, which could provide treatment options and information on future developments. From experimental studies *in vitro*, it was found that MOG antibodies, in principle, can induce complement-dependent cytotoxicity. However, a more efficient complement activation was seen with anti-AQP4 than with anti-MOG antibodies. This leads to the use of complement inhibition in treating the indication.

Among the drugs targeting the complement pathway, eculizumab was studied in a trial that showcased promising results. The drug acts by inhibiting the dissociation of C5 to C5a and C5b, thus blocking the evolution of the terminal complement complex. Eculizumab has been approved for patients with NMOSD who are positive for AQP4 antibodies. Further studies are needed to determine biomarkers that can identify patients who may benefit from complement activation inhibitors. Dr. Höftberger added that disease understanding must evolve with biomarkers and treatment options to diagnose and treat these patients earlier.


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## Industry Therapeutic Update from Genentech: Moving Upstream: The Role of Interleukin-6 in MOGAD and Autoimmune Encephalitis

Ivana Vodopivec, MD (Roche)

*During the session, a comprehensive overview of MOGAD and autoimmune encephalitis was provided, covering various aspects such as diagnosis, potential treatment options, unmet needs, and treatment targets in clinical development.*

MOGAD can affect both children and adults. Apart from clinical manifestations, the presence of IgG1 autoantibodies targeting MOG is necessary for diagnosing MOGAD. The relapse rate is highest in the first two years after diagnosis, with 45% of patients experiencing a relapse during this period.

Current treatment options for MOGAD are off-label and include high-dose corticosteroids, IVIG, rituximab (an anti-CD20 antibody targeting B cells), and plasma exchange (PLEX). While patients with MOGAD generally have better long-term outcomes compared to those with AQP4 NMOSD, the level of disability, impact on quality of life, and financial burden can still be significant due to incomplete or no recovery from myelitis or optic neuritis.

Preclinical studies on IL-6 knockout mice have suggested the involvement of IL-6 in various autoimmune diseases. Elevated levels of IL-6 have been found in the CSF of MOGAD patients, indicating a potential treatment strategy through IL-6 inhibition.

Clinical trials are currently under way to evaluate the efficacy of anti-IL-6 receptor antibodies in MOGAD patients. Additionally, FcRn inhibitors are being tested in clinical trials as an approach to disrupt the recycling of MOG IgG antibodies, thereby reducing their levels.

In the second half of the session, Dr. Vodopivec discussed autoimmune encephalitis, a rare neurological disorder characterized by brain inflammation and dysfunction.

Two autoantibodies, NMDAR IgG and LGI1 IgG, are associated with autoimmune encephalitis. However, patients positive for these autoantibodies exhibit distinct clinical phenotypes and disease courses. Approximately 80% of autoimmune encephalitis cases are either NMDAR IgG+ or LGI1 IgG+. Diagnosis involves neuroimaging (such as brain MRI and EEG), blood and CSF analysis for neuronal autoantibodies, and ruling out associated cancers.

Clinical presentations vary based on age. Children with NMDAR IgG+ autoimmune encephalitis tend to exhibit seizures more frequently, while adults often experience behavior changes. Known triggers for NMDAR IgG+ disease include Herpes simplex virus infections and ovarian teratoma.

Currently, off-label immunosuppressive drugs are recommended for the treatment of autoimmune encephalitis; however, long-term symptom improvement remains limited.

Increased levels of CSF IL-6 have been reported in NMDAR-IgG+ autoimmune encephalitis patients. Preclinical studies have suggested a potential role for IL-6 in triggering the disease in mice, indicating that targeting IL-6 receptors may benefit patients.

Clinical trials are currently under way to evaluate the efficacy of targeting IL-6 receptors, FcRn, CD19, and CD20.


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# Narcolepsy

## Samelisant (SUVN-G3031): Topline Results from the Phase-2 Proof-of-Concept Double-Blind, Placebo-Controlled Study in Patients with Narcolepsy

Poster (Suven Life Sciences)

*Samelisant as a monotherapy achieved its primary efficacy endpoint, demonstrating a statistically significant and clinically meaningful reduction in Epworth Sleepiness Scale total score compared to placebo at day 14.*

There is no cure currently available for narcolepsy. Narcolepsy is categorized into type 1 (with cataplexy; approximately 70% of all narcolepsy cases) and type 2 (without cataplexy [but often with excessive daytime sleepiness]; approximately 30% of all narcolepsy cases).

Samelisant is a histamine H3 receptor inverse agonist in development for the treatment of excessive daytime sleepiness (EDS) or cataplexy in narcolepsy.

The Phase II proof-of-concept study assessed samelisant as a monotherapy for the treatment of EDS in narcolepsy type 1 and type 2. A total of 190 patients were randomized to receive samelisant 2mg, samelisant 4mg, or placebo for 14 days.

- At day 14, there were statistically significant reductions of 1.8 points and 2.3 points in Epworth Sleepiness Scale (ESS) scores (the primary endpoint) in the 2mg and 4mg arms, respectively, compared to placebo.
- Regarding a key secondary endpoint, Clinical Global Impression of Severity (CGI-S) related to EDS, treatment with 2mg and 4mg samelisant led to 0.4-point and 0.6-point reductions compared to placebo, respectively.
- Patient Global Impression of Change (PGI-C) and Clinical Global Impression of Change (CGI-C) related to EDS were also significantly improved. Treatment with 2mg and 4mg samelisant led to 0.5-point and 0.9-point reductions on the PGI-C compared to placebo, respectively, and 0.7-point and 0.9-point reductions regarding CGI-C.
- Samelisant was generally safe and well tolerated. There were no serious AEs or deaths reported in the study.

A global Phase III trial assessing samelisant for the treatment of narcolepsy will be initiated during Q3 2024.


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An overview of the data is shown in the tables below:

| Epworth Sleepiness Scale (ESS) | | | | | |
|---|---|---|---|---|---|
| **Treatment** | **Number of patients** | **Mean at baseline** | **Mean change from baseline at day 14** | **Treatment difference at day 14 versus placebo** | |
| | | | | **Mean difference** | **p-value** |
| Placebo | 57 | 17.1 | -3.3 | - | - |
| Samelisant 2mg | 54 | 17.4 | -5.1 | -1.8 | 0.034 |
| Samelisant 4mg | 53 | 17.6 | -5.6 | -2.3 | 0.032 |

| Clinical Global Impression of Severity (CGI-S) related to EDS | | | | | |
|---|---|---|---|---|---|
| **Treatment** | **Number of patients** | **Mean at baseline** | **Mean change from baseline at day 14** | **Treatment difference at day 14 versus placebo** | |
| | | | | **Mean difference** | **p-value** |
| Placebo | 57 | 4.8 | -0.8 | - | - |
| Samelisant 2mg | 54 | 4.7 | -1.2 | -0.4 | 0.026 |
| Samelisant 4mg | 53 | 4.9 | -1.4 | -0.6 | 0.007 |

| Patient Global Impression of Change (PGI-C) related to EDS | | | | | |
|---|---|---|---|---|---|
| **Treatment** | **Number of patients** | **Mean at baseline** | **Mean change from baseline at day 14** | **Treatment difference at day 14 versus placebo** | |
| | | | | **Mean difference** | **p-value** |
| Placebo | 54 | 2.8 | 3.7 | - | - |
| Samelisant 2mg | 53 | 4.6 | 3.2 | -0.5 | 0.004 |
| Samelisant 4mg | 51 | 4.7 | 2.8 | -0.9 | <0.0001 |


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| Clinical Global Impression of Change (CGI-C) related to EDS | | | | |
|---|---|---|---|---|
| **Treatment** | **Number of patients** | **Mean change from baseline at day 14** | **Treatment difference at day 14 versus placebo** | |
| | | | **Mean difference** | **p-value** |
| Placebo | 57 | 3.5 | - | - |
| Samelisant 2mg | 54 | 2.8 | -0.7 | <0.0001 |
| Samelisant 4mg | 53 | 2.6 | -0.9 | <0.0001 |


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## Solriamfetol for Excessive Sleepiness in Narcolepsy and Obstructive Sleep Apnea: Effect Sizes and Numbers Needed to Treat or Harm

Poster (Axsome Therapeutics)

*This post-hoc analysis demonstrates favorable effect sizes and number needed to treat and number needed to harm values for solriamfetol in the treatment of EDS associated with narcolepsy and obstructive sleep apnea.*

Solriamfetol (Sunosi), a dopamine and norepinephrine reuptake inhibitor, is approved for use in adults in the US and EU for the treatment of EDS associated with narcolepsy. Preclinical data indicate that solriamfetol activates trace amine-associated receptor 1 (TAAR1), a potential target for improving cognitive functions.

The efficacy and safety of solriamfetol have been established in two Phase III studies, Treatment of Obstructive Sleep Apnea (TONES 2) and Narcolepsy Excessive Sleepiness (TONES 3). Efficacy was demonstrated based on ESS scores, Maintenance of Wakefulness Test (MWT) mean sleep latency, and PGI-C and CGI-C.

This post-hoc analysis characterized the efficacy and tolerability of solriamfetol based on effect sizes, number needed to treat (NNT), and number needed to harm (NNH), using data from TONES 2 and TONES 3.

- Effect sizes compared with placebo (Cohen's d) were determined for ESS scores and MWT mean sleep latency, based on changes from baseline to week 12 (small = 0.2; medium = 0.5; and large = 0.8). Results demonstrated favorable effect sizes for solriamfetol compared to placebo (as shown in the table below).
- NNT was determined for the percentage of participants with changes in scores that met clinically meaningful response thresholds at week 12:
    - For ESS: ESS ≤10, ≥25% decrease from baseline, and three-point decrease from baseline.
    - For MWT: achieving a mean sleep latency ≥20 minutes and a two-minute increase from baseline.
    - For PGI-C and CGI-C: improvement, defined as responses of "minimally," "much," or "very much" improved.
- Compared with placebo, with solriamfetol 150mg/day, three participants with narcolepsy or obstructive sleep apnea (OSA) would need to be treated for one additional participant to achieve PGI-C or CGI-C response.
- Compared with placebo, with solriamfetol 150mg/day:
    - Six participants with narcolepsy and three participants with OSA would need to be treated for one additional participant to achieve ≥25% decrease in ESS score.
    - Five participants with narcolepsy and four participants with OSA would need to be treated for one additional participant to achieve ESS scores in the normal range.
- Compared with placebo, with solriamfetol 150mg/day, three participants with OSA would need to be treated for one additional participant to achieve MWT ≥20 minutes.


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An overview of effect sizes and NNT with solriamfetol in TONES 2 and TONES 3:

| Study dose | ESS | | | | MWT | | | PGI-C | CGI-C |
|---|---|---|---|---|---|---|---|---|---|
| | Cohen's d | NNT (ESS≤10) | NNT (↓≥25%) | NNT (↓3 points) | Cohen's d | NNT (≥20min) | NNT (↑2min) | NNT | NNT |
| **TONES 2** | | | | | | | | | |
| 75mg/day | 0.47 | 7 | 7 | 6 | 0.29 | 48 | 5 | 4 | 4 |
| 150mg/day | 0.8 | 5 | 6 | 4 | 0.82 | 5 | 3 | 3 | 3 |
| 300mg/day | 1.03 | 3 | 3 | 3 | 1.13 | 4 | 3 | 3 | 3 |
| **TONES 3** | | | | | | | | | |
| 37.5mg/day | 0.42 | 8 | 8 | 7 | 0.46 | 10 | 7 | 16 | 11 |
| 75mg/day | 0.37 | 6 | 6 | 7 | 0.89 | 4 | 3 | 5 | 5 |
| 150mg/day | 0.99 | 4 | 3 | 3 | 1.08 | 3 | 3 | 3 | 3 |
| 300mg/day | 1.04 | 3 | 3 | 3 | 1.28 | 3 | 3 | 3 | 3 |

NNH was determined for TEAEs that were reported in ≥5% of solriamfetol-treated participants and greater than placebo. Across pooled doses with and without 300mg solriamfetol, only one TEAE had an NNH <10 (headache, in participants with narcolepsy).

## Impact of the Oral Orexin Receptor 2 Agonist TAK-994 on Sustained Attention in Patients with Narcolepsy Type 1: Exploratory Results from a Phase 2 Study

Poster (Takeda)

*A Phase 2, randomized, double-blind, placebo-controlled study evaluated the safety and efficacy of twice-daily oral TAK-994 in patients with narcolepsy type 1.*

Significant improvements from baseline in sustained attention and memory were achieved with TAK-994 doses ≥90mg twice daily in patients with narcolepsy type 1. Few serious TEAEs were associated with TAK-994, although clinical development of TAK-994 was discontinued owing to the emergence of hepatic events in Part B and its long-term extension study.


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# Neuromyelitis Optica Spectrum Disorder

## AQP4-IgG: The Impact and Evolution of Serodiagnosis

Sean J. Pittock, MD (Mayo Clinic)

*Aquaporin-4-IgG (AQP4-IgG) seropositivity has high specificity for an NMOSD diagnosis.*

NMOSD, or Devic's disease, is a severe inflammatory CNS monophasic disease. The disease is characterized by optic neuritis, transverse myelitis, and area postrema syndrome. Attacks are more severe compared to MS. Unlike MS, where progression of disease can occur without relapse, in NMOSD, progression is dependent on relapse.

Serum immunoglobulin G autoantibody binds selectively to the aquaporin-4 water channel and is a specific marker for NMOSD. The discovery of this biomarker has made it possible to differentiate between MS and NMOSD, both of which have distinct disease pathology, progression, and treatment. The role of this biomarker in NMOSD has also led to a further understanding of disease pathology, where the role of immunopathological mechanisms underlying the disease, including an increase in IL-6, the proliferation of CD19 cells, and a variety of different mechanisms which lead to complement activation and astrocyte injury, were recognized.

Diagnostic criteria for NMOSD include:

1. at least one core clinical characteristic
2. positive AQP4-IgG
3. exclusion of alternative diagnosis.

Among the various assays utilized to detect AQP4-antibody, the flow cytometry live cell-based assay is the best method to detect disease in patients. A study conducted by Redenbaugh et al. found that the live cell-based assay had a 100% positive predictive value and specificity for AQP4-IgG for NMOSD, and there were no instances of false positives. Dr. Pittock also added that the sample should be taken from the patient's serum, as up to 30% of patients can be missed when samples are collected from the CSF of patients who are AQP4-IgG positive.

Dr. Pittock emphasized that it is imperative to choose the most accurate method of AQP4-antibody detection, as it not only allows correct diagnosis of the disease, but also avoids misdiagnosis of the disease as MS. This could lead to patients missing out on FDA-approved therapies for NMOSD, and could mean patients getting MS DMTs that could make their NMOSD worse.


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## NMOSD: Acute and Preventative Treatments in the Era of Registered Therapies

Bruce Cree, MD, PhD (University of California, San Francisco)

*Dr. Cree discussed treatment options for NMOSD, with an emphasis on the efficacy and safety of eculizumab, satralizumab, inebilizumab, and ravulizumab.*

Up to 90% of patients who have AQP4-IgG-positive NMOSD show clinical manifestations that are restricted to the optic nerve and spinal cord. NMOSD also has a severe cumulative disability, where in a median follow-up of 7.7 years, 60% of patients were blind, 32% of patients had either permanent monoplegia or paraplegia, and the five-year survival rate was only 68%. This demonstrates the importance of optimal treatment of acute attacks and the use of long-term treatments that can prevent attacks.

The treatment for attacks relies on the use of high-dose corticosteroids and plasmapheresis. Delay in initiation of plasmapheresis is associated with worse optic neuritis outcomes, and IVIG can be used as a rescue treatment. Dr. Cree added that initiation of plasmapheresis in patients who come in with severe optic neuritis should not be delayed until a confirmatory diagnosis of NMOSD is completed. Dr. Cree opined that patients, irrespective of disease diagnosis, be it MS, NMOSD, or MOGAD, could benefit from plasmapheresis when presenting with acute symptoms.

The FDA has approved four therapies for the treatment of NMOSD. The first, eculizumab, was approved in 2019. Following this, satralizumab and inebilizumab were approved in 2020, and ravulizumab was approved in 2024.

Eculizumab targets the complement C5 pathway and is given intravenously. A loading dose is given once every week for five weeks, followed by a maintenance dose once every two weeks.

Satralizumab targets IL-6R and is given in a more agreeable subcutaneous formulation with no loading dose. The drug is administered conveniently every four weeks.

Inebilizumab, like eculizumab and ravulizumab, is given intravenously and targets the CD19 pathway. The drug has a split loading dose provided on day one and day 15, followed by a maintenance dose given twice a year, making it the most durable treatment option. Ravulizumab, like eculizumab, targets the C5 pathway, with a loading dose given two weeks apart and a maintenance dose given every eight weeks. The drug also demonstrated excellent efficacy in its pivotal Phase III trial, showcasing 100% overall risk reduction.

With the advent of these therapies, clinical trial design and the use of placebo in NMOSD clinical trials were also discussed. All of the approved treatments for NMOSD utilized placebo as the control arm in their Phase III pivotal trials; however, the utilization of placebo in patients with NMOSD as a control for relapse prevention is no longer practical and could also raise issues of unethical practice. Currently, regulatory bodies may still choose to allow the use of placebo if current therapies are associated with serious adverse events or if they apply to select subgroups. Dr. Cree also added that new entrants to the market must focus on conducting superiority trials or non-inferiority trials to showcase their additional value over currently approved therapies.

Although the approvals of these novel therapies in NMOSD have dramatically benefited patients, Dr. Cree reiterated that the barrier to entry for new treatments is still high, and many insurance plans still require step edits through off-label therapies before allowing patients to access approved medications.


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## Biomarkers in NMOSD

Jeffrey L. Bennett, MD, PhD (University of Colorado)

*Dr. Bennett talked about biomarkers in NMOSD that could potentially measure disease processes, thereby helping in predicting relapse while also understanding therapeutic response.*

NMOSD progression is solely based on relapse, unlike MS. Currently approved therapies greatly reduce relapse risk while also reducing the intensity of relapse, thereby decreasing the extent of disease progression.

MRI is used to diagnose NMOSD, but its role in assessing asymptomatic brain activity is not fully understood. A study by Lee et al. found that asymptomatic brain lesions are rare in clinically stable NMOSD patients; only 3.4% of clinically stable AQP4+ NMOSD patients had asymptomatic brain lesions. Multiple studies have supported these findings, where only a tiny percentage of patients had brain lesions, questioning the role of MRI in understanding asymptomatic brain activity.

Unlike MRI, damage biomarkers could give a better understanding of disease progression and therapeutic benefits. CNS astrocytes uniquely produce serum GFAP and are notably increased in NMOSD relapse as compared to other demyelinating disorders. As seen in the N-MOMENTUM study, a serum GFAP measure >170pg/ml increased the risk of NMOSD relapse by three times. The trial also found an interesting increase in GFAP levels one to seven days prior to relapse, which could help detect relapse before its occurrence, albeit this is currently impractical. NfL has gained interest among neurologists, not just in MS but also in NMOSD. In the N-MOMENTUM trial, serum NfL was correlated with EDSS change from baseline following an attack.

When using optical coherence tomography to examine the non-optical neuritis eye in NMOSD patients, ganglion cell complex thinning was evident, but was only statistically significant in patients with a history of contralateral optic neuritis.

Combining MRI and GFAP, as seen in the N-MOMENTUM study, where new and enlarging T2 lesions, Gd+T1 lesions, and an increase in GFAP were measured, showed that there was no increased risk with optic nerve lesions, but showed a signature for new T2 lesions and elevated GFAP in the spinal cord that could signify a risk of future attacks.


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## Alexion Industry Update: Management and Reduction in the Risk of NMOSD Relapses: Learnings from the Patient-Physician Relationship

Benjamin Osborne, MD (Georgetown University)

*In this industry update, the speaker described how Solaris and Ultomiris should be utilized in terms of dosing and safety precautions, and how they compare to each other.*

There are two FDA-approved treatments for NMOSD, both of which are monoclonal antibodies marketed by Alexion (since acquired by AstraZeneca). Solaris (eculizumab) became the first FDA-approved therapy for NMOSD in 2019, and a next-generation version, Ultomiris (ravulizumab), was approved in 2024.

Ultomiris is the first and only long-acting C5 complement inhibitor for the treatment of adult patients with AQP4-antibody-positive NMOSD. In the Phase III CHAMPION-NMOSD trial, zero relapses were observed among NMOSD patients treated with Ultomiris, with a median treatment duration of 73 weeks (relapse risk reduction of 98.6%). The placebo arm of the Solaris PREVENT trial was used for comparison in this trial due to the ethical issues of implementing a placebo arm when a treatment is already available for such a devastating disease.

Ultomiris is administered every eight weeks, while Solaris is dosed once every two weeks. As such, many patients are being switched to the newer product for convenience.

During this presentation, an NMOSD patient being treated with Solaris was invited on stage to talk about her experience. She explained how she had been misdiagnosed with MS for four years, and how this had a devastating effect on her health and independence. Dr. Osborne confirmed how common it is for NMOSD patients to be initially diagnosed with MS, and emphasized the importance of testing for anti-AQP4 antibodies for a correct diagnosis, particularly considering that MS medications can worsen NMOSD symptoms.


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## Indirect Treatment Comparison of Ravulizumab Versus Approved Treatment Options for Adults with Anti-Aquaporin-4 Immunoglobulin G-Positive Neuromyelitis Optica Spectrum Disorder (NMOSD)

Poster (sponsored by Alexion)

*Network meta-analysis results suggest that Ultomiris monotherapy is more efficacious in improving time to first relapse and ARR than Enspryng or Uplizna, and was comparable to Solaris.*

Considering the several treatment options that are available for AQP4-antibody-positive NMOSD, comparisons of relative treatment effects with Ultomiris versus approved therapies could facilitate shared treatment decision-making.

A Bayesian network meta-analysis (NMA) was performed to estimate the relative treatment effects based on reported trial-specific results identified via systematic literature review. Of 442 records identified, 17 reports of five studies met eligibility criteria for inclusion, comprising an evidence base of one external placebo-controlled trial for Ultomiris and four randomized, placebo-controlled trials for Solaris (eculizumab), Enspryng (satralizumab), and Uplizna (inebilizumab).

The endpoints analyzed were time to first relapse (TTFR) and ARR, with relative treatment effect measures obtained by the NMA expressed as hazard ratios and rate ratios:

- Patients treated with Ultomiris monotherapy were >90% less likely to experience a first relapse than patients treated with Enspryng and Uplizna monotherapies. TTFR was comparable between Ultomiris and Solaris.
- Patients treated with Ultomiris in combination with immunosuppressant therapy (IST) showed an 85% reduction in TTFR relative to Enspryng + IST, and was comparable relative to Solaris + IST. Patients treated with Ultomiris ± IST showed a 94% reduction in TTFR relative to Enspryng and a 76% reduction relative to Solaris ± IST.
- The ARR with Ultomiris monotherapy was 98% lower than with Enspryng and Uplizna monotherapies and was comparable to Solaris monotherapy.
- The rate ratio point estimate for ARR favored Ultomiris + IST over Enspryng + IST, but the credible interval crossed the bounds of statistical significance. The ARR was 98% lower with Ultomiris ± IST than with Enspryng ± IST and was comparable to Solaris ± IST.


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# Parkinson's Disease

## Update on Parkinson's Disease

Pinky Agarwal, MD (University of Washington)

*New research in Parkinson's disease and breakthroughs in the field were presented.*

The MANAGE-PD tool is a clinician-reported tool designed to facilitate timely identification and management of patients with advancing Parkinson's disease (PD) with suboptimal symptom control on their current treatment regimen and who may require referral for device-aided therapies. This uses a questionnaire to assess motor, non-motor, and functional impact symptoms to classify patients into either category one, two, or three depending on symptom severity (three being the most severe). A total of 2,546 real-world cases from the EU, Japan, and US were applied to this tool. Healthcare resource utilization was significantly higher for those in category three. In the US and Japan, the most expensive component was drug costs, and in the EU the highest component was cost of professional care. The proportion of patients reporting discussion with healthcare providers about device-aided therapy was also significantly higher for those in category three (55.3%, compared to 35.8% in category two and 20.5% in category one).

Deep brain stimulation (DBS) involves an implanted hardware that delivers electrical impulses to the deep brain structures. Movement disorders are characterized by altered firing patterns within the cortical, basal ganglia, and thalamocortical loop. The electric field produced by DBS induces changes in cell depolarization that can change the firing patterns of neurons within a nucleus. "Regularization" of neuronal firing patterns prevents transmission of pathologic bursting and oscillatory activity in the network, which leads to improved procession of sensorimotor information and a reduction of disease symptoms. DBS is appropriate in PD when a patient is having troubling motor symptoms, which may include motor fluctuations, dyskinesias, and refractory tremor. DBS is only considered in a window of opportunity when significant neuropsychiatric co-morbidity is still absent and before refractory symptoms (such as dementia and gait freezing) appear.

DBS has been shown to induce a 12.3-point reduction in UDPRS III over six months, compared to those taking the best medical therapy (Weaver et al., 2009). In the INTREPID trial (Vitek et al., 2020), there was a 22.1-point reduction in UDPRS III scores (49.2% improvement) after one year for PD patients who had DBS, compared to baseline. There was also a 6.1-hour increase in "on" time after one year, compared to baseline.

The future of DBS includes streamlined programming optimization that involves remote programming, image-guided programming, and brain sensing. Image-guided programming is helping clinicians to home in on the best place to deliver the stimulation. Brain sensing allows clinicians to see neurophysiological responses to stimulation in real-time. This should eventually allow for more adaptive DBS, whereby stimulation is adjusted higher or lower, which should increase the efficiency of stimulation while reducing side effects, compared to the continuous 24/7 stimulation that occurs currently.

Other surgical options for advanced PD include magnetic resonance-guided focused ultrasound (MRgFUS) and the carbidopa-levodopa (CD/LD) intestinal pump, Duopa. With a Duopa pump, CD/LD is administered over a 16-hour period. Duopa has less restrictive candidacy requirements than DBS or focused ultrasound, but a high rate of complications. In Sweden, there is a levodopa-entacapone-carbidopa intestinal gel available. The inclusion of entacapone increases the bioavailability of levodopa, therefore reducing the amount of levodopa needed.

In the Q&A session, an audience member said she was having trouble getting other medications, such as Rytary and Inbrija, covered by insurance, and asked the speaker how she manages to get any medication aside from immediate-release CD/LD covered. The speaker said she keeps an ongoing list of medications tried and failed for each patient and writes down, for example, why she thinks a certain medication would be


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appropriate for her patient or not appropriate (i.e., why it has not been tried). She will also keep written records of “off” symptoms and dyskinesia. She said these factors are what insurance companies are looking for when making reimbursement decisions.

## Safety and Tolerability of P2B001 in Patients with Early Parkinson’s Disease: Analysis of an Integrated Phase II and III Safety Database

J. Antonelle de Marcaida, MD (Hartford HealthCare Chase Family Movement Disorders Center)

*In the combined analysis, P2B001 demonstrated a favorable safety profile versus titrated pramipexole ER.*

The efficacy of P2B001 (a once-daily rasagiline/pramipexole combination drug) has been established in two previous randomized controlled trials.

The study described here evaluated and characterized the safety and tolerability profile of P2B001 in 323 patients with early-stage PD using an integrated safety analysis of Phase II (ClinicalTrials.gov identifier: NCT01968460) and Phase III (ClinicalTrials.gov identifier: NCT03329508) randomized controlled, 12-week studies.

- In the combined analysis, P2B001 demonstrated a favorable safety profile versus titrated pramipexole ER.
- The overall rate of TEAEs was 86.5% with pramipexole ER, 74.9% with P2B001, and 54% with placebo. A total of 15.6% of P2B001 patients experienced daytime sleepiness, compared to 32.4% of pramipexole ER patients.
- Furthermore, there was a lower frequency of dopaminergic TEAEs with P2B001 compared with pramipexole ER, including incidences of orthostatic hypertension, gastrointestinal side effects, and neuropsychiatric complications such as hallucinations and memory impairment.


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## Imaging Outcomes of a Dopaminergic Neuronal Cell Therapy for Parkinson's Disease: 18-Month Results from a Phase I Study of Bemdaneprocel

Claire Henchcliffe, MD (University of California)

*These analyses demonstrate bemdaneprocel survival for six months post discontinuation of immunosuppression, or 18 months post transplantation, and continued dopaminergic signaling in the putamen.*

Bemdaneprocel is an investigational therapy comprising dopaminergic neuronal progenitors derived from human embryonic stem cells. Prior results from exPDite, a Phase I open-label study, at 12 months post transplantation demonstrated bemdaneprocel was generally safe and well tolerated, supported the feasibility of stereotactic transplantation of bemdaneprocel, and suggested stability or improvement in motor outcomes.

The objective of this study was to assess changes in fluorodopa uptake and safety up to 18 months post transplantation (six months post discontinuation of immunosuppression) using PET and MRI.

- Compared with baseline, group-level analysis (n=12) revealed increased fluorodopa PET signal in the posterior putamen, which is consistent with survival of bemdaneprocel, at 12 and 18 months post transplantation.
- Decreased fluorodopa PET signal in the caudate is indicative of continuing progression of PD.
- MRI assessments of target volume did not reveal evidence of cell overgrowth, tumor formation, or other safety concerns up to 18 months post transplantation.

Additionally, a favorable safety profile, as well as stability or improvement in motor outcomes, was maintained at 18 months post transplantation.


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## Exploratory Analysis of PASADENA Open-Label Extension Evaluating the Effect of Prasinezumab on the Progression of Motor Signs and Symptoms

Patrik Brundin, MD, PhD (Roche)

*The comparison of PASADENA and PPMI data suggests that individuals treated with prasinezumab may benefit on multiple endpoints related to motor progression.*

Roche's prasinezumab is a humanized IgG1 monoclonal antibody that selectively binds aggregated α-synuclein and is potentially disease-modifying.

In this presentation, Dr. Brundin compared Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UDPRS) data from the Phase II PASADENA OLE four-year follow-up with a propensity score-balanced cohort of real-world data on the Parkinson's Progression Markers Initiative (PPMI).

Weighting with propensity scores resulted in balanced baseline demographic and clinical characteristics between the PASADENA participants and PPMI control cohort.

- Data from the open-label trial suggest that prasinezumab slowed the progression of clinician-rated motor deficits (MDS-UPDRS Part III "off" score) in early-stage PD.
- The data also suggest that prasinezumab slowed the progression of clinician-rated motor deficits (MDS-UPDRS Part III "on" score) in early-stage PD patients when receiving benefit from symptomatic treatment.
- Prasinezumab-treated individuals also progressed less than untreated individuals in the PPMI cohort regarding MDRS-UPDRS Part II (patient-reported motor experiences of daily living).

These data are exploratory and need to be confirmed in an independent trial such as the Phase IIb PADOVA study and its OLE.


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## Improvement of “On” and “Off” Times in Patients with Advanced Parkinson’s Disease Treated with Foslevodopa/Foscarbidopa: Subgroup Analyses from a Phase III Randomized Study

Drew S. Kern, MD (University of Colorado)

*A total of 141 patients with PD experienced equivalent clinical improvements with ABBV-951 that were largely unrelated to baseline demographics and disease characteristics.*

Foslevodopa/foscarbidopa (AbbVie’s ABBV-951) is a new soluble formulation of LD/CD prodrugs delivered as a 24-hour/day continuous subcutaneous infusion. In the Phase III randomized controlled trial, ABBV-951 significantly increased “on” time and reduced “off” time versus oral immediate-release LD/CD in adult patients with advanced PD.

This presentation focused on an analysis across patient subgroups by baseline demographics and disease characteristics. Subgroups included age, sex, race, country, PD duration, “off” time at baseline, levodopa equivalent daily dose (LEDD), and concomitant dopamine agonist use.

- Improvements in “on” time, “off” time, motor symptoms, and quality of life were numerically greater with ABBV-951 versus oral LD/CD across most subgroups.
- The analysis showed that improvements in “on” and “off” time with ABBV-951 treatment compared to oral LD/CD were not significantly different between any of the subgroups. However, improvements in MDS-UDPRS III and Parkinson's Disease Questionnaire (PDQ-39) were significantly greater in patients with higher versus lower PD duration. These results should be interpreted cautiously due to small sample sizes.

The safety profile of ABBV-951 was consistent across baseline age, PD duration, “off” time, and LEDD subgroups, with higher rates of TEAEs observed with ABBV-951 compared to oral LD/CD.


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## Effects of Continuous Subcutaneous Infusion of Foslevodopa/Foscarbidopa on Sleep Dysfunction in People with Parkinson's

Poster (AbbVie)

*A post-hoc analysis suggests that ABBV-951 improves sleep in PD patients.*

Sleep is commonly disrupted in people with PD, and sleep-related issues are among the most troublesome and frequent non-motor symptoms in PD.

The Parkinson's Disease Sleep Scale-2 (PDSS-2) is a 15-question assessment characterizing various aspects of nocturnal sleep disturbances experienced by PD patients, providing an overall representation of sleep problems (PDSS-2 total score) plus a breakdown of symptoms into individual factors addressed in each question/item. This can then be grouped into three subdomains: motor symptoms at night, PD symptoms at night, and disturbed sleep.

12-week and 52-week Phase III trials previously reported that 24-hour/day ABBV-951 infusion was generally safe and significantly improved motor fluctuations (versus oral therapy or baseline, respectively). These trials were analyzed post-hoc regarding sleep patterns.

- In the 12-week trial, there was a statistically significant 7.92-point improvement in PDSS-2 total scores for those treated with ABBV-951 compared to baseline, which included statistically significant improvements across all three subdomains.
- Statistically significant improvements in PDSS-2 totals compared to baseline were also observed in the 52-week trial.
- Numerical improvements versus oral therapy (nominal $p \leq 0.001$) were seen in the PDSS-2 total, the Motor Symptoms at Night, and the Disturbed Sleep subdomain scores in the 12-week trial for ABBV-951-treated patients.
- Out of the 15 PDSS-2 individual sleep/nocturnal disturbance factor items, all but one were significantly improved versus baseline in the 52-week trial for those treated with ABBV-951. In the 12-week trial, 11 items demonstrated nominally significant improvements versus baseline and nine showed nominally significant improvements versus oral therapy.


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## Efficacy of ND0612, a 24-Hour Subcutaneous Levodopa/Carbidopa Infusion for People with Parkinson's Disease Experiencing Motor Fluctuations: Subgroup Analyses from a Randomized Controlled Phase III Study

Alberto J. Espay, MD (University of Cincinnati)

*ND0612 improved "on" time across differing patient profiles and without relevant differences in safety or tolerability.*

NeuroDerm's ND0612 is an investigational continuous LD/CD infusion developed for 24-hour subcutaneous delivery.

Previously reported data from the Phase III BouNDless study showed that treatment with an optimized ND0612 regimen provided an additional 1.72 hours of "on" time without troublesome dyskinesia compared with immediate-release oral CD/LD.

- The new subgroup analysis showed a reasonably homogeneous treatment effect (ND0612 vs. oral LD/CD) for "on" time across the different subgroups (age, sex, BMI, region, baseline "on" time, and levodopa dose requirements prior to ND0612 initiation).
- Treatment effects were slightly higher for those with lower BMI, those in the US, those with higher baseline "on" scores, and those who took a levodopa dose prior to ND0612 initiation of >2,000mg.

There were also no notable differences between subgroups regarding rate of adverse events, although a lower BMI did appear to increase the TEAE rate in the ND0612 arm.


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## Supernus Industry Update: Increasing GOOD ON Time While Reducing Dyskinesia and OFF Time in Parkinson's Disease

Robert Hauser, MD (University of South Florida)

Stuart Isaacson, MD (Institute for Neurodegenerative Diseases Florida)

*In this industry session, the speakers described "off" episodes (where levodopa treatment is not working) and dyskinesia (twisting and turning) in PD patients.*

Patients often do not recognize or report these symptoms, with many confusing dyskinesia with tremor or believing "off" episodes are just a part of the disease unamenable to treatment. It is, therefore, important to educate patients and ask the right questions. Some will need to keep a diary to keep track of symptoms. The Hauser diary, which Dr. Hauser developed in the early 2000s, is still used in clinical trials today.

As PD progresses, the response to levodopa becomes less predictable (but not less effective). Adjunctive medication may be added to prolong the duration of "on" time (where treatment is working) by reducing "off" time. Consistent and predictable "on" time may not be achievable through dopaminergic medication alone, however.

Gocovri (extended-release amantadine) is the only FDA-approved treatment for dyskinesia. Gocovri differs from dopaminergic treatments by reducing excessive glutamatergic activity, which appears to benefit both dyskinesia and "off" time, as opposed to just "off" time. "On" time is, therefore, increased by widening the therapeutic window. In the Phase III EASE LID and EASE LID 3 trials, which assessed Gocovri in PD patients, "on" time was increased by 2.7 hours and 1.9 hours, respectively.

## Prodromal Symptoms in Parkinson's Disease: RBD

Joyce K. Lee-Iannotti, MD (Banner University Medical Center)

*A discussion of the evaluation and management of prodromal symptoms of Parkinson's disease and treatment for the spectrum of autonomic dysfunction in Parkinson's disease*

Prodromal PD refers to the stage at which individuals do not fulfill diagnostic criteria for PD. Understanding prodromal PD is important as it represents an opportunity for early recognition of incipient PD, and therefore could allow for the initiation of potential neuroprotective therapies at a stage when therapies might be the most effective.

Prodromal markers of PD include hyposmia, constipation, mood changes, and REM sleep behavior disorder (RBD). This speaker specialized in RBD and explained that treatment includes educating the patient and bed partner about environmental safety, which often involves removing dangerous objects in the room, placing the mattress on the floor, using bed rails, or sleeping alone.

As described by Howell et al. (2023), recommended pharmacological options for RBD include clonazepam, immediate-release melatonin, pramipexole, and rivastigmine. The speaker noted that less is more in terms of dosing these medications.


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## The Spectrum of Autonomic Dysfunction in PD

Yi-Han Lin, MD (University of Washington)

*Orthostatic hypotension and gastrointestinal involvement are components of nonmotor dysfunction that can occur in PD patients.*

Autonomic dysfunction is associated with cognitive and neuropsychiatric impairment in patients with Lewy body-related disorders.

Dr. Lin particularly focused on orthostatic hypotension (OH), which is estimated to be present in 10–50% of PD patients, and gastrointestinal (GI) dysfunction, which affects 60–80% of PD patients. Other aspects of autonomic dysfunction described included sexual dysfunction, urinary dysfunction, and difficulties with thermoregulation.

Prevalence of OH increases with age and disease duration. Regarding pharmacological treatment, midodrine and droxidopa, which promote vasoconstriction, are both FDA-approved for symptomatic OH. Although not FDA-approved in this indication, fludrocortisone, atomoxetine, and pyridostigmine are sometimes used to treat OH. There are no head-to-head trials comparing medications for OH, so an individualized approach is used, based on pre-existing co-morbidity. One limitation of treating OH is that medications can cause supine hypertension (evident in about 34–46% of PD patients). Additionally, if a patient is taking CD/LD for motor symptoms in PD, this can lead to worsening of OH.

In terms of dysfunction in the upper GI system, sialorrhea (most likely associated with impaired swallowing function) is common in PD patients, as well as dysphagia (prevalence as high as 85%) and gastric emptying (70–100% of PD patients). Dysphagia is further complicated by bradykinesia and reduced motor control of the tongue. Off-label treatments of sialorrhea include glycopyrrolate, sublingual atropine, atropine swish and spit, clonidine, and modafinil. Botox injection has been approved for sialorrhea treatment, although this is less convenient for patients. There are very limited medications for dysphagia and gastric dysmotility. Metoclopramide is contraindicated in PD, and domperidone is not available in the US due to cardiac risk.

Regarding the lower GI system, constipation is reported in 80–90% of PD patients. Most physicians will approach treatment how they would for patients with constipation without PD, which includes recommending oral bulking agents such as psyllium, probiotic and prebiotic fibers, and adequate hydration. Macrogol and lubiprostone are considered “likely efficacious,” while prucalopride and linaclotide have promising results, although the amount of data specific to PD patients is still very limited.


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## Neuropsychiatric Manifestations of Parkinson's Disease

Holly Shill, MD (Barrow Neurological Institute)

*Dr. Shill described treatment success with different options to address neuropsychiatric manifestations of PD.*

Neuropsychiatric manifestations of PD include anxiety, psychosis, impulse control disorders, delusions, dementia, and apathy.

- There are little data available for anxiety treatment in PD, but SSRIs are often used.
- Benzodiazepines can be used, but these are susceptible to cognitive side effects, fall risk, and sedation, and should not be used chronically.
- Anticholinergics, amantadine, and dopamine agonists can cause psychosis and are stopped if triggering psychotic episodes in a PD patient.
- Neuroleptics, most atypical antipsychotics, and valproic acid should be avoided when treating PD psychosis.
- Seroquel (quetiapine) is sometimes used (efficacy data are limited), as well as clozapine (although this requires weekly blood monitoring).
- Nuplazid (pimavanserin) is the only FDA-approved treatment for PD psychosis.

Dr. Shill explained the differences between PD dementia (PDD) and Alzheimer's disease (AD).

- Dementia patients tend to have better long-term memory and language than AD patients, but worse executive dysfunction and visual spatial skills.
- PDD and AD patients normally have comparable short-term memory.

Cognitive decline in PD remains disabling and difficult to treat.

- Rivastigmine, a cholinesterase inhibitor, is FDA-approved for PDD.
- Donepezil is also likely effective, although there is insufficient evidence.
- Dr. Shill noted that she has found that the rivastigmine patch is better than the rivastigmine pill, and additionally stated that the donepezil pill is better tolerated than the rivastigmine pill.
- Memantine may also be effective for PDD, although there are limited data.

Apathy (likely due to executive dysfunction) is difficult to treat, and more research is required.

- Cholinesterase inhibitors and dopamine agonists should be considered for apathy, but additional treatment options are needed.


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## Diagnosing Parkinson's Disease: How to Diagnose PD Like a Movement Specialist

Vicki Shanker, MD (Mount Sinai)

*Dr. Shanker discussed various case studies in PD and future directions for diagnosis.*

This presentation ran through several patient case studies to inform participants how to perform a movement exam to assess PD, how to apply current clinical diagnostic criteria to make a PD diagnosis, and when additional testing should be warranted.

She ended with an interesting topic on the future of PD diagnosis. New horizons include:

- Imaging for identifying select and direct radiotracers to misfolded α-synuclein protein. Neuroimaging beyond the striatum (measuring nigral dopaminergic neurons) should allow for earlier diagnosis.
- New screening methods, including CSF and skin biopsies for PD diagnosis. The α-synuclein seed amplification assay can now be used to detect misfolded aggregates in the CSF. In a paper by Concha Marambio et al. (2023), in patients who had CSF drawn at their initial assessment and were followed for 10 years, the assays had 94.6% sensitivity and 97% specificity in diagnosis (98% accuracy for synucleinopathies).

Skin biopsies can detect α-synuclein deposition in cutaneous autonomic nerves. A recent study looked at patients diagnosed with PD, multiple system atrophy (MSA), or Lewy body disease, and found that a very high rate of these patients had phosphorylated α-synuclein in their skin biopsies: 92.7%, 98.2%, and 96%, respectively. The study concluded that it needs to be understood how this could help earlier PD populations. Skin biopsies may distinguish PD from MSA, but may not distinguish PD from Lewy body disease.

A further understanding of non-White populations is needed. Dahodwala et al. (2009) found that African Americans were half as likely to be diagnosed with PD compared to Caucasian Americans. In a 2011 study by Dahodwala et al., African Americans presented to clinic at a later PD stage than White Americans. In a study by Baldwin et al. (2024), Black patients were less than half as likely as White patients to have genetic evaluation.

## Managing Motor Symptoms in PD

Jeffrey Ratliff, MD (Thomas Jefferson University)

*Dr. Ratliff explained how pharmacologic therapy for a PD patient should be initiated upon motor features becoming bothersome or disabling to the patient (considering current treatments are not disease-modifying).*

According to AAN guidelines, the recommended initial treatment for motor features is levodopa.

- Levodopa is more effective than dopamine agonists at improving motor symptoms and generally better tolerated; however, the risk of dyskinesia is higher in patients treated with levodopa.
- Dopamine agonists should be avoided in high-risk groups, which includes those over 70 years old and those with cognitive impairment, excessive daytime sleepiness, or hallucinations/psychosis.

For patients who consequently suffer from "off" episodes, the speaker notes that their medication formulation or scheduling can be adjusted, adjunctive therapies (dopamine agonists, COMT inhibitors, MAO-B inhibitors, or adenosine antagonists) can be added, or on-demand therapies such as subcutaneous apomorphine or inhaled levodopa can be tried. Data comparing these medications for "off" episodes are lacking.


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## A Drosophila Model for the Identification of Novel Glial-Based Therapeutic Targets from Parkinson's Disease

Abby Olsen, MD (Pittsburgh Institute for Neurodegenerative Diseases)

*A drosophila model supports glial adenosine as a novel therapeutic target in PD.*

Dr. Olsen's team believe that glia have been overlooked as possible therapeutic targets in PD. In a drosophila (fruit fly) model, human wild-type α-synuclein is expressed in neurons. Flies develop robust pathology within seven days of adulthood, including a loss of dopaminergic neurons, aggregation of α-synuclein, and motor dysfunction. Any gene of interest can be independently knocked down in glial cells.

In this study, investigators performed a large genetic screen and knocked down the entire Drosophila kinome (360 kinases) in the glia. Alpha-synuclein flies had impaired locomotion compared to the control flies. Additionally, purine metabolism gene expression is dysregulated in PD and in the α-synuclein flies. Most of the genes in the screen are involved specifically in adenosine metabolism. The knockdown of these genes is predicted to increase adenosine. Therefore, the investigators hypothesized that increasing glial adenosine should be neuroprotective.

They measured adenosine after the knockdown of five different genes identified in the screen and observed an increase in adenosine, as well as a rescue of neurodegeneration. These results were confirmed with a second RNAi line. Adenosine is relevant to PD in at least two ways. Secreted adenosine signals through both excitatory and inhibitory adenosine receptors, suggesting adenosine can have multiple, simultaneous, or even opposing effects in the brain. Adenosine is metabolized to urate, which has been shown to be low in PD patients and protective in animal models.

Unfortunately, the Phase III SURE-PD3 clinical trial in which participants were given inosine in order to increase their urate levels failed to slow progression in PD. The speaker explained that understanding how the adenosine pathway works is essential to future trial design, particularly whether it is adenosine that is neuroprotective or urate. The investigators consequently knocked down every gene in glia that is involved in the metabolism of adenosine down to urate. They found that the knockdown of adenosine deaminases reduces locomotion, whereas knockdown of downstream genes does not, suggesting that it is adenosine itself that is responsible for neuroprotection.

Research is ongoing regarding the best way to target adenosine metabolism. The main regulators of adenosine levels are adenosine kinases. Previous attempts to target adenosine metabolism have been met with on-target toxicity. The speaker's research group became interested in targeting a gene called Ak1, which they hypothesize is a backdoor into the adenosine metabolism pathway as it is increased in the brain and CSF of PD patients. Mice with a knocked down Ak1 gene are viable and fertile, with only mild stress-induced phenotypes, suggesting this gene could be a good therapeutic target. The investigators undertook confirmatory experiments using the fly model which showed that glial Ak1 knockdown rescues neuronal α-synuclein toxicity. They also showed that glial Ak1 knockdown rescues purine metabolite dysregulation in the α-synuclein flies.

Overall, adenosine itself may not be the best biomarker of dysfunctional adenosine metabolism. Xanthine, urate, and their derivatives are more promising in terms of pattern of change and absolute levels. In collaboration with Dr. Clemens Scherzer of the Yale Harvard Biomarkers study, Dr. Olsen's research group undertook a CSF metabolomic study in patients (both PD patients and healthy controls) and found that both xanthine and urate are potential biomarkers of dysfunctional adenosine metabolism in patients with PD.


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# Atypical Parkinsonian Syndromes

## What is Atypical Parkinsonism?

Horacio Kaufmann, MD (New York University)

*Dr. Kaufmann discussed clinical features of MSA and treatment.*

Not all patients with parkinsonism (bradykinesia, rigidity, resting tremor, and impaired postural reflexes) have PD, and not all parkinsonisms are synucleinopathies. Atypical parkinsonisms include MSA, progressive supranuclear palsy (PSP), and dementia with Lewy bodies (DLB). These diseases worsen more rapidly and have shorter survival than PD.

MSA is a rapidly progressive neurodegenerative disease involving clinical presentation of autonomic failure, parkinsonism, or cerebellar ataxia, in any combination. For patients with MSA-P, the predominant motor symptoms at onset are related to parkinsonism, while those with MSA-C show motor symptoms related to cerebellar syndrome.

MSA pathology includes glial cytoplasmatic inclusions containing α-synuclein, and neuronal loss in the striatonigral and olivopontocerebellar systems. Approximately 25% of MSA cases are misdiagnosed by a general neurologist. Supportive clinical non-motor features for established and probable MSA include stridor, inspiratory sighs, cold, discolored extremities, pathological laughter or crying, and erectile dysfunction (in men younger than 60 years). Supportive clinical motor features include rapid progression (within three years of motor onset), orofacial dystonia exacerbated by levodopa, unexplained Babinski sign, postural deformities, and jerky, irregular, myoclonic tremor.


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## Update in Atypical Parkinsonian Syndromes: Multiple System Atrophy (MSA), Progressive Supranuclear Palsy (PSP), and Corticobasal Degeneration (CBD)

Claire Henchcliffe, MD (University of California)

*Dr. Henchcliffe discussed the differential diagnosis and treatment of MSA, PSP, and corticobasal degeneration.*

The clinical diagnosis of MSA is challenging (autopsy studies are 62–79% accurate) and delayed (average 3.8 years). Sometimes, the diagnosis is not established until neuropathological studies are undertaken.

Prodromal MSA patients do not respond to levodopa or other dopaminergic medications. A patient is more likely to phenoconvert from isolated autonomic failure to MSA over PD or DLB if they have an early onset of orthostatic hypotension (mainly in their 50s) or preserved olfactory function. Patients who phenoconvert to PD or DLB tend to have a later onset of orthostatic hypotension (mid- to late-60s) and impaired olfactory function (combined with probable RBD).

When tested in the same cell lines, MSA versus PD patient α-synuclein strains display differing abilities to seed. MSA strains extract via insoluble and soluble fractions, and PD strains extract only via insoluble fractions.

The presence of exosomal α-synuclein distinguishes PD from PSP or CBD. Sometimes, patients with anti-IgLON5 disease closely resemble PSP patients; however, anti-IgLON5 patients are differentiated by sleep abnormalities.

Patients with PSP and CBD generally do not respond well to levodopa, although this is often the first line of care for motor parkinsonism in these diseases. Ancillary dopaminergic medications, such as dopamine receptor agonists and MOAB inhibitors, are unnecessary and should generally be avoided. The speaker did, however, mention that, due to the lack of medications available, these drugs are often tried. Non-dopaminergics and pure anticholinergics are also not recommended.

For gut dysfunction in PSP and CBD, treatment with amantadine and coenzyme Q-10 is recommended.


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## Imaging Biomarkers of Disease Progression in MSA

Prashanthi Vemuri, PhD (Mayo Clinic)

*MSA results in structural abnormalities on MRI imaging, and Dr. Vemuri differentiated MSA-C (predominant cerebellar ataxia subtype) and MSA-P (predominant parkinsonism subtype).*

The speaker described a recent study that her team undertook, comparing the brains of MSA-P and MSA-C patients compared to controls and PD patients. Cerebellar white matter volume was significantly decreased in MSA patients, with MSA-P patients showing earlier signs of cerebellar white matter volume reduction compared to MSA-C patients.

The speaker also brought attention to another study, which showed for the first time that the rate of decrease in the diameter of the pons and middle cerebellar peduncles in MSA-C is uniquely rapid, faster than in any other ataxia or neurological disease. The investigators, therefore, suggest this measure as a simple and powerful imaging biomarker for the diagnosis and progression of MSA-C.

Additionally, annual changes in plasma neurofilament light and whole brain volume in brain MRIs correlated best with the changes in Unified Multiple System Atrophy Rating Scale (UMSARS) scores (often used in clinical trials), and provided higher standardized effect sizes than the UMSARS, suggesting that these biomarkers have clinical relevance to track disease progression.

New methods and measures for tracking disease progression include diffusion MRI, which has shown better separation between control, MSA-P, and MSA-C in terms of cerebellum white matter volume changes compared to structural MRI. Quantitative susceptibility mapping is also being investigated for assessing iron deposition in atypical parkinsonisms, but these methods need further validation.

## A Phase 2 Study of ATH434, a Novel Inhibitor of α-Synuclein Aggregation, for the Treatment of Multiple System Atrophy

Poster (sponsored by Alterity Therapeutics)

*A description of baseline fluid biomarker, neuroimaging, and clinical data of an early MSA population enrolled in a Phase II trial.*

ATH434 is a moderate affinity iron chaperone that inhibits α-synuclein aggregation and reduces oxidative stress by redistributing excess labile iron for cellular export or sequestration. It is potentially disease-modifying.

ATH434-201 is a randomized, double-blind, placebo-controlled Phase II study in ambulatory MSA patients.

In this study, MSA patients with <4 years of motor symptoms had elevated plasma neurofilament light levels at baseline, which correlated significantly with disease severity.

Patients with clinically probable MSA had increased iron in multiple subcortical regions, with elevations most frequently observed in the substantia nigra.

The specificity of diagnosing clinically probable MSA may be increased with biomarkers such as elevated iron on MRI/quantitative susceptibility mapping or elevated plasma neurofilament light levels.


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# Tics/Tourette Syndrome

## Management of Tourette Syndrome

Irene A. C. Malaty, MD (University of Florida)

*Dr. Malaty discussed different treatment options that are currently available and upcoming for Tourette syndrome.*

Co-morbidities in Tourette syndrome (TS) patients include ADHD (60–70%), OCD (50%), anxiety (20–30%), mood disorders (20–30%), and learning difficulties (20–30%). Only 12% of patients have no co-morbidities. When it comes to treating TS, physicians decide which symptoms are most disruptive and start there. The speaker emphasized that it is important to give interventions an adequate therapeutic trial as they often take time to work. Comprehensive behavioral intervention for tics (CBIT) is the most common behavioral treatment for TS. This aims to disrupt the urge-tic-relief cycle to let the tics dissipate. Eight sessions of 60–90 minutes are required over 10 weeks.

In terms of pharmacological treatment, alpha-2 adrenergic receptor agonists are frequently used for mild tics or tics with co-morbid ADHD, although these are off-label. Clonidine (Kapvay, Catapres) and guanfacine (Tenex, Intuniv) are normally first line, not because they are the most efficacious, but because they are well tolerated and pose few long-term risks. Stimulants used for ADHD, such as methylphenidate, can exacerbate tics in the short term, but can be helpful in the long term. The most effective class of medication is neuroleptics (antipsychotics). Only haloperidol (Haldol) and pimozide (Orap) are FDA-approved for TS in adult and pediatric populations, while aripiprazole (Abilify) is approved for pediatric patients only. The side effects of neuroleptics include somnolence, weight gain, metabolic syndrome, akathisia, and acute dystonic syndrome. A side effect of tardive or withdrawal dyskinesia is rare, although not unheard of.

Topiramate (Topamax, Trokendi XR, Qudexy XR) can also be used. The speaker stated that she finds topiramate useful for patients who are obese (with whom she would worry about the metabolic side effects of neuroleptics) and for other patients who are worried about, or have experienced, the side effects of neuroleptics. Dopamine depleters, such as tetrabenazine (Xenazine), which is FDA-approved for Huntington's disease, cause less weight gain but are very hard to prescribe to TS patients as they are off-label and expensive. Newer dopamine depleters valbenazine (Ingrezza) and deutetrabenazine (Austedo) failed to meet the primary endpoints in clinical trials for TS but are used in a small subset of patients. GABA receptor agonists, for example clonazepam (Klonopin) and baclofen, are also considered for a small subset of patients, particularly those who are in crisis with extreme tics that cannot be controlled. The evidence for Botulinum toxin (botox) to treat TS is limited but its use is common.

The speaker also drew attention to a recent Phase II double-blind crossover study (Clinical Trials Registry number: ACTRN12618000545268), which assessed tetrahydrocannabinol and cannabidiol versus placebo in 22 TS patients. Yale Global Tic Severity Scale (YGTSS) scores improved by 8.9 (±7.6) in the treatment group and 2.5 (±8.5) in the placebo group. Cognitive difficulties, including slowed mentation, memory lapses, and poor concentration, occurred in eight patients. The impact of cannabinoids on the developing brain is unclear. The speaker mentioned that her colleagues in Germany, who have full access to prescribing this treatment, have had good results. There are investigations ongoing for the use of Chinese medical herbs and acupuncture, oral splints, median nerve stimulation, and non-invasive brain stimulation.


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## Effect of Ecopipam, a Selective Dopamine-1 Receptor Antagonist, on Tic Characteristics as Assessed by YGTSS: Results from the Phase 2b (D1AMOND) Randomized, Double-Blind, Placebo-Controlled Clinical Trial in Tourette Syndrome

Donald L. Gilbert, MD, MS (Cincinnati Children's Hospital)

*Ecopipam treatment for 12 weeks significantly improved motor tic characteristics in four of the five dimensions versus placebo.*

Ecopipam, a first-in-class D1 receptor antagonist, significantly reduced tics compared with placebo in the Phase IIb D1AMOND trial in 149 children and adolescents with TS.

Whether features of tics are more or less responsive to treatment is unknown. This presentation compared the effects of ecopipam treatment on individual motor and phonic tic domains that comprise the YGTSS Total Tic Score (YGTSS-TTS), which included number, frequency, intensity, complexity, and interference.

For motor tics, the largest reductions were in intensity scores, followed by number, frequency, and interference (all statistically significant). Complexity scores were not statistically significant.

For phonic tics, there was a statistically significant reduction in complexity scores, but all other subscores fell short of statistical significance.

The investigators also presented the data in a different way, which involved rating all the YGTSS-TTS scores before and after treatment on a scale of 0–5 (with 3–5 being "bad," and 0–2 being "good"). The largest difference between ecopipam treatment and placebo was observed in the motor tics' number domain (54% of ecopipam patients went from "bad" to "good," compared to 23% of placebo patients). The smallest difference was observed in the phonic tics' intensity domain, with 47% of ecopipam patients going from "bad" to "good," compared to 41% of placebo patients. Overall changes from "bad" to "good" scores were less common, but this may be a feature of YGTSS anchor points.

A Phase III trial (ClinicalTrials.gov identifier: NCT05615220) is ongoing.


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# Other Topics

## Neurology Today Panel Discussion: Best Advances in Neurology Research

Stephen Krieger, MD (Mount Sinai)

Dianna Quan, MD (University of Colorado)

Micheal Rubin, MD (Peter O'Donald Brain Institute)

*Panelists discussed recent and upcoming advances in neurology as covered in the publication Neurology Today, with specialists representing ethics and neurocritical care (Dr. Rubin), neuromuscular disorders (Dr. Quan), and MS (Dr. Krieger).*

What were the most exciting advances in your field last year?

- Dr. Krieger stated that a paper published in Nature looking at genetic predictors of disease severity was a highlight for him. Researchers found that the genetics of severity in MS were not immunological, but instead related to resilience genes, CNS adaptation, and educational attainment. Maximal brain function (coded for genetically) seemed to mitigate the risk of MS progression. The genetics of MS severity are unlike the genetics of MS causality, which are mostly immunological factors. If genetic testing becomes available and accessible to prognosticate MS, this should help with accurate diagnosis and effective treatment strategies.
- Dr. Quan believes that a recombinant adeno-associated viral vector delivering a transgene that codes for microdystrophin is a cutting-edge development. Investigators assessed a cohort of 20 boys with Duchenne muscular dystrophy (DMD) who were involved in a larger, longer-running study. The boys were given a one-time infusion of this viral vector that resulted in an increase in the amount of microdystrophin identified after just three months. One-year outcome data using the North Star Ambulatory Assessment showed that the boys had improved walking compared to external controls. The speaker stated that while the data are not overly impressive, the videos of the boys show dramatic improvements, particularly considering the natural history of DMD. She also stated that a therapy such as this is not necessarily mutation-specific, as opposed to oligonucleotide therapies that are very specific for particular mutations.
- Dr. Rubin said he is excited about the multi-society practice parameter on brain death determination. He stated that the document is very useful, with detailed guideline recommendations, focusing on the clinical biology of brain death.

What are you most excited about in your field for the next year or two?

- In MS, there are half a dozen new medicines in trials for MS that are all variations of BTK inhibitors. Dr. Krieger stated that it is rare for there to be so many Phase III trials of drugs with the same mechanism of action happening simultaneously. In 2024, we will get a real sense of whether this modality has the potential to work. When asked why no relapsing MS trials are versus placebo, he stated that it is partly as it is no longer sufficient for drugs to simply be superior to placebo, and partly due to ethical and recruitment issues.
- In neuromuscular disease, there are several gene therapies on the horizon, which use a lot of different mechanisms (CRISPR, adeno-associated viral vectors, oligonucleotides, RNA silencing), and which are now being studied in more complex diseases like ALS. There is currently an


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explosion of interest around immunology in myasthenia gravis, which is very similar to the buzz around MS 10 years ago.

- Dr. Rubin stated that he is excited about the integration of neuroethics into translational research. It is now a requirement in certain NIH funding to have an ethicist as part of the team, adding to the robustness of research planning.
- Brain-computer interface research could become the next big thing in 10 years' time, which has the potential to help people to overcome challenges involved with neurologic disease. There could also be advancements in neurorehabilitation, including exoskeletons, prosthetics, and other neurorehabilitation devices that can do what we only see in sci-fi currently. In some ways, it is an innovation-technology race to see if the biology can be fixed first or if we will work around it with external technology.

How might AI change the way you practice?

- AI could allow us to see patterns that we simply cannot see ourselves. AI could also help with EMG, by enhancing our ability to take something subjective and qualitative and make it more quantitative and uniform. It has the same potential in ultrasound and MRI, where it can look for patterns not visible to the naked eye.
- In the critical care world, AI could help differentiate a patient who potentially needs a decompressive craniectomy who could pull through with medications, and who will need surgery.


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## Gene Transfer Therapy in Neuromuscular Disorders: Is it Safe?

Julie A. Parsons, MD (University of Colorado)

*Dr. Parsons discussed the current landscape of gene transfer therapy, focusing on the different stages of development and the high costs associated with these novel therapies. She also highlighted the factors that contribute to adverse events, especially immune responses. Additionally, she touched upon the importance of anticipating and managing adverse events when using these treatments. The information provided will help gain a better understanding of gene transfer therapy and its potential risks and benefits.*

Gene transfer therapy relies on key components, including a transgene that has been optimized for codon and/or CpG, a promoter that determines tissue specificity and/or expression, and a vector typically delivered by adeno-associated virus (AAV). AAV vectors offer various serotypes that enable tissue-specific expression for a small payload, usually around 4.7 kb.

Adverse events in gene transfer therapy can be influenced by multiple factors, including capsid characteristics (total vector genome dose, ratio of filled to empty capsids), route of administration (intravenous, intrathecal, or intraventricular), and transgene properties (genotype and host susceptibility). These events are associated with the immune response, specifically the initial innate immune response (such as complement and macrophage activation) towards the capsid in the first week, followed by a subsequent adaptive immune response (B- and T-cell activation).

During the first week following gene therapy, pediatric patients may commonly experience nausea and vomiting, typically occurring three to five days after the infusion. These symptoms can indicate the possibility of heart failure, which carries a risk of dehydration. While a mild increase in troponin-I levels is often observed, there is a potential for myocardial injury or myocarditis. Patients with a higher risk of cardiomyopathy are more likely to experience a rapid progression of heart failure, as exemplified by two reported deaths in gene transfer studies for DMD. Additionally, there is a potential for thrombotic microangiopathy, necessitating close monitoring of clinical signs such as hemolysis, thrombocytopenia, and low urine output.

Monitoring laboratory results is crucial to detect acute liver injury, which typically occurs four to six weeks after injection in gene therapy. Key indicators to monitor include AST/ALT, GGT, bilirubin, PT/PTT, and INR. It is worth noting that gene therapy for spinal muscular atrophy (SMA) and X-linked myotubular myopathy has reported cases of death, and an FDA briefing document revealed that 37% of patients treated with delandistrogene experienced acute liver injury.

<u>Onasemnogene abeparvovec (Zolgensma) for treating SMA</u>

- Zolgensma has received FDA approval for the treatment of SMA. Adverse events observed in clinical experiences are summarized in the table below. Thrombotic microangiopathy, which is a response to capsid proteins mediated by complement, typically occurs within the first week following gene transfer. Patients may exhibit symptoms such as thrombocytopenia, hemolysis, decreased renal function, and renal failure. If left untreated, this condition can lead to a high mortality rate. Proactive treatment measures include the administration of increased steroids, fluids, eculizumab, plasmapheresis, and dialysis.


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| Source | Clinical experience | RESTORE Registry (Servais et al., 2024) | Clinical experience in the UK (Gowda et al., 2023) |
|---|---|---|---|
| **Adverse events** | Fever, emesis, diarrhea within the first seven days.<br>Thrombocytopenia within the first 1–3 weeks.<br>Elevated transaminases and liver injury in 4–8 weeks.<br>Thrombotic microangiopathy in 1–2 weeks. | Hepatotoxicity (29%)<br>Transient thrombocytopenia (13.8%)<br>Cardiac adverse events (13.2%)<br>Thrombotic microangiopathy (0.6%) | Transaminitis (87.9%)<br>Thrombocytopenia (71.7%)<br>Troponin-I elevation (33.7%)<br>No thrombotic microangiopathy case |

- The unexpected occurrence of necrotizing enterocolitis, typically observed in preterm infants, has been reported in three pediatric patients receiving onasemnogene abeparvovec. In addition, concerns have arisen regarding potential adverse events associated with onasemnogene abeparvovec including toxic gain of function resulting from AAV9-mediated overexpression of the SMN gene in the sensorimotor circuit. Other potential adverse effects include sensory axonal polyneuropathy and the formation of spinal cord epithelioid tumors, hypothesized to be caused by integration of AAV vector DNA into the genome.

Duchenne muscular dystrophy (DMD)

- Immune-mediated myositis, characterized by a T cell-mediated immune response to the transgene, was observed four to six weeks after infusion. This adverse event was reported in five cases from three different trials, with patients experiencing severe proximal and distal weakness resulting in loss of ambulation, as well as bulbar weakness and respiratory insufficiency. Bonnemann et al. (2023) have identified exon 8–11 of the dystrophin gene as a potential common cause for these adverse events.

X-linked myotubular myopathy

- X-linked myotubular myopathy is a severe congenital disorder characterized by profound weakness. Unfortunately, most patients with this condition experience respiratory failure and do not survive beyond one year of age. As a result, these patients require a tracheostomy for breathing and a gastrostomy tube for feeding. Additionally, there have been reports of hepatic peliosis in some affected individuals.
- Audentes Therapeutics has made significant progress in gene transfer therapy utilizing MTM1 in an AAV8 vector construct. This treatment has yielded impressive outcomes, with 16 out of 24 patients successfully weaning off ventilators, and eight patients regaining the ability to walk. However, four patients died from unrecognized hepatobiliary disease prior to treatment.
- In summary, gene therapy is safe like chemotherapy is safe, as stated by Dr. Russ Butterfield. Physicians must remain vigilant, closely monitor patients, and be prepared to anticipate and address any potential adverse events with emergency plans in place. To optimize patient care while minimizing safety concerns, it is crucial to establish an infrastructure that coordinates specialists and implements a comprehensive management plan. By learning from the experiences of others, we can enhance our understanding of the timeline of adverse events, treatment approaches, and outcomes.


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## Introduction to Hematopoietic Stem Cell Transplantation (HSCT) for Neurological Diseases

Richard Nash, MD (Colorado Blood Cancer Institute)

*Dr. Nash discussed the benefits of autologous HCT, but acknowledged its limited efficacy in underserved individuals with PPMS, suggesting allogeneic HCT and CD19 CAR-T cell therapy as potential solutions.*

- Autologous HCT has shown effectiveness in treating MS and potentially other autoimmune neurological diseases. Studies have demonstrated that patients with scleroderma who received autologous HCT had better overall survival rates compared to those receiving high-dose immunochemotherapy. Immunochemotherapy showed a 53% survival rate after 11 years of follow-up, while autologous HCT showed an 88% survival rate. Patients undergoing myeloablative HCT had lower rates of transplant-related mortality and were less likely to require post-transplant initiation of disease-modifying antirheumatic drugs (DMARDs) compared to nonmyeloablative HCT.
- Following autologous HCT, immune reconstitution occurs, including the regeneration of naive B and T cells, thymic reactivation, the emergence of a more diverse T-cell receptor repertoire, and the restoration of regulatory T cells (Tregs) and B regulatory cells.
- Although autologous HCT has shown improved survival rates, patients with PPMS did not experience any benefits as recurrent disease was observed in all cases within five years post transplantation. Allogeneic HCT, which replaces autoreactive immune cells with healthy donor immune cells, may offer potential benefits. Allogeneic stem cell grafts may suppress host immune cells and activate regulatory immune mechanisms. This approach is now associated with lower treatment-related mortality and a reduced risk of graft-versus-host disease.
- Preliminary studies have shown promising results for CD19-targeted CAR-T cell therapy in rheumatological diseases. This therapy depletes B cells through intrinsic cytotoxicity, targets antigen-expressing B-cell progenitors and plasmablasts, and can traffic to deep tissues. A recent publication from a German group demonstrated the efficacy of CD19 CAR-T cell therapy in treating autoimmune disease patients with heart or kidney involvement who are ineligible for stem cell transplantation. The therapy showed impressive clinical efficacy without neurotoxicity events. A proposed Phase I trial aims to evaluate CD19-targeted CAR-T cell therapy in patients with relapsing/remitting or progressive MS.


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## HSCT Treatment Trials in Neurologic Disorders – A Focus on Multiple Sclerosis and Stiff Person Syndrome

Amanda L. Piquet, MD (University of Colorado)

*Dr. Piquet presented current clinical trial data on HSCT as a treatment for neurologic disorders, highlighting anecdotal benefits but emphasizing the need for larger controlled trials and prospective studies to assess long-term remission and disease progression.*

Multiple Sclerosis (MS)

- RPMS is an immune-mediated, demyelinating disorder of the CNS. While several FDA-approved DMTs are available, some patients do not respond fully, and others experience early aggressive disease.
- Studies of autologous HSCT in MS have consistently demonstrated high efficacy and durable outcomes in RRMS. Recent research has indicated significant improvements in the safety of autologous HSCT, with lower mortality rates.

| MS International Stem Cell Transplant (MIST) Randomized Clinical Trial (Burt et al., 2018) | Autologous HSCT | Disease-modifying therapy |
|---|---|---|
| Mean EDSS change at one year | -1.02 points | 0.67 points |
| Between group difference | -1.7 points (p<0.01) | |
| Patient number with disease progression | Three of 55 patients | 34 of 55 patients |

- A study published in 2023 by Kalincik et al. investigated the comparative effectiveness of autologous HSCT versus high efficacy disease-modifying drugs (fingolimod, natalizumab, and ocrelizumab) in highly active RRMS. The study found that autologous HSCT was considerably superior to fingolimod in preventing relapses and facilitating recovery from disability, and marginally superior to natalizumab. However, no significant difference in effectiveness was observed between autologous HSCT and ocrelizumab within the available shorter follow-up time. Larger randomized clinical trials are needed to determine whether autologous HSCT offers advantages over the most efficacious currently available DMTs. The ongoing BEAT MS clinical trial (ClinicalTrials.gov identifier: NCT04047628) aims to evaluate the best available therapy compared to autologous HSCT, assessing how current treatments compare to transplantation in a randomized controlled trial, with MS relapse-free survival as the primary outcome measure.

Stiff person syndrome (SPS)

- SPS is a rare autoimmune neurological disorder characterized by progressive and episodic muscle spasms and stiffness. Triggers for these symptoms can include noise, touch, or emotional stress. The condition is often associated with high-titer GAD65 antibodies, although, less commonly, glycine receptor, amphiphysin, or DPPX antibodies may also be present.
- Currently, there are no FDA-approved drugs specifically for the treatment of SPS. IVIG is commonly used as a first-line therapy. However, a positive control trial (Dalakas et al., 2001) showed that around one third of patients experienced a loss of IVIG efficacy after three years of treatment.


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Additionally, a placebo-controlled trial found that rituximab did not provide any benefits for SPS patients.

- In small-scale clinical trials, autologous HSCT seemed to benefit patients with mild disease, but those with advanced disease remained underserved.
- It is important to develop appropriate SPS-specific outcome measures that include objective measures for qualifying stiffness, using validated scales. Ultimately, an ideal scenario would involve a randomized trial that includes SPS patients with early disease who are unresponsive to current therapies, weighing potential side effects.

Chronic inflammatory demyelinating polyneuropathy (CIDP)

- CIDP is a chronic autoimmune disorder affecting the peripheral nervous system, leading to progressive or relapsing-remitting sensorimotor neuropathy. Approximately 70–80% of CIDP patients respond to established first-line immunomodulatory treatments such as IVIG, steroids, and plasma exchange. However, within this group, 12–29% eventually become refractory to treatment. As the condition progresses, secondary axonal loss contributes to increased disability.
- While anecdotal studies have suggested improvement in disability with autologous HSCT, research on HSCT in CIDP treatment is limited by trial design and the number of patients studied. A randomized trial is necessary to determine the potential benefits of autologous HSCT and to confirm whether HSCT can reverse disability and provide long-term independence from immune therapy.

Myasthenia gravis (MG)

- MG is an antibody-mediated autoimmune neurological disorder affecting the neuromuscular junction. Approximately 85% of MG patients have autoantibodies against the acetylcholine receptor (AChR), with less common targets including MuSK and LRP4. While most patients respond to current therapies, 10–20% may develop refractory MG, leading to severe disability.
- Anecdotal evidence from case reports suggests complete remission in severe MG patients treated with autologous HSCT. A planned Phase II clinical study aims to establish the effectiveness of HSCT as a therapy for severe refractory MG and to gain further insights into disease pathogenesis.


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## Regenerative Stem Cell Treatments and Complications of Medical Tourism: How Do We Counsel Patients?

Andrew Wolf, MD (University of Colorado)

*Dr. Wolf highlighted patients' motivations to engage in stem cell tourism despite risks, emphasizing the impact of permissive legislation, and urged physicians to promote evidence-based discussions prioritizing safety.*

Stem cell tourism has emerged as a significant aspect of medical tourism, particularly for neurodegenerative diseases, where conventional therapeutics offer limited benefits. While numerous clinics, both domestic and international, offer stem cell treatments, it is important to note that there are currently no FDA-approved regenerative stem cell treatments for neurological disorders.

Regulation of stem cell treatments within the US remains an ongoing issue. Various states, including Texas, Mississippi, and North Carolina, have enacted legislation that allows physicians to administer adult stem cell therapies to patients with severe chronic diseases or terminal illnesses as long as those therapies are already being tested in humans. Additionally, legislation in Utah does not require physician administration of cells nor does it mandate vetting for manufacturing standards, safety, cleanliness, or effectiveness. Consequently, patients may feel compelled to seek out these treatments due to the limitations of conventional therapies.

Due to the lack of safety monitoring and manufacturing oversight, patients undergoing stem cell treatments may experience complications stemming from the procedure or the product itself, which can result in permanent disability or even death. Additionally, the efficacy of these treatments can vary.

Physicians are encouraged to remain open to reviewing treatment options that patients may come across. This approach fosters ongoing dialogue about the scientific and safety aspects of stem cell therapies. When discussing treatment options with patients, it is helpful to provide information about future prospects and limitations of current stem cell therapies, supported by reliable sources such as AboutStemCells.org.


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## CAR-T Therapy: Indications for Use and Clinical Management

Bianca Santomasso, MD (Memorial Sloan Kettering Cancer Center)

*Dr. Santomasso discussed the challenges of managing neurotoxicities, including immune effector cell-associated neurotoxicity syndrome (ICANS), tumor inflammation-associated neurotoxicity (TIAN), and movement and neurocognitive treatment-emergent events (MNTs) in CAR-T therapy, highlighting the potential of the IL-1R inhibitor anakinra in preventing ICANS, and emphasizing the importance of understanding risk factors and effective management to improve patient outcomes.*

Immune effector cell-associated neurotoxicity syndrome (ICANS)

- CAR-T cell therapy has received approval for treating various cancers; however, it is associated with neurotoxicity in a significant number of patients, in the range of 15–65%. Severe neurotoxicity occurs in 3–32% of cases. Cytokine release syndrome (CRS) is a common side effect of CAR-T therapy, occurring typically two to three days after the infusion and characterized by fever, hypotension, capillary leak, and respiratory insufficiency, etc. It can be managed with IL-6R blockade, and tocilizumab is FDA-approved for this purpose. ICANS, on the other hand, occurs 5–10 days after infusion and presents with global encephalopathy, expressive aphasia, tremor, somnolence, seizures, hallucinations, and motor weakness, among other symptoms. It may occur during or after CRS symptoms have gone, and can last for a few hours to several days. Unlike CRS, ICANS does not resolve with IL-6R blockade. Most cases of ICANS are reversible, with symptoms typically subsiding within the first month. Of note, ICANS without CRS is very uncommon (<2%).
- Expressive aphasia and handwriting change are the most characteristic features of severe neurotoxicity. To assess the severity of these symptoms, the immune effector cell-associated encephalopathy (ICE) tool was developed. This tool utilizes a 10-point measurement to evaluate patients' orientation, naming ability, command-following skills, writing, and attention. A lower ICE score indicates more severe symptoms.
- ICANS after CAR-T cell therapy is influenced by both host/tumor factors and therapy-related factors. Host factors include cancer type, tumor burden, pre-existing inflammation or infection, and baseline elevated CRP levels. Notably, patients with CNS lymphoma who received CAR-T therapy did not experience an increase in ICANS events. Additionally, direct intrathecal injection of IL-13Ra or EGFR CAR-T therapy for glioblastoma did not induce ICANS. Therapy-related factors include the lymphodepleting/conditioning method, CAR-T cell dose, CAR-T cell design, and prior severe CRS. For instance, CAR-T with a CD28 costimulatory domain triggers more neurotoxicity compared to those with a 4-1BB domain. Similarly, CD19-directed CAR-T therapy has a higher frequency of neurotoxicity compared to CD22 or BCMA-directed CAR designs. Patients who have experienced severe CRS in the past are more likely to develop severe ICANS. Higher temperature, CRP, and ferritin levels have also been correlated with severe ICANS.
- A preclinical study indicates that IL-1 may serve as a target for mitigating toxicity associated with CAR-T cell therapy. Antagonizing IL-1 with anakinra has shown comparable effectiveness to tocilizumab in protecting against CRS-related mortality and a greater efficacy in treating neurotoxicity. Multiple studies suggest that ICANS is primarily caused by off-target cytokine production that affects the CNS.
- Managing ICANS involves understanding the product and patient risk factors, reducing baseline tumor burden, conducting baseline exams including the ICE tool, and utilizing prophylactic anti-seizure medications, as well as MRI and EEG scans. While tocilizumab does not play a role in managing ICANS, corticosteroids and off-label IL-1 blockade with anakinra can be considered for severe cases.


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- Anakinra, an IL-1 blocker, was tested in a Phase II study involving lymphoma patients receiving CD19 CAR-T cell therapy. The drug was administered either two days after CAR-T infusion or on the same day. The results were positive, with no reported grade 4 ICANS events and only 10% of patients experiencing grade 3 ICANS, which was better than historical control. Approximately 81% of patients did not develop ICANS, and no pulse-dose steroids were administered. Anakinra was detected not only in peripheral blood but also in CSF.

Tumor inflammation-associated neurotoxicity (TIAN)

- CAR-T cell therapy is now being utilized as a treatment for brain tumors and can be administered through intratumoral, intracerebroventricular, and intravenous routes. However, clinicians must be mindful of TIAN, a distinct form of toxicity observed in patients receiving cell therapies for CNS tumors such as glioblastoma and CNS lymphoma. TIAN may occur as a result of CAR cells infiltrating the tumor site to target the tumor, ultimately leading to cerebral edema.

Movement and neurocognitive treatment-emergent events (MNTs)

- Emerging data suggest the occurrence of new manifestations of neurotoxicity with prolonged timelines and atypical features, particularly associated with BCMA CAR-T therapy. In the CARTITUDE-1 study, while 16.5% of patients experienced ICANS, 5% of patients (five out of 97) developed MNTs. The median time to onset for MNTs was 27 days, which differed from the eight-day onset observed for ICANS. These patients exhibited parkinsonism symptoms but were not diagnosed with PD. Despite receiving intensive medical interventions, including chemotherapy, anti-Parkinson drugs, anakinra, and antibiotics, no improvement was observed. Unfortunately, three patients did not recover, and one fatal outcome was reported. These side effects were attributed to a T cell-mediated on-target off-tumor effect due to the expression of BCMA in the basal ganglia. The high level of circulating CAR-T cells in these patients suggests that the absolute lymphocyte count or CD4 T-cell levels may serve as clinical indicators. High-dose cyclophosphamide, which eliminates immune cells, is currently being investigated as a potential treatment option.

In summary, the remarkable clinical efficacy of CAR-T therapy is accompanied by unique and serious toxicities, including ICANS. It is crucial to understand the risk factors, grading, and management of ICANS to improve patient outcomes. Effective management of both common neurotoxicities (ICANS and TIAN) and uncommon neurotoxicities (MNTs) is essential for optimizing patient survival and quality of life. The future holds promise for the rapid development of safer CAR designs for CNS tumors and autoimmune diseases.


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## What Do We Know About the Mechanisms of Action of IVIG in Autoimmune and Neuromuscular Diseases?

Marinos Dalakas, MD (Thomas Jefferson University)

*This presentation, sponsored by Octapharma, aimed to introduce the scientific knowledge and clinical data regarding the use of IVIG in the treatment of dermatomyositis and CIDP. IVIG is an approved treatment for autoimmune neuromuscular disorders, working through various mechanisms to improve symptoms, while pharmacogenomics analysis of IVIG can provide insights into optimal dosing and the impact of genetic variations on treatment outcomes.*

IVIG has been approved for the treatment of various autoimmune neuromuscular disorders (A-NMD) such as Guillain-Barre syndrome, CIDP, multifocal motor neuropathy, and dermatomyositis. The underlying contributors to A-NMD include antibodies of different subclasses (IgG 1–3, IgG4, and IgM), macrophages with reduced expression of FcγRIIB, complement, activated T cells, co-stimulator molecules, and cytokines. IVIG has demonstrated efficacy in improving A-NMD through multiple mechanisms, including the broad neutralization of autoantibodies associated with autoimmune neuropathies, partial saturation of FcRn to enhance IgG catabolism, interception of complement-mediated microangiopathy in dermatomyositis patients leading to immunohistopathological and clinical improvement, downregulation of adhesion molecules and cytokines in muscle biopsies of dermatomyositis patients, and upregulation of inhibitory FcγRIIb receptors on monocytes and B cells to suppress macrophage-mediated inflammation.

In contrast to IgG1 antibodies, IgG4 antibodies do not initiate inflammatory processes or complement-mediated immune responses. Instead, they exert pathogenic effects on targeted antigens by blocking enzymatic activity, disrupting protein-protein interactions, or interfering with signal transduction pathways. IgG4-mediated autoimmune diseases include MuSK-positive MG (but not AChR-positive), CIDP with paranodal antibodies, and CNS and peripheral nervous system disorders associated with LGI1 or CASPR2 (such as Morvan syndrome, neuromyotonia, and pain).

To gain a deeper understanding of the varied responses and optimal dosing of IVIG treatment, the analysis of IVIG pharmacogenomics has been suggested. IVIG has been implicated to directly modulate biologically significant genes in the relevant tissues, and gene polymorphisms may potentially influence these effects. For instance, individuals with heterozygous FcRn VNTR2/3 genotype exhibit impaired FcRn saturation, leading to accelerated degradation of IVIG.


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## Shedding Light on CIDP and Dermatomyositis – A Deep Dive into the Latest Evidence

Hans Katzberg, MD (University of Toronto)

*Dr. Katzberg shared the findings of the ProDERM and ProCID studies, which explored the use of IVIG as a treatment for dermatomyositis and CIDP, respectively.*

IVIG for dermatomyositis

- Dermatomyositis, an inflammatory myopathy characterized by skin manifestations and associated with specific autoantibodies, can now be treated with Octagam 10% following its approval for this condition.
- In the Phase III study ProDERM, the total improvement score (TIS) was measured in dermatomyositis patients receiving monthly IVIG or placebo treatment. While the placebo effect was notable, IVIG demonstrated both statistical and clinical improvement, as evidenced by the key primary endpoints.

| Endpoint | IVIG | Placebo |
|---|---|---|
| Percentage of patients who had an increase of >20 points on TIS at Week 16 From Baseline | 79% | 44% |
| Total improvement score at Week 16 | 48.4 | 21.6 |

In conclusion, after 16 weeks of treatment, a significantly higher number of patients in the IVIG group demonstrated at least minimal improvement compared to the placebo group, regardless of their autoantibody status. The effectiveness of IVIG in treating dermatomyositis and the effects on specific autoantibody subsets are yet to be established. The high placebo rate observed may be attributed to factors such as a low threshold for minimal improvement, background immunosuppression, and subjective endpoint measures.

Chronic inflammatory demyelinating polyneuropathy (CIDP)

- CIDP presents with both proximal and distal symmetric weakness, hyporeflexia to areflexia, and sensory disturbances that gradually develop over a period of eight weeks to several months. Steroids and IVIG are commonly effective treatments for CIDP, and if patients do not respond to these therapies, physicians may reconsider the diagnosis. While nerve conduction studies and nerve biopsies can identify demyelination neuropathy, these analyses are less frequently performed. The Inflammatory Neuropathy Cause and Treatment (INCAT) disability score is often utilized in clinical trials to assess the level of impairment in the arms and legs caused by the disease.
- The ProCID study evaluated various doses of IVIG (Panzyga) for CIDP in an international, multicenter setting. After a loading dose of 2g/kg Panzyga, patients received maintenance doses of 1g/kg or 2g/kg. Selected endpoint results showed that response rates in the 2.0g/kg group did not significantly differ from the 1.0g/kg group, and 56% of patients experienced improved adjusted INCAT scores after the induction dose alone.


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| Endpoint | 2g/kg Panzyga | 1g/kg Panzyga |
|---|---|---|
| Patients with decrease of at least 1 point on the adjusted INCAT disability score at Week 24 | 91.7% | 79.7% |

In summary, the study found that a maintenance dose of 1g/kg IVIG following a 2g/kg induction dose effectively treated active CIDP, including patients previously treated with corticosteroids. Further research is needed to confirm the potential benefits of lower or higher maintenance doses. Limitations of the study include the exclusion of newly diagnosed and untreated CIDP patients, lack of assessment of long-term efficacy, safety, and relapse rates, absence of a placebo control or statistical power to detect dose response, and low rate of deterioration after Week 6 across all dose groups.

## Optimizing Clinical Practice – From Studies to Patient Cases

Mazen Dimachkie, MD (University of Kansas)

*In this presentation, Dr. Dimachkie reviewed the safety profile of IVIG in the ProDERM and ProCID studies.*

Dermatomyositis

- Based on the findings of the ProDERM study, nearly half of the reported adverse events were related to the infusion and occurred either during or within 72 hours of the infusion cycle. The most commonly reported adverse events in the IVIG group were headache (37%), pyrexia (19%), and nausea (12%).
- Notably, dermatomyositis patients have an elevated risk of thromboembolic events (TEEs), which increases with age and is highest within the first year after diagnosis. The occurrence of TEEs is likely due to an inflammation-induced imbalance, with increased procoagulant factors, decreased anticoagulants, and impaired fibrinolysis. By reducing the maximum infusion rate, the incidence of TEEs could be decreased.

Chronic inflammatory demyelinating polyneuropathy (CIDP)

- In the ProCID study, one out of 142 patients experienced a serious adverse event related to IVIG, specifically a serious headache and vomiting, but still completed the study. Common side effects in the standard dose group (1g/kg IVIG) included headache (4.5%), pyrexia (4.5%), and dermatitis (6%), with only headache being dose-dependent. IVIG was generally well tolerated, with no reported hemolysis or thromboembolic events.
- IVIG has shown efficacy and safety in trials and real-life cases. Dosing can be adjusted to improve efficacy with careful monitoring. Infusion rate adjustments can manage adverse events, such as lower TEE incidence after reducing the infusion rate.


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## Social Determinants of Brain Health

Joshua Budhu, MD (Memorial Sloan Kettering Cancer Center)

*The social determinants of health are not necessarily positive or negative; they affect everyone, but in underserved communities, the interplay of these factors can result in severe inequities that lead to measurably worse health outcomes.*

Environmental determinants of health include factors such as pollution, climate change, environmental toxins, and radiation. These are interconnected and span from global to local.

Lead is extremely neurotoxic, leading to cognitive dysfunction, neuropathy, paralysis, headache, and encephalopathy. In children, this can manifest as loss of IQ, aggressiveness, behavioral disruptions, and language delay, and may even have contributed to rising crime rates observed in the second half of the 20$^{th}$ century.

A 2021 study found that living in pre-1950s housing, high poverty, and residing in zip codes that were predominantly Black or Hispanic were all strongly correlated with higher levels of lead in children's blood. Practices like redlining, which pushes racial or ethnic minority families, who may already be struggling with poverty, to live in more undesirable neighborhoods, contributed to this pattern in exposure to toxins. Importantly, these factors combine to negatively impact overall life expectancy in these ethnic and racial groups.

Climate change, including rising temperatures and sea levels, extreme weather, and increasing $CO_2$ levels, can lead to a variety of health issues through impact on water quality, pollution, and general environmental degradation. These factors drive changes in nutrition, infectious disease incidence, allergen presence, forced migration, and even civil conflict. The degree of harm caused by these changes is heavily dependent on social and behavioral context, such as age, gender, race and ethnicity, poverty, education, and access to health infrastructure.

Interestingly, the healthcare sector in the US is responsible for 8.5% of the country's share of greenhouse gas emissions, which has only increased over the past several years. In all, 82% of this contribution is from supply chain emissions related to testing and research, medical supplies, pharmaceuticals, transport, water and energy usage, and more.


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## Political Determinants of Brain Health

Adys Mendizabal, MD (University of California)

*The political determinants of brain health involve the process of distributing resources and power in ways that mutually reinforce one another and shape opportunities to either advance health equity or exacerbate health inequity.*

Brain health begins with general health, so policies that support nutritious food availability, safe housing and community, employment, and access to preventive health services will also support brain health.

The Affordable Care Act, a 2014 act that made insurance plans more affordable, expanded state-sponsored Medicaid, and allowed people to stay on their parents' insurance until age 26. This not only directly improved access to healthcare and medications and reduced out-of-pocket medical spending, but also reduced the racial disparities in the use of emergency room visits for non-emergent or primary care. Indirectly, Black and Hispanic communities, as well as those living in low-income neighborhoods, experienced a reduction in hypertension and diabetes, as well as improved traumatic brain injury outcomes, due to increased access to care.

The US has the highest expenditure on prescription drugs in the world, partially because of the range of measures in place that extend patent and exclusivity protections, keeping drug costs high. Additionally, until the Inflation Reduction Act was passed in 2022, Medicare did not negotiate drug prices, but starting in 2026, the government will negotiate pricing for some drugs in Medicare Part B and Part D. The act also caps out-of-pocket spending for Medicare Part D starting in 2025, limits insulin costs per month, and requires that drug companies rebate to Medicare any increases in price beyond regular inflation.

Less obvious political determinants of brain health include racist and discriminatory legislature and policies that contribute to generational trauma, leading to worse mental health outcomes. For instance, the forced relocation of Indigenous Americans in the 1800s and 1900s has pushed these groups onto reservations, effectively reducing access not only to healthcare and nutritious food, but also cultural heritage. This is directly correlated with higher rates of suicidal ideation and suicide attempts.

Moreover, policies that support housing inequities also result in lower access to quality public education for many oppressed populations. Higher education attainment is associated with lower odds of cognitive impairment, mental health disorders, and insomnia, as well as less severe outcomes in PD and a 21% lower risk of ALS.


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## Neurologic Conditions in Transgender Patients

Gwen Zigler, DO (Albany Medical College)

*Many physicians do not realize the impact that sexual orientation and gender identity have on neurologic health, but like other marginalized groups, transgender individuals and LGBTQIA+ patients as a whole may be at a higher risk for mood disorders, cardiovascular diseases, migraine, and many others.*

A 2019 survey of AAN members found that while the majority of respondents felt comfortable assessing LGBTQIA+ patients, 43% believed that sexual orientation and gender identity had no bearing on neurologic management. A more recent 2023 survey of Italian neurologists revealed that only 2.8% felt they had adequate training and resources for caring for gender diverse patients, despite 86.4% being interested in learning this skill. Both of these results highlight the lack of knowledge and resources available to neurologists regarding neurologic care for the LGBTQIA+ community.

Social determinants of health such as housing, legislative barriers, poverty, and other societal factors create vast inequities in this community, like other marginalized groups.

Gender-affirming healthcare, such as hormone therapy, can increase the risk of cerebrovascular disease and venous thromboembolism in those taking estradiol, while exogenous testosterone may increase blood pressure and reduce high-density lipoprotein cholesterol. Although hormone therapy or surgeries like hysterectomy, oophorectomy, or orchiectomy might put someone at a higher risk for some of these health conditions, it is important to remember that gender-affirming care is lifesaving.

Like many marginalized populations, transgender patients, as well as the LGBTQIA+ community as a whole, are widely underrepresented in clinical trials, and data on sexual orientation and gender identity are rarely collected.


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## Batman & Robin vs. The Riddler: Is ChatGPT a Reliable Sidekick to Neurologists for Diagnosis and Management of Functional Movement Disorders?

Pushpraj Poonia (Government Medical College and Hospital)

*ChatGPT has shown promising use as a clinical decision-making tool in multiple studies, at certain instances even outperforming trainee doctors in licensing exams, and has shown to be accurate in making final diagnosis.*

Functional movement disorders (FMDs) are defined as movement disorders where clinical features such as distractibility suggest voluntary movements, but they are experienced by patients as involuntary.

FMDs pose a major challenge in diagnosis for clinicians. This complexity in diagnosis of FMDs calls for a multidisciplinary approach in complex cases involving physicians and neurologists. Having different specialists might not be possible in the case of remote medical setups, especially in underdeveloped nations, hence the need for a clinical assistant.

In this study, 30 patients diagnosed with functional movement disorders were randomly selected from the neurology clinics. The case summaries of these 30 patients, including patient history, physical examinations, and diagnostic assessments, were presented to ChatGPT-v3.5 in separate chat sessions to remove the bias of ChatGPT. No differential diagnosis or patient identification information was provided to ChatGPT. These case studies were also provided to seven independent neurologists practicing in geographically different areas with various levels of experience.

Two prompts given were: “What is the best adjuvant treatment?” and “What is the treatment regimen to be followed?” The responses generated were converted into sets of 10, and three sets were created. Two of the three sets of 10 were randomly allocated to seven neurologists and they were asked to grade the responses on a scale of 0–10 (10 being complete agreement) on the following parameters:

- diagnosis
- treatment recommendations (adjuvant therapy)
- therapy regimen (complete management suggestions)
- patient’s coordination (functional status assessed by pain, fatigue, gait, weakness, and motion)
- reliability in general of ChatGPT as a clinical assistant (overall concordance with recommendations).

Statistical analysis was performed using R software. Among the patients, 21 (70%) were diagnosed with FMDs, while nine (30%) presented with alternative movement disorders, according to ChatGPT. Neurologists tended to agree with the treatment recommendations provided by ChatGPT, but less so with diagnosis, partly because the treatment algorithms are similar for several movement disorders.

The speaker concluded that ChatGPT still has a long way to go to become a reliable “sidekick” to neurologists to fight FMDs. There were limitations regarding the accurate diagnosis of FMDs, but ChatGPT demonstrated potential in recommending management planning, as assessed by neurologists recruited for the study. While ChatGPT cannot supplant clinical expertise, it may serve as a valuable adjunctive tool within a human-in-the-loop clinical decision-making framework, furnishing supplementary insights for the management of FMD patients.


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## From Mario to Mechs: The Way Video Games Alter Neural Connections

Jose H. Posas, MD (Ochsner Health)

*Video games have been shaping our brains since their inception, both positively and negatively, and will continue to do so in the future.*

Previous studies have shown that playing video games leads to increases in gray matter, changes in brain activity and functional connectivity, and increases in visuospatial processing memory.

Current limitations on our knowledge of the effects of video games include the lack of any long-term studies, with only small studies showing diminishing benefits over time, and lack of control for any proposed long-term studies due to the prevalence of games in many forms, including mobile games.

Future development of video games into augmented and virtual reality can be developed for rehabbing to mimic activities of daily living.

The development of brain-computer interfaces (BCIs) has the potential for motor restoration with myoelectric prosthetics and mitigation of danger by operating machinery remotely in dangerous working environments.

Privacy and ethical issues are a possibility with BCIs, such as invasive advertising and further marginalization of groups due to selective information being fed directly to the brain.

## Generative Artificial Intelligence versus Clinicians: Who Diagnoses Disease Faster and with Greater Accuracy?

Mahi Patel (University of Texas Southwestern Medical Center)

*The use of AI will only increase in prevalence, especially by upcoming generations considered digital natives who tend to be reliant on self-learning and technology.*

AI is already prevalent in our daily lives in areas such as face ID, social media, and search engines. AI will be used by patients for medical purposes.

Gen Z are considered digital natives, having had access to the internet since an early age. Gen Z tends to be more cost conscious due to less access to health insurance, and has a reduced tendency to seek face-to-face healthcare from medical professionals.

Using MS data, a study was conducted to assess whether ChatGPT could diagnose MS in individuals faster than physicians did in real-time.

The study examined patients over the age of 18 years with at least one symptom suggestive of CNS demyelination, MRI data available for analysis, and seen by a provider within one year of initial symptom onset.

The results showed that the model diagnosed people three months faster on average, but the difference was due to limitations on appointments and waiting for test results. Providers were also held to higher standards due to liability, and provided more comprehensive evaluations to arrive at a more correct diagnosis.

The results suffer from biases due to the use of existing data, such as females having higher prevalence among Black Americans, increasing incidence in Asians, and stability in incidence among White Americans.

Generative AI models could be used by providers to urge specialty care sooner, as long as the models are developed correctly.


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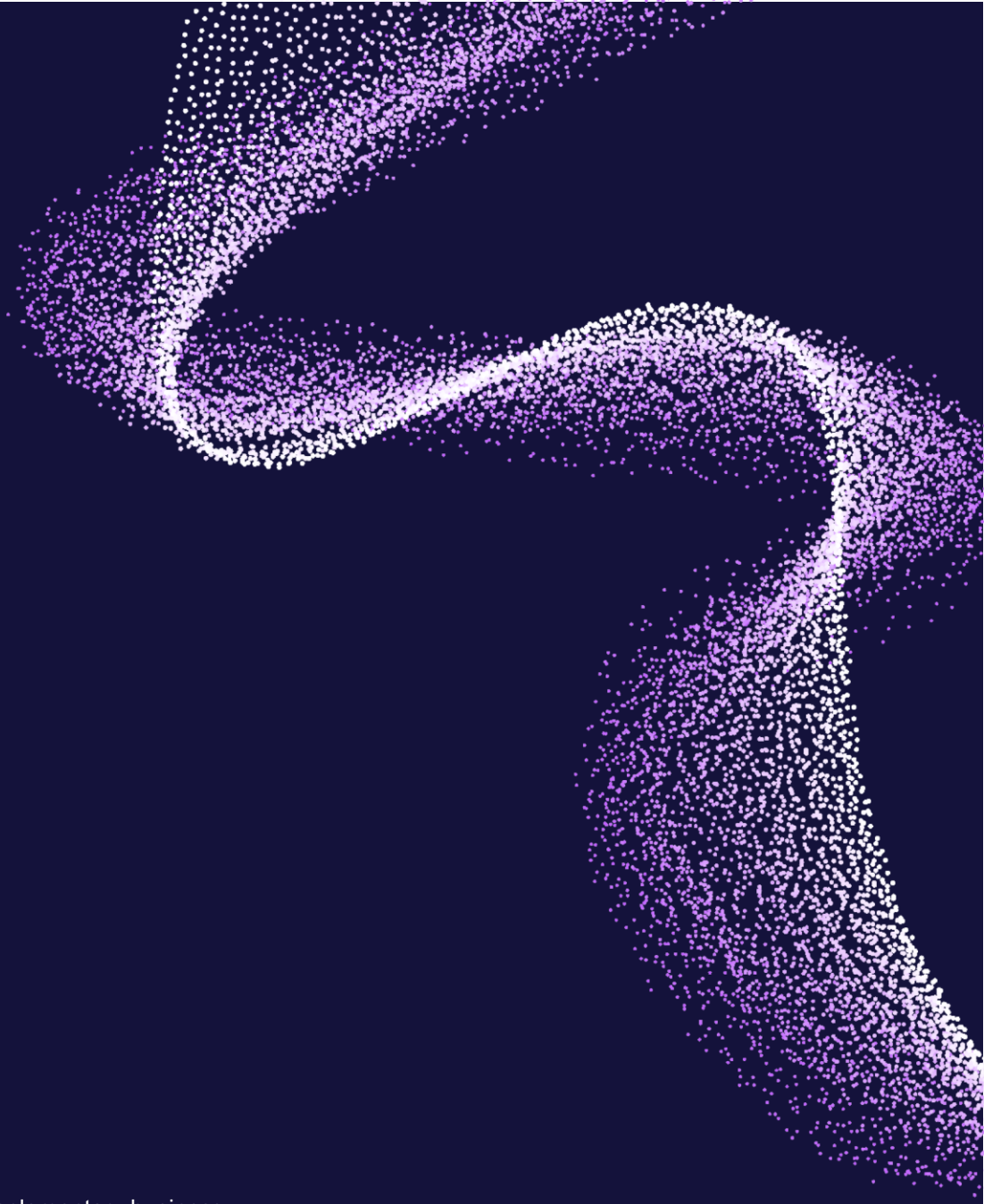

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