Medicom International Conference Series in Neurology

AAN 2021 Annual Meeting

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PEER-REVIEWED CONFERENCE REPORT

Persistent Chemosensory Dysfunction After COVID-19

About half of patients with COVID-19 who experienced a loss of smell had not regained this sense 5 months later. Of patients losing their sense of taste, almost 40% had not regained this after 5 months.

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Severe COVID-19 and Stroke Risk

Of critically ill patients with COVID-19, 2% experienced a stroke after they were admitted to the intensive care unit. Haemorrhagic stroke was associated with a higher risk of death in these patients.

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Serum NfL Associated with Clinical Disability, Brain Atrophy

Elevated neurofilament light (NfL) in serum of patients with multiple sclerosis was associated with clinical disability and brain atrophy, and also with comorbidities including diabetes and smoking.

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Editor Prof. Hans-Peter Hartung, Heinrich-Heine-University Düsseldorf, Germany

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MEDICOM
MEDICAL PUBLISHERS

Head Office
Medicom Medical Publishers
Faas Eliaslaan 5
3742 AR Baarn
The Netherlands

Postal address
Medicom Medical Publishers
PO Box 90
3740 AB Baarn
The Netherlands

Telephone +31 85 4012 560
E-mail publishers@medicom-publishers.com

Letter from the Editor

Prof. Hans-Peter Hartung

Dear colleagues,

Due to the prevailing COVID-19 pandemic, this year the AAN community again gathered only virtually. Nevertheless, it turned out to be yet another big success with more than 13,000 colleagues from around the world digitally joining the proceedings and multiple high class educational programs. As always, the meeting provided a unique opportunity to get authoritative updates about the latest developments in clinical and translational neurological research, disease diagnosis and management, healthcare, and topics on the borderland of healthcare, economics, and politics.

Clearly, of the entire spectrum of neurological disorders studied, the impact of COVID-19 stood out. Leading experts shared and critically analyzed the constantly accumulating evidence for involvement of the central and peripheral nervous system in this grave SARS-CoV2 disease and discussed how it impacts several aspects of disease management. Here, efficacy and potential risks of disease-modifying drugs were discussed also in relation to COVID-19 vaccinations.

In all the major disease groups cared for by neurologists, new advances were presented both regarding diagnosis and therapies. We have been witnessing astounding progress in utilizing anti-sense technology to provide therapeutic benefits in hitherto untreatable diseases of both the brain and peripheral nerve. Clearly, assessing cognitive impairment in many diseases and therapeutic avenues for improvement as well as deciphering the mysteries of dementia and the various subgroups continue to be a major challenge. This will certainly persist after the recent approval by FDA of aducanumab for Alzheimer dementia. Prominently discussed were also the recent therapeutic advances noted in migraine and multiple sclerosis.

The organizers did a great job in hosting this mega-virtual event. Mission accomplished. Congratulations! However, we would all be happy to see our colleagues at AAN 2022 in person again.

Hans-Peter Hartung, MD FRCP FAAN FANA FEAN

Biography

Prof. Hartung is currently Professor of Neurology at Heinrich-Heine-University Düsseldorf, Honorary Professor at Brain and Mind Center, University of Sydney, Visiting Professor at Medical University Vienna and Palacky University Olomouc. He was chairman of the Department of Neurology, Heinrich-Heine-University Düsseldorf from 2001-2020, director of the Center for Neurology and Neuropsychiatry from 2012-2020 and director of the Department of Conservative Medicine from 2012-2019.

Prof. Hartung's clinical and translational research interests are in the field of basic and clinical neuroimmunology and in particular multiple sclerosis and immune neuropathies, development of new immunological, neuroprotective and neural repair promoting strategies. He has (co-)authored more than 950 articles in peer-reviewed journals and 100 book chapters. He has been involved as member of the Steering Committee in numerous international multicentre therapeutic phase 2 and 3 trials in multiple sclerosis, Guillain-Barré Syndrome and CIDP.

He was President of ECTRIMS and has served/serves amongst others on the executive boards of the European Charcot Foundation, the European Neurological Society, and the International Multiple Sclerosis Cognition Society (IMSCOGS). He is/was also member of the Editorial Board of a number of international journals. Prof. Hartung is a Fellow of the AAN and EAN, and has been chair/member of the management group of the EAN scientific panels on general neurology and multiple sclerosis. He is Corresponding and Honorary Fellow of several international societies.

Conflict of Interest Statement:
Hans-Peter Hartung has received fees for consulting, speaking, and serving on steering committees from Bayer Healthcare, Biogen, GeNeuro, MedImmune, Merck, Novartis, Opexa, Receptos Celgene, Roche, Sanofi Genzyme, CSL Behring, Octapharma, Teva, TG Therapeutics, and Viela Bio, with approval by the Rector of Heinrich-Heine University.

"I am grateful for the opportunity to have led the AAN through these challenging, unprecedented times."

Interview with AAN president '21

Dr James C. Stevens, MD, FAAN,

conducted on 17 April 2021 by Michiel Tent

Dr James Stevens has been a private practicing neurologist and specialist in sleep disorders medicine at the Fort Wayne Neurological Center for 32 years. He completed his 2-year term as president during the 2021 virtual edition of the AAN annual meeting, where he was succeeded by Dr Orly Avitzur, MD, MBA, FAAN, who holds office in Tarrytown and Carmel, New York. On the meeting's first day, Dr Stevens discussed organising this meeting and shared some personal highlights with Medicom.

How has the AAN 2021 meeting been faring thus far?

"Fantastic! It has exceeded our expectations. When we first realised that our meeting needed to be totally virtual due to the pandemic, we expected about 7,000 attendees. But even before the meeting started, we already exceeded 12,000 registrations. The technology involved is cutting edge; reactions have been overwhelmingly positive."

The downsides of a virtual meeting are obvious. What are the upsides?

"The scientific and educational content is still of the highest quality. You can attend at your convenience and at you leisure, without paying for a flight, hotel room, and restaurants. Anyone who misses a session of his interest, can go to the rewind section to access scientific and educational content until 1 month after the meeting.

Still, nothing can truly replace the face-to-face interaction with others. But we try to do our best by offering a very creative networking area at our meeting. There you can connect with people from all over the world who have a common interest in your area of research or study, or whom you can contact about specific subjects such as leadership, or making your way through your training, for example."

Which presentations would you specifically like to draw attention to?

"Anyone who is new to the meeting and wants an excellent overview of the latest in science and in our knowledge, should focus on the plenary sessions [as this conference report primarily does]. For example, a hot topics plenary session deals with the COVID-19 pandemic, with updates for neurologists by Dr Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases and Chief Medical Advisor to the US President, and by Dr Walter Koroshetz, Director of the National Institute of Neurological Disorders and Stroke."

As a specialist in sleep disorders medicine, what is the most exciting news at the meeting?

"There are exciting advances and new therapeutics in the treatment of patients with narcolepsy. There are also advances in the area of sleep apnoea, among others. Furthermore, we are learning about the overall importance of sleep, which affects our health, well-being, and longevity. So, a lot of information comes out of this meeting concerning sleep, which is critically important for the medical community as a whole."

Do you think the pandemic will forever change the way meetings like the AAN 2021 are organised?

"Without a doubt. From now on, meetings like ours are likely to always provide the opportunity to attend virtually as well as in person. This offers the advantage of having a tremendous reach across the globe, and to enable access for people who are unable to make all the necessary travel arrangements."

What have been the biggest challenges of your presidency?

"When I started my term 2 years ago, we had a retreat with a futurist. He helped us envision scenarios for the future, from the very optimistic, down to the abject disaster. But we did not foresee anything like the disastrous pandemic we have seen. Neurological practices had to close; as neurologists we had to pivot to delivering virtual healthcare. Medical education changed dramatically, turning from hands-on instructions to e-learning. Still, the AAN set records for membership and member satisfaction; and financially we are healthy."

Your term as president of the AAN draws to a close. How do you look back on it and what message would you have to your successor?

"I am grateful for the opportunity to have led the AAN through these challenging, unprecedented times. What I would say to my successor Dr Orly Avitzur, who is very capable and accomplished, is that there are always solutions – no matter how challenging and difficult things look. It is through persistence and determination that she will find these solutions. The talented AAN staff and the neurologic community are more than willing to help and find them. As AAN president, she will '*knock it out of the park*'."

LISTEN TO THE INTERVIEW

COVID-19 and Neurology

The neurological impact of COVID-19

In a special hot-topics session at the AAN 2021 meeting, top experts Dr Anthony Fauci and Dr Walter Koroshetz provided an update on the neurological implications of COVID-19. Dr Fauci is director of the National Institute of Allergy and Infectious Diseases and chief medical advisor to the US President; Dr Koroshetz is director of the National Institute of Neurological Disorders and Stroke.

The wide variation in response to COVID-19 infection is one of the most puzzling and unprecedented aspects of this disease, according to Dr Fauci [1]. He could only guess at possible explanations, such as underlying pre-existing immunity, or the density of ACE2 receptors in the nasopharynx and the lungs. He called this "one of the most exciting areas of research". Dr Fauci also stressed that the pandemic has highlighted "very disturbing health disparities" in the US. People of colour have a higher rate of infection, but they also suffer more severe consequences as a result of having more comorbidities. The Biden administration has taken measures to improve access of minorities to vaccination.

Can vaccinated people still transmit the virus? Due to the relatively low levels of virus in the nasopharynx of vaccinated people, Dr Fauci deemed this unlikely. He said a study on college campuses will assess this question. If the answer is negative, people who are vaccinated will not have to worry about wearing a mask. Asked about advances in treatment, Dr Fauci said that monoclonal antibodies and convalescent plasma are most valuable in an early stage of the infection. He added that dexamethasone is a "life saver", effectively decreasing 28-day mortality. However, Dr Fauci thinks the future belongs to targeted antiviral therapy, to be administered when symptoms emerge, to prevent hospitalisation.

Dr Koroshetz addressed safety issues of COVID-19 vaccines [1]: "The question of vaccines and different neurological conditions has been studied over the years. We don't have any real concerns about the COVID-19 vaccine being any different." He observed that COVID-19 does not appear neurotropic, even though it infiltrates nasal mucosa. Whether the virus invades the brain is controversial. What it certainly can do, is affect vital systems that support the brain, which for example may result in encephalopathy, delirium, acute necrotising encephalitis, and transverse myelitis.

Also in want of more research is the chronic fatigue syndrome after infection, officially known as 'post-acute sequelae of SARS-CoV-2' (PASC). Possible symptoms include fatigue, memory and attention problems, dysautonomia, postural orthostatic tachycardia, sleep disorder, and pain syndromes. Dr Koroshetz observed that the percentage of COVID-19 patients who develop PASC may be below 10%, but that this is still a huge number of people.

1. Hot topics: Neuro-COVID plenary session. COVID-19 Keynote Address. AAN 2021 Virtual Congress, 17-22 April.

Chemosensory dysfunction often persistent after COVID-19

About half of patients with COVID-19 who experienced loss of smell during the initial illness had not regained their sense of smell 5 months later. Similarly, of patients losing their sense of taste, almost 40% still had not regained it after 5 months.

Chemosensory dysfunction (CD) is a key symptom of COVID-19. About 60% of patients experience alterations in smell and about 50% in taste. Moreover, persistent CD is reported in 20% of patients after viral upper respiratory tract infections [1]. In a cohort of 813 Quebec healthcare workers with a positive COVID-19 diagnosis (mean age 42 years, 84% female), the duration, severity, and trajectory of CD symptoms were evaluated [2]. Subjects were invited to complete a questionnaire on average 5 months after diagnosis, evaluating CD retrospectively during the acute phase, and at the time of questionnaire completion. Results were reported on a scale from 0 to 10 (0: no perception; 10: very strong perception). Additionally, a chemosensory dysfunction home test (CD-HT) was used to objectify olfactory and gustatory symptoms. Results were presented by Dr Nicolas Bussière (University of Quebec, Canada).

Average self-reported olfaction rates were 8.98/10 before the infection, 2.85/10 during the acute phase, and 7.41/10

at the time of answering the questionnaire. Rates for taste were 9.20/10, 3.59/10, and 8.05/10, respectively. Of 580 respondents with a compromised sense of smell during the acute phase, 297 (51.2%) had not regained olfactory functions at the time of completion. Of 527 participants who lost their sense of taste during the initial illness, 200 (38%) had not regained this sense when completing the questionnaire 5 months later. Assessed objectively with the CD-HT, 134 (17%) had persistent loss of smell and 73 subjects (9%) had persistent loss of taste. Dr Bussière mentioned that the possibility of recall bias and variability in CD-HT (product quality, expiration date, brand) are limitations of this study.

In conclusion, persistent CD occurred in approximately 1 out of 5 COVID-19 patients in this study. Reported chemosensory alterations differed between subjective and objective data collection.

1. Hajikhani B, et al. Physiol Rep. 2020;8(18):e14578.
2. Bussière N, et al. Persistent Chemosensory Dysfunction Associated with COVID-19 Infection in a Cohort of Over 700 Health Care Workers. S21.005, AAN 2021 Virtual Congress, 17-22 April.

Pandemic results in decreased global stroke care

The volume of global stroke hospitalisations, intravenous thrombolysis (IVT), and IVT interfacility transfers have declined during the COVID-19 pandemic. The consequences of the pandemic on global stroke care were the subject of a cross-sectional, observational, retrospective study.

Data was collected from 457 stroke centres in 70 countries, covering 6 continents [1]. Under-resourced countries, low-income regions, and primary stroke centres were the main targets. Results were presented by Dr Thanh Nguyen (Boston University School of Medicine, MA, USA).

During the first pandemic peak from March to June 2020, there were 11.5% fewer stroke admissions (n=80,894) than in the 4 preceding months (n=91,373; P=0.0001). Reduction rates were especially high in Africa and North America (see Table). COVID-19 hospitalisations per site correlated with declined rates in stroke admissions. There were similar drops in the rate of IVT attempts (-13.2%; P<0.0001) and in IVT transfers during the pandemic peak months (-11.9%; P=0.001).

A recovery of stroke hospitalisation volume by 9.5% was observed over the 2 later months (May/June) versus the 2 earlier months (March/April) of the pandemic, with greater recovery in hospitals with lower COVID-19 hospitalisation volume, high volume stroke centre, and in comprehensive stroke centres (P<0.0001). This recovery did not apply to IVT. Stroke rate was 1.48% across 119,967 COVID-19 hospitalisations; COVID-19 infection was diagnosed in 3.3% of stroke admissions.

Table: Change in stroke admission and IVT volume immediately before and during the COVID-19 pandemic [1]

Continent	% Change in stroke admission	% Change in IVT volume
Africa	-30.2% (95% CI -32.2 to -28.3; P<0.0001)	-23.5% (95% CI -29.8 to -18.2; P<0.01)
Asia	-7.1% (95% CI -7.4 to -6.9; P<0.0001)	-10.1% (95% CI -11.2 to -9.1; P<0.0001)
Europe	-10.0% (95% CI -10.4 to -9.6; P<0.0001)	-13.4% (95% CI -14.3 to -12.5; P<0.0001)
North America	-18.8% (95% CI -19.3 to -18.3; P<0.0001)	-14.4% (95% CI -15.6 to -13.3; P<0.0001)
South America	-17.4% (95% CI -18.5 to -16.3; P<0.0001)	-24.2% (95% CI -27.6 to -21.0; P<0.0001)
Oceania	-1.9% (95% CI -2.5 to -1.5; P=0.3)	-1.9% (95% CI -3.9 to -0.92; P=0.7)

Dr Nguyen considered the global decline in stroke care during the first pandemic wave to be irrespective of COVID-19 hospital burden or pre-pandemic stroke and IVT volumes.

1. Nguyen TN, et al. Global impact of the COVID-19 pandemic on stroke care and intravenous thrombolysis. N3.002, AAN 2021 Virtual Congress, 17-22 April.

Stroke uncommon in critically ill COVID-19 patients

In a large, year-long study, stroke was an infrequent complication in critically ill patients admitted to an intensive care unit (ICU) with COVID-19. Of 2,699 patients registered across more than 370 sites spanning 52 countries, 59 (2.2%) experienced acute stroke during their ICU stay. In these patients, haemorrhagic stroke was associated with a higher risk of death, but not ischaemic stroke.

Cerebrovascular complications of COVID-19 occur in 1-6% of COVID-19 patients. The incidence of stroke seems higher than expected, especially in younger patients. The COVID-19 Critical Care Consortium (CCCC) is a prospective observational study that focuses on critically ill patients requiring admission to the ICU [1]. The study selected 2,699 eligible patients registered across over 370 sites in 52 countries. Median age was 53 years, 65% were male.

During their ICU stay, 59 patients (2.2%) experienced an acute stroke. Of these, 19 (32%) were ischaemic, 27 (46%)

haemorrhagic, and 13 (22%) unspecified. Haemorrhagic stroke increased the cumulative hazard of death (HR 2.7; 95% CI 1.4–5.3), while ischaemic stroke did not (HR 1.0; 95% CI 0.5–2.4). Of patients with haemorrhagic stroke, 72% died. However, only 15% of these died of stroke, with multiorgan failure being the leading cause of death.

"For people with COVID-19 in intensive care, our large study found that stroke was not common, and it was infrequently the cause of death," said leading author Dr Jonathon Fanning (University of Queensland, Australia). "Still, COVID-19 is a new disease and mutations have resulted in new variants, so it is important to continue to study stroke in people with the disease. More importantly, while the proportion of those with a stroke may not be as high as we initially thought, the severity of the pandemic means the overall absolute number of patients around the world who will suffer a stroke and the ongoing implications of that for years to come could create a major public health crisis."

1. Fanning J, et al. Stroke complicating critically ill patients with SARS-CoV-2: Analysis of the COVID-19 Critical Care Consortium (CCCC) international, multicenter observational study. AAN 2021 Virtual Congress, 17-22 April.

Neurologic symptoms in children with multisystem inflammatory syndrome

There is a new inflammatory syndrome associated with COVID-19, called paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), also known as multisystem inflammatory syndrome in children (MIS-C). In a single-centre study, over half of these patients had neurologic symptoms at presentation affecting central and peripheral nervous system; after 6 months, symptoms persisted in one third of these patients.

Between 4 April and 1 September 2020, a total of 46 children (median age 10.2) who fulfilled the PIMS-TS criteria were admitted to the Great Ormond Street Hospital, UK [1]. The children were predominantly male (65.2%) and of non-white ethnicities (80.4%). Neurologic symptoms in these patients were analysed at baseline and at 6 weeks and 6 months post-discharge.

At baseline, 24 children (52%) showed neurological symptoms they had not had before, while respiratory symptoms were absent. Both central and peripheral nervous system manifestations were reported. The most commonly described symptoms were headache (52%), encephalopathy (30.4%), voice abnormalities (30.4%), coordination deficits (19.6%), myopathy/neuropathy (17.4%), and hallucinations (13.0%). Brain MRI was performed for 16 patients at baseline, 7 of which showed abnormalities. In all 17 patients who underwent EEG monitoring at baseline, abnormalities were found. Children with neurological involvement of PIMS-TS had higher peak inflammatory markers and were more likely to be ventilated and require inotropic support (P<0.05).

At 6 months follow-up, neurological manifestations persisted in one-third of the population, but with few functional problems. Commonly reported neurological symptoms at 6 months follow-up were dysmetria (26%), ataxia (13.0%), abnormal saccades (15.2%), proximal myopathy (17.4%), peripheral neuropathy (6.5%), and emotional lability (15.2%).

1. Abdel-Mannan O, et al. Neurologic and radiographic findings associated with Pediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 (PIMS-TS) in Children. ES.008, AAN 2021 Virtual Congress, 17-22 April.

COVID-19 could cause novel seizures in patients without epilepsy

New research showed a higher incidence of new-onset seizures among COVID-19 patients without a known history of epilepsy, compared with patients with a known history of epilepsy. Further investigation into the pathophysiology of this phenomenon is required; the authors hypothesise it includes cytokine storm, increased permeability of the blood-brain barrier, hypoxia, and vascular events.

Anecdotal reports have indicated a possible relationship between COVID-19 infections and novel seizures. For this retrospective study, data was gathered of 917 patients who were admitted with COVID-19 and who received standard antiepileptic medication for any reason [1]. Patients were divided into 4 groups: patients with a history of epilepsy, presenting with or without breakthrough seizures, and patients without a history of epilepsy, presenting with or without new-onset seizures.

Results demonstrated that patients without a known history of epilepsy had 3 times greater odds to have a new-onset seizure than patients with a history of epilepsy: of 451 patients with a history of epilepsy, 48 (11%) had a novel seizure; of 466 patients without a history of epilepsy, 127 (27%) had a novel seizure (OR 3.15; P<0.0001). Patients with new-onset seizures had a significantly longer length of stay at the hospital: 128 patients with new-onset seizures and no

history of epilepsy (22%) had an average stay of 26.9 days; 48 patients with a history of epilepsy and breakthrough seizures (8%) had an average stay of 12.8 days, and 40 patients with a history of epilepsy and no new seizures (70%) had an average stay of 10.9 days.

Mortality rates were higher among patients who had a novel seizure (29%) than among those who did not (29% vs 23%, respectively; OR 1.41; P=0.045). There was no difference in mortality rates between patients who had and did not have a history of epilepsy (OR 0.90; P=0.47).

The researchers offered multiple hypotheses for the mechanism of action for seizures during COVID-19: cytokine storm, disruption and increased permeability of the blood-brain barrier, hypoxia, and/or coagulation abnormalities resulting in strokes.

1. Bhaskar H, et al. Association of COVID-19 infections with novel and breakthrough epileptic seizures. ES.003, AAN 2021 Virtual Congress, 17-22 April.

MS therapies influence COVID-19 severity

Preliminary outcomes of a retrospective Italian study on the impact of disease-modifying treatments (DMTs) on COVID-19 disease course, showed that multiple sclerosis (MS) patients treated with anti-CD20 therapies have an increased risk of severe COVID-19 disease. In contrast, treatment with interferon or teriflunomide may decrease this risk.

A total of 844 MS patients were enrolled in the study; 565 had suspected COVID-19 and 279 confirmed COVID-19 [1]. Groups were classified based on COVID-19 severity as 1) mild disease not requiring hospitalisation; 2) pneumonia or hospitalisation; 3) intensive care unit (ICU) admission or death. Mean age was 45 years, 593 (70.3%) were women. The median expanded disability status scale (EDSS) score was 2; 16% had progressive MS.

Of the included patients, 38 (4.5%) were admitted to an ICU, 99 (11.7%) had pneumonia, and 96 (11.4%) were hospitalised. The number of fatalities was 13 (1.54%), 11 of which had progressive MS; 8 were not on any therapy.

The use of anti-CD20 therapy (ocrelizumab or rituximab) was significantly associated with increased risk of severe COVID-19 (OR 2.37; 95% CI 1.18–4.74; P=0.015). Recent use (<1 month) of methylprednisolone was also associated with a worse outcome (OR 5.24; 95% CI 2.20–12.53; P=0.001). In contrast, a protective effect against severe COVID-19 was observed for interferon (OR 0.36) and teriflunomide (OR 0.49, trending). Additional analysis revealed that duration of anti-CD20 treatment may be associated with severe infection (≤6 months: OR 1.56; >2 years: OR 2.75). Other factors that significantly impacted infection severity were age, sex, EDSS scores, presence of comorbidities, and high-dose steroid use one month before symptoms (see Table).

Table: Risk factors for severe COVID-19 in 1,584 confirmed cases: multivariate analysis [1]

Variable	OR (95% CI)*	P-value
Age <45 years	Reference	
Age 45-60 years	1.9 (1.3–2.8)	0.001
Age >60 years	7.7 (4.4–13.4)	<0.001
Sex (female vs male)	0.65 (0.48–0.89)	0.007
EDSS	1.17 (1.07–1.27)	<0.001
Comorbidities	2.03 (1.45–2.86)	<0.001
Methylprednisolone 1 month before symptoms	2.33 (1.08–5.01)	0.03
Disease-modifying therapy		
No therapy	Reference	
Interferon	0.36 (0.16–0.79)	0.012
Glatiramer acetate	0.84 (0.42–1.67)	0.57
Teriflunomide	0.49 (0.24–1.01)	0.054
Dimethyl fumarate	0.90 (0.51–1.58)	0.72
Natalizumab	0.80 (0.42–1.67)	0.47
Fingolimod	0.79 (0.44–1.41)	0.30
Anti-CD20 (ocrelizumab or rituximab)	1.89 (1.15–3.10)	0.012
Other	0.61 (0.30–1.38)	0.10

*Ordinal logistic regression applies: the outcome is a severity scale that is "ordered".
Level 0 = mild disease, no pneumonia, not requiring hospitalisation (n=1,363)
Level 1 = pneumonia or hospitalisation (n=184)
Level 2 = ICU or death (n=36)
The OR represents the risk increase passing from one classification to the next.

1. Sormani MP, et al. Different disease modifying therapies can increase or decrease COVID-19 severity in Multiple Sclerosis. S28.002, AAN 2021 Virtual Congress, 17-22 April.

Cognitive Impairment and Dementias

Obstructive sleep apnoea associated with lower cognition

Over half of cognitively impaired patients have obstructive sleep apnoea (OSA). Severity of OSA correlates with the degree of cognitive impairment and sleep quality. This was found in a study of patients with cognitive impairment primarily attributable to an underlying neurodegenerative and/or vascular aetiology.

Previous research has linked OSA to cognitive impairment [1]. In a new study, prevalence of OSA was assessed in cognitively impaired patients in a tertiary care clinic [2]. A total of 67 participants who contributed complete home sleep apnoea test (HSAT) recordings were included for analysis. Mean age was 73 years, 45% were male, and mean BMI was 25.6. OSA was assessed with HSAT, which is an alternative to polysomnography. Also, patients completed various assessments and questionnaires related to sleep, cognition, and mood. Dr David Colelli (University of Toronto, Canada) presented the results.

Within the study population, 52% was diagnosed with OSA; 31.3% had moderate or severe OSA. Of studied variables (see Table), OSA was only significantly associated with lower Montreal Cognitive Assessment (MoCA) score (OR 0.40; P=0.048). Severity of OSA was correlated with the degree of cognitive impairment and actigraphy-derived sleep variables (lower total sleep time, greater sleep-onset latency, lower sleep efficiency, and greater awakenings). Dr Colelli added that future research should examine the prevalence of OSA in larger cohorts and assess predictors in specific neurodegenerative and/or vascular aetiologies for cognitive impairment.

Table: Predictors of obstructive sleep apnoea [2]

	Coefficient ± SE	OR (95% CI)	P-value
Age	0.01 ± 0.03	1.14 (0.48–2.67)	0.767
Male sex	0.56 ± 0.76	1.75 (0.39–7.77)	0.463
Neck circumference	0.27 ± 0.31	1.70 (0.51–5.63)	0.383
Sleep efficiency	-0.04 ± 0.04	0.70 (0.34–1.43)	0.327
Montreal Cognitive Assessment	-0.19 ± 0.09	0.40 (0.16–0.99)	0.048

1. Bradley TD, Floras JS. Lancet. 2009;373(9657):82-93.
2. Colelli DR. Frequency and predictors of obstructive sleep apnea in a cognitively impaired clinic population. S9.003, AAN 2021 Virtual Congress, 17-22 April.

NfL is a better marker for neurodegeneration than T-tau

Compared with plasma total tau (T-tau), elevated neurofilament light chain (NfL) plasma level is a better prognostic biomarker, more strongly associated over time with cognitive decline and neuroimaging changes. This was the conclusion of a study comparing both biomarkers cross-sectionally and longitudinally. T-tau adds cross-sectional value to NfL with the combination being useful in diagnostic settings.

Plasma T-tau and NfL were directly compared in a study to better establish which marker can best be applied in which clinical trials and to evaluate their utility in the diagnosis and prognosis of cognitive decline in daily clinical practice [1]. Included were 995 participants without dementia at baseline of whom plasma NfL and T-tau, cognitive status, and neuroimaging data were available. For a median 6.2 years, follow up was performed approximately every 15 months. The study results were presented by Mr Jordan Marks (Mayo Clinic, MN, USA).

Elevated baseline plasma NfL levels were more strongly associated with cognitive and neuroimaging outcomes than plasma T-tau in all analyses: cross-sectional and longitudinal, global- and domain-specific, both for cognitive degeneration and neuroimaging outcomes. Cross-sectional differences between both biomarkers were small, whereas the longitudinal differences were more pronounced. Over time, baseline NfL levels were strongly associated with cognitive decline, decreasing cortical thickness and hippocampal volume, and an increased number of infarcts. On the other hand, the combination of NfL and T-tau levels in the top quartile at baseline was associated with lower memory and global cognitive z-scores, decreased temporal lobe thickness, and a higher number of infarcts.

Mr Marks concluded that plasma NfL may be a useful marker of neurodegenerative changes and has a prognostic value, whereas the combination of NfL and T-tau may be useful in a diagnostic setting. The replicability of these findings across community-based and clinical cohorts lends further credibility to their feasibility in clinical practice.

1. Marks J, et al. Comparison of Neurofilament Light and Total Tau as Blood-Based Biomarkers of Neurodegeneration: Associations with Cognition and Neuroimaging Outcomes. ES.001, AAN 2021 Virtual Congress, 17-22 April.

Monoclonal antibody rapidly reduces brain amyloid

Lecanemab, a monoclonal antibody (mAb) that binds amyloid-beta, elicits rapid reductions of brain amyloid at a dose of 10 mg/kg biweekly, over 12 months of treatment in a controlled study. Although superior to placebo, lecanemab did not meet the primary endpoint of reducing the Alzheimer's Disease Composite Score (ADCS).

Lecanemab is a humanised IgG1 mAb that selectively binds amyloid-beta (Aβ) protofibrils. It is 1 of 4 mAbs that have recently shown anti-amyloid efficacy, the others being aducanumab, donanemab, and gantenerumab. In subjects with early AD, lecanemab demonstrated dose-dependent reductions in brain amyloid in an 18-month, placebo-controlled, phase 2 study (NCT01767311) [1]. The primary endpoint –demonstrating an 80% probability that lecanemab was superior to placebo by 25% at reducing the ADCS after 12 months– was not met. After 18 months, this probability was 76%, just missing the 80% threshold, explained Dr Chad Swanson (Neurology Business Group, Eisai Inc., NJ, USA). This prompted the open-label extension (OLE), of which he shared the preliminary results over 12 months [2].

Subjects received lecanemab 10 mg/kg biweekly for up to 24 months. There were 143 subjects who contributed to the longitudinal amyloid PET imaging dataset of the OLE. The observed reductions in brain amyloid depended on the treatment received during the core study. "Patients initially assigned to placebo showed the greatest reductions, with effects noted as early as 3 months," Dr Swanson said. Estimated reductions on PET standard uptake value ratio (SUVr) in this group were -0.08, -0.17, and -0.33 at 3, 6, and 12 months, respectively. The reductions were lower in patients who had received lecanemab in the core study, dependent on baseline PET SUVr values at the start of the OLE.

Of 180 dosed patients, 14 (7.8%) had cerebral oedema (ARIA-E) during the OLE. This occurred in 8.9% of patients allocated to placebo in the core study, all of which were ApoE4+. Some patients with mild or moderate ARIA-E resumed treatment.

1. Swanson CJ, et al. Alzheimer's Res Ther. 2021;13(1):80.
2. Swanson C. Preliminary analysis of BAN2401 effects on brain amyloid and ARIA-E findings over 12 months of treatment in the open-label extension of the Phase2b study BAN2401-G000-201 in subjects with early Alzheimer's Disease. S19.001, AAN 2021 Virtual Congress, 17-22 April.

Breast cancer treatment decreases risk of dementia

In a retrospective review study, women with breast cancer who were taking oestrogen-modulating therapy (EMT) had a decreased risk of neurodegenerative diseases, specifically Alzheimer's disease (AD) and dementia.

As the number of women with a diagnosis of breast cancer increases and survival rates improve, the number of women living with breast cancer who are at risk of other diseases will escalate. The presented study involved a review from medical records of 57,843 perimenopausal to postmenopausal women from the United States with breast cancer [1]. Of these, 18,126 (31.3%) received EMT –tamoxifen or steroidal aromatase inhibitors, mainly exemestane– for breast cancer treatment.

Using EMTs was associated with a significantly lower risk of a neurodegenerative disease, especially AD (RR 0.827; 95% CI 0.759–0.901; P<0.0001). Overall rate and proportion of neurodegenerative disease-free survival were determined in patients who developed neurodegenerative disease. Results indicated that reduction of neurodegenerative disease risk increased with age. Current research aims to identify molecular mechanisms by which EMT protects against AD and dementia.

1. Branigan GL. Breast Cancer Therapies Reduce Risk of Alzheimer's Disease and Dementia: Clinic to Bench Translation. S19.004, AAN 2021 Virtual Congress, 17-22 April.

Pimavanserin does not worsen motor function in patients with neurodegenerative disease

Pimavanserin did not have a negative impact on motor function in patients with neuropsychiatric symptoms of neurodegenerative disease [1]. This selective serotonin 5-HT2A receptor inverse agonist/antagonist did not seem to affect cognitive function either [2].

Psychosis and other neuropsychiatric symptoms are common among patients with dementia. Use of (off-label) antipsychotics in these patients is associated with significant adverse outcomes, including declining motor function and accelerated cognitive decline. The effect of pimavanserin on motor function changes was evaluated in 3 studies: 2 double-blind, parallel-group studies (019 [NCT02035553] & 046 [NCT03575052]) and the HARMONY randomised withdrawal study (NCT03325556). Patients had neuropsychiatric manifestations of neurodegenerative

disease (n=626 receiving pimavanserin), including dementia-related psychosis (n=562 receiving pimavanserin). In all 3 studies, mean changes in motor function were minimal in pimavanserin-treated patients and similar to placebo. Motor-related treatment-emergent adverse events were reported at rates ≤2.2%, which was similar to placebo.

A review of 4 studies (adding 032 [NCT02992132] to the 3 mentioned above) evaluated the impact of up to 9 months of treatment with pimavanserin on cognitive measures in patients with neuropsychiatric manifestations of neurodegenerative disease. Cognitive function was measured by Mini-Mental State Examination (MMSE). Overall, pimavanserin did not have a negative impact on cognitive function in patients with neurodegenerative disease. Across all 4 studies, mean changes in MMSE score were small and similar to placebo. Confusion and memory impairment were the only cognition-related treatment-emergent adverse events reported. They were infrequent and occurred at rates similar to placebo.

1. Weintraub D. Motor function in patients with neuropsychiatric manifestations of neurodegenerative disease treated with pimavanserin. S19.005, AAN 2021 Virtual Congress, 17-22 April.
2. Ballard C. Impact of pimavanserin on cognitive measures in patients with neurodegenerative disease (NDD): results from 4 placebo-controlled clinical studies. P1.012, AAN 2021 Virtual Congress, 17-22 April.

Epilepsy

Extraordinary transformation of epilepsy care in Ontario

A system-wide restructuring of epilepsy services over the last decade has transformed epilepsy care in Ontario, Canada. A novel partnership between government, epilepsy caregivers, patients, and families has resulted in the provision of unique end-to-end epilepsy care including knowledge translation, with a high increase in patients evaluated for and receiving epilepsy surgery.

The Ontario Ministry of Health (MOH) instigated a partnership between epilepsy healthcare providers, hospital administrators, critical care services, provincial Neurosurgery Advisory Committee, the Ontario Brain Institute, community epilepsy agencies, and epilepsy patients and their families. Dr O. Carter Snead III (University of Toronto, Canada) explained what this partnership entailed and which objectifiable results it had thus far [1].

The MOH started in 2013 with the development of District Epilepsy Centers (DEC) and Regional Epilepsy Surgery Centers of Excellence (RESC) throughout Ontario. It issued a total of 6 provincial guidelines on Epilepsy Care. It also created a provincial knowledge translation (KT) strategy for epilepsy. To provide epilepsy KT in Ontario, project ECHO (Extension for Community Healthcare Outcomes; https://oen.echoontario.ca) was consequently launched in 2018. This is an innovative (and forward-looking) model for medical education that uses Zoom meetings to connect academic health centres to community healthcare providers. Project ECHO is very different from telehealth, explained Dr Snead. "The idea is to create a cadre of community health providers knowledgeable in epilepsy to serve as a resource not only for their epilepsy patients, but for the community as well." Each regional district centre represents a hub. Each hub recruits community partners from their respective regions of referral. A hub team consists of an epileptologist, a social worker, a nurse psychologist, a nurse practitioner, a pharmacist, and a psychiatrist. The Hospital for Sick Children (SickKids) in Toronto serves as the administrative hub. Nine adult and paediatric epilepsy project ECHO team hubs are currently "up and running" across Ontario. Learner satisfaction was very high.

Dr Snead provided results in terms of Epilepsy Monitoring Unit (EMU) volumes before (2012) and after (2019) full implementation of the project. EMU volumes increased from 450 to over 2,000, while epilepsy surgery volumes increased by 92%, from 208 to 400.

1. Snead OC, et al. A Unique Population Based Epilepsy Network in Ontario Enhances Epilepsy Care and the Availability of Epilepsy Surgery. S10.004, AAN 2021 Virtual Congress, 17-22 April.

No neurodevelopmental effects of foetal antiseizure medication

Children born to women taking anti-seizure medication during pregnancy either as monotherapy (lamotrigine

[LTG] or levetiracetam [LEV]) or polytherapy (LTG+LEV) have no developmental delays at the age of 3. This was found in the prospective, multicentre Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) study.

"Having a seizure during pregnancy may not only harm the mother but possibly the baby as well, so seizure control is an important part of prenatal care," said study author Dr Kimford Meador (Stanford University, CA, USA). "While the risks for some medications are known, and careful planning can result in healthy pregnancies, there are some newer medications for which the longer-term effects are still not fully known."

The MONEAD study (NCT01730170) enrolled women with epilepsy and otherwise healthy women during pregnancy [1]. The primary outcome for children at age 3 was a Verbal Index score, calculated by averaging scores on a series of cognitive and developmental tests that measured skills such as vocabulary, listening comprehension, number recall, and pattern recognition. At enrolment, 74% of pregnant women with epilepsy were on monotherapy, primarily lamotrigine (43%) or levetiracetam (37%). Lamotrigine plus levetiracetam was the most prevalent polytherapy (44%).

The current preliminary analysis assessed 275 children from women with epilepsy and 77 children of healthy women. Results showed that the children of women with epilepsy had similar Verbal Index scores (LS mean 103.4; 95% CI 102.1–104.6) compared with children of healthy women (LS mean 102.7; 95% CI 100.2–105.1). In addition, there were no developmental differences between children of women with epilepsy and healthy women that could be linked to the different levels of antiseizure medications in mothers' blood samples (n=251) during the third trimester (adjusted parameter estimate -1.2 [-6.2 to 3.8]).

1. Meador K, et al. Fetal Antiseizure Medication Effects on Neuropsychological Outcomes at Age 3 Years in the MONEAD Study. S1.001, AAN 2021 Virtual Congress, 17-22 April.

Durable seizure frequency reduction with cenobamate

In a post-hoc efficacy analysis of an open-label phase 3 safety study of cenobamate, this anti-seizure medication was effective in the long term, yielding high rates of sustained (≥12 months) 100% seizure reduction. The results further support durable seizure frequency reduction with cenobamate in adults with uncontrolled focal seizures.

During the development of cenobamate, 3 cases of drug reaction with eosinophilia and systemic symptoms (DRESS) occurred at starting doses of 50 or 100 mg/day. To mitigate the rate of DRESS, daily doses were started at 12.5 mg/day and slowly increased at 2-week intervals to the target dose of 200 mg/day over a 12-week period in an open-label, multicentre phase 3 study mandated by the FDA (NCT02535091). In 1,339 participants, no cases of DRESS were seen [1]. At the AAN 2021 meeting, post-hoc efficacy data from 10 US study sites from this study were presented [2]. Included in the analysis was available efficacy data of 240 patients with focal aware motor, focal impaired awareness, or focal to bilateral tonic-clonic seizure data while on treatment. Median duration of treatment was 30 months. Mean baseline seizure frequency per 28 days was 18.1.

A 100% seizure reduction with a duration of ≥12 months at the last visit or at any visit was seen in 62 patients (25.8%) and in 87 (36.3%), respectively. A 100% seizure reduction of ≥6 and ≥3 months at the last visit occurred in 84 (35.0%) and 107 (44.6%) patients, respectively. At the last visit, 177 patients (73.8%) were still using cenobamate. During the entire maintenance phase, 162 of 214 patients (75.7%) had a ≥50% responder rate; 29 (13.6%) had a ≥100% responder rate.

Another study analysed steady state trough plasma concentrations in patients who achieved 50% seizure reduction and seizure freedom in order to determine a reference concentration range for cenobamate [3]. A reference range of 5–35 µg/mL covered 95% of patients; it should be noted this is not a target therapeutic range.

1. Sperling ME, et al. Epilepsia. 2020 Jun;61(6):1099-1108.
2. Sperling MR, et al. Efficacy of Cenobamate for Uncontrolled Focal Seizures: Post-hoc Analysis of a Phase 3, Multicenter, Open-Label Study. S1.002, AAN 2021 Virtual Congress, 17-22 April.
3. Greene SA, et al. Cenobamate Trough Plasma Concentrations in Patients With Uncontrolled Focal Seizures Achieving 50% and 100% Seizure Reduction in Two Randomized Clinical Studies. S1.003, AAN 2021 Virtual Congress, 17-22 April.

Soticlestat in children with Dravet and Lennox-Gastaut

In the phase 2 ELEKTRA study, soticlestat treatment resulted in a statistically significant and clinically meaningful reduction in median convulsive seizure frequency in children with Dravet syndrome, and in a directional reduction in median drop seizure frequency in patients with Lennox-Gastaut syndrome. Soticlestat was generally well tolerated.

Dravet syndrome and Lennox-Gastaut syndrome are rare childhood epilepsies that are often resistant to current treatment with antiseizure medications. Soticlestat is a first-in-class, selective inhibitor of cholesterol 24-hydroxylase which catabolises cholesterol to 24S-hydroxycholesterol in the brain. The phase 2 ELEKTRA trial (NCT03650452) was a randomised, placebo-controlled, parallel-group study of soticlestat (≤600 mg/day weight-adjusted) in children (2–17 years) with Dravet syndrome with ≥3 convulsive seizures (n=51), or Lennox-Gastaut syndrome with ≥4 drop seizures per month (n=88) [1].

In the combined patient population, soticlestat-treated patients demonstrated a statistically significant median placebo-adjusted reduction in seizure frequency of 30.5% (P=0.0007) in the 12-week maintenance period. Over the full 20-week treatment period, patients receiving soticlestat demonstrated a median placebo-adjusted reduction of seizure frequency of 25.1% (P=0.0024). In the soticlestat group, there was a decrease of 36.5% in convulsive frequency during the maintenance period, while the placebo group experienced a median increase of 10.1%. This results in a significant placebo-adjusted median reduction in convulsive seizure frequency of 50% (P=0.0002). Patients with Lennox-Gastaut syndrome showed a median reduction in drop seizure frequency of 18.9% during the maintenance period, compared with a 2.2% median reduction in the placebo group. This resulted in a median reduction in a placebo-adjusted median reduction of 17.1% (P=0.1166). Results of the full treatment period were consistent with the changes in seizure frequency observed during the maintenance period.

The incidence of treatment-emergent adverse events was similar between the soticlestat and placebo groups (80.3% vs 74.3%). Serious adverse events were reported in 15.5% vs 18.6%. Lethargy and constipation were the most frequent treatment-emergent adverse events reported in soticlestat-treated patients with at least 5% difference from placebo. Safety findings were consistent with previous studies.

1. Hahn CD, et al. Efficacy, Safety and Tolerability of Soticlestat (TAK-935/OV935) as Adjunctive Therapy in Pediatric Patients with Dravet Syndrome and Lennox-Gastaut Syndrome (ELEKTRA). S1.005, AAN 2021 Virtual Congress, 17-22 April.

Migraine and Other Headaches

Long-term safety of atogepant as migraine prophylaxis

Daily oral atogepant (60 mg) for the preventive treatment of migraine showed no considerable safety or tolerability issues. Common treatment-emergent adverse events were upper respiratory tract infection, constipation, nausea, and urinary tract infection. Most constipation cases were mild to moderate in severity. There were no hepatic safety issues.

Prof. Messoud Ashina (University of Copenhagen, Denmark) discussed the results of the randomised, multicentre, open-label safety trial that followed 744 adult migraine patients for 1 year [1]. Participants were randomised with a 5:2 ratio to atogepant 60 mg/day or standard-of-care (SOC) to assess safety and tolerability of atogepant. Visitations were scheduled every 4 weeks. The intention-to-treat analysis included 739 participants.

In the atogepant group (n=543), 67% of patients experienced treatment-emergent adverse events. Of these, 31 (5.7%) discontinued the study. Treatment-related adverse events were reported by 98 patients (18.0%), serious adverse events by 24 patients (4.4%). Importantly, no serious adverse event occurred in more than 1 patient and none of them were considered related to atogepant treatment. Upper respiratory tract infection (10.3%), constipation (7.2%), nausea (6.3%), and urinary tract infection (5.2%) were the most frequently reported adverse events. Only 1 case of obstipation was rated severe; it was resolved before the end of the study. In the SOC group (n=196), treatment-emergent adverse events were reported by 154 (78.6%) of patients. Treatment-related adverse events were reported by 71 patients (36.2%).

1. Ashina M, et al. Long-term Safety and Tolerability of Atogepant 60 mg Following Once Daily Dosing Over 1 Year for the Preventive Treatment of Migraine. S5.001, AAN 2021 Virtual Congress, 17-22 April.

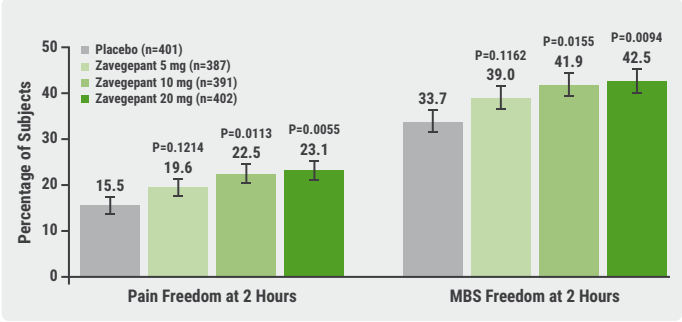
Intranasal zavegepant effective treatment for acute migraine

In a randomised, dose-ranging, placebo-controlled, phase 2/3 trial, intranasal zavegepant 10 or 20 mg met the co-primary endpoints freedom from pain and freedom from the most bothersome symptom (MBS) after 2 hours. Intranasal zavegepant demonstrated rapid onset of pain relief and had a favourable safety profile.

Zavegepant is the only intranasal CGRP receptor antagonist in late-stage development for the acute treatment of migraine. In the presented trial (NCT03872453), subjects with a single attack of migraine with moderate-to-severe pain intensity were treated with intranasal zavegepant 5, 10, 20 mg, or placebo [1]. A total of 1,673 adults with migraine were randomised, 1,581 of whom were included in the intention-to-treat population. Median age was 40 years, 85.5% were female, and 14% took prophylactic migraine medication.

The co-primary endpoints of freedom from pain and freedom from MBS were significantly more often reached in the zavegepant 10 mg and 20 mg groups than in the placebo group (see Figure). The onset of pain relief occurred as early as 15 minutes post-dose. There was no significant difference in the secondary endpoint of pain relief at 2 hours post-dose (P=0.0167) for any zavegepant dose group.

Figure: Intranasal zavegepant is superior to placebo on co-primary endpoints of a phase 2/3 trial [1]



MBS, most bothersome symptom (photophobia, phonophobia, or nausea).

The most common (>5%) adverse events were dysgeusia (13.5–16.1% with zavegepant vs 3.5% with placebo) and nasal discomfort (1.3–5.2% with zavegepant vs 0.2% with placebo). The majority of adverse events were mild or moderate and not related to the study drug. There was no signal of hepatoxicity.

1. Croop R, et al. Intranasal Zavegepant is Effective and Well Tolerated for the Acute Treatment of Migraine: A Phase 2/3 Dose-Ranging Clinical trial. S5.003, AAN 2021 Virtual Congress, 17-22 April.

Ubrogepant for acute treatment of perimenstrual migraine

Menstruation is a significant risk factor for migraine; over 50% of patients report an association between migraine attacks and monthly menstruation. Perimenstrual migraine can be also difficult to treat. In a randomised, 52-week extension trial, ubrogepant was efficacious in the acute treatment of perimenstrual migraine (pmM), comparable with that observed for non-pmM.

Perimenstrual migraine can be relatively difficult to treat, as attacks are often longer in duration and resistant to treatment. In a phase 3, randomised, open-label, 52-week extension trial, adults with migraine were randomised to ubrogepant 50 mg, ubrogepant 100 mg, or usual care. The intention-to-treat population consisted of 808 ubrogepant users who treated 21,419 migraine attacks with ubrogepant. Of this population, 354 (43.8%) were menstruating women. A post-hoc analysis was presented which included all 278 women (78.5%) who treated at least 1 pmM attack [1]. In total, 8,620 pmM attacks were treated, 40.2% of all treated migraine attacks.

In the ubrogepant 50 mg dose group, significantly more pmM patients (28.7%) achieved pain freedom at 2 hours than non-pmM patients (22.3%; P=0.046). In the 100 mg dose group, these percentages were 29.7% and 24.8%, respectively (P=0.406). In the 50 mg dose group, pain relief at 2 hours was achieved by 64.8% and 64.9%, respectively (P=0.396), and in the 100 mg dose group by 67.1% and 67.8% (P=0.253). Absence of photophobia, phonophobia, and nausea were seen in similar percentages of patients with pmM and non-pmM attacks. Treatment-related adverse events were reported by 18/137 (12.8%) and 12/141 (8.8%) in the ubrogepant 50 mg and 100 mg subgroups.

In conclusion, this post-hoc analysis showed that the overall efficacy of ubrogepant for the treatment of pmM was comparable with that observed for non-pmM.

1. Pavlovic JM, et al. Ubrogepant Was Safe and Well Tolerated in the Acute Treatment of Perimenstrual Migraine. S5.004, AAN 2021 Virtual Congress, 17-22 April.

CGRP antagonists and complications in patients with Raynaud's phenomenon

CGRP antagonists may lead to microvascular complications in patients with underlying primary or secondary Raynaud's phenomenon (RP). A retrospective

observational study showed that these complications are uncommon (seen in 5.3% of patients), but that caution is warranted when CGRP agents are considered in RP patients.

CGRP antagonists can decrease reflex vasodilatory response. This may lead to exacerbation of microvascular disease in susceptible patients, for example with RP. To date, this condition is not listed as a contraindication for the use of any of the 6 CGRP modulators subjected to clinical trials. A retrospective observational study reviewed patients with diagnoses of migraine and RP who were prescribed, and exposed to, CGRP antagonists [1].

Of 169 eligible patients, 9 (5.3%) had microvascular complications. They were all female; median age was 45 years. Most (5/9) had previously diagnosed RP, of which 3 were primary and 2 secondary to scleroderma. The other 3 patients were newly diagnosed with RP. The 9 patients were using galcanezumab (n=3), erenumab (n=5), or fremanezumab (n=1). Observed microvascular complications ranged from worsening RP to digital gangrene and auto-necrosis requiring distal digit amputation (n=2). The authors observed that digital ulcerations/infarctions rarely occur in primary RP alone and almost always reflect a secondary aetiology, which may include associated connective tissue diseases or exposure to precipitating medication. Although rare, the incidence of serious adverse events warrants caution when considering the use of CGRP modulators in patients with RP.

1. Breen I, et al. Calcitonin Gene-Related Peptide Inhibitor Use for Migraine Associated with Exacerbation of Raynaud Phenomenon. S15.005, AAN 2021 Virtual Congress, 17-22 April.

Efficacy and safety of eptinezumab in acute migraine

In the phase 3 RELIEF study, preventive therapy with eptinezumab during a migraine attack resulted in rapid and sustained freedom from headache and most bothersome symptom (MBS) compared with placebo. Eptinezumab also delayed the time to a next migraine attack by a median of 10 days, versus 5 days with placebo.

In the parallel-group, double-blind RELIEF study (NCT04152083), adult migraine patients were randomised to eptinezumab 100 mg (n=238) or placebo (n=242), administered intravenously within 1–6 hours of a moderate-to-severe migraine attack onset [1].

Patients in the eptinezumab group achieved freedom from headache significantly faster (median 4 vs 9 h, respectively; HR 1.54; P=0.0006), as well as absence of their MBS (median 2 vs 3 h; HR 1.75; P<0.0001). Two hours after the start of infusion, freedom from headache was reported by 23.5% and 12.0%, respectively (P=0.0009), and absence of MBS by 55.5% and 35.5% (P<0.0001); differences were still significant after 4 hours. Significantly fewer patients in the eptinezumab group used rescue medication within 24 hours (31.5% vs 59.9%; P<0.0001). There were similar rates of treatment-emergent adverse events (10.9% vs 10.3%); no serious adverse events occurred.

In a second presentation, results of exploratory endpoints were reported [2]. The median time to next migraine was 10 days in the eptinezumab group and 5 days in the placebo group (HR 0.60; P<0.0001). Results also showed that 4 weeks after infusion, eptinezumab improved the total score of the 6-item Headache Impact Test (HIT-6) to a clinically meaningful extent compared with placebo. Mean change from baseline was -8.7 and -4.5 points, respectively (P<0.0001).

1. Winner P, et al. Efficacy and Safety of Eptinezumab Initiated During a Migraine Attack: Results from the RELIEF Study. P10.033, AAN 2021 Virtual Congress, 17-22 April.
2. McAllister P, et al. Eptinezumab Treatment Initiated During a Migraine Attack Prolonged the Time to Next Migraine and Improved HIT-6 Outcomes in the RELIEF Study. P10.022, AAN 2021 Virtual Congress, 17-22 April.

Multiple Sclerosis

Mast cell and neutrophil involvement in MS activity

Preliminary results of a genome-wide association study (GWAS) demonstrate a possible involvement of mast cells and neutrophils in disease activity of patients with relapsing-remitting multiple sclerosis (MS). These results may provide important knowledge on mechanisms underlying disease activity and could lead to future therapeutic developments.

Evidence on the genetic basis of the broad heterogeneity in the clinical spectrum of MS is still limited. Italian researchers performed the first GWAS that targeted disease activity in MS [1]. A total of 790 patients with confirmed relapsing-remitting MS were followed for 2 years from the moment they started a first-line disease-modifying treatment. Disease activity was assessed according to No-Evidence/Evidence of Disease Activity-3 (NEDA/EDA-3) status. After quality controls, 778 patients and 607,864 single nucleotide polymorphisms (SNPs) were subjected to the GWAS.

Two SNPs at chromosome 14 passed the threshold for genome-wide significance: rs1956932 and rs17104242. These polymorphisms were found to protect EDA status at 2 years (OR 0.35 and 0.36, respectively). For 3 other SNPs –also located at chromosome 14– an association was found that suggested protection from disease activity, safeguarding NEDA status. There is a possible involvement of the chymase-1 (CMA-1) and cathepsin-G (CTSG) pathways. These pathways are involved in the activity and degranulation of mast cells and neutrophils, respectively. Neutrophils and mast cells have been associated with disease mechanisms in MS, such as the regulation of the blood-brain barrier, inflammatory response, and evoking a CNS-directed immune response through peripheral activation.

1. Giordano A, et al. A Genome-Wide Association Study Highlights a Possible Involvement of Mast Cells and Neutrophils in Disease Activity in Multiple Sclerosis. S11.002, AAN 2021 Virtual Congress, 17-22 April.

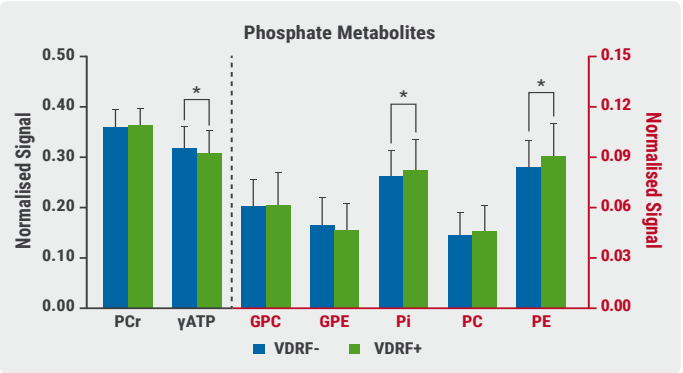
Dysmetabolism may drive MS progression

Multiple sclerosis (MS) patients without vascular disease risk factors (VDRF) had reduced brain adenosine triphosphate (ATP), lower total brain parenchymal volume, and higher EDSS scores when compared with patients with VDRF. This was demonstrated in a 3-year, prospective, observational study measuring ATP changes in MS by 7T magnetic resonance spectroscopy (MRS).

VDRF are common in MS, affecting over 50% of patients, with hyperlipidaemia, hypertension, and obesity being most prevalent [1]. Disease progression in MS is accelerated by the presence of VDRF, but the mechanisms behind this association are not well known. Dr Vijayshree Yadav (Oregon Health & Science University, USA) and her group hypothesised that VDRF leads to a reduced substrate delivery, which increases mitochondrial dysfunction. Subsequently, this could lead to increased high-energy phosphate metabolite deficiencies, increased neurodegeneration, and disease progression. Dr Yadav presented results from the first study using 7T MRS to longitudinally assess brain metabolism in MS subjects with and without VDFR [1].

The study included 52 patients with MS; 29 were VDRF-positive and 23 VDRF-negative at baseline. They were subjected to 7T MRS/MRI to assess differences in high-energy phosphate metabolites, brain volumes, and associated disease progression. Brain volumes were reduced in VDRF-negative patients. VDRF-positive patients had approximately 5% lower brain ATP than VDRF-negative patients (see Figure). The MRI signal changes were consistent in white and grey matter. Patients in the VDRF-positive group had higher neurological disability as assessed by EDSS.

Figure: Brain ATP is reduced in VDRF-positive MS patients [2]



VDRF, vascular disease risk factors; PCr, phosphocreatine; ATP, adenosine triphosphate; GPC, glycerophosphocholine; GPC, glycerophosphoethanolamine; Pi, inorganic phosphate; PC, phosphocholine; PE, phosphoethanolamine.

Dr Yadav concluded that ATP reductions in VDRF-positive MS patients are possibly caused by lower cranial blood flow and are related to mitochondrial dysfunction, which could contribute to accelerated disease progression.

1. Marrie R, et al. Neurology. 2010 Mar 30;74(13):1041-7.
2. Yadav V, et al. Vascular Disease Risk Factors in Multiple Sclerosis (MS) is Associated with Brain Adenosine Triphosphate Abnormalities: Dysmetabolism May Drive MS Disease Progression. S2.004, AAN 2021 Virtual Congress, 17-22 April.

Plasma NfL and GFAP predict disability worsening in non-active secondary progressive MS

In a post-hoc analysis of the EXPAND study, a bio-signature of combined high plasma neurofilament light chain (pNfL) and high plasma (p)GFAP consistently indicated an elevated risk of disability worsening in non-active secondary progressive MS patients. The added value of combining GFAP and NfL was less apparent in active secondary progressive MS.

EXPAND (NCT01665144) was a randomised, double-blind, phase 3 trial of siponimod in secondary progressive MS patients [1]. In this post-hoc analysis, which included the open-label extension period, baseline pNfL and pGFAP levels were determined using Single Molecule Array technology [2]. Samples from 1,369 patients were available for analysis.

In 704 patients with non-active secondary progressive MS, combined high pNfL and high pGFAP had relatively higher hazard ratios for all disability outcomes versus combined low pNfL and low pGFAP:

- time to EDSS 7.0 (HR 2.65; P=0.0014);
- time to 1-point sustained EDSS worsening (HR 1.57; P=0.0176);
- time to 3-month confirmed disability worsening (HR 1.45; P=0.0151).

Hazard ratios were also higher (range: 2.09–1.17) with a high pNfL + low pGFAP signature across all 3 outcomes (P=0.05). In 665 patients with active secondary progressive MS, the prognostic value of baseline levels of pNfL and pGFAP individually or in combination was weaker. Further analyses are ongoing, investigating other cut-offs and considering potential differential and time-dependent treatment effects.

1. Kappos L, et al. Lancet. 2018;391(10127):1263-73.
2. Kuhle J, et al. Plasma Neurofilament Light Chain and Glial Fibrillary Acidic Protein Levels Are Prognostic of Disability Worsening: A Biosignature That Helps Differentiating Active From Non-active SPMS. P11.001, AAN 2021 Virtual Congress, 17-22 April.

Serum NfL projects development of definite MS

In patients who experienced a first clinical demyelinating event, baseline levels of serum neurofilament light chain (NfL) were associated with conversion to McDonald 2005 MS. This was found in a post-hoc analysis of the phase 3 REFLEX trial.

Serum NfL is a known biomarker for disease activity and treatment efficacy in multiple sclerosis (MS) patients. The phase 3 REFLEX trial (NCT00404352) demonstrated that treatment with subcutaneous interferon-beta-1a (scIFNβ-1a) delayed the onset of MS (as defined by the 2005 McDonald criteria) in patients with a first clinical demyelinating event [1]. This treatment also reduced serum NfL levels from 6 months post-baseline.

A post-hoc analysis of the REFLEX trial showed that baseline levels of serum NfL predicted the conversion to McDonald 2005 MS after 2 years of follow-up in all 3 groups: scIFNβ-1a thrice-weekly (n=171), once-weekly (n=175), and placebo (n=171) [2]. Prof. Jens Kuhle (University of Basel, Switzerland) explained that patients with high serum NfL levels at baseline (>26.1 µg/mL) had an increased risk of developing clinically definite MS within 2 years. Serum NfL subgroup analyses demonstrated that treatment with scIFNβ-1a delayed MS onset in both patients with low and high baseline levels of serum NfL. Younger age, multifocal first clinical demyelinating event, and the number of T1 and T2 lesions predicted the onset of definite MS in all groups of the REFLEX trial.

1. Comi G, et al. Lancet Neurol. 2012;11(1):33-41.
2. Kuhle J, et al. Baseline Serum Neurofilament Light Chain Levels Predict Conversion to McDonald 2005 Multiple Sclerosis (MS) Within 2 Years of a First Clinical Demyelinating Event in Patients with MS. P5.080, AAN 2021 Virtual Congress, 17-22 April.

Serum NfL associated with clinical disability and brain atrophy

In a large and heterogeneous, multicentre cohort of multiple sclerosis (MS) patients, elevated serum neurofilament light chain (NfL) was associated with clinical disability and brain atrophy, and with comorbidities including diabetes and smoking. These results may help advance the utilisation of serum NfL in clinical practice.

Serum NfL was measured in baseline samples from 6,968 MS patients and 201 healthy control participants in the MS PATHS cohort [1].

Serum NfL was elevated in 1,202 MS participants (17.2%). Factors associated with elevated NfL included:

- progressive MS (OR 1.63; 95% CI 1.38–1.92);
- non-white race/ethnicity (OR 1.43; 95% CI 1.17–1.74);
- diabetes mellitus (OR 1.89; 95% CI 1.42–2.49);
- smoking (OR 1.49; 95% CI 1.20–1.85);
- younger age, and shorter symptoms duration.

An inverse relation was found between BMI and serum NfL: higher BMI was associated with lower odds of elevated sNfL (OR 0.83 per 5 kg/m^2 increase; 95% CI 0.78–0.88). Similar results were reported recently [2]. MS participants with elevated NfL exhibited worse neurological function (walking speed, manual dexterity, and processing speed), lower brain parenchymal fraction, lower thalamic volume, and higher T2 lesion volume (P<0.001 for all).

1. Sotirchos E, et al. Associations of Serum Neurofilament Light Chain with Clinico-Radiological Characteristics in the MSPATHS Network: A Cross-Sectional Evaluation. S25.001, AAN 2021 Virtual Congress, 17-22 April.
2. Manouchehrinia A, et al. Ann Clin Transl Neurol. 2020;7(1):139-143.

Natalizumab versus fingolimod in subgroups of MS patients

An analysis of 3 international cohorts revealed natalizumab to be associated with lower relapse frequency and higher odds of disability improvement than fingolimod. This difference was most pronounced in patients with relapses 12 months prior to starting treatment. Women and patients with lower disability also derived more benefit from natalizumab.

Natalizumab has proven to be more effective than fingolimod in reducing disease activity in relapsing-remitting multiple sclerosis (MS) in different studies. The current analysis was performed to assess whether natalizumab is more effective across all patient groups [1]. A total of 5,148 relapsing-remitting MS patients who received treatment with natalizumab (n=1,989) or fingolimod (n=3,159) for at least 3 months were identified in 3 international registries: the French Observatoire of MS, the Danish MS Treatment Register, and the global MSBase registry. Mean age at baseline was 37.91 years; the majority (71.83%) were women. The median on-treatment follow-up was 25.05 months.

A significantly lower on-treatment relapse rate on natalizumab versus fingolimod was observed in patients with the following characteristics:

- women (IRR 0.76; 95% CI 0.65–0.88);
- age group ≤38 years (0.64; 95% CI 0.54–0.76);
- disease duration ≤7 years (0.63; 95% CI 0.53–0.76);
- EDSS score <4 (0.75; 95% CI 0.64–0.88);
- EDSS <6 (0.80; 95% CI 0.70–0.91);
- EDSS ≥6 (0.52; 95% CI 0.31–0.86);
- patients with pre-baseline relapses (0.74; 95% CI 0.64–0.86).

Confirmed disability improvement on natalizumab was more likely in women (OR 1.36; 95% CI 1.10–1.66), age >38 years (1.34; 95% CI 1.04–1.73), disease duration >7 years (1.33; 95% CI 1.01–1.74), EDSS score <6 (1.21; 95% CI 1.01–1.46), EDSS score ≥6 (1.93; 95% CI 1.11–3.34), and patients without new MRI lesions (1.73; 95% CI 1.19–2.51). In a more progressive MS phenotype, natalizumab and fingolimod showed equal effectiveness.

1. Sharmin S, et al. Comparative effectiveness of natalizumab and fingolimod in subgroups of patients with relapsing-remitting multiple sclerosis from three international cohorts. P15.073, AAN 2021 Virtual Congress, 17-22 April.

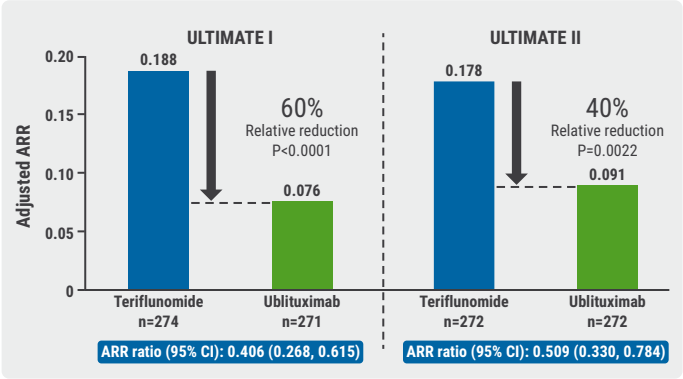
Ublituximab versus teriflunomide in relapsing MS

In the phase 2 ULTIMATE I and II trials, ublituximab significantly reduced annualised relapse rate (ARR) and MRI parameters compared with teriflunomide in relapsing multiple sclerosis (MS) patients. A very low rate of disability progression was observed with ublituximab, with >94% of patients showing no 12-week confirmed disease progression.

ULTIMATE I (NCT03277261) and ULTIMATE II (NCT03277248) are identical phase 3, randomised, multicentre, double-blinded, active-controlled studies. The studies' objective was to evaluate the efficacy and safety of ublituximab compared with teriflunomide in relapsing MS patients [1]. In both trials, participants were randomised 1:1 to intravenous ublituximab every 24 weeks or daily oral teriflunomide for 96 weeks. The primary endpoint was ARR at week 96. Key secondary endpoints included MRI-related outcomes, no evidence of disease activity (NEDA), and 3-month confirmed disability progression.

In both studies, ublituximab was associated with a relative reduction in ARR of 60% (P<0.0001) and 49% (P=0.0022), respectively (see Figure on the next page). There was a relative reduction in the total number of Gd-enhancing T1 lesions with ublituximab of 97% and 96%, respectively, relative to teriflunomide (P<0.0001). The relative reduction in the total number of new or enlarging T2 lesions was 92% and 90%, respectively, relative to teriflunomide (P<0.0001). In a prespecified pooled tertiary analysis, there was a 100% improvement in the proportion of patients who reached

Figure: ARR at 96 weeks in ULTIMATE I and II trials [1]



ARR, annualised relapse rate.

12-week confirmed disability improvement (CDI) with ublituximab versus teriflunomide (12% vs 6%; HR 2.158; 95% CI 1.406–3.3133). There was an 88% improvement in 24-week CDI (9.6% vs 5.1%; HR 2.031; 95% CI 1.269–3.248). In ULTIMATE I, 44.6% of patients in the ublituximab group achieved NEDA, which is a relative increase by 198% over teriflunomide (P<0.0001). In ULTIMATE II, 43% achieved NEDA, an increase of 277% over teriflunomide (P<0.0001). Ublituximab had a favourable safety and tolerability profile with no unexpected safety signals.

1. Steinman L, et al. Efficacy and safety of ublituximab versus teriflunomide in relapsing multiple sclerosis: Results of the Phase 3 ULTIMATE I and II trials. P15.074, AAN 2021 Virtual Congress, 17-22 April.

Tolebrutinib reduces brain lesions in very active MS

A subgroup analysis of a phase 2b trial demonstrated that tolebrutinib 60 mg effectively reduced new Gd-enhancing and new/enlarging T2 lesions in relapsing multiple sclerosis (MS) patients with highly active disease.

The randomised, double-blind, placebo-controlled, cross-over phase 2 study (NCT03889639) assessed the dose-response relationship after 12 weeks of treatment with tolebrutinib (5, 15, 30, and 60 mg), by measuring the number of new brain lesions on MRI. This study had a novel design which limited placebo exposure to only 4 weeks. At a dose of 60 mg, tolebrutinib was associated with an 85% relative reduction of new Gd-enhancing T1 hyperintense lesions [1]. Of 130 enrolled MS patients, 61 (47%) met the criteria for highly active disease at baseline; 29 of those started in the placebo cohort and later crossed over to tolebrutinib, evenly distributed across each dose arm.

After 4 weeks of placebo treatment, patients with highly active disease had a mean of 0.89 Gd-enhancing lesions and 1.44 new/enlarging T2 lesions. After 12 weeks of tolebrutinib treatment, mean numbers of new Gd-enhancing lesions in the subgroup with highly active disease were lowest in the 60 mg group: 0.82 (5 mg), 0.5 (15 mg), 0.38 (30 mg), and 0.08 (60 mg). The numbers of new/enlarging T2 lesions showed a very similar pattern: 1.09 (5 mg), 0.89 (15 mg), 0.75 (30 mg), and 0.15 (60 mg). Tolebrutinib was well tolerated over 12 weeks. Safety in the highly active disease group was consistent with the overall population.

1. Traboulsee A, et al. Efficacy and Safety of Tolebrutinib in Patients With Highly Active Relapsing MS: Subgroup Analysis of the Phase 2b Study. S25.004, AAN 2021 Virtual Congress, 17-22 April.

Fenebrutinib at highest dose generally well tolerated

In 13 completed randomised controlled and open-label extension trials, the oral Bruton's tyrosine kinase inhibitor (BTKi) fenebrutinib was generally well tolerated at the highest dose. There were no increases in infection rates. The observed safety profile of fenebrutinib supports testing in phase 3 clinical trials in multiple sclerosis (MS).

Of currently investigated BTKis in MS, fenebrutinib has the largest clinical safety database, allowing for assessment of its potential in MS management. A total of 13 completed phase 2 trials and extensions in rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and chronic spontaneous urticaria (CSU) were analysed [1]. Safety assessments included adverse events (AEs), laboratory results, ECGs, and vital signs. This analysis only included patients who received fenebrutinib at the highest dose of 200 mg twice daily (n=792) or placebo.

In the fenebrutinib and placebo groups, 299 and 278 patients experienced one or more AEs, respectively; these were mostly not serious. AEs reported in >5% of fenebrutinib-treated patients were nasopharyngitis (6%), nausea (5.7%), and headache (5.4%). Serious infections were reported in 6 patients (2%) receiving fenebrutinib and 5 patients (1.8%) receiving placebo. Asymptomatic, reversible grade 2 and 3 alanine aminotransferase elevations were seen in 11 (3.7%) and 3 (1.1%) patients, respectively. Bleeding or bruising was reported in 23 (7.7%) and 9 (3.2%) patients, with no major haemorrhage. AEs generally became less frequent with prolonged exposure during open-label extension trials.

1. Oh J, et al. The Safety of Fenebrutinib in a Large Population of Patients With Diverse Autoimmune Indications Supports Investigation in Multiple Sclerosis (MS). S25.005, AAN 2021 Virtual Congress, 17-22 April.

Predicting long-term prognosis in paediatric MS patients

By using clinical and easily obtainable MRI measures, an Italian group identified early predictors of long-term multiple sclerosis (MS) course in paediatric patients. High-efficacy disease-modifying treatment (DMT) exposure over the first year reduced disease activity over a 9-year follow-up. Baseline spinal cord, brain stem, and optic nerve involvement of lesions have an important role in predicting long-term outcomes.

The aim of the study by Dr Ermelinda De Meo (San Raffaele Hospital, Italy) was to assess early predictors of long-term clinically relevant outcomes in a cohort of 123 paediatric MS patients through clinical and MRI assessments [1]. Expanded Disability Status Scale (EDSS) scores were collected at disease onset, after 1 and 2 years, and at the last visit. The number, distribution, and features of MS lesions were assessed at baseline, as well as number of new T2 or Gd+ lesions after 1 and 2 years.

Observed were only 2 main independent factors that predicted time to first relapse: optic nerve lesions (HR 2.1; P=0.02) and exposure to high-efficacy DMT (HR 0.3; P=0.005). Predictors of annualised relapse rate are shown in the Table. Predictors of 9-year disability worsening were: at baseline, presence of optic nerve lesions (OR 6.45; P=0.01) and presence of brain stem lesions (OR 6.17; P=0.10); from baseline to 1 year: 1-year EDSS change (OR 13.40; P<0.001); and from baseline to 2 years: 1-year EDSS change (OR 26.05; P<0.001), 2-year EDSS change (OR 16.38; P=0.02), and ≥2 new T2-lesions in 2 years (OR 4.91; P=0.02). These results underscore the need for complete MRI assessment at baseline, concluded Dr De Meo.

Table: Predictors of annualised relapse rate in paediatric MS [1]

	Coefficient	95% CI	P-values	R^2 (adjusted R^2)
Baseline (n=123)				0.17 (0.15)
Presence of cerebellar lesions	-0.15	-0.25 to -0.05	<0.001	
Presence of cervical spinal cord lesions	0.16	0.05–0.26	0.003	
High versus moderate efficacy DMT	-0.14	-0.25 to -0.03	0.01	
Baseline – 1 year (n=115)				0.26 (0.22)
Number of 1-year relapses	0.14	0.05–0.23	0.002	
Presence of cerebellar lesions	-0.16	-0.26 to -0.06	0.002	
Presence of cervical spinal cord lesions	0.15	0.05–0.25	0.004	
High versus moderate efficacy DMT	-0.12	-0.23 to 0.01	0.04	
Baseline – 2 years (n=105)				0.26 (0.22)
Time to first relapse	-0.12	-0.20 to -0.02	0.01	
Number of 2-year relapses	0.06	0.01–0.12	0.02	
Presence of cerebellar lesions	-0.12	-0.22 to -0.01	0.03	
Presence of cervical spinal cord lesions	0.10	0.00–0.21	0.04	

DMT, disease-modifying treatment.

1. De Meo E, et al. Early clinical and MRI predictors of long-term disability in pediatric multiple sclerosis patients. S28.005, AAN 2021 Virtual Congress, 17-22 April.

Neuromuscular Disorders

Functional and survival benefits of AMX0035 in ALS

AMX0035, aimed at decreasing neuronal cell death, significantly reduced the risk of death in amyotrophic lateral sclerosis (ALS) patients compared with placebo, regardless of concomitant use of riluzole and/or edaravone. This was the result of the long-term survival analysis of the phase 2 CENTAUR trial. The study used a novel approach of collecting survival data.

AMX0035 is an oral, fixed-dose combination of 2 compounds (sodium phenylbutyrate and taurursodiol), which decreases neuronal cell death. The phase 2 CENTAUR trial (NCT03127514) included 137 patients, who were randomised 2:1 to AMX0035 or placebo. After 6 months, the primary safety, tolerability, and efficacy endpoints (ALSFRS-R slope reduction of 2.32 points) were met. Subsequently, 92% of participants entered the open-label extension (OLE). Long-term survival data was collected through a participant-locating service, a method new to ALS trials [1]. In this way, survival data could be retrieved from all original participants. Results were presented by Dr Sabrina Paganoni (Massachusetts General Hospital, MA, USA).

Participants originally randomised to AMX0035 had a 44% lower risk of death than participants in the placebo group (HR 0.56; 95% CI 0.34–0.92; P=0.023), with corresponding

improved median survival (25.0 vs 18.5 months) and median duration of exposure (8.8 vs 1.9 months). Dr Paganoni emphasised that these results were obtained despite all participants already using riluzole and/or edaravone at baseline. Participants in the AMX0035 group survived longer without tracheostomy, permanent assisted ventilation, and first hospitalisation. Dr Paganoni added that the true impact of AMX0035 on survival may be underestimated, since many participants in the original placebo group were exposed to AMX0035 in the OLE. An exploratory analysis suggested that the placebo group had a 6.4-month longer median survival than predicted, suggesting a higher long-term survival benefit of AMX0035.

1. Paganoni S, et al. Long-Term Survival of Participants in the CENTAUR Trial of AMX0035 for ALS. AAN 2021 Virtual Congress, 17-22 April.

Remission with rituximab in refractory generalised myasthenia gravis

In a retrospective case series, rituximab was effective in refractory myasthenia gravis, either with anti-muscle-specific kinase (MuSK) or anti-acetylcholine receptor (AChR) autoantibodies. Early start of treatment may be associated with a more rapid and sustained clinical response.

Rituximab, a monoclonal antibody targeted against CD20, is a therapeutic option in myasthenia gravis, especially in refractory patients. In a single-centre study, 16 patients (13 females) with generalised myasthenia gravis who had been referred to a specialised clinic in Buenos Aires (Argentina) and were treated with rituximab were included [1]. Of the 16 participants, 8 had AChR and 8 had MuSK autoantibodies. Outcomes were assessed using the Myasthenia Gravis Status and Treatment Intensity (MGSTI) score. Patients received 2 immunosuppressants and had received at least one cycle of intravenous immunoglobulin. During induction, they received low-dose rituximab: 1,000 mg (n=7), 1,500 mg (n=2), or 2,000 mg (n=7); only 5 patients received maintenance doses. Follow-up data of a minimum of 2 years were available.

All 16 patients achieved and maintained undetectable CD20 levels at 6 and 12 months, without new relapses. All patients had MGSTI scores ≤2; the earlier rituximab treatment was initiated, the faster this score was reached.

1. Castiglione J, et al. Long-term remission with rituximab in refractory generalized myasthenia gravis. S12.001, AAN 2021 Virtual Congress, 17-22 April.

Novel AAV-based gene therapy for Duchenne muscular dystrophy

rAAVrh74.MHCK7.micro-dystrophin (SRP-9001) is a novel adeno-associated virus (AAV)-based gene transfer therapy for the treatment of Duchenne muscular dystrophy (DMD). Findings of the first part of a placebo-controlled trial reinforced a favourable benefit-risk profile. Treatment was well tolerated and appeared to improve muscle function.

The novel gene therapy was subjected to the randomised, double-blind, placebo-controlled trial SRP-9001-102 (NCT03769116) that evaluated safety, efficacy, and tolerability of a single intravenous dose of SRP-9001 in boys with DMD gene mutation (exons 18–58) aged 4–7 years [1]. This phase 2 trial has 3 parts: two 48-week randomised, double-blind, placebo-controlled periods with crossover design (part 1 and 2) and an open-label follow-up period of up to 212 weeks (part 3). Results from the 41 randomised patients in part 1 were communicated.

There were 1.6 copies of the transgene DNA per nucleus at week 12. Micro-dystrophin expression at week 12 was achieved (28.1% of normal), and the percentage of dystrophin-positive fibres was 33% of normal. Functional outcomes were measured in terms of North Star Ambulatory Assessment (NSAA). In the 6- and 7-year-olds, a large imbalance in baseline NSAA was present; this is why the results (not reaching statistical significance; P=0.37) are hard to interpret. In 4- and 5-year-olds, baseline function was well matched. Change in NSAA in this subgroup was significantly higher in the experimental group than in the placebo group (4.3 vs 1.9; P=0.0172). Treatment was generally well tolerated, with treatment-emergent adverse events in the SRP-9001 and placebo group being reported in 85% and 43%. The most common treatment-emergent adverse event was vomiting (60% vs 19%).

1. Mendell J, et al. A Multicenter Randomized, Double-Blind, Placebo-Controlled, Gene-Delivery Clinical Trial of rAAVrh74.MHCK7.micro-dystrophin for Duchenne Muscular Dystrophy. S32.004, AAN 2021 Virtual Congress, 17-22 April.

Parkinson's Disease and Other Movement Disorders

Autoimmune mechanisms implicated in Parkinson's disease

Monocyte-derived dendritic cells from patients with Parkinson's disease present a dysregulated cytokine profile. The subset of cytokines that is altered promotes T-cell polarisation towards autoimmune-related Th1/Th17 cells. The authors conclude that this data supports the hypothesis that autoimmune mechanisms may be implicated in Parkinson's disease.

One of the major hallmarks of Parkinson's disease is inflammation. Furthermore, the Parkinson's disease-related genes *PINK1* and *Parkin* regulate the mitochondrial antigen presentation pathway. PINK1 aggregates on damaged mitochondria and recruits Parkin, thus triggering mitophagy. If PINK1 or Parkin are missing, mitochondrial-derived vesicles (MDV) may form. The mitochondrial antigens contained within the MDVs may be expressed at the cell surface. To better understand the processes taking place in the periphery in Parkinson's disease, Canadian researchers investigated whether antigen-presenting cells (APCs) from patients display a dysregulated cytokine expression profile [1]. Monocyte-derived dendritic cells were generated from peripheral blood mononuclear cells (PBMCs) of patients with Parkinson's disease and healthy controls to characterise their cytokine expression profile after lipopolysaccharide (LPS) or bacterial (Enteropathogenic *Escherichia coli* [EPEC]) stimulation. The results were presented by Dr Camille Michaud (University of Montreal Hospital Research Centre, Canada).

The results demonstrated that inflammation and ageing regulate expression of *PINK1* and *Parkin*. Treatment of inflammation induced by LPS/EPEC reduced the expression of *PINK1* and *Parkin*. Loss of co-localisation between patients' monocyte-derived dendritic cells could indicate activation of the MDV/mitochondrial antigen presentation pathway. Monocyte-derived dendritic cells of patients with Parkinson's disease produced more pro-inflammatory cytokines in response to LPS and EPEC.

1. Michaud C, et al. Antigen-presenting cells from PD patients exhibit an autoinflammatory cytokine profile. S27.001, AAN 2021 Virtual Congress, 17-22 April.

Stable long-term effects of deep brain stimulation in Parkinson's disease

Long-term results of the CSP468 VA/NINDS trial demonstrated that deep brain stimulation (DBS) therapy had a significant and stable effect on motor function of patients with Parkinson's disease, regardless of whether the globus pallidus interna (GPi) or the subthalamic nucleus (STN) were targeted. This is remarkable in view of the progressive nature of Parkinson's disease.

DBS of the GPi and STN are well-established therapies of Parkinson's disease, but outcomes on the very long-term are lacking. At the AAN 2021 meeting, extended long-term outcomes – of up to 10 years in some cases – from the landmark CSP468 VA/NINDS multicentre, randomised-controlled trial (NCT01076452) were presented [1].

A subset of patients originally randomised to GPi or STN DBS and with visits completed at 2 years were followed for up to 10 years. Data included analyses at baseline (GPi n=152; STN n=147), 2 years (GPi n=85; STN n=70), 7 years (GPi n=68; STN n=49), and 10 years (GPi n=49; STN n=28). The primary outcome was change in score of the Unified Parkinson's Disease Rating Scale (UPDRS) part III (motor subscale) in the off medication/on stimulation state. At baseline, these scores were 43.2 in both groups.

Improvement in UPDRS motor scores was maintained across all times analysed, in both groups. In the STN group, the scores declined from 43.2 to 27.7 after 2 years (P<0.001), to 34.4 after 7 years (P<0.001), and to 28.3 after 10 years (P<0.001). In the GPi group, the scores were 25.8 after 2 years (P<0.001), 35.4 after 7 years (P<0.001), and 34.0 after 10 years (P=0.10). Improvements were generally similar over time, but with a trend favouring STN (P=0.09). Tremor subscales showed the greatest reduction, followed by rigidity. Bradykinesia subscores showed greater improvement at 7 and 10 years with STN DBS (P=0.03). The UPDRS I, II, and IV scores and quality of time based on motor diaries also demonstrated significant long-term improvements, regardless of target.

The tremor subscales showed the greatest reduction over time, followed by rigidity subscores. Both targets had equal and significant medication reduction. Parkinson's Disease Questionnaire-39 (PDQ-39) total score no longer showed improvement at 7 or 10 years (either target).

The 4-year follow-up results of the INTREPID trial (NCT01839396) showed that use of a multiple-source, constant-current rechargeable DBS system is safe and effective for the long-term in patients with Parkinson's disease [2]. INTREPID was a double-blinded, randomised, sham-controlled trial of a novel DBS device capable of Multiple Independent Current Control (MICC). Results of 120 patients showed continued improvement of the UPDRS part III in the off medication/on stimulation state (43.4 at baseline; 21.2 at 1 year; 22.6 at 2 years; 22.6 at 3 years; 25.6 at 4 years). Medication reductions were maintained, and PDQ-39 scores indicated ongoing improvements in most aspects of quality of life.

1. Ostrem J, et al. 10 Year Clinical Outcomes of Subthalamic Nucleus versus Pallidal Deep Brain Stimulation for Parkinson's Disease: VA/NINDS CSP #468F. S8.003, AAN 2021 Virtual Congress, 17-22 April.
2. Vitek J, et al. Long-Term Evaluation of Deep Brain Stimulation for Treatment of Parkinson's Disease Using a Multiple-Source, Constant-Current Rechargeable System: 4-year Follow-Up of a Prospective, Double-Blind RCT. S8.004, AAN 2021 Virtual Congress, 17-22 April.

Novel non–D2-receptor-binding treatment for Parkinson's disease psychosis

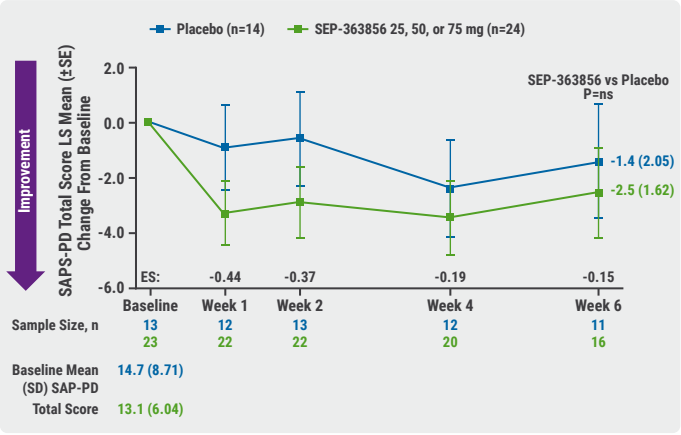
Parkinson's disease psychosis (PDP) is a frequent, debilitating symptom of Parkinson's disease and current treatments may worsen motor function. In a proof-of-concept study, a novel non–D2-receptor-binding treatment for PDP called SEP-363856 improved PDP symptoms without worsening the motor parkinsonism manifestations and was well tolerated.

PDP is progressive, debilitating, and common, with a prevalence of around 60% as Parkinson's disease progresses. Most treatment options are limited due to lack of efficacy, safety concerns, and/or exacerbation of motor symptoms. SEP-363856 is a full agonist of the TAAR1 and 5HT1A receptors. It is a potent regulator of dopamine neurotransmission and represents a novel way to prevent hyperactivity of the dopaminergic system. In a previous study, SEP-363856 demonstrated antipsychotic-like activity [1]. A proof-of-principle study evaluated safety and efficacy of SEP-363856 in PDP patients [2]. The results were shared by Dr Stuart Isaacson (Parkinson's Disease and Movement Disorders Center of Boca Raton, FL, USA).

PDP patients requiring treatment were randomised to SEP-363856 (25, 50, or 75 mg/day) or placebo. Primary endpoint was change in Scale for Assessment of Positive Symptoms–Parkinson's Disease (SAPS-PD) after 6 weeks. The intention-to-treat population included 38 patients (SEP-363856, n=24; placebo, n=14). Mean time since onset of Parkinson's disease and PDP were 9.0 and 2.4 years, respectively. Mean baseline SAPS-PD total score was 13.6; mean Mini-Mental State Examination (MMSE) score was 25.0.

Improvements in SAPS-PD total scores for SEP-363856 compared with placebo occurred as early as week 1; least-squares mean change from baseline at week 6 was -2.5 versus -1.4 (P=0.681; see Figure). A ≥100% improvement in SAPS-PD total score was seen in 25% versus 0% of patients. Regarding SAPS-PD subscores, there was a greater effect of SEP-363856 on hallucinations (-3.6 vs -1.9; P=0.339). Dr Isaacson also noted that SEP-363856 was relatively more effective in patients with cognitive impairment. SAPS-PD total score in patients with baseline MMSE score ≤24 was -5.2 versus -2.1 (P=0.460). No change at 6 weeks in motor parkinsonism was noted.

Figure: SAPS-PD total score over 6 weeks [2]



SAPS-PD, Scale for Assessment of Positive Symptoms–Parkinson's Disease; SE, standard error; LS, least squares; ES, effect size.

Adverse events occurring in ≥15% with SEP-363856 versus placebo included hallucinations (24% vs 14%), confused state (20% vs 14%), dizziness (16% vs 7%), and falls (12% vs 21%). CNS adverse events seemed dose-related. Adequately powered studies are needed to confirm these findings.

1. Koblan KS, et al. N Engl J Med. 2020;382(16):1497-1506.
2. Isaacson S, et al. Efficacy and Safety of SEP-363856, a Non–D2-Receptor Binding Drug With Antipsychotic Activity, in Patients With Parkinson's Disease Psychosis. S3.005, AAN 2021 Virtual Congress, 17-22 April.

Troriluzole for spinocerebellar ataxia

Long-term results of the BHV4157-201 trial among patients with spinocerebellar ataxia (SCA) suggest an attenuation of disease progression in patients treated with troriluzole for up to 3 years. This analysis focused on the continued assessment of change from baseline to 96 weeks in the total score on the Scale for the Assessment and Rating of Ataxia (SARA) [1].

The phase 2/3 BHV4157-201 study (NCT02960893) comprised an 8-week randomisation phase, followed by a 48-week open-label phase. Encouraging data at 1 year were a reason to add another 48 weeks of open-label treatment. Enrolled were 136 patients with hereditary SCAs; mean age was 53 years; 53% were female; baseline SARA score was 14.4. Patients in BHV4157-201 were treated with 140 mg of troriluzole administered daily for 1 year. SARA scores after 96 weeks of open-label treatment were compared with the expected score in untreated patients, which is an increase of 1-2 points per year, based on cumulative historical data [2]. Dr Melissa W. Beiner (Biohaven Pharmaceuticals, CT, USA) presented the results.

Least squares mean change from baseline in total SARA score after 96 weeks was -0.34 (95% CI -0.94 to 0.26), a significant improvement compared with the cumulative historical data (P=0.0007). While the primary analysis suggests a therapeutic benefit from troriluzole in this patient population, these results need to be confirmed in a prospective placebo-controlled trial. Dr Beiner added that patients with a gap in troriluzole treatment (3 weeks to 12 months) had a ≥1 point worsening during off-treatment, increasing with longer duration off troriluzole. "When patients experience a gap in troriluzole dosing, the decline in total SARA scores was in accordance with the duration of the gap. When troriluzole was then resumed, patients experienced an improvement in total SARA scores similar to the 48-week open-label observation."

1. Beiner M, et al. Analysis of 96 Week, Long-Term Open Label Extension Phase of Study BHV4157-201: A Phase IIb/III, Randomized, Double-blind, Placebo-controlled Trial of the Safety and Efficacy of Troriluzole in Adult Subjects with Spinocerebellar Ataxia. S3.002, AAN 2021 Virtual Congress, 17-22 April.
2. Diallo A, et al. J Neurol. 2020 Apr 7. doi: 10.1007/s00415-020-09815-2.

Stroke

Can linoleic acid help prevent stroke?

A Mendelian randomisation study provided evidence for an inverse causal association of circulating linoleic acid levels with risk of ischaemic stroke, particularly large artery stroke.

Linoleic acid is an essential fatty acid involved in the human diet. Epidemiological studies have suggested an inverse association between circulating linoleic acid levels and ischaemic stroke [1], but it was unclear whether the observed association is causal or due to confounding or reverse causation. To evaluate the potential causal relationship between circulating linoleic acid levels and risk of ischaemic stroke, summary statistics for ischaemic stroke were obtained from the MEGASTROKE consortium [2]. These data included 34,217 ischaemic stroke cases and 404,630 controls of European ancestry. First author David Wu (University of Minnesota Medical School, MN, USA) explained that 17 single nucleotide polymorphisms (SNPs) associated with circulating linoleic acid levels were used as instrumental variables in the Mendelian randomisation analysis, with another 2 SNP sets used in sensitivity analyses.

"We found an inverse causal relationship between circulating linoleic acid levels and ischaemic stroke overall, and especially in large artery stroke," Dr Wu said. Every 1% increase in genetically predicted linoleic acid levels was inversely associated with a 2% reduction in ischaemic stroke incidence. There was a significant causal association for large artery stroke (OR 0.95; 95% CI 0.92–0.98; P=0.00034), but not for cardioembolic stroke (OR 0.98; 95% CI 0.96–1.00; P=0.05) and small vessel stroke (OR 1.02; 95% CI 0.99–1.05; P=0.11). These findings are robust, as sensitivity analyses using 2 additional SNP sets as instrumental variables resulted in consistent findings.

1. Zhang W, et al. Nutrition. 2020;79-80:110953.
2. Wu D, et al. Effect Of Linoleic Acid On Ischemic Stroke: A Mendelian Randomization Study. S21.001, AAN 2021 Virtual Congress, 17-22 April.

No association between SSRIs and risk of ICH

Antidepressants are commonly prescribed to patients with intracerebral haemorrhage (ICH) in routine clinical practice. A new preliminary population-based study has found that the most commonly prescribed

antidepressants, selective serotonin-reuptake inhibitors (SSRIs), are not associated with an increased risk of ICH.

"By interfering with serotonin, which also plays a role in blood clotting, SSRIs may increase the risk of bleeding," explained Dr Mithilesh Siddu (University of Miami, FL, USA). "To determine if these antidepressants increase the risk of bleeding strokes, we looked at a large population of stroke patients." This study population consisted of 127,915 cases in whom information on antidepressant use was available [1]. Of these, 17,009 patients were prior SSRI users, while the other 110,906 had never had an SSRI prescription. The rate of ICH in both groups was 11% and 14%, respectively. Prior antidepressant users were more likely to be female, non-Hispanic white, have hypertension, diabetes mellitus, use oral anticoagulants, antiplatelets, and/or statins prior to hospital presentation.

After adjusting for other factors that could affect stroke risk, such as age, race, hypertension, diabetes mellitus, prior oral anticoagulant, antiplatelet, or statin use, SSRI users had the same ICH risk as non-users (OR 0.92, 95% CI 0.85–1.01). A total of 3.4% of all ICH patients and 9% of those for whom antidepressant information was available, were discharged from the hospital on an antidepressant (74% SSRI). "These findings are important, especially since depression is common after stroke and SSRIs are some of the first drugs considered," Dr Siddu said. "More research is needed to confirm our findings and to examine if SSRIs prescribed after a stroke may be linked to risk of a second stroke."

1. Siddu M, et al. Association Between Antidepressants Use and Intracerebral Hemorrhage: Florida Stroke Registry. P5.080, AAN 2021 Virtual Congress, 17-22 April.

Effectiveness of public awareness campaigns on stroke signs

The impact of FAST (Face-Arm-Speech-Time) public awareness campaigns on stroke signs recognition was assessed in Quebec, Canada. After multiple campaigns, FAST stroke signs identification improved by 26% overall. However, 1 in 3 people could still not identify FAST stroke signs and 1 in 5 people still would not activate emergency medical services.

Rapid community recognition of stroke signs is crucial to the timely activation of pre-hospital care. The Heart and Stroke Foundation of Canada launched the bilingual English/French FAST/VITE campaign in 2014 (see Table). Using data from 4 repeated cross-sectional surveys within 2.5 years, the impact of public awareness campaigns was investigated. Participants (1: n=450; 2: n=450; 3: n=451; 4: n=1,100), were asked to name stroke signs. A public awareness campaign preceded the first 3 surveys, and 2 more campaigns preceded the fourth survey [1].

Table: FAST/VITE – Learn the signs of stroke

Face	**V**isage	Is face drooping?
Arms	**I**ncapacité	Can you raise both arms?
Speech	**T**rouble de la parole	Is speech slurred or jumbled?
Time	**E**xtrême urgence	Call 911 right away

The identification of FAST stroke signs improved by 25% overall (OR 1.25; 95% CI 1.01–1.54; P=0.039). However, the proportion of respondents unable to identify any FAST stroke signs remained high after each survey (1: 37.7%; 2: 26.9%; 3: 30.4%; 4: 30.5%). Factors associated with worse FAST stroke sign identification were male sex, retirement, lower income, and lower education. Coincidental, people in these groups are also at higher risk of incident stroke.

1. Brissette V, et al. Improved Identification of FAST Stroke Signs in the Population After Multiple Public Awareness Campaigns in Quebec, Canada. S30.003, AAN 2021 Virtual Congress, 17-22 April.

Blood pressure reduction after LVO potential target for intervention

In patients with large vessel occlusion (LVO), marked and frequently iatrogenic blood pressure reductions occur around the time of initial imaging and prior to endovascular therapy (EVT), and may present a potential target for therapeutic intervention.

Decrease in blood pressure before reperfusion may increase the risk of infarct progression and poor functional outcome. A new study looked at the relation of blood pressure reductions during the hyperacute period of stroke with infarct progression and functional outcome [1]. Patients with LVO undergoing EVT were prospectively enrolled. To study timing of blood pressure reductions, high-frequency blood pressure and haemodynamic monitoring were used. Outcomes were analysed of 45 patients who underwent continuous blood pressure monitoring. Mean age was 72 years, 26 (58%) were female, mean NIH Stroke Scale score was 13.

There was a marked blood pressure reduction around the time of imaging, from which patients recovered, as well as

a sustained decrease in blood pressure after groin puncture, without return to baseline. After adjusting for age and admission NIH Stroke Scale score, mean arterial pressure difference from baseline (ΔMAP) was independently associated with infarct growth (P=0.02). On average, there was a 16 mL increase in infarct volume for every 10 mmHg reduction in ΔMAP (P=0.054) in the hyperacute phase before reperfusion. The authors suggested that the observed changes in haemodynamic variables throughout the acute stroke period indicate that fluid resuscitation could be used for haemodynamic optimisation.

1. Peshwe KU, et al. Blood Pressure Reductions in the Hyperacute Phase of Large Vessel Occlusion Ischemic Stroke Are Associated With Infarct Progression And Poor Functional Outcome. S6.003, AAN 2021 Virtual Congress, 17-22 April.

Other Topics

Lower-sodium oxybate for hypersomnia

In participants with idiopathic hypersomnia, lower-sodium oxybate (LXB) led to a clinically meaningful decrease in excessive daytime sleepiness, self-reported global change, and overall idiopathic hypersomnia symptom severity. The overall safety profile was consistent with that of sodium oxybate (SXB).

LXB contains calcium, magnesium, potassium, and sodium oxybate, representing a novel oxybate treatment with 92% less sodium than SXB. It was tested in patients with idiopathic hypersomnia, a condition for which currently no approved treatment exists [1]. All participants started with 16 weeks of treatment with LXB, during which period the dose was titrated, optimised and, during the last 2 weeks, stabilised. They were then randomised to placebo or to continue LXB for a 2-week withdrawal period. The primary efficacy endpoint was change in Epworth Sleepiness Scale (ESS) score. The safety population included 154 participants, who had a mean ESS of 16; mean dose was 6.0 g/night.

At the end of the double-blind withdrawal period, ESS scores were significantly worse in the placebo group compared with the LXB group, with a mean difference in change of -6.51 (95% CI -7.99 to -5.03; P<0.0001). Patient Global Impression of Change (PGIc) was also significantly worse (21.4% for LXB vs 88.1% for placebo; P<0.0001), as was Idiopathic Hypersomnia Severity Scale (IHSS) score, with an estimated median difference of -12.00 (95% CI -15.0 to -8.0; P<0.0001). Overall incidence of treatment-emergent adverse events was 80%. Treatment-emergent adverse events which occurred in at least 5% of participants were nausea (21.4%), headache (16.2%), dizziness (11.7%), anxiety (10.4%), and vomiting (10.4%). Serious treatment-emergent adverse events occurred in 4 participants, but none were deemed related to study drug.

Results of LXB in patients with narcolepsy with cataplexy were also presented [2]. All participants received LXB during a 12-week optimised treatment and titration period, followed by a 2-week stable-dose period. They were then randomised to placebo or continued LXB treatment during a 2-week withdrawal period. Health-related quality of life worsened in those randomised to placebo but remained stable in participants who continued LXB treatment. The overall safety profile of LXB was similar to SXB.

1. Dauvilliers Y, et al. Efficacy and Safety of Lower-Sodium Oxybate in a Phase 3, Placebo-Controlled, Double-Blind, Randomized Withdrawal Study in Adult Participants With Idiopathic Hypersomnia. AAN 2021 Virtual Congress, 17-22 April.
2. Foldvary-Schaefer N, et al. Quality of Life in a Phase 3, Placebo-Controlled, Double-Blind, Randomized Withdrawal Study of Lower-Sodium Oxybate in Adults With Narcolepsy With Cataplexy. S9.002, AAN 2021 Virtual Congress, 17-22 April.

Gene therapy for Leber hereditary optic neuropathy

An indirect comparison of 76 treated patients with an external control group of 208 untreated patients showed a clinically meaningful effect of gene therapy on visual outcomes in patients with Leber hereditary optic neuropathy with ND4-mutations (ND4-LHON).

The treated population consisted of 76 patients with ND4-LHON who had received unilateral treatment with rAAV2/2-ND4 gene therapy –showing unexpected sustained bilateral improvement– in two phase 3 multicentre clinical trials: RESCUE (NCT02652767) and REVERSE (NCT02652780). Of this cohort, 62 patients enrolled in a long-term follow-up study. The untreated population consisted of 208 *ND4*-LHON patients, the large majority of whom

participated in 10 historical studies. Best corrected visual acuity (BCVA) in both groups was compared 12, 18, 24, 36, and 48 months after onset of vision loss [1].

In the treated group, BCVA demonstrated gradual, progressive, and sustained improvement from month 12 to the last available observation (on average 51.5 months). In untreated patients, there was no improvement. After 48 months, mean BCVA in the treated and untreated cohort was 1.26 and 1.59 logMAR, respectively (P<0.01).

1. Newman N, et al. Evaluation of rAAV2/2-ND4 Gene Therapy Efficacy in Leber Hereditary Optic Neuropathy Using an External Control Group of Untreated Patients. P21.011, AAN 2021 Virtual Congress, 17-22 April.

Patisiran for hATTR amyloidosis: 24-month efficacy and safety

In patients with hereditary transthyretin-mediated (hATTR) amyloidosis with polyneuropathy, patisiran continued to demonstrate durability of efficacy after 24 months of treatment in the ongoing open-label extension (OLE) of the APOLLO study.

APOLLO (NCT01960348) is the largest randomised clinical trial of patients with hATTR amyloidosis with polyneuropathy to date. Patients were eligible to enter the OLE if they had completed the parent study, notably APOLLO participants randomised to placebo (APOLLO/placebo, n=49) or patisiran (APOLLO/patisiran, n=137), as well as phase 2 OLE patients (n=25) [1]. For 178 patients, 24-month data was available.

Modified Neuropathy Impairment Score +7 (mNIS+7) demonstrated durable improvement. Mean change in the APOLLO/patisiran and phase 2 OLE groups was -5.9 and -4.9, respectively, compared with baseline scores in the parent study. Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) also continued to show durable improvement in APOLLO/patisiran patients (mean change -2.4). The safety profile of patisiran remained consistent with previous studies.

Another presentation described the impact of patisiran on functioning in daily life of 225 APOLLO participants [2]. For the majority of these, patisiran preserved the ability to perform activities of daily living and functional status versus placebo. The odds of stabilising or improving these assessments were also higher.

1. Adams D, et al. Global Open-label Extension: 24-month Data in Patients with hATTR Amyloidosis. S32.001, AAN 2021 Virtual Congress, 17-22 April.
2. Peltier A, et al. Impact of Patisiran on Activities of Daily Living and Functional Status in hATTR Amyloidosis. S32.002, AAN 2021 Virtual Congress, 17-22 April.

Vutrisiran for hATTR amyloidosis with polyneuropathy

Vutrisiran offers an additional treatment option for patients with hereditary transthyretin-mediated (hATTR) amyloidosis, also known as ATTRv amyloidosis. This investigational RNA interference (RNAi) therapeutic agent significantly improved neuropathy impairment, quality of life, and gait speed compared with an external placebo group.

hATTR amyloidosis is a rare, underdiagnosed, rapidly progressive, and fatal disease caused by misfolded transthyretin that accumulates as amyloid fibrils in multiple tissues and organs. Vutrisiran is an RNAi therapeutic which targets liver-expressed variant and wild-type transthyretin. Dr David Adams (Centre Hospitalier Universitaire Bicêtre, France) presented the 9-month efficacy and safety from the phase 3, open-label HELIOS-A study (NCT03759379) of vutrisiran [1]. The study enrolled 164 patients, who were randomised 3:1 to vutrisiran or to patisiran, a reference comparator RNAi therapeutic approved for hATTR amyloidosis with polyneuropathy. The placebo group from the APOLLO trial (n=77; NCT01960348) served as external control.

Vutrisiran met the primary endpoint, which was change in neuropathy impairment as measured by Modified Neuropathy Impairment Score +7 (mNIS+7) versus placebo after 9 months. Mean change was -2.24 and +16.76 in the treatment and placebo group, respectively (P<0.00001). Both secondary endpoints were also met after 9 months; there were statistically significant improvements versus placebo in quality of life (Norfolk QoL-DN): -3.3 and 12.9, respectively (P<0.00001), as well as in gait speed (10-Meter Walk Test [10-MWT]): -0.001 and -0.133 (P=00003). The effects on neuropathy and QoL were seen across all patient subgroups. Vutrisiran also led to rapid and sustained reduction in serum transthyretin levels. It had an acceptable safety profile and favourable benefit-risk profile.

1. Adams D, et al. HELIOS-A: 9-month Results from the Phase 3 Study of Vutrisiran in Patients with Hereditary Transthyretin-Mediated Amyloidosis with Polyneuropathy. S13.001, AAN 2021 Virtual Congress, 17-22 April.

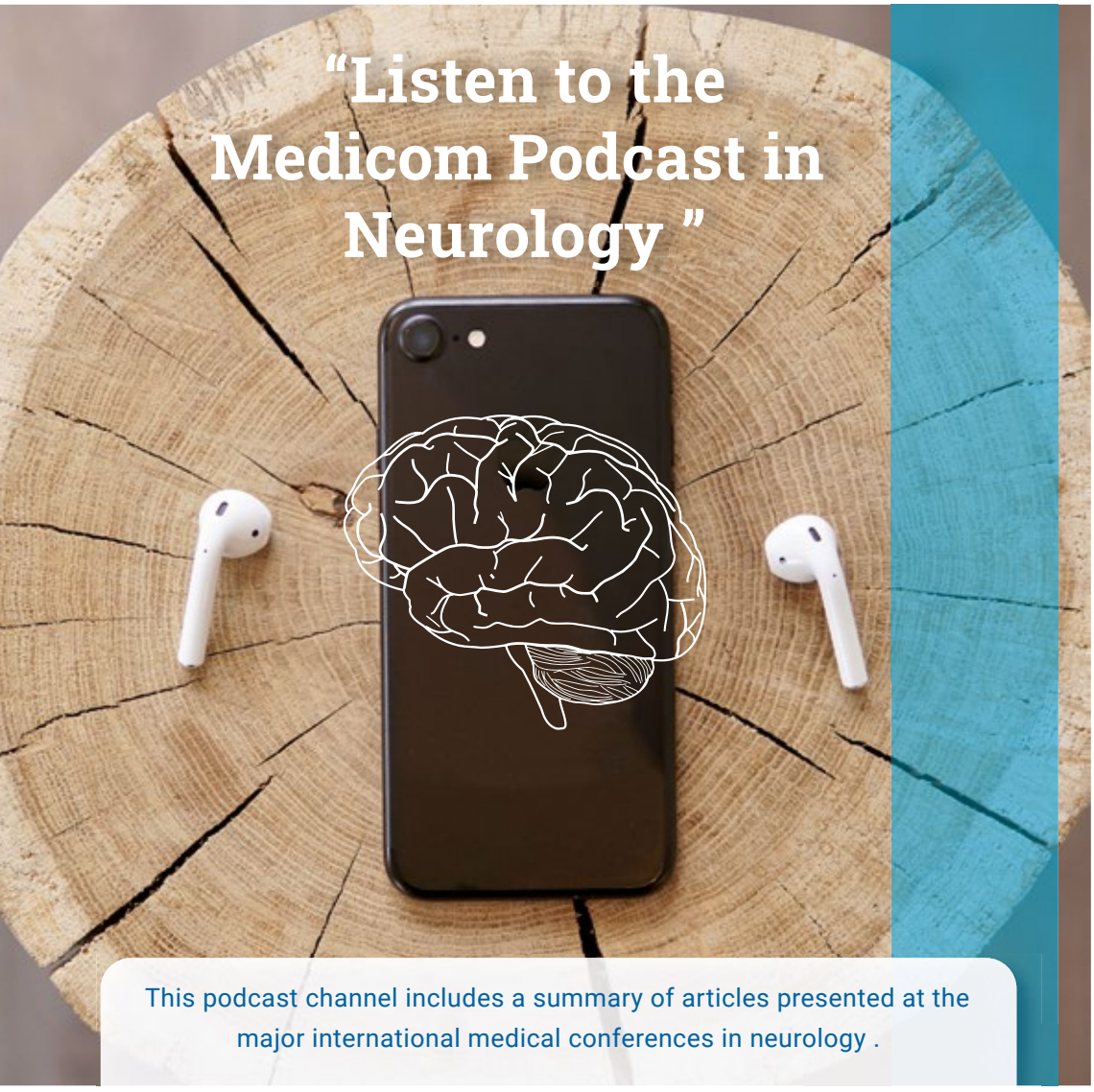
10 kHz spinal cord stimulation for painful diabetic neuropathy

In the large, randomised-controlled SENZA-PDN trial, most subjects with painful diabetic neuropathy (PDN) benefitted from treatment with 10 kHz spinal cord stimulation. The results showed clear differences compared with the best available conventional medical treatments.

Most of the pharmacological treatments available for PDN, such as pregabalin and duloxetine, have a number needed to harm that is close to the number needed to treat. In the SENZA-PDN trial (NCT03228420), 216 PDN patients were randomised 1:1 to 10 kHz spinal cord stimulation plus conventional medical management or to conventional medical management alone. Subjects had a clinical diagnosis of PDN with symptoms ≥12 months; they were refractory to medications and had a lower limb pain intensity ≥5 on a 0–10 visual analogue scale (VAS). The combined primary endpoint was ≥50% pain relief and no worsening of baseline neurological deficits. Prof. Erika Petersen (University of Arkansas, USA) presented the results [1].

In the experimental group, average VAS scores decreased from 7.6 at baseline to 1.7 at 6 months. Only 2.3% of subjects had worsened symptoms, whereas 85% were deemed responders, defined as ≥50% pain relief. In the conventional management group, average VAS scores were 7.0 at baseline and 6.9 at 6 months; over half of subjects (52%) reported worsening pain. Just 6.3% of conventional management subjects were deemed responders (P<0.001). Neurological examination showed improvements for 65.9% and 8.5%, respectively, in the experimental and control group (P<0.001). Prof. Petersen noted that the primary endpoint as well as 7 of 8 prespecified secondary endpoints were met. Durability of treatment effects was demonstrated for 12 months; study follow-up will continue for another 12 months.

1. Petersen E, et al. Sustained Benefits for 10 kHz Spinal Cord Stimulation Treatment of Painful Diabetic Neuropathy - Six Month Results from a Multicenter Randomized Controlled Trial. AAN 2021 Virtual Congress, 17-22 April.



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