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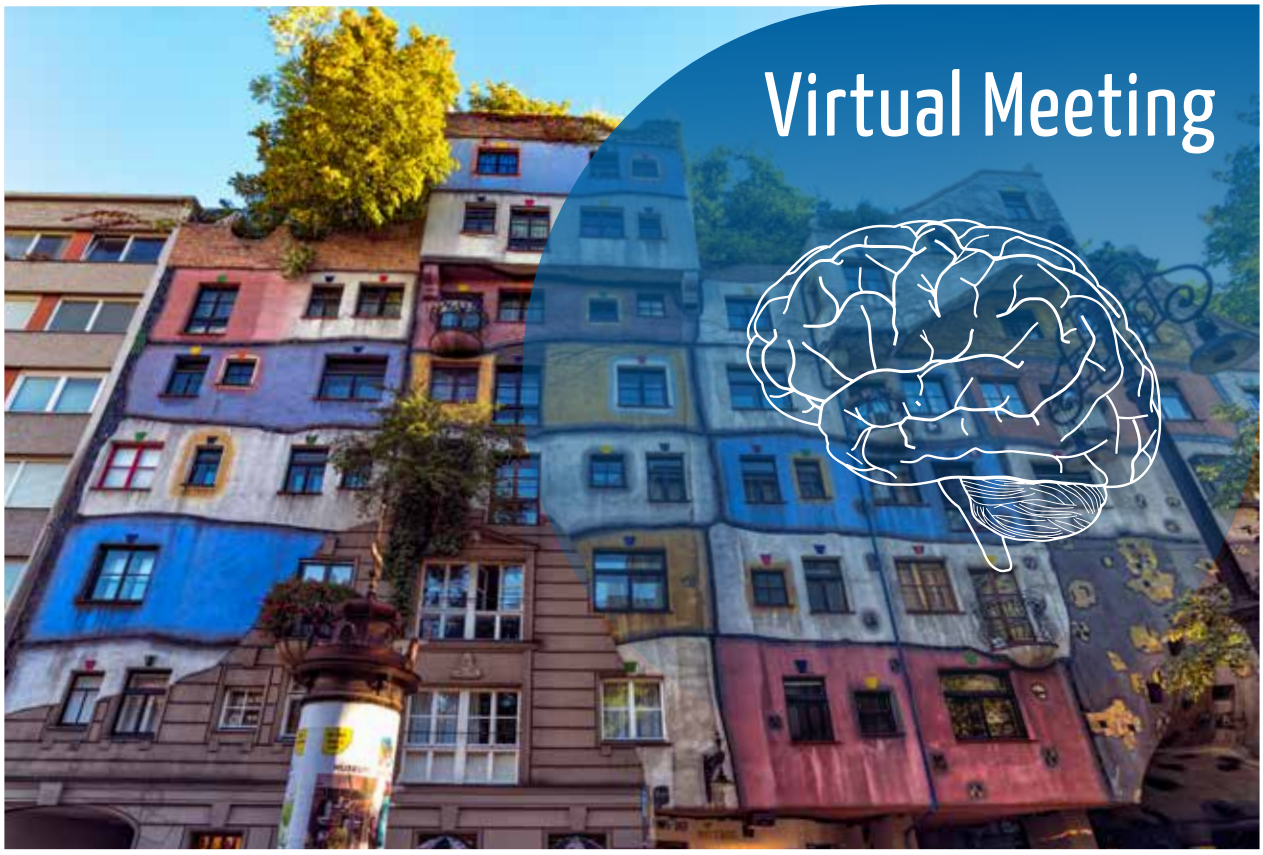
PEER-REVIEWED CONFERENCE REPORT



Dexamethasone Not Indicated for Chronic Subdural Haematoma

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

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Letter from the Editor

Prof. Hans-Peter Hartung

Dear colleagues,

Like last year`s EAN meeting and almost any of the big international congresses, EAN 2021 was again held as a virtual meeting. So, while the splendour of Vienna and the chats in the Kaffeehäuser (coffee houses) were missed, the extensive program provided a very up-to-date overview of our quickly moving field.

Much news was communicated regarding diagnostic, therapeutic, and pathogenetic advances in subdisciplines like multiple sclerosis, movement disorders, epilepsy, the dementias, and neuromuscular disorders. Appropriately, one focus was on COVID-19, its nervous system manifestations, vaccinations, and specific management issues.
There were lively discussions during live Q&A sessions and in the chatrooms.
As always, the main meeting was preceded by a range of excellent teaching courses providing high level postgraduate educational sessions.

I hope you will find this report highlighting some outstanding contributions useful.
We all expect and long for a face-to-face meeting at EAN 2022.

With best wishes,
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.

COVID-19

First evidence of brainstem involvement in COVID-19

Respiratory failure in COVID-19 patients is likely to have a neurogenic component. An Italian study provided the first combined neuropathological, neurophysiological, and clinical evidence of brainstem involvement, suggesting viral trafficking via the vagus nerve between lung and brainstem.

Dr Tommaso Bocci (University of Milan, Italy) and colleagues acquired neuropathological data from people who died of COVID-19 and healthy controls to assess brainstem involvement in COVID-19 [1]. Histopathological analysis was performed in 2 patients who died of respiratory failure due to COVID-19-related pneumonia. The results were compared with 2 COVID-19-negative patients who died of non-neurological conditions. To clarify whether neuropathological findings had a functional correlate, the blink reflex was assessed in 11 patients with severe COVID-19, healthy subjects, and non-COVID-19 ICU patients. The glabellar and corneal reflexes were also evaluated.

Autopsies showed extensive neuronal damage and a higher number of corpora amylacea in the medulla oblongata of COVID-19 patients. Immunohistochemistry revealed the presence of SARS-CoV-2 virus in the brainstem. Latencies of the first response (RI) did not differ. However, the medullary second response (RII) of the supraorbital blink reflex was impaired in COVID-19 patients compared with controls and non-COVID-19 ICU patients. Clinically, the glabellar reflex was reduced or absent.

The results suggest that brainstem involvement likely contributes to respiratory failure in COVID-19 patients, as was postulated by Manganelli et al. [2] and Baig et al. [3], Dr Bocci concluded. "Most importantly, SARS-CoV-2 immunohistochemically detected in the vagus nerve fibres is an original and previously unreported finding, which suggests viral trafficking between brainstem and lung."

1. Bulfamante G, et al. Brainstem damage in COVID-19. OPR-054, EAN 2021 Virtual Congress, 19–22 June.
2. Manganelli F, et al. Neurol Sci. 2020;41:1663–5.
3. Baig AM, et al. ACS Chem. Neurosci. 2020;11(7):995–8.

Cognitive/behavioural alterations persistent after COVID-19

COVID-19 is associated with significant cognitive and behavioural problems which persist several months after remission of the disease [1]. Cognitive and behavioural alterations were more severe in the youngest patients and were independent of brain structural integrity.

Around 30% of COVID-19 survivors manifest with cognitive disturbances and 30–40% with psychopathological disorders. It is still unclear whether these disturbances persist after COVID-19 infection. An Italian study set out to explore psychopathological features within 2 months (subacute phase) and 10 months (post-COVID-19 phase) after hospital discharge in a cohort of 49 subjects with confirmed COVID-19. Participants underwent comprehensive neuropsychological assessment and a brain MRI within 2 months from hospital discharge; age range was 40–75 years. Prof. Federica Agosta (Vita-Salute San Raffaele University, Italy) presented the results.

In the subacute phase, 53% of participants had ≥1 cognitive deficit. Domains affected the most were executive functions (39%), memory (6%), visuospatial functions (6%), and non-executive functions (2%). Also, 16% had depressive symptoms and 18% reported post-traumatic stress disorder (PTSD). Lower performance at information processing was associated with higher severity of respiratory COVID-19 symptoms ($r=0.44$; $P=0.002$). Lower performance on memory tests was associated with more white matter brain lesions. Cognitive and psychopathological problems were more severe in younger people, with most patients aged <50 having executive dysfunctions. In the post-COVID-19 phase, at 10 months of follow-up, the percentage of patients with cognitive deficits decreased from 53% to 36%. The incidence of depression and PTSD did not change.

1. Agosta F, et al. Cognitive and behavioral features of a cohort of patients in COVID-19 post-acute phase. EPR-067, EAN 2021 Virtual Congress, 19–22 June.

Neural base of persistent hyposmia after COVID-19

An Italian group provided the first evidence of cortical hypometabolism in patients with isolated persistent hyposmia

after COVID-19 without severe respiratory distress. They conclude that ^{18}F-FDG-PET may play a role in the identification of long-term brain functional sequelae of COVID-19.

Hyposmia is often not only the first symptom of COVID-19, but its persistence is also a relatively frequent neurological complication of the infection. Little is known about the neural bases of hyposmia persisting after the patient's recovery from COVID-19. Dr Matteo Pardini (University of Genoa, Italy) and colleagues evaluated the presence of regional brain hypometabolism in patients with persistent isolated olfactory dysfunction after recovery from COVID-19 [1]. A total of 22 patients underwent whole-body ^{18}F-FDG-PET at least 4 weeks after their recovery, 14 of whom had isolated persistent hyposmia. A voxelwise analysis was used to identify brain regions of relative hypometabolism in patients with hyposmia, compared with 61 healthy controls.

Patients with hyposmia after COVID-19 were characterised by relative hypometabolism in parahippocampal and fusiform gyri in both hemispheres and in left insula compared with controls. Structural connectivity maps showed that the hyposmia cluster was included in the bilateral longitudinal fasciculi, with a probability score of 0.82 and 1.0 for the right and left inferior longitudinal fasciculus, respectively.

"One of the hypotheses to explain hyposmia in COVID-19 patients –in the absence of nasal congestion– is that the virus enters the CNS through the first neurons of the olfactory pathway located in the olfactory mucosa," Dr Pardini explained. "The present evidence of hypometabolism in two symmetrical, similar regions within the limbic cortex may support the occurrence of a distal involvement of the olfactory pathway. Moreover, the involvement of the inferior longitudinal fasciculus is in line with observations of its role in hyposmia in Parkinson's disease, HIV, and hepatitis C."

1. Pardini M, et al. Brain metabolism and persistent olfactory deficits after SARS-CoV-2 infection: an FDG-PET study. OPR-142, EAN 2021 Virtual Congress, 19–22 June 2021.

Neurological symptoms and complications of COVID-19 affect outcomes

New findings from a large German registry study shed more light on the neurological implications of COVID-19 and the factors affecting outcomes. Patients with pre-existing neuro-immunological diseases and prior cerebrovascular events did not seem to have an elevated risk of unfavourable outcomes or complicated disease course.

Dr Nina Kleineberg (University Hospital Cologne, Germany) presented findings from the Lean European Open Survey on SARS-CoV-2-Infected Patients (LEOSS), based on data from 6,537 patients from 127 centres across Europe with a diagnosis of SARS-CoV-2 infection between January 2020 and February 2021 [1].

In total, 92.1% of patients in this cohort were hospitalised. More than half (54.4%) had ≥1 neurological symptom, 3.3% had a new neurological complication, and 18.1% had ≥1 pre-existing neurological comorbidities. The neurological manifestations (see Table 1) and complications (see Table 2) in this study were mostly in agreement with previously published data. Overall, 33.5% of patients had a complicated, and 19.4% a critical disease course. Total death rate was 14.7%. This was higher in patients with dementia (38.0%), movement disorders (32.8%), and prior cerebrovascular disease (32.3%). Age (OR 1.53), cardiovascular diseases (OR 1.74), muscle weakness (OR 1.40), pulmonary diseases (1.49), and male sex (OR 1.52) were associated with a significantly increased risk of a critical COVID-19 disease course, failed recovery, and death. Patients with pre-existing neuro-immunological diseases and prior cerebrovascular events did not seem to have an elevated risk of unfavourable outcome or complicated disease course. Most unspecific neurological symptoms at baseline were not associated with unfavourable short-term outcome. Headache may predict a favourable outcome. Excessive fatigue at baseline was associated with a higher risk of less favourable short-term outcome.

Table 1: Neurological symptoms of patients in LEOSS [1]

Neurological symptoms	All phases/total (n=6,537)
Nausea/emesis	16.6 % (867/5,227)
Muscle aches	19.1% (976/5,121)
Muscle weakness	17.0% (890/5,242)
Delirium	6.7% (340/5,045)
Excessive tiredness	28.0% (1,466/5,240)
Headache	18.5% (942/5,096)
Impaired smell	9.0% (443/4,964)
Impaired taste	12.8% (636/4,972)

Table 2: Neurological complications of patients in LEOSS [1]

Neurological complications	Total n=3,451	Complicated phase n=2,965	Critical phase n=1,264
Intracerebral bleeding	2.2% (57/2,605)	0.4% (9/2,565)	5.0% (51/1,027)
Ischaemic stroke	1.0% (26/2,578)	0.5% (14/2,562)	1.3% (13/1,019)
Meningitis/encephalitis	0.6% (16/2,578)	0.2% (5/2,564)	1.3% (13/1,019)
Seizure	0.8% (20/2,577)	0.3% (8/2,564)	1.2% (12/1,018)
Critical illness myopathy	2.6% (55/2,146)	0.0% (0/2,114)	6.3% (55/874)
Critical illness polyneuropathy	3.2% (68/2,150)	0.1% (3/2,113)	7.6% (66/873)

1. Kleineberg N, et al. Neurological implications of COVID-19 – results of the LEOSS registry. OPR-056, EAN 2021 Virtual Congress, 19–22 June.

Cerebrovascular Disease

Intracerebral haemorrhage only slightly increases mortality in COVID-19 patients

An Italian study addressing the clinical course of patients with intracerebral haemorrhage (ICH) and simultaneous SARS-CoV-2 infection confirmed that age, ICH location, and previous antiplatelet or anticoagulant treatment predict in-hospital death. Unlike ischaemic stroke, ICH in COVID-19 patients only slightly increased mortality.

The study, presented by Dr Davide Sangalli (Alessandro Manzoni Hospital, Italy), was initiated by the Italian Society of Hospital Neurosciences (SNO) as a retrospective, observational study in 20 Northern Italian medical centres [1]. Included were 949 consecutive patients admitted to neurological departments from 1 March to 30 April 2020 with cerebrovascular disease. Average age was 73.4 years, 52.7% were men. A total of 127 patients (13.4%) had primary ICH, 68 (53.5%) of whom were women. Only 16 ICH patients (12.6%) had laboratory-confirmed SARS-CoV-2 infection. There were no gender differences.

During hospitalisation, 32 patients (25.2%) died; 6 were SARS-CoV-2-positive (37.5%), 26 were negative (23.4%); the difference was not statistically significant (OR 1.96; 95% CI 0.65–5.91; P=0.20). The need for respiratory support negatively affected prognosis: 8 patients required continuous positive airway pressure (CPAP), 7 were eventually intubated. Most deaths in COVID-19 patients occurred in the severe pneumonia and respiratory distress group: 4 of 7 died (57.2%), while only 2 of 9 patients (22%) in the group with no or mild COVID-19 symptoms died (OR 4.4; 95% CI 0.9–20.8; P=0.06).

SARS-CoV-2-related pneumonia or respiratory distress, lobar location, and previous antiplatelet or anticoagulant treatment were the only factors significantly associated with increased mortality in ICH. SARS-CoV-2 infection, regardless of respiratory involvement, led to a non-significantly increased risk of in-hospital death, which was not as marked as that observed in ischaemic stroke or myocardial infarction. In this cohort, a massive inflammatory response with increased CRP values appeared to be related with a worse prognosis in SARS-CoV-2 patients, whereas elevated D-dimer levels increased mortality risk in both SARS-CoV-2-positive and -negative patients.

1. Sangalli D, et al. Primary intracerebral haemorrhage during SARS-CoV-2 outbreak. OPR-143, EAN 2021 Virtual Congress, 19–22 June 2021.

Stroke with covert brain infarction indicates high vascular risk

Chronic covert brain infarction (CBI) was present in more than one-third of patients with a first-ever acute ischaemic stroke in a single-centre cohort study. These patients represent a subgroup with a high vascular risk.

Of patients with a first-ever acute ischaemic stroke, 1 in 3 has an additional chronic CBI on acute imaging. Dr Thomas Meinel (Bern University Hospital, Switzerland) and his group set out to assess the frequency, imaging phenotypes, and distribution of CBI in patients with a first-ever clinically evident acute ischaemic stroke; determine the vascular risk factor profile according to CBI phenotypes; and disentangle the association of CBI and undifferentiated white matter hyperintensities (WMH) [1]. They assessed 1,546 consecutive patients with first-ever acute ischaemic stroke with MRI on admission between 2015 and 2017.

A total of 950 CBI lesions were found in 574 of 1,546 patients (37%). The most frequent CBI locations were cerebellar (31%), subcortical supratentorial (31%), and cortical (24%). CBI phenotypes included cavitary lesions (49%), combined grey and white matter lesions (30%), grey matter lesions (13%), and large subcortical infarcts (7%). Vascular risk profile and WMH severity (19% in absence of WMH, 63% in severe WMH; P<0.001) were associated with CBI. NIH Stroke Scale scores on admission were higher in patients with an embolic CBI phenotype (median NIHSS 5; P=0.025).

Dr Meinel concluded that additional CBI indicates an elevated vascular risk, as several vascular risk factors and WMH severity are associated with CBI. Different phenotypes of CBI were associated with differing risk factor profiles, potentially pointing towards discriminative ischaemic stroke aetiologies. For example, a consistent association was observed between cortical CBI and atrial fibrillation (adjusted OR 2.03). At least 25% of CBIs found in this stroke population were not part of the small vessel disease spectrum. "Although not incorporated in current guidelines for acute stroke management, chronic CBI is associated with certain stroke subtypes and might be used to develop individualised diagnostic work-up and therapeutic approaches for patients with a first-ever acute stroke," Dr Meinel elaborated.

In a separate talk on CBI and precision medicine [2], Dr Meinel gave the following take-home messages:

- CBI is the most frequent incidental finding on brain MRI, present in 30% of 70-year-old patients. This percentage is higher in cardiovascular risk populations.
- Look for CBI and then act upon them: as a neuroradiologist, describe them according to the STandards for ReportIng Vascular changes on nEuroimaging (STRIVE), but also when they are not part of the small vessel disease spectrum; ask the patient if it was truly covert and if full workup was done; were there covert deficits, such as visual field defects; assess and treat modifiable cardiovascular risk factors; assess depression, cognition, and mobility.
- CBI can be used as a prognostic tool in, for example, atrial fibrillation.
- Incident CBI offers the opportunity to reduce cardiovascular morbidity and mortality.

1. Vynckier J, et al. Phenotypes of chronic covert brain infarction in first-ever ischemic stroke patients – a cohort study. OPR-128, EAN 2021 Virtual Congress, 19–22 June.
2. Meinel T. Covert brain infarction: Towards precision medicine in research, diagnosis, and therapy for a silent pandemic. SYMP11-1, EAN 2021 Virtual Congress, 19–22 June.

Expanding precision medicine to stroke care

The stroke community needs a philosophical and paradigm shift as well as a higher level of care, argued Dr Svetlana Lorenzano (Sapienza University of Rome, Italy) in a focused workshop on precision medicine in stroke care [1]. Individualised treatments, based on prognostic prediction models incorporating precision medicine-based variables, represent the next frontier in stroke care.

Applying precision medicine to stroke care in order to identify diagnostic and prognostic markers is challenging but crucial. "Guidelines are essential to support the clinician's decision-making process, but in daily care they are not always helpful, particularly because we face the challenges posed by the heterogeneity of cerebrovascular disease phenotypes and the complexity of individual cases," Dr Lorenzano said. Strong recommendations in guidelines are based on randomised controlled trials, which generally cannot fully consider the complexity of cerebrovascular disease pathophysiology for reasons of feasibility and study design. Exactly these shortcomings of trials could be overcome by precision medicine. The continuous forming and applying of large datasets, the growing collection of omics data (genomics/transcriptomics/proteomics/metabolomics), and the development of advanced neuroimaging techniques (including metabolic imaging, imaging of functional connectivity, and radiomics) have established a basis for precision medicine in stroke. Precision medicine can improve primary/secondary prevention, diagnosis, phenotyping, treatment, and prognosis.

Implementation of precision medicine into clinical practice is still far from being a reality, however, and healthcare disparities around the world may slow this down. Nevertheless, stroke patients already request personalised management. Multidisciplinary teams including clinicians, biostatisticians, and experts in omics, imaging techniques, computational science, digital health, and big data are needed. Multicentre collaborative efforts should be put in place through the establishment of consortia and adequate infrastructure for proper and standardised data collection.

In a down-to-earth conclusion of the session, Prof. Louis Caplan (Harvard Medical School, MA, USA) argued precision medicine and personalised medicine should be combined in daily practice [2]:

- Find out exactly what is wrong with each patient in as much detail as possible. (Here Prof. Caplan quoted Miguel de Cervantes, author of Don Quixote: "For when the cause of the complaint is unsure, 'Twould be a miracle to find a cure.")
- Get to know each patient and their circumstances: family situation, psychosocial and economic stress, thoughts, fears, biases, and wishes.
- Therapeutic decisions are made with, by, and for complex individuals.

1. Lorenzano S. Precision medicine in stroke – Current applications. FW08-1, EAN 2021 Virtual Congress, 19–22 June.
2. Caplan LR. Precision medicine or personalized medicine? FW08-3, EAN 2021 Virtual Congress, 19–22 June.

Dexamethasone not indicated for chronic subdural haematoma

Results of the DECSA trial demonstrated that dexamethasone is not indicated for the treatment of symptomatic chronic subdural haematoma; surgery is the appropriate treatment. In the trial, both treatments were directly compared.

The incidence of chronic subdural haematoma is rising due to the ageing population and the increasing use of oral anticoagulant therapy. Surgery by burr hole craniotomy with closed subdural drainage is still the mainstay of therapy, but dexamethasone is widely applied as an alternative or adjuvant treatment.

The DECSA trial (EUCTR 2015-001563-39) tested the hypothesis that dexamethasone is non-inferior to surgical treatment in achieving favourable functional outcome [1]. DECSA was a randomised, multicentre, phase 4 trial with blinded endpoint assessment. Patients with chronic subdural haematoma were allocated to dexamethasone 16 mg daily for 4 days, then tapered to 50% every 3 days over 19 days; or surgery by burr hole craniotomy with closed subdural drainage within 24–48 hours. Primary endpoints were favourable functional outcome at 3 months (modified Rankin Scale score 0–2) and, in a separate study, cost-effectiveness at 12 months. Results were presented by Dr Ishita Miah (Leiden University Medical Center, the Netherlands).

An interim-analysis including 252 participants revealed between-group differences in efficacy and safety, after which immediate termination of the trial was recommended. Favourable functional outcome was seen in 79 of 124 patients (63.7%) in the dexamethasone group versus in 97 of 124 patients (78.2%) in the surgery group (adjusted OR 0.70; 95% CI 0.33–2.95). No symptoms were observed in 21 of 124 patients (16.9%) versus 44 of 124 patients (35.5%), respectively. Eight (6.5%) versus 2 patients (1.6%) died (adjusted OR 2.74; 95% CI 0.45–16.65). The number of patients with serious adverse events was 61 (65.6%) versus 32 (34.4%), respectively. In the dexamethasone group, 67 of 127 (52.8%) needed additional surgery.

1. Miah IP, et al. Dexamethasone versus Surgical Treatment for Chronic Subdural Hematoma: The DECSA trial. OPR-202, EAN 2021 Virtual Congress, 19–22 June.

Cognitive Impairment and Dementia

Severe outcomes of COVID-19 in patients with dementia

In patients with dementia, COVID-19 frequently revealed itself by confusion and asthenia, and was associated with a high fatality rate. A group of French researchers recommend SARS-CoV-2 testing after any significant change in frequency of confusion and delirium in patients with dementia.

Dementia appears independently associated with higher mortality in COVID-19 patients. However, large cohort studies of patients with dementia have been lacking so far. Dr Agathe Vrillon (Hôpital Lariboisière Fernand-Widal, France) reported on the outcomes of 125 patients with dementia hospitalised for confirmed COVID-19 [1]. Median age was 86 years; 67.2% had ≥2 comorbidities. Male sex (41.6%) was associated with mortality (P=0.029).

The most common symptoms at COVID-19 onset were confusion and delirium (82.4%) and asthenia (76.8%). Signs of infection were frequent: fever (72.8%), cough (49.6%), and expectorations (21.6%). Falling was an initial symptom in 35.2% of patients. Dyspnoea (P<0.001) and desaturation (P=0.002) were associated with mortality. Complications significantly associated with death were acute respiratory distress syndrome, cardiac injury, and acute kidney injury (see Table). The most frequently applied treatment was antibiotics (61.6%). Oxygen support was given in 60% of cases, more often in non-survivors (P<0.0001). Steroids were prescribed in only 8%.

Table: Complications of COVID-19 and their relation to survival [1]

Complications	Total (n)	P-value (non-survivors vs survivors)
Acute respiratory distress syndrome	26.6% (32)	<0.0001
Cardiac injury	13.6% (17)	0.024
Acute kidney injury	16.8% (21)	0.021
Bacterial superinfection	14.4% (18)	0.122
Persisting behavioural disorder	19.2% (24)	0.278
Diabetic ketoacidosis	2.4% (3)	1.00
Seizure	2.4% (3)	0.536
Stroke	2.4% (3)	1.00

The fatality rate at 21 days was 22.4% (n=28). "This is a significant rate, but lower than was reported in similar studies," according to Dr Vrillon. Median delay between admission and death was 8.5 days. Median length of hospital stay for survivors was 16 days; 40.2% were discharged before end of follow-up. There were 2 independent risk factors of death: chronic renal disease (ExpB=4.631) and CRP at admission (ExpB=1.013).

1. Vrillon A, et al. COVID-19 in patients with dementia: clinical features and predictive factors of mortality in a cohort of 125 patients. OPR-144, EAN 2021 Virtual Congress, 19–22 June.

Hypertension pathology visible in white matter lesion volume

White matter lesions (WMLs) seem to represent a marker of advanced hypertension pathology, calling for early markers of brain damage such as structural and functional connectivity. Longitudinal studies are required to establish the possible long-term benefits of blood pressure control for brain health.

WMLs of presumed vascular origin are a frequent finding in older people. These are attributed to small vessel disease, involved in the pathogenesis of cognitive decline. Vascular risk factors, especially arterial hypertension, predispose for small vessel disease, and offer a potential for prevention. The population-based 1000BRAINS study aims to unravel the variability of brain structure, function, and connectivity, as well as cognition in relation to influences such as genetic factors, lifestyle, urban environment, and health conditions [1].

In the study, the association of systolic (SBP) as well as diastolic blood pressure (DBP), antihypertensive medication, and treatment efficacy with WML volume were analysed. Treatment efficacy was evaluated using a classification based on antihypertensive medication and BP:
1) untreated BP <120/<80 mmHg (n=180), 2) untreated SBP 120–139 mmHg or DBP 80–89 mmHg (n=159), 3) untreated BP 140/90 mmHg (n=75), 4) treated BP <120/<80 mmHg (n=62), 5) treated SBP 120–139 mmHg or DBP 80–89 mmHg (n=81), 6) treated BP 140/90 mmHg (n=71).

In 560 participants (65.2 years, 51.4% men), the following variables were significantly associated with WML volume in multivariable regression models adjusting for age, sex, education, depression, alcohol consumption, and smoking:

- continuous SBP (B=0.63 per 10 mmHg, 95% CI 0.32–0.94);
- DBP (B=0.64, 95% CI 0.37–0.91);
- antihypertensive treatment (B=1.23, 95% CI 0.14–2.23).

Participants with hypertension despite treatment (treated BP 140/90 mmHg) had significantly increased WML volume compared with normotension without treatment (untreated BP <120/<80mmHg).

1. Gronewold J, et al. Association of blood pressure, its treatment and treatment efficacy with white matter lesions in the 1000BRAINS study. OPR-126, EAN 2021 Virtual Congress, 19–22 June.

Promising diagnostic accuracy of plasma GFAP

Glial fibrillary acidic protein (GFAP) in plasma accurately differentiated patients with Alzheimer's disease (AD) from healthy controls and thus holds promise as a diagnostic biomarker for AD. This could be a non-invasive and cost-effective method to detect people at risk, early in the neuropathological cascade.

GFAP is an intermediate cytoskeletal filament protein of astrocytes and is regarded as a promising non-invasive biomarker for neurodegeneration. It has been shown that GFAP levels are increased in patients with AD compared with healthy controls. Dr Tandis Parvizi (Medical University of Vienna, Austria) examined the utility of GFAP as a biomarker along the AD continuum [1]. In a retrospective, cross-sectional study they included 185 subjects: 44 healthy controls and 141 patients with either subjective cognitive decline (SCD, n=18), mild cognitive impairment (MCI, n=63), or AD (n=60). Concentrations of GFAP in plasma and CSF were quantified using ultrasensitive single-molecule array (SIMOA).

The results showed a gradual increase of GFAP, with the lowest concentration in healthy controls and the highest in AD. The median concentration of GFAP in plasma was:

- healthy controls: 79 pg/mL (53.7–120.6);
- SCD: 111 pg/mL (71.0–154.0);
- MCI: 167.5 pg/mL (93.9–256.3);
- AD: 181.9 pg/mL (129.6–269.6).

Diagnostic discrimination between controls, MCI, and AD groups was good (P<0.001). Analysis of GFAP in plasma could further distinguish between groups with SCD and AD (P=0.01). To establish the value of these biomarkers for clinical diagnosis, the researchers constructed a diagnostic panel combining GFAP and neurofilament light chain (NfL) with well-known risk factors (age, sex, *ApoE4* genotype). Results for distinguishing people with AD from healthy controls were promising, with an area under the curve (AUC) of 0.92. The AUC for distinguishing people with MCI and healthy controls was 0.82.

1. Parvizi T, et al. Promising diagnostic accuracy of Plasma GFAP within the AD continuum. OPR-121, EAN 2021 Virtual Congress, 19–22 June.

Sex modulates effect of cognitive reserve on subjective cognitive decline

In an Italian study, premorbid intelligence was associated with age at onset and severity of cognitive complaints in men. However, premorbid intelligence and years of education had opposite effect on age at onset of subjective cognitive decline (SCD) in women.

Demographic factors, genetic factors, and cognitive reserve influence SCD, which in turn increases the risk of Alzheimer's

disease (AD). The study presented by Dr Giulia Giacomucci (University of Florence, Italy) aimed to analyse how sex might modulate the influence of cognitive reserve on SCD [1]. The study included 381 patients with SCD aged >40, who had self-reported symptoms of cognitive decline during ≥6 months. Patients underwent clinical evaluation, neuropsychological assessment, the Test di Intelligenza Breve (TIB) to evaluate premorbid intelligence, the Memory Assessment Clinics-Questionnaire (MAC-Q) to evaluate cognitive complaints, Hamilton Depression Rating Scale (HDRS) to evaluate depressive symptoms, and ApoE genotyping.

The cohort contained about twice as many women as men: 68.7% versus 31.3%. Women were younger at SCD onset and at study baseline (P=0.02), had less years of education (P=0.007), lower TIB scores (P<0.001), and higher HDRS (6.3 vs 5.12; P=0.007) and MAC-Q scores (26.3 vs 25.0; P=0.012). The number of years of education was inversely associated with age at onset only in women (ρ=0.259; P<0.001). The only factor influencing MAC-Q was sex. TIB was directly associated with MAC-Q only in men (ρ=-0.292; P<0.005). Sex and cognitive reserve influenced severity of cognitive complaints, which was higher in women. In men, higher cognitive reserve was associated with worse cognitive complaints in a linear fashion.

This result contradicts previous studies reporting that less educated individuals showed a higher degree of cognitive complaints. Dr Giacomucci said this discrepancy may be explained by the different cognitive reserve proxy, and/or the different recruitment method. "Sex and cognitive reserve interact in influencing age at onset and severity," Dr Giacomucci concluded. She added it is not possible to describe the relationship between sex and cognitive reserve in SCD in a complete and uniform model.

1. Giacomucci G, et al. Sex influences the effect of cognitive reserve on subjective cognitive decline. OPR-043, EAN 2021 Virtual Congress, 19–22 June.

Hypersensitivity to uncertainty in subjective cognitive decline

A behavioural and imaging study investigated the mechanisms of subjective cognitive decline (SCD) and its relation to depression and anxiety. It demonstrated that SCD patients have hypersensitivity to uncertainty, which is associated with strong insular-hippocampal connectivity.

In SCD, there is by definition no evidence of significant dysfunction. However, depression and anxiety are common, and the severity of SCD has often been found to correlate with the severity of this affective burden. Despite this correlation, the mechanisms behind this affective burden are not well understood, explained Dr Bahaaeddin Attaallah (University of Oxford, United Kingdom) [1]. The key factor underlying affective burden in SCD may be the processing of uncertainty. People prone to anxiety or depression may overact to uncertainty, i.e. gather more information than needed; likely due to an overestimation of uncertainty.

The presented study focused on the gathering of information (quantity and speed) when faced with uncertainty. A behavioural paradigm was used in which subjects were required to make decisions involving uncertainty and gather information before committing to these decisions. Participants were 27 SCD patients and 27 controls; mean age was 61 years. Participants also completed self-reported questionnaires of anxiety and depression. To investigate the brain networks involved, resting-state functional MRI was used.

Results showed that SCD patients require uncertainty to be lower; they do this by gathering more information prior to committing to a decision and doing this quicker than controls. However, no difference was observed in sampling efficiency. As expected, SCD patients were more depressed and more anxious. Affective burden was associated with rapid and extensive sampling.

In a network functional connectivity analysis, 40 regions of interest (ROIs) and 780 connections were analysed. These results showed that SCD patients, compared with controls, had specifically increased functional connectivity between the insular cortex and the hippocampus. Increased insular-hippocampal connectivity was also associated with overacting to uncertainty.

"Hyperreactivity to uncertainty mediates the association between increased insular-hippocampal connectivity and affective burden," Dr Attaallah concluded. "This could be a key mechanism underlying psycho-cognitive manifestations in SCD and may be a possible treatment target."

1. Attaallah B, et al. Hypersensitivity to uncertainty in subjective cognitive impairment. OPR-204, EAN 2021 Virtual Congress, 19–22 June.

Epilepsy

Minimally invasive device to detect focal seizure activity

A minimally invasive sub-scalp device (Minder® system) can capture continuous EEG data and detect focal seizure activity. This monitoring system captured all seizure events identified during the video-EEG period. Devices implanted beneath the scalp may be of considerable clinical utility in forecasting seizures.

Prof. Mark Cook (University of Melbourne, Australia) stated there is a clear need for a long-term recording system in patients with epilepsy. "These patients are often unaware of their seizures, which may both complicate diagnosis and optimisation of treatment." Potentially, it could be used for safety alerts and seizure forecasting. They could have a role in clinical trials as well. So far, such systems have been relatively invasive. Ideally, the device would be inserted as a day procedure and involve an unobtrusive external unit such as a smartphone to store and process data. Prof. Cook's group developed such a minimally invasive system themselves, the Minder system, a sub-scalp device. Four electrode contacts are deployed in a coronal plane posterior to the vertex, providing 2 channels of data. EEG data is continuously captured and transferred to a smartphone, from where it is accessible remotely by internet.

Prof. Cook presented preliminary results of a registered clinical trial of the Minder system in 9 patients with refractory epilepsy with at least 1 seizure weekly [1]. Recordings were compared to a 1-week in-patient video-EEG monitoring session for 4 of these subjects. EEG recordings from both systems were reviewed blindly by 2 neurologists. The procedures were uncomplicated and well tolerated, without any significant complications and with excellent compliance. High-quality EEG data was captured continuously. The monitoring system captured all 31 events identified during the video-EEG period from the 4 subjects. Two events were initially identified on the system alone. Of the 20 patient-reported events, 12 were not associated with clinical or EEG changes on either system. Prof. Cook added that seizure forecasting is feasible using this system.

1. Cook M, et al. Preliminary experience using a minimally invasive sub-scalp device for ultra-long term seizure monitoring. EPR-311, EAN 2021 Virtual Congress, 19–22 June.

Long-term effectiveness of ANT-DBS in epilepsy confirmed

The benefit and safety of deep brain stimulation (DBS) of the anterior nucleus of the thalamus (ANT) in drug-resistant epilepsy patients was confirmed in a real-world setting. Two years following implantation, seizure frequency decreased by 33%. Patients without cognitive impairment may benefit more from this therapy.

The randomised, double-blind SANTE trial previously established the efficacy of ANT-DBS in patients with drug-resistant epilepsy [1]. ANT-DBS is an established third-line therapy for patients with drug-resistant focal epilepsy, but real-world data remains scarce. The Medtronic Registry for Epilepsy (MORE; NCT01521754) is an open-label, observational study to evaluate the long-term effectiveness, safety, and performance of ANT-DBS in this patient group in routine clinical practice [2].

Participants were 191 adult patients with focal drug-resistant epilepsy from 13 European countries. Seizure frequency, health-related quality of life (QOLIE-31), depression, and safety at 2 years were reported. Both prospective and retrospective clinical data were obtained and analysed. The 170 participants included in this interim analysis had a mean age of 36 years, 73 (43%) were women, and 65 (38%) reported cognitive impairment at baseline.

After 2 years, median monthly seizure frequency had progressively decreased by 33.1% ($P<0.0001$). Factors influencing seizure frequency reduction included seizure type, absence of cognitive impairment, and site implant volume. QOLIE-31 simultaneously increased by a median of 2 points. Depression severity did not significantly alter. Among the most frequent adverse events were new or worsening seizures (16%), memory impairment (15%), and depression (13%).

1. Fisher R, et al. Epilepsia 2010;51:899-908.
2. Peltola JT, et al. Deep brain stimulation of the ANT for drug resistant epilepsy in a real-world setting: MORE registry 2-year results. OPR-152, EAN 2021 Virtual Congress, 19–22 June.

Good safety and efficacy of cenobamate for focal seizures

Onset of cenobamate efficacy in patients with uncontrolled focal seizures occurred early, occurred at lower doses than the target dose for maintenance therapy, and continued to improve at higher doses [1]. Adverse events (AEs) occurred primarily during titration, were generally self-limited in duration, and mainly mild or moderate in severity [2]. Slower titration reduced their severity.

In Europe, cenobamate is approved for the adjunctive treatment of focal-onset seizures with or without secondary generalisation, in adult patients who have not been adequately controlled despite a history of treatment with at least 2 anti-epileptic drugs. In C013 (NCT01397968) [3] and C017 (NCT01866111) [4], 2 international, double-blind, placebo-controlled trials with open-label extensions (OLE), efficacy and safety were assessed. A pooled post-hoc analysis established time to onset of efficacy during titration [1].

In C013, participants were randomised to placebo (n=108) or cenobamate 200 mg/day (n=113). Cenobamate was titrated by 50 mg/day every 2 weeks until the maintenance dose of 200 mg/day was reached. Patients in the cenobamate group had significant reductions in median percentage seizure frequency of -26.7% versus -15.1% in the placebo group (P<0.05), starting as early as in the first 1–2 weeks of titration at 50 mg/day.

In C017, participants were randomised to placebo (n=106), cenobamate 100 mg/day (n=108), 200 mg/day (n=109), or 400 mg/day (n=111). The initial starting dose of 100 mg/day was reduced to 50 mg/day, after which the titration rate to target dose was slowed to improve tolerability. As in C013, participants had significant reductions in median percentage seizure frequency (-36.4%) versus placebo (-20.0%; P<0.05), starting in the first week of titration at 50 mg/day.

In both studies, sustained significant decreases in seizure frequency with cenobamate versus placebo were seen throughout the 6-week titration period. The median reduction in seizure frequency was progressively higher with increasing cenobamate doses of 100, 200, and 400 mg/day.

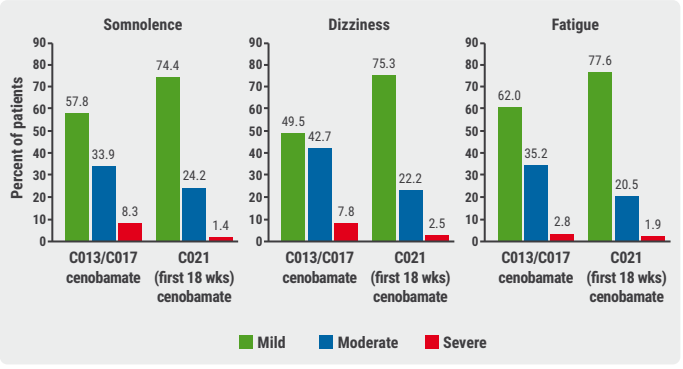
In a second pooled ad-hoc analysis, time to onset, duration, and severity of the most common AEs were assessed in 3 studies: C013, C017, and the large international open-label safety study C021 (NCT02535091) [2,5]. In C021 (n=1,339) cenobamate titration started at a lower dose, which was also up-titrated slower than in C013/C017 ("start low, go slow"). Patients initiated cenobamate at 12.5 mg/day for 2 weeks, followed by 25 mg/day for 2 weeks and 50 mg/day for 2 weeks; the dose was then increased by 50 mg/day at 2-week intervals to the target dose of 200 mg/day. Maximum dose was 400 mg/day. The analysis focused on the most common AEs: somnolence, dizziness, and fatigue.

AEs emerged throughout the double-blind period and OLE, mostly during titration. In C021, AEs peaked when dose reached 50 mg/day. Median duration in days during the double-blind period shows AEs were generally self-limited in duration:

- somnolence: cenobamate 32%, placebo 22%;
- dizziness: cenobamate 11%, placebo 8%;
- fatigue: cenobamate 34%, placebo 20.5%.

AEs in the double-blind period of C013 and C017 were primarily mild or moderate, with few severe AEs. In C021, AEs were more often mild and fewer were moderate and severe (see Figure). The authors concluded that slower titration, using the currently recommended schedule, reduced severity of the most common AEs.

Figure: Severity of most common adverse events in C013, C017, and C021 [5]



1. Steinhoff BJ, et al. Cenobamate as adjunctive therapy in adults with uncontrolled focal seizures: time to onset of efficacy during titration. EPR-307, EAN 2021 Virtual Congress, 19–22 June.
2. Steinhoff BJ, et al. Safety of adjunctive cenobamate in adults with uncontrolled focal seizures: time to onset, duration, and severity of Aes. OPR-153, EAN 2021 Virtual Congress, 19–22 June.
3. Chung SS, et al. Neurology. 2020;94(22):e2311-22.
4. Krauss GL, et al. Lancet Neurol. 2020;19(1):38-48.
5. Sperling MR, et al. Epilepsia. 2020;61(6):1099-108.

Prenatal valproate exposure increases risk of adverse neurodevelopmental outcome

In a very large nationwide study in 5 Nordic countries, prenatal exposure to the anti-seizure medications (ASM) valproate and topiramate was associated with an increased risk of autism spectrum disorder (ASD) and

intellectual disability. Valproate was also associated with early-onset psychiatric disorders compared with non-exposed children.

SCAN-AED is a population-based cohort study (www.scanaed.org) of singleton births using linked health and social register data from Denmark, Finland, Iceland, Norway, and Sweden. The association between prenatal exposure to ASM and adverse neurodevelopmental outcomes was established in 2 prospective population-based studies. One assessed the risk of ASD and intellectual disability [1], the other assessed the risk of psychiatric disorders [2].

In the first study, the total study population was 4,493,373 singletons, of whom 31,019 (0.7%) had prenatal ASM exposure [1]. ASM exposure was associated with an increased risk of ASD and intellectual disability, especially when exposed to valproate or topiramate. For valproate (n=3,042) the adjusted HR (aHR) was 2.9 for ASD, and 4.3 for intellectual disability. For topiramate (n=879) the aHR was 2.5 and 2.8, respectively. For oxcarbazepine and carbamazepine, the risk of ASD and intellectual disability was also significantly increased. Prenatal exposure to valproate and topiramate was also associated with neurodevelopmental disorders when accounting for maternal epilepsy. For valproate and topiramate, association strength for neurodevelopmental disorders compared with unexposed children was dose dependent.

The second analysis included 25,306 singletons of mothers with epilepsy, 15,914 (63%) of whom had had prenatal ASM exposure [2]. An increased risk of early-onset psychiatric disorders was found for prenatal exposure to valproate (aHR 1.85). This risk seemed to be mainly driven by intellectual disorders (HR 3.15), ASD (HR 2.74) and attachment disorders (HR 2.31). For lamotrigine, carbamazepine, and oxcarbazepine there was no increased risk across the spectrum of psychiatric disorders. For other therapies such as topiramate and levetiracetam, there was some evidence indicating an increased risk of psychiatric morbidity in the child, but statistical power was limited.

1. Bjork M, et al. Prenatal antiseizure medication exposure and risk of autism and intellectual disability. SCAN-AED: a Nordic cohort study. OPR-154, EAN 2021 Virtual Congress, 19–22 June.
2. Dreier J, et al. Prenatal exposure to antiseizure medication and the full spectrum of diagnosed psychiatric disorders: A SCAN-AED study. OPR-185, EAN 2021 Virtual Congress, 19–22 June.

'Mozart effect' in epilepsy: why Mozart tops Haydn

A new study confirms the 'Mozart effect' in epilepsy and provides evidence that the acoustic characteristics of music are responsible for suppressing brain epileptic activity. In this study, listening to Mozart's Sonata for Two Pianos (K448) decreased epileptiform discharges (EDs), but listening to Haydn's Symphony No. 94 caused an increase in EDs.

Music exposure is a potential therapy in neuropsychiatric diseases including epilepsy. The 'Mozart effect' in epilepsy has been the subject of numerous previous studies. It refers to the observation that listening to Mozart lowers the number of epileptic seizures and the frequency of abnormal brain activity in patients with epilepsy. Prof. Ivan Rektor (Masaryk University, Czech Republic) presented a study comparing the effects of listening to Mozart with listening to Haydn [1].

A total of 18 candidates for epilepsy surgery had intracerebral electrodes implanted in the temporal cortex. They listened to Mozart's piano sonata and to Haydn's 'Surprise' symphony. Musical features with respect to rhythm, melody, and harmony were analysed. "To our surprise, the effects of listening to Mozart and Haydn were significantly different," Prof. Rektor said. "Listening to Mozart's K448 led to a 32% decrease in EDs, but listening to Haydn's No. 94 caused a 45% increase." The acoustic features of music composition appear to have a different effect on men compared with women. Listening to Haydn's music was associated with a suppression of EDs in women, but with an increase in men. The reduction in EDs was larger in the lateral temporal lobe, which participates in translating acoustic signals, rather than in the mesiotemporal limbic region, which plays an important role in the emotional response to music.

"The effects of listening to music on epilepsy cannot be explained by the effect of dopamine released by the reward system," according to Prof. Rektor. "Our patients were not music connoisseurs and said they were emotionally indifferent to both pieces of music." Since the acoustic characteristics of music seem to be responsible for suppressing brain epileptic activity, Prof. Rektor suggested the use of musical pieces with well-defined acoustic properties to reduce epileptic activity in epilepsy patients.

1. Rektor I, et al. The Mozart effect. Why is Mozart better than Haydn? EPR-145, EAN 2021 Virtual Congress, 19–22 June.

Migraine and Headache

Factors associated with decreased migraine attack risk

In two-thirds of individuals with migraine, at least one factor associated with decreased risk of a migraine attack could be identified using prospective daily data. Most common protectors included feeling refreshed after waking, happiness, and good sleep quality. Although highly individualised, these behavioural factors are relevant in diminishing migraine attack risk.

For the management of migraine, potential protective factors may be equally important as trigger factors, but have been widely ignored. A study set up by Prof. Christian Wöber (Medical University of Vienna, Austria) and colleagues aimed to identify factors associated with decreased migraine attack risk in patients with migraine [1].

A total of 866 individuals with migraine registered to use N1-Headache®, a mobile app that connects patients to their clinicians and is specifically designed to identify migraine risk factors. Median age of participants was 43 years; 88% were women. In total, 88.7% had a diagnosis of migraine by a physician; 83% had episodic migraine; median number of migraine days was 8.8 per months; and 55.1% of women recorded at least one menstrual cycle. For 90 days, participants entered daily data about potential attack risk factors (e.g. diet, mood), migraine symptoms, and headache characteristics. A factor was defined as a potential protector if it was significantly associated with a decreased risk of migraine attack (unadjusted HR <1.0; P<0.05).

In 31.4% of patients no protectors were found, 65.9% had between 1 and 8 protectors, and 2.7% had 9 or more. The most common protectors were feeling refreshed after waking (32%), happiness (23%), good sleep quality (16%), being relaxed (13%), activity (9.0%), and coffee/caffeine (8.5%). Prof. Wöber stated that, similar to migraine triggers, migraine protectors are highly individual, and that behavioural factors are the most relevant protectors. Knowledge on these migraine 'protectors' may help patients adopt behavioural changes that may ultimately decrease migraine attack risk.

1. Wöber C, et al. Potential migraine "protectors": factors associated with decreased attack risk in individuals. OPR-069, EAN 2021 Virtual Congress, 19–22 June.

Eptinezumab shows acute benefits during migraine attack

Eptinezumab is an approved migraine-preventive treatment, but can also be effective as a treatment for acute migraine. In the placebo-controlled RELIEF study, infusion of this CGRP monoclonal antibody during a migraine attack resulted in rapid and sustained freedom from headache pain and most bothersome symptom (MBS).

The results of the phase 3 RELIEF study (NCT04152083) were presented at the EAN Virtual Congress and simultaneously published in JAMA [1,2]. Participants were 18–75 years of age and had migraine on 4–15 days per month in the 3 months prior to screening. During a moderate-to-severe migraine attack, they were randomised to eptinezumab 100 mg (n=238) or placebo (n=242), administered intravenously. There were 2 primary efficacy endpoints: time to headache pain freedom and time to absence of MBS (nausea, photophobia, or phonophobia).

The eptinezumab group achieved significantly faster headache pain freedom than the placebo group (median 4 vs 9 hours; HR 1.54; P<0.001) as well as absence of MBS (median 2 vs 3 hours; HR 1.75; P<0.001). Two hours after infusion, the percentage of patients reporting headache pain freedom was 23.5% and 12.0% (P=0.0009), respectively. The percentage reporting absence of MBS was 55.5% and 35.8% (P<0.0001). This difference remained significant after 4 hours.

In the eptinezumab group, statistically significantly fewer patients used rescue medication within 24 hours than in the placebo group (31.5% vs 59.9%; P<0.0001). There was no difference in treatment-emergent adverse events, occurring in 10.9% and 10.3% of eptinezumab and placebo-treated patients. The most common was hypersensitivity (2.1% vs 0%). No notable safety findings were identified.

1. Winner P, et al. Efficacy and safety of eptinezumab initiated during a migraine attack: Results from the RELIEF study. EPR-101, EAN 2021 Virtual Congress, 19–22 June.
2. Winner PK, et al. JAMA. 2021;325(23):2348–56.

Erenumab superior to topiramate for migraine treatment

In the direct head-to-head HER-MES study, in patients with episodic and chronic migraine, erenumab showed significantly better tolerability and efficacy versus topiramate. Fewer patients discontinued erenumab during the 24-week treatment phase, and a greater proportion achieved ≥50% reduction in monthly migraine days.

Erenumab is a CGRP receptor blocker, while the anticonvulsant topiramate is one of the most commonly prescribed prophylactic migraine drugs. For the first time, erenumab was directly compared with topiramate in a randomised, double-blind, double-dummy study [1]. The HER-MES study (NCT03828539) comprised a 24-week double-blind treatment period in which patients were randomised to either 70 mg or 140 mg subcutaneous erenumab (investigator's choice) and an oral placebo; or to the maximally tolerated dose of oral topiramate (50–100 mg daily) and a subcutaneous placebo. The primary endpoint was treatment discontinuation due to adverse events (AEs). The secondary endpoint was achieving a ≥50% reduction from baseline monthly migraine days (MMDs) over months 4, 5, and 6. The study enrolled 777 adult patients with ≥4 MMDs who were naïve to, were unsuitable for, or had previously failed ≤3 prophylactic migraine treatments. Participants had a mean age of 41 years; about 86% were women.

Both primary endpoints were met, showing significant differences in favour of erenumab compared with topiramate. During the double-blind period, 10.6% of patients in the erenumab group versus 38.9% in the topiramate group discontinued medication due to AEs (OR 0.19; P<0.001). The total number of study treatment-related AEs was 215 (55.4%) versus 315 (81.2%); the number of patients experiencing a serious AE was 1 and 2, respectively. The safety profile in the HER-MES study was generally consistent with that observed in previous clinical erenumab trials. Erenumab was also significantly more efficacious in terms of MMDs. In the erenumab and active control group, 55.4% and 31.2% of patients experienced a ≥50% reduction of MMD (OR 2.76; P<0.001).

1. Reuter U, et al. Erenumab versus topiramate for the prevention of migraine: Results of a randomised, active controlled double-dummy trial (HER-MES). OPR-200, EAN 2021 Virtual Congress, 19–22 June.

Pregnant migraine patients at higher risk of complications

Women who suffer from migraine are at increased risk of having obstetric and post-partum complications, especially women who have migraine with aura. They should be included in a high-risk pregnancy protocol of care throughout pregnancy. These are the main conclusions of a study carried out in Israel, in which the pregnancies of 145,102 women between 2014 and 2019 were analysed.

Dr Nirit Lev (Rabin Medical Center, Israel) and colleagues aimed to assess whether women with migraine have a higher risk of developing pregnancy and post-partum complications than women without migraine, and to evaluate their characteristics and medical needs [1]. Mode of delivery, medical and obstetric complications per trimester, and use of medications throughout the pregnancy were studied. A total of 12,222 women had a diagnosis of migraine (1,576 with aura), though Dr Lev warned that migraine is not always diagnosed. The remaining 132,880 women served as control group.

In the migraine group, there was an increased risk of high-risk admissions:

- 6% in the control group;
- 6.9% in the migraine group without aura (P<0.0001 vs controls);
- 8.7% in the migraine group with aura (P<0.0001 vs controls and P=0.03 vs migraine without aura).

The risk of obstetric complications was higher in the total migraine group, this included the risk of gestational diagnosis of diabetes, hyperlipidaemia, and diagnosis of a psychiatric disorder (P<0.0001 for all). The risk of pre-eclampsia and stroke was significantly higher as well. Dr Lev noted that pregnant women with migraine sought more medical consultations and consumed more medication during pregnancy. The use of epidural anaesthesia was significantly higher in women with migraine without aura (45.7%) and with aura (47.5%) than in women without migraine (40.5%; P<0.0001). Women with migraine also tended to have laboratory examinations post-partum more often. Dr Lev recommended a specialised neurological follow-up to women with migraine during pregnancy and the post-partum period.

1. Lev N, et al. Migraine in pregnancy and post-partum epidemiological and clinical characteristics. OPR-066, EAN 2021 Virtual Congress, 19–22 June.

Occipital nerve stimulation in drug-resistant cluster headache

Long-term experience in a Spanish tertiary centre showed that occipital nerve stimulation (ONS) is a beneficial treatment of drug-resistant chronic cluster headache (CCH). ONS reduced attack frequency without causing serious adverse events (AEs); this makes it a valid option for drug-resistant CCH management.

Dr Javier Membrilla (University Hospital La Paz, Spain) presented results from a retrospective observational study of 22 consecutive drug-resistant CCH patients who underwent ONS in a tertiary clinic [1]. This kind of study with long follow-up is scarce. The participants had drug-resistant CCH according to the EHF 2014 criteria and underwent ONS between March 2008 and July 2020. Baseline characteristics are listed in the Table. The procedure had 2 phases: temporary ONS for 2–7 weeks, followed by definitive ONS if there was a >50% improvement. The study's primary endpoint was weekly CCH attack reduction. Secondary endpoints were pain intensity on the visual analogue scale (VAS), patient-perceived overall improvement, and a decrease in oral medication use.

Table: Baseline patient characteristics [1]

n (% women)	22 (41%)
Mean duration of CCH	12.2 ± 11.6 years
Mean number of oral preventive medications	4.5 ± 1.7
Median weekly attacks	30.0 (24.6–58.3)
Median follow-up (years)	5.0 (1.5–8.3)
ONS failure during trial period	4/22 (18%)
ONS status at the end of follow-up	Active: 9/18 (50%) Deactivated: 2/18 (11%) Removed: 7/18 (39%)

After a median follow-up of 5 years, the weekly number of CCH attacks decreased from 30 at baseline to 22.5 after 3 months (P=0.012); 7.5 after 12 months (P=0.006); and 15.0 at the end of follow-up (P=0.023). From a median of 10, the VAS score decreased to 9.0 at 3 months (P=0.011); 7.0 at 12 months (P=0.008) and 7.0 at the end of follow-up (P=0.002). After 3 and 12 months, and after the end of follow-up, 23.5%, 41.2%, and 27.8% of patients had a perceived overall improvement of 70%. Of 22 participants, 13 (59%) reduced their prophylactic oral medication, while 3 (14%) stopped taking it altogether. All 22 participants decreased triptan use, 3 (14%) stopped using it. AEs were reported by 9 of 22 patients (41%) and were all mild. The most common AE was superficial surgical wound infection (n=4).

Dr Membrilla stated that further research is needed to identify characteristics of responders, so that ONS therapy can be offered to properly selected cases.

1. Membrilla J, et al. Occipital nerve stimulation in drug-resistant chronic cluster headache: a third-level hospital experience. OPR-067, EAN 2021 Virtual Congress, 19–22 June.

Rhythmicity in primary headache disorders

Chronobiology plays a major role in primary headache disorders, Dr Christoph Schankin (University Hospital of Bern, Switzerland) argued in a lecture on the relationship between headache and the biological clock [1]. The hypothalamus is a key structure for rhythm generation and pain modulation. Medication altering rhythmicity might be helpful as treatment.

Dr Schankin explained that circadian rhythm is present at single-cell level, and that organs function together as a single circadian unit (the peripheral clock). They run independently and are synchronised by a central 'pacemaker', the suprachiasmatic nucleus (SCN). The SCN is calibrated by 'Zeitgeber': light, food, temperature, exercise, and circadian hormones (most notably steroids, melatonin). Steroids and melatonin not only change the SCN, but are also changed by it.

There is clinical evidence of circadian rhythmicity in migraine and other primary headache disorders: most attacks start between noon and 1 PM. Furthermore, 'early risers' in general have migraine attacks that start early in the day. Cluster headache mostly seems to start very early in the morning: at 1 or 2 AM. There is also a possible circaceptan (weekly) rhythmicity in migraine, with more attacks on Fridays and fewer on Sundays. Women often have migraine attacks at the beginning of the menstrual period. Migraine attacks seem to originate in the subcortical areas, and/or from the hypothalamus, as was confirmed in imaging studies. There is a clear circannual rhythmicity in cluster headache, which can be provoked by very long and short days (in June and December, respectively). Other patients have relatively very few attacks in summer.

It is unclear which factors drive rhythmicity in migraine and other primary headache disorders. There is evidence for involvement of the hypothalamus and its major mediators (CLOCK, CK1, PACAP, melatonin, orexins). The association with sleep is bidirectional: sleep is affected by headache, and headache by sleep.

Dr Schankin said medication altering rhythmicity may be helpful as migraine treatment. Among the interventions that have been studied thus far are melatonin and corticosteroids (to reset the body clock), orexin A and B (involved in sleep, arousal, feeding), lithium and valproic acid, and PACAP. Solid evidence for any of these options is still lacking.

1. Schankin C. Rhythmicity in Headache Disorders. SYMP10-2, EAN 2021 Virtual Congress, 19–22 June.

Multiple Sclerosis and NMOSD

Typing behaviour to remotely monitor clinical MS status

Real-world smartphone typing behaviour ('keystroke dynamics'; KD) can effectively distinguish between MS patients and healthy controls, and between MS patients with different levels of disability. These findings show the potential of KD as a digital biomarker to remotely monitor clinical MS status.

Physical and cognitive functions required for typing are affected in MS patients. Dr Ka-Hoo Lam (Amsterdam UMC, the Netherlands) and colleagues studied KD data in people using an app called Neurokeys [1]. The information collected included typing speed features (alphanumeric keys) and processing speed features (backspaces and punctuation marks), based on hold time, release time, or both. The study aimed to verify if KD collected by smartphone could discriminate between MS patients and healthy controls and between MS patients with different levels of disability, as defined by Expanded Disability Status Scale (EDSS) scores.

A logistic regression and random forest algorithm were combined in a model to capture linear and non-linear trends. It was tested in 97 MS patients and 22 healthy controls, from whom 2 weeks of KD were aggregated per hour. MS patients were divided into 2 sub-groups: low disability (EDSS ≤3.5; n=61) and higher disability (EDSS >3.5; n=36). In the low disability group, 44 patients had relapsing-remitting MS, 12 had secondary progressive MS, and 5 had primary progressive MS. In the higher disability group, 14 had relapsing-remitting MS, 17 had secondary progressive MS, and 5 had primary progressive MS.

The best performing model for distinguishing between MS patients and controls had an area under the curve (AUC) of 0.78, indicating good sensitivity and specificity. This model included 2 typing speed features, number of suggestions, age, and gender. Similarly, the AUC for distinguishing between low and higher disability groups was 0.78. This model included 3 typing speed features, a mental processing feature, and age. Both models were primarily driven by KD.

1. Lam K, et al. Real-world smartphone keyboard interactions discriminate between different levels of disability in multiple sclerosis. EPR-114, EAN 2021 Virtual Congress, 19–22 June.

Machine-learning method accurately classifies patients with MS

A combination of different machine-learning principles applied to functional MRI (fMRI) scans accurately classified patients with MS by clinical phenotype, and distinguished them from healthy controls. Distinct sub-network abnormalities contributed to accurate phenotype classification.

Graph theoretical analysis helps to gain insight into functional reorganisation in MS. Italian researchers developed advanced machine-learning methods to analyse data on resting-state functional connectivity and classify MS patients according to disease phenotype [1]. They obtained fMRI scans from 46 healthy controls and 113 MS patients (62 with relapsing-remitting MS and 51 with progressive MS). By way of dominant set clustering, functional connectivity matrices were grouped into patients with similar network configurations. Disease phenotypes were classified using linear support vector machines.

This approach helped to distinguish relapsing-remitting MS patients from healthy controls with an accuracy rate of 72.5%. A sensitivity analysis revealed the following key features that differentiated relapsing-remitting MS as well as progressive

MS patients from healthy controls: increased connectivity within the basal ganglia sub-network and decreased functional connectivity within the temporal sub-network. Decreased functional connectivity within the occipital and parietal sub-networks contributed to differentiate progressive MS patients from healthy controls. Altered thalamic and frontal resting-state functional connectivity occurred in all phenotypes and may be a hallmark of MS. The involvement of occipitotemporal subnetworks in relapsing-remitting MS patients may be secondary to damage of associative sensory regions. The involvement of the parietal regions in progressive MS suggests a spreading of damage to high-order, associative regions, leading to impaired network integration.

In another very recent study, machine learning applied to brain MRI scans from 6,322 MS patients resulted in the definition of 3 MS subtypes: cortex-led, normal-appearing white matter-led, and lesion-led [2]. The lesion-led subtype had the highest risk of confirmed disability progression and the highest relapse rate, but also predicted positive treatment response in clinical trials.

1. Rocca MA, et al. Classifying and characterizing multiple sclerosis disease phenotypes with functional connectivity and machine learning. OPR-112, EAN 2021 Virtual Congress, 19–22 June.
2. Eshaghi A, et al. Nat Commun. 2021;12(1):2078.

Positive results from ublituximab versus teriflunomide

Results from the identical ULTIMATE I and II phase 3 trials showed that the novel anti-CD20 monoclonal antibody ublituximab significantly reduced the annualised relapse rate (ARR) and MRI abnormalities compared with teriflunomide in patients with relapsing MS.

Ublituximab targets a unique epitope on the CD20 antigen and is glycoengineered for enhanced B-cell depletion through antibody-dependent cellular cytotoxicity (ADCC). The increased ADCC may offer benefit over available anti-CD20 agents in terms of lower doses and shorter infusion times.

In the global, active-controlled, phase 3 studies ULTIMATE I (NCT03277261) and ULTIMATE II (NCT03277248), ublituximab was compared with teriflunomide in relapsing MS patients [1]. Overall, 1,094 patients (ULTIMATE I, n=549; ULTIMATE II, n=545) participated in 10 countries. They were randomised 1:1 for 96 weeks to 450 mg ublituximab via 1-hour IV-infusions every 24 weeks (following 150 mg on day 1) or to 14 mg oral teriflunomide once daily. Participants were between 18 and 55 years of age (mean 36 years), with scores on the Expanded Disability Status Scale (EDSS) between 0 and 5.5. The primary endpoint was ARR, key secondary endpoints included MRI, no evidence of disease activity (NEDA), confirmed disability progression (CDI), and safety/tolerability.

Both studies met their primary endpoint of significantly reduced ARR (P<0.005 in each study). In ULTIMATE I, ARR was 0.076 in the ublituximab group and 0.188 in the teriflunomide group (adjusted ARR ratio 0.406; 95% CI 0.268–0.615). In ULTIMATE II, the ARR was 0.091 and 0.178, respectively (ARR ratio 0.509; 95% CI 0.330–0.784). The total number of relevant MRI abnormalities was reduced by 97% and by 96% with ublituximab versus teriflunomide in ULTIMATE I and II, respectively. In ULTIMATE I and II, 44.6% and 43.0% of ublituximab-treated patients achieved NEDA, respectively, representing a 198% and 277% improvement over teriflunomide (P<0.0001 for both studies). Ublituximab also significantly improved disability: compared with teriflunomide, the chance of CDI was 116% (P=0.003) in the first trial, and 103% (P=0.0026) in the second trial.

Ublituximab was generally well tolerated, with no significant differences in the percentage of adverse events (AEs) in the 2 study groups. In the ublituximab group, 9.5% reported a serious AE, compared with 6.2% in the teriflunomide group. Infection was more frequent in the ublituximab group: 4.0% versus 2.6%.

1. Steinman L, et al. Ublituximab versus teriflunomide in relapsing multiple sclerosis (RMS): Results of the Phase 3 ULTIMATE I and II trials. OPR-086, EAN 2021 Virtual Congress, 19–22 June.

Alemtuzumab in treatment-naïve patients with aggressive MS

In an observational study of treatment-naïve patients with aggressive MS, alemtuzumab yielded positive efficacy results. No evidence of disease activity (NEDA)-3 was reached by almost 70% after 3 years. The authors stress the importance of rigorously selecting the ideal patients for this treatment modality to achieve a positive risk/benefit ratio.

Alemtuzumab is a powerful anti-CD52 monoclonal antibody for the treatment of active MS. It induces depletion of T- and B-cell populations and a possible immune system 'reset', but also has many possible side effects.

The multicentre, prospective, observational study presented by Dr Lucia Moiola (IRCCS San Raffaele Hospital, Italy) evaluated efficacy and safety of alemtuzumab in treatment-naïve patients with aggressive early MS [1]. Between 2015 and 2019, a total of 133 patients were included. Efficacy data were analysed after the end of the complete therapeutic cycle (2 courses of alemtuzumab). Follow-up data at 24 and 36 months was available for 99/133 and 61/133 subjects, respectively.

At year 2 and year 3, mean annualised relapse rate (ARR) was 0.06 and 0.10, respectively. The reduction in ARR was 94.4% compared with pre-treatment (P<0.0001). The percentage of relapse-free patients at years 2 year 3 was 97% and 82%, respectively. Mean time to first relapse was 27.4 months. Female sex (OR 2.05) and a high ARR (OR 1.21) were significantly associated with relapse risk. After 3 years, 43 of 61 patients (69.4%) reached NEDA-3. Overall, 99 patients (74.4%) reported adverse events: 94 (70.1%) had infusion-associated reactions, 21 (15.8%) thyroid dysfunction, and 13 (9.8%) infections.

Dr Moiola stressed that alemtuzumab yielded more favourable efficacy and safety outcomes in this cohort of treatment-naïve patients with aggressive disease than in other randomised controlled trials and real-world studies. This is likely due to young age, short disease duration, and low disability. She added that a neurologist must know and understand the mechanism of action and adverse events of alemtuzumab to be able to confidently propose it to the right patient.

1. Moiola L, et al. Observational study on real-life experience with alemtuzumab in naïve patients with aggressive Multiple Sclerosis. OPR-191, EAN 2021 Virtual Congress, 19–22 June.

No higher early MS relapse frequency after stopping ponesimod

In a post-hoc analysis of the OPTIMUM study, short-term observational data in patients who stopped ponesimod for 6-168 days did not suggest a higher early relapse frequency than during treatment, or compared with teriflunomide. Furthermore, there was no clear pattern of disease reactivation, nor an indication that post-treatment relapses were usually severe or leading to persistent disability.

Ponesimod is an orally active, selective S1P1-receptor modulator that induces rapid, dose-dependent, and reversible reductions in peripheral blood lymphocyte count. In the phase 3 OPTIMUM study (NCT02425644), ponesimod 20 mg demonstrated superior efficacy versus teriflunomide 14 mg in reducing annualised relapse rate (ARR) in patients with relapsing MS [1]. Cases of exacerbation of MS activity have been reported after discontinuation of S1P1-receptor modulators.

Prof. Ludwig Kappos (University of Basel, Switzerland) reported on the post-treatment relapse activity in the OPTIMUM study [2]. He explained that all patients who completed treatment in the OPTIMUM study after 108 weeks, regardless of treatment group, interrupted treatment for at least 2 weeks and, for teriflunomide, underwent an accelerated elimination procedure. All patients who stopped treatment, either prematurely or not, entered safety follow-up (at least 30 days after the last dose), and a post-treatment observation period (from the last dose up to 108 weeks after randomisation).

Of 1,133 randomised patients, 1,124 had post-treatment observation. In the ponesimod and teriflunomide group, 88 and 92 patients stopped treatment prematurely, respectively. Eight patients in the ponesimod group and 14 in the teriflunomide group experienced a total of 23 post-treatment relapses within 182 days of the last received dose of either study drug. Post-treatment ARR did not exceed on-treatment ARR for both drugs. Including non-confirmed relapses, ARR in the ponesimod group was 0.246 on-treatment, and 0.186 off-treatment; ARR in the teriflunomide group was 0.348 and 0.294, respectively. These findings are consistent with the main OPTIMUM results up to the end of the study. There were 8 confirmed on-treatment relapses in 5 ponesimod-treated patients, and 9 relapses (3 confirmed) in 8 patients between 6 and 168 days post-treatment, without any pattern of latency or severity.

1. Kappos L, et al. JAMA Neurol. 2021 May 1;78(5):558-67.
2. Kappos L, et al. Analysis of post-treatment relapse activity in the phase 3 OPTIMUM study of ponesimod compared with teriflunomide. OPR-208, EAN 2021 Virtual Congress, 19–22 June.

Satralizumab efficacious in AQP4-IgG-positive patients with NMOSD

In adults with AQP4-IgG-seropositive neuromyelitis optica spectrum disorder (NMOSD), satralizumab significantly reduced relapse risk, was well tolerated and showed a favourable safety profile compared with placebo. This was shown by efficacy and safety results from the phase 3 SAkura studies.

SAkuraSky (NCT02028884) tested satralizumab in combination with baseline immunosuppressants; SAkuraStar (NCT02073279) tested satralizumab as monotherapy. In both placebo-controlled studies, satralizumab reduced the risk of protocol-defined relapse. In a pooled subgroup analysis, efficacy

and safety of satralizumab in adults with AQP4-IgG-positive NMOSD were assessed [1]. Between-group comparisons were made for time to first relapse, rates of adverse events (AEs), serious AEs, infections, and serious infections that occurred during the double-blind period. To assess safety, data from the overall satralizumab treatment periods were evaluated, including open-label extension periods.

The analysis included 116 adult AQP4-IgG-positive NMOSD patients. Compared with placebo, satralizumab significantly reduced protocol-defined relapse risk by 78% in SAkuraSky and by 74% in SAkuraStar. The percentages of patients who were relapse free after 96 weeks were 91.1% in the satralizumab group and 56.8% in the placebo group in SAkuraSky (HR 0.22; 95% CI 0.06–0.82; P=0.014). These percentages were 76.5% and 41.1%, respectively, in SAkuraStar (HR 0.26; 95% CI 0.11–0.63; P=0.001).

In both studies, rates of AEs and serious AEs were similar in the experimental and placebo groups (see Table). Risk of infection or serious infection was not elevated by satralizumab in the double-blind nor in the overall treatment period. Decreases in neutrophil and platelet counts and elevations in liver enzymes were more frequently observed with satralizumab, but were not associated with serious infections or bleeding events.

1. Bennett J, et al. Satralizumab in adults with AQP4-IgG seropositive NMOSD: Efficacy and safety results from the phase 3 SAkura studies. OPR-163, EAN 2021 Virtual Congress, 19–22 June.

Good long-term safety and efficacy of inebilizumab in NMOSD

In patients with neuromyelitis optica spectrum disorder (NMOSD), inebilizumab continued to be efficacious, with up to 77% of patients free of attacks for at least 4 years, and no additional safety concerns. This was concluded from interim analyses of the open-label extension of the randomised N-MOmentum trial, presented in 2 abstracts.

The placebo-controlled N-MOmentum study (NCT02200770) evaluated efficacy and safety of inebilizumab in patients with NMOSD. After 28 weeks, inebilizumab was well tolerated, decreased the risk of an NMOSD attack, and decreased disability worsening [1]. After the randomised controlled period, participants could enter the open-label extension period (OLE) for a minimum of 2 years. Prof. Bruce Cree (University of California San Francisco, CA, USA) presented interim efficacy and safety analyses of the OLE [2,3].

OLE participants received inebilizumab 300 mg every 28 weeks. For analysis, 4 groups of participants were distinguished:

- INE/INE: participants who received inebilizumab during the randomised controlled period and the OLE;
- PBO/INE: participants who received placebo during the randomised controlled period, inebilizumab during the OLE;
- Any INE: all participants who received inebilizumab at some point during the study;
- Long-term INE: participants who received inebilizumab ≥4 years.

In total, 51/56 (91.1%) of those originally randomised to placebo and 165/174 (94.8%) of those originally randomised to inebilizumab entered the OLE. Mean exposure was 3.2 years.

Regarding efficacy, attack risk was reduced in all patients who were treated with inebilizumab. Annualised attack rate (AAR) decreased with long-term treatment. In total, 77.1% of the 'Any INE' group remained free of attacks for at least 4 years. Benefits in terms of disability and of NMOSD-related rates of hospitalisation were sustained in the OLE, as were radiological benefits.

Long-term inebilizumab treatment was generally well tolerated. Overall treatment-emergent adverse event (AE) rate in the INE/INE, PBO/INE, and 'Any INE' group was 1.54, 1.55, and 0.28, respectively. Rates of AEs of special interest

Table: Adverse event rates in the double-blind and overall treatment periods of the SAkura studies [1]

	SAkuraSky (combination therapy)			SAkuraStar (monotherapy)		
	Double-blind period		Overall	Double-blind period		Overall
Events per 100 patient years (PY)	Placebo (n=26; 33.0 PY)	Satralizumab (n=26; 52.7 PY)	Satralizumab (n=44; 137.4 PY)	Placebo (n=23; 26.8 PY)	Satralizumab (n=41; 80.4 PY)	Satralizumab (n=62; 150.6 PY)
AEs	657.5	458.9	417.9	519.7	440.5	379.8
Serious AEs	30.3	17.1	16.0	11.2	17.4	12.6
Infections	184.8	115.7	129.6	157.0	93.3	77.0
Serious infections	9.1	3.8	4.4	3.7	5.0	3.3

did not increase during the OLE. Immunoglobulin levels decreased with long-term treatment, but were not associated with increased infection risk. Rates of infection or serious infection did not increase.

1. Cree BAC, et al. Lancet. 2019 Oct 12;394(10206):1352–63.
2. Cree BAC, et al. Long term efficacy outcomes with inebilizumab treatment in neuromyelitis optica spectrum disorder: the N-MOmentum trial. OPR-161, EAN 2021 Virtual Congress, 19–22 June.
3. Cree BAC, et al. Long term safety outcomes with inebilizumab treatment in neuromyelitis optica spectrum disorder: the N-MOmentum trial. OPR-160, EAN 2021 Virtual Congress, 19–22 June.

Neuromuscular Disorders

24-month pooled FIREFISH data of risdiplam in SMA

In the phase 2/3 FIREFISH trial, infants with spinal muscular atrophy (SMA) treated with risdiplam continued to improve their ability to sit without support and other motor milestones after 24 months. Event-free survival time was greatly improved compared with natural history, while the rate of serious adverse events almost halved during the second 12-month period, compared with the first.

Risdiplam is approved for the treatment of patients with SMA aged ≥2 months. FIREFISH (NCT02913482) is an ongoing, multicentre, open-label study of risdiplam in infants with Type 1 SMA. Patients were aged 1–7 months at enrolment and had 2 *SMN2* gene copies. Part 1 of the trial (n=21) assesses safety, tolerability, and pharmacokinetics/pharmacodynamics (PK/PD) of different risdiplam doses; part 2 of the trial (n=41) assesses efficacy and safety of risdiplam at the dose selected in part 1. Presented were the pooled safety and efficacy data of 58 participants in FIREFISH part 1 (high-dose cohort, n=17) and part 2 (n=41), who have been treated over 24 months [1].

Treatment over 24 months led to further improvement in the ability to sit without support. After 12 months of treatment, 19 of 58 infants (33%) could sit without support for ≥5 seconds; 11 of 58 (19%) could sit without support for ≥30 seconds. After 24 months of treatment, 35 of 58 (60%) could sit without support for ≥5 seconds; 23 of 58 (60%) for ≥30 seconds. Treatment also resulted in continued gains in motor milestones (HINE-2) after 24 months: 48 of 58 infants (83%) had treatment response using the HINE-2 scale and prespecified response criteria. Swallowing and feeding ability was maintained by the majority of infants alive at month 24. Event-free survival time was greatly improved in infants treated with risdiplam compared with historical data: 91% were alive after 24 months and 83% were event-free. The rate of hospitalisations and of serious adverse events both almost halved during the second 12-month period compared with the first 12 months.

1. Masson R, et al. FIREFISH Parts 1 and 2: 24-Month Safety and Efficacy of Risdiplam in Type 1 SMA. EPR-281, EAN 2021 Virtual Congress, 19–22 June.

Inability to recognise disgust as first cognitive symptom of ALS

A study in amyotrophic lateral sclerosis (ALS) patients without cognitive/behavioural symptoms demonstrated an impaired ability to correctly recognise disgust, suggesting that this could be the first emotion to be hit in ALS cognitive decline. Basal ganglia could play a role in the altered processing of disgust.

Ms Veronica Castelnovo (Vita-Salute San Raffaele University, Italy) and colleagues aimed to verify the hypothesis that in ALS, the impairment in detecting disgust is related with the integrity of subcortical structures [1]. To do this, 20 ALS patients without cognitive/behavioural symptoms and 52 matched healthy controls underwent MRI and a neuropsychological assessment, which included the Comprehensive Affect Testing System (CATS), evaluating emotion recognition. In ALS patients, significant CATS findings were then correlated with subcortical volumes, Edinburgh Cognitive and Behavioural ALS Screen (ECAS) performance, patients' mood, and behaviour.

Compared with healthy controls, ALS patients had significantly worse CATS outcomes in general, and were significantly less able to recognise disgust in particular. In ALS patients, a low performance in the ability to recognise disgust was associated with a reduced volume of the left pallidum and with unfavourable ECAS performance. There

were no grey matter volume differences apparent between ALS patients and controls. The authors concluded that these results offer new potential markers for monitoring extra-motor progression in ALS.

1. Castelnovo V, et al. Impaired recognition of disgust is related to subcortical volume loss in amyotrophic lateral sclerosis. OPR-002, EAN 2021 Virtual Congress, 19–22 June.

Pathogenic T-cell signature identified in myasthenia gravis

A Swiss in-depth analysis of the immune dysregulation underlying myasthenia gravis (MG) provided valuable insight into potential disease pathogenesis and the role of the thymus in connection with disease severity.

The auto-antigen and effector mechanisms of MG are well defined, but the cellular and molecular drivers of this auto-immune disease remain elusive. Dr Bettina Schreiner (University of Zürich, Switzerland) presented a study which employed high-dimensional single-cell mass and flow cytometry in a cohort of mainly newly diagnosed MG patients in order to:

- screen the peripheral blood for an MG disease signature;
- identify map correlations between immune clusters and MG severity; and
- create a leukocyte map of the diseased thymus [1].

B-cell frequencies were found to be highly increased in the inflamed thymus, but not in the peripheral blood of MG patients. A comprehensive immune map identified a decrease of inflammatory circulating memory T-helper subsets such as Th_{GM} and Th_{CD103} cells that migrated to the inflamed thymus. Circulatory TNF-producing Th_{CD103} cells populated the diseased thymus, were reduced in the blood of MG patients, and were strongly inversely correlated with clinical disease severity of MG patients.

After surgical removal of the thymus, both of these signature T-helper subsets seemed to rebound in the blood –underlining their role as cellular markers of disease activity– and were effectively targeted by azathioprine treatment.

1. Ingelfinger F, et al. Single-cell profiling of myasthenia gravis identifies a pathogenic T cell signature. OPR-209, EAN 2021 Virtual Congress, 19–22 June.

Parkinson's Disease

Effect of prasinezumab on motor features in early PD

Results of the first stage of the PASADENA study showed that treatment with prasinezumab slows motor progression and delays time to clinically meaningful worsening of motor features in early Parkinson's disease (PD). These results were confirmed in subgroup populations with faster disease progression. Prasinezumab had a favourable safety profile.

Prasinezumab is the first monoclonal antibody that binds aggregated alpha-synuclein at the C-terminus with high selectivity, and is more effective in preclinical models than N-terminal antibodies.

PASADENA (NCT03100149) is a randomised, double blind, placebo-controlled, phase 2 study with 3 stages. In stage 1, 316 patients with early PD were randomised for 52 weeks to placebo, prasinezumab 1,500 mg, or prasinezumab 4,500 mg [1]. In stage 2, the original placebo group is re-randomised to prasinezumab 1,500 mg or 4,500 mg. In stage 3, all eligible patients will receive open-label prasinezumab 1,500 mg for up to 60 months. The primary endpoint is change in Movement Disorder Society-Unified Parkinson's disease Rating Scale (MDS-UPDRS) total score (sum of parts I, II, and III) after 52 weeks.

A real-world study previously showed that over a 1-year period, only progression in MDS-UPDRS part III (motor examination) is clinically meaningful [2]. In PASADENA as well, MDS-UPDRS progression in parts I (non-motor experience of daily living) and II (motor experience of daily living) remained below the threshold for clinical meaningfulness. Taken together, the primary endpoint was not met. MDS-UPDRS total scores were:

- -1.30 (80% CI -3.18 to 0.58) for pooled doses versus placebo;
- -2.02 (80% CI -4.21 to 0.18) for prasinezumab 1,500 mg;
- -0.62 (80% CI -2.82 to 1.58) for prasinezumab 4,500 mg.

MDS-UPDRS part III did give a signal of efficacy:

- -1.44 (80% CI -2.83 to -0.06) for pooled treatment versus placebo;
- -1.88 (80% CI -3.49 to -0.27) for prasinezumab 1,500 mg;
- -1.02 (80% CI -2.64 to 0.61) for prasinezumab 4,500 mg.

MDS-UPDRS part III site rating, MDS-UPDRS part III bradykinesia subscore, digital motor endpoints, and time to worsening of motor symptoms supported this efficacy signal. Prasinezumab delayed time to clinically meaningful worsening of motor signs (≥5 points increase in MDS-UPDRS part III) versus placebo (pooled HR 0.84).

Subgroup analyses revealed that slowing of clinical decline was more evident in groups with faster disease progression, namely patients treated with a MAO-B inhibitor and patients with a diffuse malignant sub-phenotype (n=59) versus mild motor predominant (n=106) and intermediate (n=151) sub-phenotypes. There were no life-threatening adverse events or immunogenicity concerns.

1. Pagano G, et al. Phase II PASADENA Part one Week 52 results: Evaluating safety and efficacy of prasinezumab in early Parkinson's. OPR-104, EAN 2021 Virtual Congress, 19–22 June.
2. Simuni T, et al. Mov Disord. 2018;33(5):771-82.

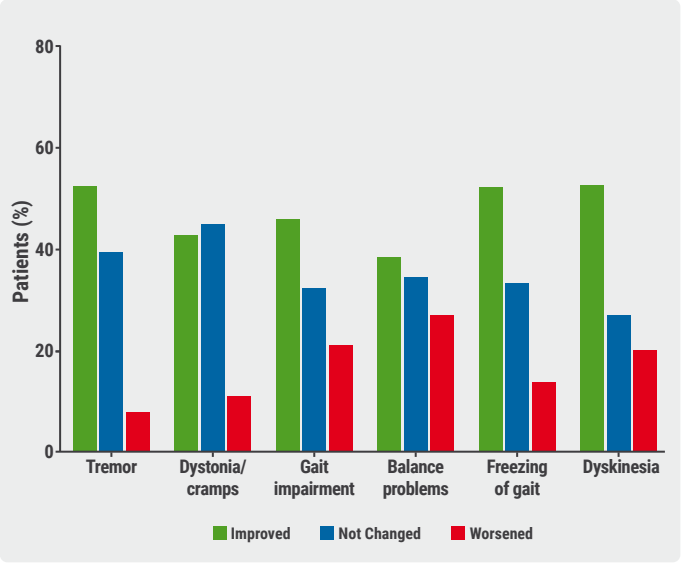
Levodopa-carbidopa intestinal gel in patients with advanced PD

Despite natural progression of the disease, over half of patients with advanced Parkinson's disease (PD) experienced improvement or no change in symptoms after at least 12 months of treatment with levodopa-carbidopa intestinal gel (LCIG). The authors concluded that LCIG may help control symptoms that impact healthcare resource use.

LCIG is a long-term treatment option for advanced PD patients with symptoms not controlled by oral medication. It is delivered continuously via a percutaneous endoscopic gastroscopy with a jejunal extension tube (PEG-J), with the option to provide symptom control as monotherapy when possible. The post-marketing observational COSMOS study (NCT03362879) was the first to evaluate LCIG as monotherapy or in combination with oral medication in routine clinical practice. A subanalysis of COSMOS was presented by Dr József Szász (University of Târgu Mures, Romania), assessing changes in individual PD symptoms following LCIG treatment [1]. A total of 409 participants were evaluated at a single study visit conducted at least 12 months after LCIG initiation. They had had continuous LCIG treatment for ≥80 days in the past 12 months.

Most patients reported improvement or no change in individual motor symptoms following LCIG initiation (see Figure). This was also true for balance problems, but more patients experienced worsening of this symptom than of other symptoms. In general, patients not experiencing worsening of symptoms were younger, had shorter disease duration, greater improvements in "Off" time following LCIG treatment, and greater improvements in dyskinesia severity following LCIG treatment. Non-motor symptoms were also assessed. More patients reported improvement than worsening in anxiety, pain, depression, fatigue, and constipation; more patients reported worsening than improvement in cognitive impairment, apathy, urinary symptoms, and orthostatic hypotension. Adverse events were similar to those reported in other LCIG studies.

Figure: Percentage of patients reporting individual motor symptoms after LCIG treatment [1]



1. Fasano A, et al. Parkinson's disease Symptoms Before and After Levodopa-Carbidopa Intestinal Gel: a Subanalysis From the COSMOS Study. OPR-150, EAN 2021 Virtual Congress, 19–22 June.

Safinamide improves non-motor symptoms in PD

An open-label study confirmed previously observed beneficial effects of safinamide on non-motor symptoms of Parkinson's disease (PD). Safinamide was well tolerated and improved both non-motor symptom burden and quality of life (QoL) in PD patients after 6 months.

Safinamide is a new monoamine oxidase (MAO) B inhibitor which also exerts a non-dopaminergic effect. The SAFINONMOTOR trial is a prospective, open-label, single-arm study to assess the effectiveness of safinamide on non-motor symptoms in PD patients [1]. The study's primary endpoint is change from baseline (V1) after 6 months (V4) in the Non-Motor Symptoms Scale (NMSS) total score. A total of 50 PD patients were included. Median age was 68.5; 58% were women; they had been diagnosed a mean of 6.4 years before. A total of 44 (88%) completed the follow-up observational period of 6 months.

The NMSS total score was reduced by 38.5% (P<0.0001) after 6 months: at baseline, it was 97.5; after 1 month, 65.9; after 3 months, 59.4; and after 6 months, 59.9. Improvement was observed in the following domains: sleep/fatigue (-35.8%; P=0.002), mood/apathy (-57.9%; P<0.0001), attention/memory (-23.9%; P=0.026), gastrointestinal symptoms (-33%; P=0.010), urinary symptoms (-28.3%; P=0.003), and pain/miscellaneous (-43%; P<0.0001). QoL, as measured by the 39-item Parkinson's Disease Questionnaire summary index (PDQ-39SI) improved by 29.4%: from 30.1 at baseline to 21.2 at 6 months (P<0.0001).

Eleven patients (22%) reported a total of 21 adverse events (AEs). Five AEs were severe, but none were deemed treatment related. The most frequent were dyskinesias and nausea (6%).

1. Santos Garcia D, et al. Safinamide Improves Non-Motor Symptoms Burden in Parkinson´s Disease: An Open-label Prospective Study. OPR-108, EAN 2021 Virtual Congress, 19–22 June.

New Frontier – Navigated Transcranial Ultrasound

Exploring the possibilities

A special symposium at the EAN 2021 meeting explored the possibilities of navigated transcranial ultrasound for surgery, blood-brain barrier (BBB) opening, and neuro-modulation. It could be a new frontier in neurotherapy.

Prof. Andres Lozano (University of Toronto, Canada) delivered a lecture on focused ultrasound energy across the skull as a novel, non-invasive method to make therapeutic lesions in the brain [1]. "Deep brain stimulation (DBS) is effective, and it would almost seem like a step backwards to make lesions in the brain," Prof. Lozano noted. However, an important difference is that focused ultrasound is a non-invasive procedure, often done in an outpatient basis. "There is a general trend to use non-invasive therapy in outpatient neurosurgery. Some patients and physicians who are shunning surgery, will accept magnetic resonance-guided focused ultrasound. There is no delay in its effects, they are immediate." In the eyes of Prof. Lozano, another important aspect of this technique is the harmonisation and blurring of boundaries between neurology, radiology, and neurosurgery. "I think there will be a new discipline of interventional neurology or interventional radiology, where perhaps neurologists and radiologists will work together with neurosurgeons to do these procedures. In some centres, neurologists are leading these efforts; in my personal belief, anyone with a proper training should be able to carry out these procedures."

The first indication is tremor. Another possibility is lesioning the globus pallidus and subthalamic nucleus in addition to the thalamus to treat Parkinson's disease. The anterior limb of the internal capsule, the subgenual cingulate, and other neuropsychiatric targets are also being considered to treat obsessive-compulsive disorder or depression, among others. In addition, several new indications are in development. "Particularly exciting are the possibilities to non-invasively treat epilepsy, trigeminal neuralgia, brain tumours, and maybe even dissolving blood clots."

Prof. Jean-François Aubry (Physics for Medicine Paris, France) talked about focal BBB opening by focused ultrasound [2]. He said there is a need to safely and transiently open the

BBB to enable drug delivery in the brain. This paves the way to more efficient drug therapies, such as chemotherapy for glioblastomas. He explained the principles and first results in humans of pioneering BBB opening with magnetic resonance guidance. The same clinical systems were used to induce thermal lesions, but at lower frequency (220 kHz) and in conjunction with intravenous injection of ultrasonic contrast (micro-bubble) agents. In a feasibility study, this was applied in 5 patients with high-grade glioma to deliver chemotherapy, in most cases temozolomide [3]. Focused ultrasound was also used to open the BBB in 5 patients with early-to-moderate Alzheimer's disease (AD) in a phase 1 safety trial as a potential novel treatment and delivery strategy for AD patients [4]. Low-cost, lightweight handheld, and neuro-navigated systems specifically for BBB opening are now available. Prof. Aubry also said BBB opening can be used to deliver neuroactive drugs to modulate brain activity.

Focal neuromodulation with ultrasound transcranial pulse stimulation (TPS) was the third application of transcranial ultrasound that was discussed, by Prof. Roland Beisteiner (Medical University of Vienna, Austria) [5]. He said that highly focal brain stimulation and non-invasive DBS are feasible with modern ultrasound neuromodulation technologies. "These allow for unprecedented precision in targeting brain areas in pathological brains with altered connectivity." Brain heating and generation of secondary stimulation maxima can be avoided with TPS. Clinical benefits of TPS are likely for all diseases which benefit from neuroplastic reorganisation (neurodegenerative diseases, psychiatric disorders). Secondly, benefits are likely for all diseases which rely on deep network nodes, since focused ultrasound allows for the first time for non-invasive DBS. Thirdly, TPS could be effective to treat diseases and conditions with focal pathologies which require precise targeting, most notably Parkinson's disease, stroke, pain, and MS.

Data of the University of Vienna has shown:

- modulation of neuronal responses (SEP data);
- stimulation of neuroplastic reorganisation (fMRI data);
- reduction of cortical atrophy (MR data);
- improvement of brain performance in AD;
- motor improvements in Parkinson's disease, as shown by very recent clinical observations.

TPS data of application in over 2,000 patients have shown that ultrasound neuromodulation is safe.

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