pulmonary dysregulation are two assumed mechanisms. However, there are no valid nor reliable biomarkers to help identify patients who are at risk of SUDEP. Patients at substantially high risk are those with epilepsies caused by sodium channel (SCN) gene mutations.[9] Heart rate variability has been investigated as a potential biomarker in 40 drug-resistant patients with SCN mutations.[10] Prolonged telemetry EEGs in these patients were compared restrospectively with those in 40 age-matched controls with non-SCN drug-resistant epilepsy. In the SCN group, ten (25%) patients experienced SUDEP. Awake heart rate variability was lower in these patients than in patients without SUDEP and in patients with SCN mutations, when compared with those with non-SCN mutations. These findings support that autonomic dysfunction is a contributing factor in SUDEP in the presence of SCN mutations and that heart rate variability could be a potential biomarker of SUDEP risk in epilepsy that could be incorporated into standard EEG protocols and used as a risk indicator. Heart rate variability could also be captured by wearable devices for the identification of patients with epilepsy at high risk of SUDEP.

In summary, the results of these studies expand our knowledge of the safety and efficacy of old, new, and investigational antiepileptic drugs, but still the long-term prognosis of epilepsy and drug resistance cannot be accurately predicted, and the prevention of SUDEP relies on further research on the role of autonomic dysfunction in patients with epilepsy.

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EB has received grants from UCB-Pharma and from the Italian Ministry of Health. GG declares no competing interests.

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Movement disorders in 2018: tackling this evil at the roots

In 2018, several initiatives that have aimed to slow progression or prevent development of movement disorders have provided encouraging results. In mouse models of Parkinson's disease, drugs that activate glucagon-like peptide 1 (GLP-1) receptors have been shown to target neuroinflammation, reduce microglial activation following exposure to aggregated α-synuclein, and prevent microglial-mediated conversion of astrocytes to a neurotoxic phenotype.[1] Mild improvements of motor scores in patients with Parkinson's disease who were treated with the GLP-1 receptor agonist exenatide compared with placebo[2] need to be confirmed in other studies (NCT02953665 for liraglutide, NCT03659682 for semaglutide).

Another approach being investigated for Parkinson's disease is to target α-synuclein aggregates directly. In cell cultures and mice, pharmacological inhibition of poly (ADP-ribose) polymerase (PARP) 1, which is involved in DNA damage repair, prevents α-synuclein fibril aggregates from causing neuronal death. PARP inhibitors, which are currently used as cancer chemotherapy, could hold potential as disease-modifying drugs in Parkinson's disease,[3] but chronic use would require assessment of tolerability and safety. A humanised monoclonal antibody (prasinezumab) targeting aggregated α-synuclein, has been used in a randomised, double-blind, placebo-controlled, safety and tolerability trial.[4] In this trial, 80 patients with Parkinson's disease (Hoehn and Yahr stages 1–3) received single or ascending doses (0·3–60 mg/kg monthly as intravenous infusions) and were monitored for 24 weeks.[4] The investigators reported a marked dose-dependent reduction of free

α-synuclein in serum and penetration of prasinezumab into the CSF. Further phase 2 clinical trials of anti-α-synuclein immunotherapies are ongoing (eg, PASEDENA, number NCT03100149; SPARK, number NCT03318523).

Although the results of these and other studies are awaited, currently available treatments have demonstrated clinical effectiveness and reasonable cost in real-world practice in the past year. In a study comparing habitual exercise (three times per week, eight patients) with sedentary habits (nine patients), habitual exercise was associated with improved motor function, lower apathy scores, and greater release of dopamine in the caudate nucleus as assessed by raclopride PET scans before and after 30 min of stationary cycling.[5] In a double-blind, randomised, placebo-controlled trial (TOLEDO)[6] in 128 patients with non-optimally controlled motor fluctuations, subcutaneous infusion of apomorphine (mean final dose 4·68 mg/h, SD 1·50) was well tolerated, with a significant reduction in off time compared with placebo. In a secondary analysis of the EARLY-STIM open-label randomised trial,[7] patients with Parkinson's disease and early motor complications who were treated with deep brain stimulation of the subthalamic nucleus (n=124) were compared with similar patients treated with medical therapy alone (n=127) over 2 years. In the stimulation group, neuropsychiatric fluctuations decreased, with a 39% decrease of levodopa-equivalent dose, whereas hyperdopaminergic behaviours increased with medical treatment alone, and levodopa-equivalent doses needed to be increased by 20%. These results support the benefit of subthalamic nucleus stimulation for dopaminergic behavioural complications as well as for disabling motor complications.[7]

Translational therapeutic approaches addressing disease mechanisms are rapidly expanding in hyperkinetic disorders, such as pantothenate kinase-associated neurodegeneration (PKAN) disease and Huntington's disease. PKAN disease is a devastating childhood-onset or adolescent-onset disorder associated with severe dystonia, parkinsonism, impaired balance, and cognitive and visual alteration, and it is related to a mutation in *PANK2* that causes a deficiency in coenzyme A. In a mouse model of PKAN disease, PZ-2891, an allosteric pantothenate kinase (PANK) activator that crosses the blood–brain barrier, increased coenzyme A concentrations in the brain and liver, improved locomotor activity, and caused weight gain.[8] This work paves the way for future safety and tolerability trials in patients who have the PKAN disease mutation.

Huntington's disease is a completely penetrant autosomal dominant degenerative disorder related to the presence of more than 36 CAG expansions in the huntingtin gene. Clinically it presents with psychiatric, behavioural, and cognitive manifestations, and choreic movements that can be associated with dystonia, parkinsonism, and gait and balance impairment. Antisense oligonucleotides are short stretches of DNA with a sequence complementary to the mutated huntingtin mRNA; they bind to the mRNA and block production of mutant huntingtin, leaving the normal copy untouched. In a mouse model of Huntington's disease, the use of antisense oligonucleotides reduced cognitive and behavioural impairments and reduced expression of mutated huntingtin in cortical and limbic brain regions.[9] In preliminary results from the phase 1–2 IONIS-HTTRx trial,[10] an antisense oligonucleotide injected once a month intrathecally reduced the level of mutant huntingtin in CSF.

Potential disease-modifying therapies for movement disorders, based on disease mechanisms, are developing rapidly. Findings published in the past year are starting to pave the way towards a personalised interdisciplinary approach to management of movement disorders, with re-enforcement of compensatory systems for better motor, cognitive, and behavioural control.

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I have received travel expenses from the European Academy of Neurology, the Movement Disorders Society, and the Movement Disorders Society European Section. I thank Aurelie Meneret, Eavan Mc Govern, and Emmanuel Roze for helpful discussions.

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Multiple sclerosis in 2018: new therapies and biomarkers

2018 has been a year of substantial progress in multiple sclerosis research, with breakthroughs in experimental medicine and translational research. Advances have ranged from successful clinical trials to new reports of promising biomarkers and improved understanding of the pathophysiology of multiple sclerosis.

More than a dozen disease-modifying therapies exist for relapsing-remitting multiple sclerosis, but only one therapy has been approved by regulators to slow progression in primary progressive multiple sclerosis (ocrelizumab), and no therapies have been approved with that specific indication in secondary progressive multiple sclerosis. Ibudilast, a phosphodiesterase inhibitor that crosses the blood–brain barrier, reduced the rate of brain atrophy by about 48% compared with placebo in the phase 2 SPRINT-MS randomised trial[1] of 255 patients with progressive multiple sclerosis, thereby leading the way to a phase 3 trial. Beyond the promise of this new therapy, this trial is important for a few reasons: it was a multicentre trial that provided data from five advanced imaging metrics (transverse and longitudinal diffusivity in the corticospinal tract, magnetisation transfer ratio in normal-appearing tissue, thickness of the retinal nerve fibre layer, and cortical thickness), demonstrating that it is feasible to include advanced methods in trials to detect the effect of experimental therapies on brain microstructure. Furthermore, SPRINT-MS[1] also showed the potential for drug repurposing in multiple sclerosis (ie, the application of a drug that is already used for a different indication), because ibudilast is used in Asia for treatment of patients with asthma or post-stroke vertigo. Drug repurposing is an attractive strategy that could lead to the discovery of an effective treatment sooner and at a lower cost than de novo drug development. About half of the patients enrolled in the SPRINT-MS trial[1] had primary progressive multiple sclerosis, confirming that secondary progressive and primary progressive multiple sclerosis can be studied together because they share more similarities than differences. Another notable result was that the rate of brain atrophy in the placebo group was lower than that reported in observational studies and in other trials of progressive multiple sclerosis, making it difficult to generalise this finding to the general population.

A disease-modifying treatment that has followed a standard development pathway is siponimod, a selective sphingosine-1-phosphate receptor modulator that inhibits the egress of lymphocytes from lymph nodes and crosses the blood–brain barrier. Siponimod induced a 21% reduction of the risk of 3-month confirmed disability progression compared with placebo in the phase 3 EXPAND study[2] of 1651 patients with secondary progressive multiple sclerosis. The safety profile was similar to that of other sphingosine-1-phosphate receptor modulators, and the dose titration during the first 6 days of treatment mitigated the risk of cardiac adverse events associated with these drugs. The patient characteristics were as expected for secondary progressive multiple sclerosis, but 21% of patients showed gadolinium-enhancing lesions on MRI at baseline and about a third had a relapse in the 2 years before screening, suggesting that some patients had active inflammatory disease. The trial was an event-driven and exposure-driven study, so median exposure to the drug was 18 months (range 0–37 months), which is shorter than other trials in secondary progressive multiple sclerosis, after which the open-label extension of the trial commenced. Subgroup analyses showed that patients with higher disease activity, younger age, lower disability, and shorter disease duration were more likely to benefit from siponimod than patients with the opposite characteristics. Whether the