Treatment of epilepsy in light of the most recent advances

The long-term effects of antiepileptic drugs are still disputed. Although the response to the available antiepileptic drugs is favourable in up to 80% of cases, seizure control in the long term is still ill-defined. This issue was addressed by a clinic-based cohort study on treatment outcomes in 1795 patients with newly diagnosed epilepsy, followed up for up to 30 years.[1] The study reported that 820 (46%) patients remained seizure-free for 1 year or longer with the first antiepileptic drug. Only 324 (18%) additional patients became seizure-free after change in treatment, despite an increasing use of second-generation and third-generation antiepileptic drugs. The authors concluded that modern antiepileptic drugs have not substantially improved the long-term prognosis of epilepsy.

The elusive results of this and other previous reports on the long-term effects of antiepileptic drugs did not stop the study of new compounds. Following the positive results of a phase 3 trial on the use of cannabidiol for drug-resistant seizures in patients with Dravet syndrome,[2] the compound was also tested on drop seizures in two randomised placebo-controlled trials in patients with Lennox-Gastaut syndrome[3,4] The first of these studies[3] investigated in 225 children and adults two daily doses of cannabidiol oral solution (67 patients assigned to 10 mg/kg and 82 patients assigned to 20 mg/kg) against placebo (n=76) administered for 14 weeks, and found a median reduction from baseline in the frequency (28-day period) of drop seizures of 37·2% for the 10 mg/kg group, 41·9% for the 20 mg/kg group, and 17·2% for the placebo group. However, adverse events were reported in 77 (94%) of 82 patients in the 20 mg/kg group and 56 (84%) of 67 patients in the 10 mg/kg group, most commonly somnolence, decreased appetite, diarrhoea, upper respiratory tract infection, fever, and vomiting. Eight patients (six taking 20 mg/kg, one taking 10 mg/kg, and one in the placebo group) discontinued treatment because of adverse events. A similar reduction in the median percentage of monthly drop seizure frequency (43·9%) was reported in another randomised trial of 86 patients with Lennox-Gastaut syndrome aged 2–55 years, who received 20 mg/kg of cannabidiol.[4] Adverse events occurred in 74 (86%) of 86 patients in the cannabidiol group and led to study withdrawal in 12 (14%) patients. The results of these studies confirm the antiseizure activity of cannabidiol. Cannabinoids, however, have complex pharmacokinetics: they interact with other compounds, including antiepileptic drugs, and the mechanism through which they act to reduce seizure frequency is still unknown.[5] In spite of these concerns, both studies are encouraging, but the long-term safety and efficacy of the drug are currently assessed in the ongoing open-label extension trials (NCT02564952 and NCT02607904, ClinicalTrials.gov).

Sodium valproate is still the drug of choice for treatment of several types of epilepsy, in particular generalised epilepsy syndromes (ie, juvenile myoclonic epilepsy). However, the report of major congenital malformations and impaired cognitive development in children born to mothers treated with valproate during pregnancy[6,7] led the US Food and Drug Administration and the European Medicines Agency to issue recommendations for the restricted use of the drug in women of childbearing potential. The teratogenic risk of other antiepileptic drugs during pregnancy is still unclear. A prospective cohort study of the International Registry of Antiepileptic Drugs and Pregnancy (EURAP) assessed the occurrence of major congenital malformations in 7355 pregnancies in women with epilepsy who used one of the eight most common antiepileptic drugs as monotherapy at conception.[8] The prevalence of major congenital malformations was 10·3% for valproate, 6·5% for phenobarbital, 6·4% for phenytoin, 5·5% for carbamazepine, 3·9% for topiramate, 3·0% for oxcarbazepine, 2·9% for lamotrigine, and 2·8% for levetiracetam. The prevalence increased with daily dose and, for valproate, doses of 650 mg/day or less were still associated with increased risk of major congenital malformations. However, because of the absence of alternative treatments, in some pregnant women valproate use cannot be avoided. The decision to stop or continue valproate should be based on the needs of each individual patient. The results of the EURAP study should also be taken into account when therapeutic alternatives are considered for women of childbearing potential.

Sudden unexpected death in epilepsy (SUDEP) is—along with status epilepticus, unintentional injuries, and suicide—among the commonest causes of death attributed to epilepsy. The pathophysiology of SUDEP is still poorly understood. Autonomic cardiac and

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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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