Editorial

Cannabis in neurology

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Constituents of the cannabis plant, cannabinoids, may be of therapeutic value in neurologic diseases. The most abundant cannabinoids are D9-tetrahydrocannabinol (THC), which possesses psychoactive properties, and cannabidiol (CBD), which has no intrinsic psychoactive effects, but exhibits neuroprotective properties in preclinical studies. A small number of high-quality clinical trials support the safety and efficacy of cannabinoids for treatment of spasticity of multiple sclerosis, pain refractory to opioids, glaucoma, chemotherapy induced nausea and vomiting and rare severe forms of childhood refractory epilepsies. Lower level clinical evidence indicates that cannabinoids may be useful for dystonia, tics, tremors, epilepsy, migraine and weight loss. Data are also limited in regards to adverse events and safety.

Common nonspecific adverse events are similar to those of other CNS 'depressants' and include weakness, mood changes and dizziness. Cannabinoids can have cardiovascular adverse events and, when smoked chronically, may affect pulmonary function. Fatalities are rare even with recreational use. There is a concern about psychological dependence, but physical dependence is less well documented. Cannabis preparations may presently offer an option for compassionate use in severe neurologic diseases, but at this point, only when standard-of-care therapy is ineffective.

There is public (and producer) interest in cannabis containing medicinal products and currently there seems to be an interest in the Sri lankan community mostly in public and political domain to have these products available for illnesses in our patients. With the licensing of CBD for Dravet and Lennox Gastaut syndromes in USA and UK, two rare but severe forms of epilepsy resistant to other drugs, our colleague paediatricians are naturally interested in offering this treatment to selected patients of theirs, but they have justifiable concerns about exposing a group already vulnerable to mental health and neuro behavioural comorbidities to the associated additional risks associated with the use of cannabis products.

The cannabis plant produces at least 144 naturally occurring compounds known as cannabinoids. The most widely researched cannabinoids are THC and CBD. THC is the primary constituent of cannabis that causes the "high" whereas CBD is not intoxicating at typical doses. Several products exist for medicinal use and these differ in THC/CBD profile, formulation, licensed indications, and conditions for prescribing. Cannabis based products that were previously listed in Schedule 1 (Drugs belonging to schedule 1 are thought to have no therapeutic value and therefore cannot be lawfully possessed or prescribed) can now be prescribed by doctors on the General Medical Council Specialist Register in the UK, on a named patient basis. Currently, general practitioners in the UK cannot prescribe them. Some cannabis-based products were already available for medicinal use before rescheduling in 2018. Sativex, an oral spray derived from the cannabis plant containing THC and CBD in a 1:1 ratio, is licensed for the treatment of spasticity in multiple sclerosis in 29 countries, including the UK, Israel, Canada, Brazil, and Australia. However, a meta-analysis suggests its effectiveness may be limited and it is not recommended by the UK's National Institute for Health and Care Excellence (NICE) because of poor cost effectiveness.

Epidiolex, an oral CBD solution derived from the cannabis plant, was licensed by the US Food and Drug Administration in June 2018 for the treatment of seizures in two rare and severe forms of childhood epilepsy – Lennox-Gastaut syndrome and Dravet syndrome based on data from randomized controlled trials supported by selected case videos, and "emotional testimony" from parents. FDA has approved its use recently for seizures in tuberous sclerosis based on a recently completed trial. Of note is that two recently completed randomized controlled trials failed to show efficacy of CBD and CBDV for the treatment of refractory focal onset epilepsy in adults. With the licensing of cannabidiol for drug resistant seizures in Dravet and Lennox Gastaut syndromes in the United states in 2018, interest in the potential for cannabis-based-medicinal products to meet currently unmet needs for people with epilepsy continues to grow. Only pure cannabidiol formulations have been rigorously evaluated in controlled trials thus far, with modest but significant improvements in motor seizures.

In the last 2 years, five randomized controlled trials of pharmaceutical grade CBD have been completed. The first study reported on the use of CBD (Epidiolex) for the treatment of convulsive seizures in patients with Dravet syndrome. In this double-blind, placebo controlled study, patients were randomized to receive either CBD at 20 mg/kg/day or placebo in addition to their standard

AEDs. The primary outcome measure was the change in convulsive seizures over a 14-week treatment period compared to a 4-week baseline. The authors were able to show a significant decrease in convulsive seizures per month from 12.4 to 5.9 with CBD vs. 14.9 to 14.1 with placebo (p=0.01 after adjusting for baseline differences). The responder rate of convulsive seizures in this study was 43% for CBD vs. 27% for placebo (p=0.08). The authors also reported on the overall seizure frequency (all seizure types) which has improved in the CBD group (p=0.03). However, there was no significant improvement in the nonconvulsive seizures. There was an overall improvement in the Caregiver Global Impression of Change scale in 62% of the CBD compared to 34% of the patients treated with placebo. Of the two LGS studies, the first study included 171 patients with drop seizures who were randomized to receive either placebo or CBD (Epidiolex) at 20 mg/kg/day after a 4-week baseline; the primary endpoint was change from baseline in drop seizure frequency. After 14 weeks of treatment, the median percentage reduction in drop seizure frequency per month from baseline was 43.9%in the CBD group and 21.8% in the placebo group (p=0.0135). Forty-four percent of patients were considered responders in the treatment phase and 46% in the maintenance phase of the study with respect to a reduction of drop seizures. The second randomized and placebo-controlled study also evaluated the efficacy of CBD in LGS with the primary endpoint being change in the rate of drop seizures. In this dose ranging study, patients were randomized to placebo, 10 mg/kg/day or 20 mg/kg/day of CBD with response measured at 14 weeks when compared to 4-week baseline. Of the 225 enrolled patients, 41.9% in the 20 mg/kg/day CBD group, 37.2% in the 10 mg/kg/day CBD group, and 17.2% in the placebo group responded to therapy with comparisons between treatment and placebo groups being significant. Responder rates for drop seizures were 39%, 36%, and 14% in the 20 mg/kg/day, 10 mg/kg/day, and placebo groups, respectively.

Dronabinol and nabilone are synthetically produced medicinal products that mimic the effects of THC. Dronabinol has an identical structure to THC, while nabilone has a related structure and is more potent than dronabinol, requiring lower doses to achieve clinical efficacy. Countries including the US, the Netherlands, Germany, Austria, and Croatia have licensed the use of both products. They are licensed for the treatment of weight loss in patients with AIDS and of nausea and vomiting in people receiving chemotherapy who have failed to respond adequately to conventional antiemetics. Nabilone is licensed in the UK while dronabinol is not licensed but can be prescribed on a named patient basis.

A combination of △ 9-THC and CBD, nabiximols (Sativex), showed >20% improvement in spasticity in patients with MS after 4 weeks in over half of patients treated. This has led to approval of use of nabiximols in multiple sclerosis for management of severe spasticity. The preparation, nabiximols (Sativex) has currently attained regulatory approval in 30 countries for spasticity associated with multiple sclerosis (MS), and in Canada for central neuropathic pain in MS, and for opioid-resistant cancer pain. Recent surveys find usage rates for cannabis of 20%-60% among MS patients. Cannabis may improve quality of life in some patients with multiple sclerosis. Patients' perception of the benefit of cannabis is often vastly different from their clinicians.

Other areas where a keen interest exists in studying the value of cannabinoids are intractable epilepsy, brain tumors, Parkinson disease (PD), Alzheimer disease (AD) and traumatic brain injury (TBI)/chronic traumatic encephalopathy (CTE). Available studies and data in these conditions are of low quality mainly observational and needs further properly designed studies before considering use in these conditions.

Adverse effects of CBD include diarrhoea, somnolence and reduced appetite, with mostly acceptable tolerability, but a not insignificant (up to 1 in 23) risk of serious adverse events. Recognized drug interactions include with valproate (increased risk of hepatotoxicity) and clobazam (contributing to somnolence, increased secretions, probably chest infections, and potentially efficacy).

A significant gap exists between the actual evidence, and public beliefs, fueled by media and anecdote. Pro cannabis lobby brings out sympathy and emotional aspects of the illnesses to promote their cause. Continued education of the public, policymakers, researchers and healthcare providers about what is and isn't yet known, together with on-going good quality research is essential to counter future potential risks, particularly in relation to vulnerable populations like disabled MS patients, severe epilepsies, and patients with intractable pain syndromes.

Based on current evidence in terms of efficacy or tolerability it is not yet a "game changer", and there is much still to be done. There are justifiable concerns about the use of THC containing products, particularly in children and adolescents and moreover being used for unlicensed conditions resulting in wide abuse with significant drawbacks and repercussions. So when the evidence is not strong and the consequences can be detrimental to the cause, best is to practice caution – "*Primum non nocere*".

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