Therapeutic Use of medicinal cannabis in difficult to manage epilepsy

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Introduction

Intractable epilepsy is currently defined by the International League Against Epilepsy as failure of adequate trials of two tolerated and appropriately chosen antiepileptic drugs (AED) to achieve sustained seizure freedom (1). Approximately 33% of adults and 20% of children with epilepsy meet that definition (2). This is despite the fact that there are 25 registered AED with a particular explosion of new drugs over the past three decades. That increased number of drugs surprisingly has not led to a significant reduction in the proportion of people who have intractable epilepsy.

Thus there was great hope in the epilepsy community (mainly patients and their families) that medicinal cannabis would bridge this gap. Cannabis had been used for millennia (especially in Asia) to treat a great variety of ailments including epilepsy. In the 19th century, its use became more mainstream in the Western world with several neurologists documenting its efficacy and safety in small case series (3). Used alone or in combination with other treatments such as bromide, cannabinoids were the mainstay of epilepsy treatment until the development of phenobarbital (1912) and phenytoin (1937) which were proven to be efficacious.

So why the recent resurgence of interest? A combination of the power of the internet, vested interests such as agri-business and marijuana legalisation groups and growing public distrust of institutions and science (4). One just has to search the internet for ‘epilepsy and cannabis’ and often the same individual cases are recycled as examples of the next miracle cannabis cure of epilepsy. This internet magnified, confirmation bias of anecdotal reports has polarised views, bred distrust of doctors (and their requirement for evidence-based medicine) and provided considerable hope but minimal help to those suffering with epilepsy and their carers. This review will focus mainly on cannabidiol (CBD), the most researched compound of the cannabis sativa derivatives.

Efficacy of medicinal cannabis products in epilepsy.

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When a clinician faces the question of which medication to choose next in managing a patient with intractable epilepsy, their choice is generally based on selecting from a bank of AED that have been proven to be effective from randomized double-blind placebo-controlled trials. When selecting an AED for a specific patient, they mainly rely on personal experience and local practice in tailoring their choice to the patient’s epilepsy syndrome or seizure type. There are published guidelines such as from the AAN(5) that provide estimates of comparative efficacy, adverse events and tolerability. While there are significant differences in adverse events, comparative efficacy is surprisingly similar across the multiple AED although good practice dictates the need to tailor the drug to the patient’s epilepsy syndrome as not all AED are appropriate for all epilepsies. There are very few head to head comparisons of AED. One must rely on metanalyses of predominantly add-on trials to gauge relative efficacy and side effects; these trials often do not reflect the real-life situation of a patient. Where does CBD place in this schema?

Three recent publications (involving the same product) contain the best evidence we have of the short-term efficacy and adverse events of CBD. These double-blind, randomised, placebo-controlled trials (DBRCT) utilising an alcohol/sesame oil based oral plant-derived CBD solution were similar in their design and outcomes. The initial study(6) was of 120 children (aged 2-18 years) with Dravet syndrome, a rare, devastating genetic epilepsy. The second and third trials (7, 8) involved 171 and 225 subjects respectively (age range 2-55 years) with Lennox-Gastaut syndrome (LGS) a notoriously pharmacoresistant, childhood-onset, severe epilepsy. In the initial two trials, subjects were randomly assigned 1:1, to receive 20 mg/kg/day CBD or placebo for 14 weeks compared to a baseline 4 week period. In the most recent LGS trial there were 3 comparative groups; placebo, 10mg/kg/day and 20mg/kg/day. Efficacy outcomes were similar in the Dravet and LGS trials with significant median seizure frequency reductions of 17% to 23%, respectively, adjusted for placebo group response. A small percentage in all trials became seizure free.

These trials were pivotal to the approval of a New Drug Application for Epidiolex (cannabidiol) 100 mg/mL oral solution by the US Food and Drug administration in June 2018. This is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients two years of age and older. The drug may not be marketed until the US Drug Enforcement Agency makes a scheduling decision as it is currently listed as Schedule 1. (9)

A criticism of these publications(10, 11) is that the efficacy may be partly related to drug interactions such as with clobazam and that this important secondary endpoint data has not
been published for review. The implication here is that the CBD is merely increasing the available clobazam and its metabolites to achieve its anti-epileptic effect; an issue that still remains to be resolved.

Adult epilepsy data is scarce. One recently reported (12) but, as yet, unpublished DBRCT of an adjuvant topical CBD gel in 188 adults aged 18-70 years with intractable focal epilepsy (no patients on clobazam) failed to show a significant reduction in median seizure frequency at two dose levels compared to placebo at the 12 week endpoint. Adverse events did not differ significantly from placebo. A critical question for this trial was whether adequate doses of CBD were delivered by the transdermal route.

Historical literature is sparse and of limited value. Several older case series are well detailed in the 2014 Cochrane Review (13) with the outcome that no reliable conclusions could be drawn on efficacy or long term safety of cannabinoids for epilepsy. A more recent large open label multicentre trial of oral CBD was published (14) adding to the body of safety data. An open-label Israeli CBD paediatric trial similarly showed high levels of efficacy but only provided class IV evidence for efficacy. (15)

Safety

There is considerable reassuring safety data on the short and medium term effects of CBD derived mainly from the GW Pharma ongoing DBRCT’s. There is also a large multi-national compassionate use program of the oral cannabidiol solution which has over 2000 subjects who have been periodically monitored and, for some cases, now includes up to 5 years of regular CBD use. This data although not publically available has been used for submission to the US and European drug regulatory agencies. The significant adverse events in this large cohort mirror that of the published RCT’s (personal communication GW Pharma).

In the three published DBRCT’s, adverse events led to a withdrawal rate of 8% to 14%, respectively in the treatment groups (6-8). The adverse events in general could be considered mild and reversible but frequent with 36% reporting somnolence. Somnolence was often addressed by reducing the dose of clobazam, if the patient was on concomitant clobazam. Gastrointestinal side effects such as anorexia, weight loss, vomiting and diarrhoea occurred in a third of subjects. A small increased risk of status epilepticus is noted but this requires greater sample sizes to confirm. The majority of the side effects resolved with dose reduction and/or alteration of concomitant drugs. Elevated liver aminotransferase enzymes more than 3 times the upper limit of normal occurred in 20% of subjects leading to
withdrawal from both trials in 5%. Over three-quarters of these patients were also on valproate. No permanent liver injury occurred.

Longer term safety remains a question and rarer short term side effects may emerge as the exposed patient population numbers and years of exposure increase. There are the well established concerns about chronic recreational marijuana use (such as risk of psychosis and poor educational outcome) summarised in recent excellent reviews (16, 17). The relevance of these concerns to pure CBD products is very uncertain.

A particular worry is the effect on children as little is known about the potential adverse side effects of CBD on brain development and behaviour. Preclinical studies of cannabis derivatives such as those on the early post-conception zebrafish (18) produced dysmorphic and behavioural abnormalities at lower concentrations of CBD than THC. In humans there has been minimal evaluation of the effect of cannabinoids on the fetus. There is no evidence that cannabis is a classic teratogen. Global IQ in children born to mothers using cannabis in pregnancy is unaffected but a negative effect on executive function has been demonstrated (19). Prenatal cannabis exposure leads to higher rates of anxiety and depression in adolescence. The extrapolation of these concerns to the young child and the developing brain is uncertain but of concern. These risks cannot be ignored but need to be balanced against the known impact of severe epilepsy.

**Practical issues in prescribing**

One practical issue is that cannabidiol (as a medicinal cannabis product) is currently classified as a narcotic in most jurisdictions. Under the Single Convention of the United Nations in 1961 cannabis and extracts were listed as Schedule I and Schedule IV. Schedule I refers to those substances having a liability to abuse; whereas, schedule IV refers to substances that are particularly liable to abuse and to produce ill effects, and such liability is not offset by substantial therapeutic advantages. A United States federal law from 1970, but remains current, lists cannabis as a schedule I drug with its use prohibited for any purpose. (20)

**Pharmacokinetics**

There is considerable complexity to the delivery of cannabinoids as a medicine. These are well summarised in a recent review (11) and include marked instability of compounds when exposed to light, heat or air. Unknown effects of downstream metabolites and marked individual variability in absorption and metabolism are not well understood. Differing delivery methods such as capsules, oils, vaporisers or skin gels result in vastly different
serum concentrations and PK profile. An oral cannabinoid dose can result in an 8 fold difference of the pharmacokinetic (pK) value of area under the curve depending on whether one is in the fasted or fed state!

A separate issue is the significant interaction with metabolism of other AED through induction of liver CYP and UGT enzyme systems. One study (21) highlighted the increased levels of topiramate, rufinamide and clobazam when CBD was added. Although this requires further investigation, in a practical sense, the interaction of clobazam and valproate appear most clinically relevant. Levels of the active metabolite of clobazam, nor-clobazam, showed increased plasma levels up to 8X when used in conjunction with CBD that were associated with somnolence (and possibly contributing to CBD efficacy)(22). Those on valproate and CBD had a high rate of elevated liver transaminases, through an unknown mechanism.

Conclusions

What do these results mean for the clinician at the coalface (or the green pasture)? One could cautiously construe that cannabidiol has modest efficacy and is appropriate for children with severe epilepsy with due attention to important adverse effects and potential drug interactions. There is no evidence to guide its ranking in AED prescribing choices. Currently, CBD but must be considered a third-line agent because of the comparatively low patient-years of use in terms or exposure and adverse events, and the presence of well-established first and second line agents, not to mention the costs involved in making purified CBD (>95%) formulations. Cannabidiol is a medicine, not a miracle and should be managed as such. Epilepsy care will not improve if we as a community support a laissez-faire approach. It is hoped that further investment in class I trials and high level research is encouraged and continues, otherwise we may return to the days of snake oil.

References

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*Note: The N Engl J Med article has been cited with the correct DOI.*

**Effect of Cannabidiol on Drop Seizures in the Lennox-Gastaut Syndrome.**

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