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Prescribing Patterns of Medicinal Cannabis for Epilepsy

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Abstract

Aims

Evidence for the use of medicinal cannabis in epilepsy has emerged in recent years. Data on the prescribing practices of medicinal cannabis for epilepsy has not been collected to date in Ireland. This project aims to survey prescribers of medicinal cannabis for epilepsy in Ireland in 2019.

Methods

We sent an anonymous survey to all adult and paediatric consultant neurologists in the Republic of Ireland in 2019. The survey included questions regarding the product prescribed, indication, estimated efficacy, and adverse effects.

Results

62 consultant neurologists were surveyed with 23 respondents (37%). Five (23%) of the respondents had prescribed medicinal cannabis. The most common indication was Lennox-Gastaut syndrome (3) followed by Dravet syndrome (2) and Focal Epilepsy (2). Four (80%) of the prescribers had ceased a prescription; reasons cited included: side-effects (2), lack of effect (2) and cost (1). Side effects noted included drowsiness (2), lethargy (1) and nausea (1). Efficacy was estimated at 'no improvement' by 2 prescribers, 'mild improvement' by 2 prescribers; 1 prescriber noted 'significant improvement'.

Conclusion

Our survey revealed a small number of medicinal cannabis prescribers for epilepsy in the Republic of Ireland, suggesting a limited clinical exposure in the country to date. Resurvey at future intervals is recommended as product availability and familiarity increases, to guide clinical use and prescription programs.

Introduction

The utility of medicinal cannabis has come to represent an area of growing interest in the medical literature.[1] Cannabinoids derived from the cannabis plant include Tetrahydrocannabinol (THC) and cannabidiol (CBD).[2] THC is the psychoactive component of the cannabis plant whereas CBD does not have psychoactive properties at typical doses.[2]

Historically, medicinal properties of the cannabis plant have been described for the treatment of convulsions.[10] Accounts exist of its medical use from a range of cultures including Assyria, India and sources from China which date as far back as 2700 BC.[10] In addition, European physicians in the nineteenth century described its use in the treatment of convulsive disorders.[11]

More recently, evidence for the use of medicinal cannabis has emerged in the treatment of epilepsy .[3] This includes two recent placebo-controlled trials that studied the use of CBD as adjunctive therapy in two paediatric epilepsy syndromes.[4,5]

In 2017, Cannabidiol was studied as an adjunctive treatment in children with Dravet Syndrome, also known as Severe Myoclonic Epilepsy of Infancy.[4,12] This trial demonstrated a >50% reduction in seizure frequency among 43% of patients who received cannabidiol, as compared to only 27% of the placebo group.[4] A similar trial in 2018 considered the use of cannabidiol in patients with Lennox-Gastaut syndrome, again as an adjunctive treatment.[5] This found a median percentage reduction of seizure frequency from baseline of 43.9% in the cannabidiol group versus 21.8% in the placebo group.[5] Adverse effects of cannabidiol noted in both studies included diarrhoea, reduced appetite, somnolence, pyrexia and liver function test derangement.[4,5]

Lennox-Gastaut syndrome accounts for 4% of all childhood epilepsy with a incidence of 2 in 100, 000.[20,21] Dravet syndrome is estimated to have an incidence of 1 per 15, 700 births.[22]

In Ireland, in 2017, a report by the Health Products Regulatory Authority (HPRA) found that there was 'at best, a moderate benefit for cannabis in a small number of conditions and conflicting evidence, or no evidence at all, in a large number of other medical conditions.'[15] The report went on to state that 'the effectiveness and safety of cannabis in large numbers of medical conditions is simply not proven' and 'there is not currently evidence that cannabinoids are an effective treatment in epilepsy'.[13,15]

However, the report recommended that should a policy decision make medicinal cannabis available it should remain limited to a particular set of medical circumstances.[15] One of the conditions highlighted included 'severe, refractory (treatment-resistant) epilepsy that has failed to respond to standard anticonvulsant medications whilst under expert medical supervision'.[13,15]

As a result, in 2019 the Irish government signed legislation to allow for the operation of a pilot Medical Cannabis Access Programme for a duration of five years.[6] Eligible patients were considered to be those, under the care of an appropriate specialist consultant, with Dravet syndrome or severe drug-resistant epilepsy. Other conditions within the Access Program include spasticity associated with Multiple Sclerosis, and intractable nausea and vomiting secondary to chemotherapy. Although this scheme is not yet operational, physicians are able to prescribe other CBD products, as well as THC-containing products if a ministerial licence is granted, but at personal cost to the patient. A ministerial licence is required if there is more than 0.2% THC content, as the product can no longer be classified as a dietary product, and falls under the drugs of misuse act 1977.[7]

Data on prescribing practices for medicinal cannabis products in epilepsy have not been collected to date in the Republic of Ireland. We aimed to collect data on the prescribing practices, as well as estimated clinical efficacy, tolerability and adverse effects.

Methods

We sent an anonymous survey to all consultant adult and paediatric neurologists in the Republic of Ireland in 2019. The survey comprised ten questions and included questions regarding the product prescribed, indication, estimated clinical efficacy, tolerability issues and adverse effects.

Results

62 consultant neurologists were surveyed with 23 respondents giving us a responder rate of 37%. (Figure 1) Of the respondents, 19 (83%) were adult neurologists while 4 (17%) were paediatric neurologists. (Figure 2)

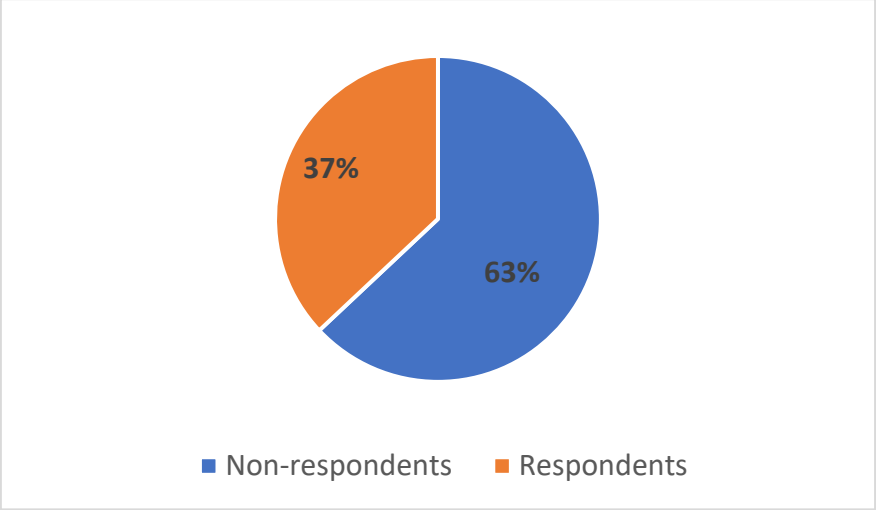

Figure 1: Respondents (%)

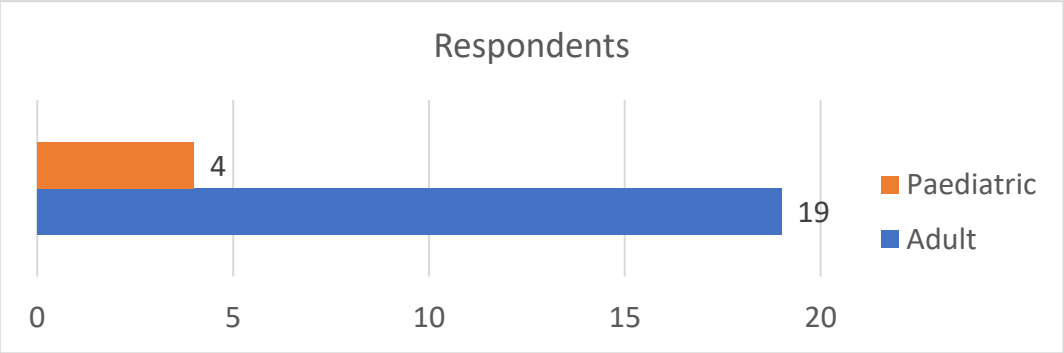

Figure 2: Proportion of adult and paediatric neurologists among respondents

	Practice	Prescriptions	Product	Indications	Estimated efficacy	Side effects	Sourcing
Prescriber 1	Adult	2	CBD & THC + CBD	LGS	No Improvement	Drowsiness	Netherlands
Prescriber 2	Adult	2	THC + CBD	Focal Epilepsy	Mild improvement	Nil	Netherlands
Prescriber 3	Adult	15	CBD & CBD + THC	Dravet Syndrome, LGS, SGE	Mild Improvement	Nausea	Ireland
Prescriber 4	Paediatric	10	CBD & CBD + THC	Dravet Syndrome, LGS, DRE	Significant Improvement	Drowsiness, weight loss, thrombocytopaenia, LFT derangement	Unspecified
Prescriber 5	Adult	Unsure	CBD & CBD + THC	Focal Epilepsy	n/a	Constipation	Ireland

***Acronyms**: LGS: Lennox Gastaut Syndrome; SGE: Symptomatic Generalised Epilepsy; DRE: Drug-resistant Epilepsy*

Table 1: Side effects recorded by prescribers

Five respondents (23%) prescribed medicinal cannabis products. (Table 1) At least 27 patients in this group were prescribed medical cannabis products for Epilepsy in 2019. The clinician with the highest number of medicinal cannabis prescriptions had prescribed to 15 patients, accounting for a majority of all prescriptions in our survey. Four prescribers had prescribed pure CBD products. All prescribers had prescribed products containing both THC and CBD, at some point. The most common indication was Lennox-Gastaut syndrome (3) followed by Dravet syndrome (2) and Focal Epilepsy (2). Four (80%) of prescribers had ceased a prescription. Reasons cited included: side-effects (2), lack of effect (2) and cost (1). In the case of 5 patients (19%) reimbursement was received via the Primary Care Reimbursement Service (PCRS).

Estimated Efficacy & Side effects

Efficacy was estimated at 'no improvement' by 1 prescriber, and 'mild improvement' by 2 prescribers. One prescriber noted 'significant improvement'. Side effects noted by the prescribers included drowsiness (2), lethargy (1) and nausea (1). Other side effects reported included constipation (1), Liver Function Test (LFT) derangement (1), weight loss (1) and thrombocytopaenia with concomitant Sodium Valproate use (1). Interaction with Clobazam causing somnolence was also noted.

Sourcing

Product sourcing was specified by four of the five prescribers. Two prescribers noted medicinal products sourced in Ireland, and an additional two prescribers sourced medicinal cannabis products in the Netherlands (Transvaal Pharmacy).

Discussion

Our survey revealed a relatively small number of prescribers of medicinal cannabis for epilepsy in the Republic of Ireland in 2019. The responder rate is likely a consequence of participation bias and may not be a true reflection of the proportion of Irish neurologists who prescribe medicinal cannabis in epilepsy. However, the numbers are lower than expected given the intense public attention to this treatment over the last few years.[13]

Surveyed clinical outcomes were modest, with mild or no improvement noted by the majority of prescribers, suggesting limited usefulness in clinical practice. However, a study of this nature is not powered or designed to assess the true clinical efficacy of these products. As noted, the efficacy of cannabidiol as an adjunctive treatment in cases of Dravet syndrome and Lennox-Gastaut syndrome has been robustly demonstrated through placebo-controlled clinical trials.[4,5] Outside of these clinical trials, there is a paucity of evidence for the efficacy of medicinal cannabis in a wider range of epilepsy syndromes.[16] In experimental studies, positive anticonvulsant effects have been demonstrated using cannabinoids in rodent models of acute seizures.[17]

Side effects recorded by prescribers are listed in Table 1. Known interactions were observed between medicinal cannabis products, Clobazam and Valproate, highlighting the importance of specialist input in assessing for drug interactions.

The most common adverse effects associated with cannabidiol use include somnolence, decreased appetite, diarrhoea, pyrexia, fatigue, and vomiting.[14]

Cannabidiol, through modulation of Cytochrome P450 enzymes, has been shown to interact with many commonly-prescribed anti-epileptic medications.[8] Levels of Clobazam and N-desmethylclobazam, its active metabolite, have been shown to increase in response to increasing doses of CBD.[9] This is postulated to be the mechanism responsible for an increased risk of sedation when CBD and Clobazam are co-prescribed.[8] Interactions between CBD and Valproate are also described, in particular an elevated risk of liver function test derangement.[8] This is the most common reason for discontinuation of cannabidiol therapy. [14]

The above interactions also highlight the importance of medicinal cannabis prescriptions occurring under specialist guidance. Products containing cannabidiol are commercially available in health food shops or possible to order on the internet. Where patients source these products in non-medical settings, the quantity of cannabidiol can be variable or inaccurate in these formulations.[2] The European Union mandates that the content of THC in such products cannot exceed 0.2%.[18] Furthermore, the quantity of cannabidiol is typically much lower than the doses used in clinical trials.[2] Despite this, the potential still exists for interaction with other anti-epileptic medications.[8] This is of concern particularly in circumstances where the supervising consultant is unaware of patient's use of such products.

Four prescribers had ceased a prescription due to lack of efficacy and side-effect concerns. Cost was also noted as a reason for ceasing a prescription. Financial barriers and inequity of access to such products are suggested by the relatively low number of patients who received PCRS reimbursement. Despite difficulty in accessing such products, interest remains high in the potential benefits of medicinal cannabis among patients with epilepsy, as demonstrated by a recent nationwide survey in Australia.[19] In this survey patient interest in medicinal cannabis products was highest among those with medication-refractory epilepsy and those searching for a therapy with a more favourable side effect profile than conventional anti-epileptic medications.[19]

One of the primary strengths of this study is in the accrual of previously uncollected data within the Republic of Ireland. This will be of value for future researchers, especially should the practice of medicinal cannabis prescriptions become more widespread. An additional strength is the invitation of all consultant neurologists on the Republic of Ireland to participate in the survey. This will allow for comparison with any future interval survey of prescribing patterns. Such work would inform on how levels of physician engagement with medicinal cannabis for epilepsy changes over time.

Our limitations include the low number of medicinal cannabis prescribers in the Republic of Ireland. This remains nonetheless informative as it allows us to conclude that in 2019 there are a very small number of prescribers of medicinal cannabis for epilepsy. An additional limitation is that as this study was designed to collect preliminary data on prescribing practices for medicinal cannabis in epilepsy, we are unable to reach any conclusions on the clinical efficacy of these products. Although we noted side-effects reported by clinicians, we are unable to reach any conclusion on the prevalence of these adverse effect upon the wider patient population. Data on subspeciality interest in epilepsy was not collected.

Additionally, our study only included adverse effects and clinical response reported by clinicians which may be at variance with those reported by patients. We did not collect doses of medicinal cannabis prescribed. Future studies may expand upon our work in order to assess the impact of the Medicinal Cannabis Access Scheme once it becomes fully operational and as access to these products expands. These findings represent a preliminary survey of data on prescribing practices of medicinal cannabis for epilepsy in the Republic of Ireland.

Our study reveals a small number of prescribers of medicinal cannabis for epilepsy, suggesting limited clinical exposure in the country to date. Surveyed clinical outcomes were modest, with mild or no improvement reported by the majority of prescribers. Side effects such as drowsiness and nausea led to discontinuation in some patients.

Future research is needed to monitor the clinical uptake and patient response to medicinal cannabis project as the Irish government's Medicinal Cannabis Access Programme becomes operational. Ongoing survey of the use of cannabis-based products in Ireland will aid in monitoring evolving practice as well as to guide clinical use and prescription programs.

Declaration of Conflicts of Interest:
Neither of the authors have conflicts of interests to disclose.

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