Cannabis derived medicinal products in child neurology

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The review of cannabinoids for the treatment of spasticity by Nielsen et al. is topical and timely. The use of cannabis derived medicinal products (CDMPs) has had a high profile in the media in the UK and worldwide and attempts are being made to assess their efficacy and safety in conditions such as spasticity, chronic pain and epilepsy. All this is being done in a highly charged emotive atmosphere as the public, sometimes aided, abetted and financed by vested interests in the cannabis industry and their public relations consultants, place pressure on clinicians to prescribe CDMPs in the absence of any good quality safety and efficacy data.

Manipulation of the endocannabinoid system theoretically holds promise for the treatment of both spasticity and epilepsy in children. Cannabinoids reduce release of the excitatory neurotransmitter glutamate and this is probably mediated through the CB1 receptor. In animal models, CB1 agonists reduce spasticity and cannabinoid antagonists have the opposite effect.

The problem for clinicians, ably highlighted by the Nielsen review, is that there is a paucity of good quality evidence demonstrating efficacy and safety of CDMPs in human studies. There are only 5 paediatric studies, including a total of 117 children and young adults, looking at the use of CDMPs for spasticity. The causes of spasticity were heterogenous. These studies include one case report, two case series and two small trials. Most of these studies are flawed because they deal inadequately with confounding and do not use standardized objective outcome measures. The first trial conducted by Libzon et al was limited by its small size, used no placebo controls, did not clearly describe its randomization methods and lacked a standardized objective outcome measure[1]. However, it did report improvements in spasticity, dystonia and quality of life. The second trial was larger (n=72), did include a placebo group and utilized a standardized outcome measure and this showed no significant difference in spasticity reduction between the active treatment and placebo[2].

There is a clear need for further research into the use of CDMPs in spasticity and epilepsy. It will not be enough to extrapolate from adult studies to children as the different pharmacokinetics and pharmacodynamics in children and the particular vulnerability of the developing central nervous system may mean that the effects and safety profile of CDMPs may be very different in the paediatric population.

One of the problems clinicians face is that the marijuana plant contains many compounds, any of which may have a pharmacological effect. Most interest has focused on cannabidiol (CBD) and tetrahydrocannabinol (THC) but there are also advocates of using whole cannabis plant extracts. CBD has been shown to be

efficacious in two rare epilepsy syndromes and, as yet, there is no evidence that adding THC improves the anti-epileptic effect of the CBD[3-5]. In the context of spasticity there has been more interest in using THC or its synthetic analogues because of their direct effect on CB1 receptors. The use of whole plant extracts may be perceived by clinicians as too crude an approach and the use of more selective products may minimize side-effects and toxicity and improve efficacy.

There is legitimate concern about the possible effects of CDMPs on the developing CNS. We do not know, for example, what is a safe level of exposure to tetrahydrocannabinol (THC) and we do not know what are the effects of chronic exposure to THC, cannabidiol or any of the other cannabinoids. In particular, we do not know what are the effects on cognition and these may be difficult to discern in children with spasticity and epilepsy who often already have sustained damage to the CNS.

There are many challenges ahead but we should not be deterred from doing the necessary research in this area. The recent change in legislation in the UK that allows clinicians and scientists to investigate the use of CDMPs in patient populations is to be welcomed. As a priority, we need to establish objective standardized outcome measures of efficacy and we need to design studies that have a chance of establishing an accurate safety profile for these drugs. Clinicians should continue to practice evidence-based medicine in this area and until good quality evidence exists should resist public or political pressure to prescribe medicines that have no proven benefit or safety profile.

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