Potential therapeutic uses of cannabinoids to treat behavioural problems in children and adolescents with developmental disorders

CPD

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Background
There is a great deal of interest in the potential symptomatic benefits of medicinal cannabis among parents of children and adolescents with developmental disorders.

Objective
This article provides an overview of what is known about medicinal cannabis as a treatment for paediatric developmental disorders.

Discussion
While there is emerging evidence in support of medicinal cannabis for some adult mental health disorders, to date the evidence in children and adolescents is scant. Reports from uncontrolled observational studies suggest that cannabidiol-rich products may be helpful in reducing behavioural problems in autistic youth. Cannabidiol appears to have a relatively benign adverse effect profile and therefore may be worth considering as a treatment option in some cases. Several controlled clinical trials are underway that will provide more definitive information on the therapeutic value of medicinal cannabis in paediatric developmental and behavioural disorders.

CHILDREN AND ADOLESCENTS with developmental disorders such as intellectual disability commonly exhibit challenging behaviours, including agitation, irritability, aggression and self-injury.[1] Aggression is observed in up to two-thirds of autistic children and adolescents,[2] and self-injurious behaviours – such as head banging, eye poking, arm biting and skin scratching – in more than one-quarter.[3] Approximately half of individuals with intellectual disability have psychopathology,[4] commonly manifesting as severe behavioural problems. These behaviours can pose a threat to the individual and/or their carers.

Behavioural problems are a major contributor to morbidity, functional impairments and reduced quality of life in autistic children and adolescents and those with intellectual disability, and cause great distress for their families and carers. Parents and siblings often live in fear of their family members with behavioural problems and are at increased risk of mental health problems. Behavioural problems in youth with developmental disorders also place an enormous burden on the health, education and disability sectors. In severe cases, carer burnout and relinquishment is a genuine risk.

Behavioural problems in patients with developmental disorders can be difficult to treat.[1] Psychological interventions are often ineffective, leaving environmental modification and medication as the main strategies available. Management is commonly crisis-oriented, including calls to emergency services and presentations to hospital emergency departments.

Psychotropic medications including antipsychotics, stimulants and antidepressants are prescribed for a high proportion of patients with developmental disorders in Australia,[5] despite limited evidence for their efficacy[6,7] and a high risk of serious adverse effects, including weight gain, metabolic syndrome, extrapyramidal movement disorders and serotonin syndrome.[8] Off-label prescribing, polypharmacy and frequent changes to medications are common practices in treating these patients, and medications are sometimes added to treat adverse effects (eg metformin to control weight gain caused by antipsychotics).[9]

Medicinal cannabis for child and adolescent behavioural problems

The potential for medicinal cannabis to treat a range of adult psychiatric conditions is beginning to be understood,[10] and there is now intense interest from parents and physicians as a treatment for behavioural problems in youth with developmental disorders. Australian parents are asking paediatricians whether they can prescribe medical cannabis for

their children,[11] and some parents have reported giving unregulated cannabis products to their children. There are many anecdotal reports on the internet from parents of children with developmental disorders describing major improvements in behaviour with the administration of either unregulated or prescribed cannabis products. In recent years, some Australian general practitioners (GPs), paediatricians and child and adolescent psychiatrists have begun prescribing medicinal cannabis products for paediatric developmental disorders (the Therapeutic Goods Administration Special Access Scheme [Category B] now includes autism as a listed indication for medicinal cannabis approval applications), with anecdotal reports of good responses in some patients. Reported effects have included reductions in agitated anxiety and aggression, as well as the ability to reduce or cease antipsychotic medications, with associated elimination of adverse effects from these medications. However, at present there is little research evidence to support the use of medical cannabis. The Royal Australasian College of Physicians[12] has highlighted the need for research into therapeutic cannabis in youth, a position supported by a recent systematic review.[13]

The endocannabinoid system appears to play an important part in neurodevelopment and behaviour.[14] There are two cannabinoid receptors; CB1 receptors are expressed mostly in the central nervous system, while CB2 receptors are expressed mostly in lymphoid tissue, on the surface of white blood cells. Activation of CB1 receptors is thought to play a part in the modulation of neurotransmitter release. CB2 receptor function is less well understood but may have a role in immune regulation.[15] Alterations in endocannabinoid signalling have been found in mouse models of autism[16] and fragile X syndrome.[17] Immune dysregulation and neuroinflammation are believed to be key cellular mechanisms underpinning autism[18] and are likely to be involved in intellectual disability also, given the aetiological and phenotypic overlap between these two disorders. Therefore, there is some biological plausibility for cannabis as a possible treatment for a range of emotional and behavioural symptoms in developmental disorders.

The primary psychoactive compound in the cannabis plant, Δ^9-tetrahydrocannabinol (THC), has been associated with paranoia and hallucinations in habitual recreational users. Although illicit cannabis use is likely to involve higher doses than prescribed medicinal cannabis, these are potential adverse effects if THC is prescribed, particularly in high doses. In contrast, the non-psychoactive cannabidiol (CBD) appears to cause relatively few adverse effects.[19] The most common adverse effects reported in clinical trials of CBD in children have been somnolence, diarrhoea and decreased appetite. CBD has anti-inflammatory and neuroprotective properties[20] and so has biologically plausible potential for treating behavioural problems in youth with developmental disorders. Furthermore, there is evidence from both preclinical and human studies that CBD has anxiolytic effects,[21] and so it may be efficacious in youth with developmental disorders, as anxiety is commonly a prominent symptom and a primary driver of behavioural problems in these patients.[22]

In children, the only strong evidence for the effectiveness of medicinal cannabis is for high-dose CBD oil (20 mg/kg/day) in the treatment of two severe epilepsy syndromes.[23,24] Sedation was observed in some participants in these studies, and it was considered to have been mostly caused by interactions with clobazam. Improvements in mood, behaviour and alertness were reported by parents in both a chart review (n = 75)[25] and a Facebook survey (n = 19)[26] of parents of children given various oral cannabis extracts for epilepsy. However, there has been very little research into the effect of medicinal cannabis on behavioural problems in children with developmental disorders. The published studies are summarised in Table 1.

A number of high-quality clinical trials of medicinal cannabis products for treating behavioural problems in youth with developmental disorders are currently being conducted internationally, including a large randomised placebo-controlled trial of CBD to treat severe behavioural problems in children and adolescents with intellectual disability in Melbourne and Sydney.[27] Most studies are using oil preparations, though sublingual spray and gel preparations have also been used.

In summary, it is possible that CBD-rich cannabis may be a useful treatment for behavioural problems in children and adolescents with developmental disabilities. However, at present the evidence base for treating this patient group is weak.

Practice recommendations

It is likely that parents of children and adolescents with developmental disorders will be increasingly asking their GPs about medicinal cannabis as a treatment for behavioural problems in their children. Although any doctor can apply to the Therapeutic Goods Administration for a permit to prescribe for any patient (under the Special Access Scheme [Category B]), at present, few doctors in Australia have experience in prescribing medicinal cannabis for children and adolescents.

Several considerations need to be factored into decisions to prescribe a trial of medicinal cannabis to treat paediatric behavioural problems. These include the pattern of the behavioural presentation, the patient's comorbidity profile, the relative toxicity of current medication treatments when compared with medicinal cannabis, and the substantial cost of medicinal cannabis. It is also important to ask parents if they have tried unregulated cannabis products, as this experience (ie type of product used, symptomatic response, adverse effects) may inform prescribing choices.

The potential role for medicinal cannabis needs to be considered alongside other conventional psychotropic medications, weighing up risks and possible benefits. At present, there is insufficient evidence to inform clear clinical guidance regarding the preferred medicinal cannabis product or dose to treat behavioural problems in various paediatric developmental disorders. Published case series in children and adolescents with developmental disorders

Table 1. Published studies of medicinal cannabis in children and adolescents with developmental disorders

Reference	Study design	Population	Product details	Findings
Aran et al 2019[28]	Retrospective	60 children aged 5–17 years with ASD and severe behaviour disturbance	Initial product contained whole-plant extract CBD and THC in a 20:1 ratio. Twenty-nine patients with an insufficient response commenced strains with a CBD/THC ratio up to 6:1. Mean total daily dose was 3.8 mg/kg/day CBD and 0.29 mg/kg/day THC for those taking three daily doses (n = 44), and 1.8 mg/kg/day CBD and 0.22 mg/kg/day THC for those taking two daily doses (n = 16).	• 'Much improved' or 'very much improved': behaviour in 61%, anxiety in 39%, communication in 47%. • Adverse events included sleep disturbances (14%) irritability (9%) and loss of appetite (9%). • One serious adverse event was noted: a transient psychotic event, which was considered related to the THC content.
Aran et al 2021[29]	Placebo-controlled double-blind comparison of two oral cannabinoid solutions	150 participants with ASD, aged 5–21 years	1) Whole-plant cannabis extract containing CBD and THC at a 20:1 ratio and 2) purified CBD and THC at a 20:1 ratio. Average treatment dose was 5.7 mg/kg/day of CBD in the whole-plant extract arm and 5.9 mg/kg/day of CBD in the pure cannabinoid arm.	• No significant difference was found between the groups in changes on the primary-outcome measure of noncompliant behaviour or the secondary-outcome measure of parenting stress. • Median social responsiveness score (secondary outcome) improved by 14.9 points on whole-plant extract versus 3.6 after placebo (P = 0.009). • Common adverse events included somnolence, decreased appetite, weight loss, tiredness, euphoria and anxiety. No serious adverse events were reported.
Barchel et al 2019[30]	Prospective	53 youth with ASD, aged 4–22 years	CBD:THC in a 20:1 ratio. Individualised dose: median (IQR) CBD daily dose was 90 (45–143) mg.	• Overall improvement was reported in 75% of participants. • Changes in the following symptoms were reported (improved, worsened): self-injury and rage attacks 68%, 9%; hyperactivity 68%, 3%; sleep 71%, 5%; anxiety 47%, 24%. • Adverse effects were described as mild; most common were somnolence and decreased appetite.
Bar-Lev Schleider et al 2018[31]	Prospective open label	During the study period, 188 ASD patients initiated the treatment. Mean age was 12.9 ± 7.0 years.	Products varied – most patients received 30% CBD/1.5% THC. Mean daily dose was CBD 240 mg and THC 12 mg.	• After one month, 179 patients remained on treatment and data were collected from 119: 49% reported significant improvement, 31% reported moderate improvement, and 14% reported no improvement. • The most common symptoms improved were restlessness, rage attacks and agitation. • The most common adverse effects were restlessness and sleepiness.

ASD, autism spectrum disorder; CBD, cannabidiol; IQR, interquartile range; THC, Δ^9-tetrahydrocannabinol

have used CBD-predominant products (no or minimal THC) and have started with low doses (eg 1–2 mg/kg/day) and titrated up slowly according to tolerance and response.[15–17] As with any medication, it should only be prescribed after a comprehensive clinical assessment, and only if the prescriber has the capacity to monitor closely for adverse effects. If GPs are considering this therapy, then referral to a paediatrician or child and adolescent psychiatrist may be appropriate.

Key points

- There is a growing belief in the community that medicinal cannabis could be a safe and effective treatment for behavioural problems in children and adolescents.
- Observational studies have reported symptomatic benefits from CBD-rich products in autism; however, there have been no controlled trials published to date.
- Until data from randomised controlled trials are published, CBD-rich medicinal cannabis should be prescribed judiciously; patients should be closely monitored, and non-GP specialist consultation is recommended.

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