BMJ Open

Does cannabidiol reduce severe behavioural problems in children with intellectual disability? Study protocol for a pilot single-site phase I/II randomised placebo controlled trial

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To cite: Efron D, Taylor K, Payne JM, *et al*. Does cannabidiol reduce severe behavioural problems in children with intellectual disability? Study protocol for a pilot single-site phase I/II randomised placebo controlled trial. *BMJ Open* 2020;**10**:e034362. doi:10.1136/bmjopen-2019-034362

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2019-034362).

Received 17 September 2019
Revised 30 January 2020
Accepted 11 February 2020

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ABSTRACT

Introduction Severe behavioural problems (SBPs) are a common contributor to morbidity and reduced quality of life in children with intellectual disability (ID). Current medication treatment for SBP is associated with a high risk of side effects. Innovative and safe interventions are urgently needed. Anecdotal reports and preliminary research suggest that medicinal cannabis may be effective in managing SBP in children with developmental disabilities. In particular, cannabidiol (CBD) may be a plausible and safe alternative to current medications. Families who are in urgent need of solutions are seeking cannabis for their ID children with SBP. However there is no evidence from randomised controlled trials to support the use of CBD for SBP. This pilot study aims to investigate the feasibility of conducting a randomised placebo-controlled trial of CBD to improve SBP in children with ID.

Methods and analysis This is a single-site, double-blind, parallel-group, randomised, placebo-controlled pilot study of 10 participants comparing 98% CBD oil with placebo in reducing SBP in children aged 8–16 years with ID. Eligible participants will be randomised 1:1 to receive either CBD 20 mg/kg/day or placebo for 8 weeks. Data will be collected regarding the feasibility and acceptability of all study components, including recruitment, drop-out rate, study visit attendance, protocol adherence and the time burden of parent questionnaires. Safety outcomes and adverse events will be recorded. All data will be reported using descriptive statistics. These data will inform the design of a full scale randomised controlled trial to evaluate the efficacy of CBD in this patient group.

Ethics and dissemination This protocol has received ethics approval from the Royal Children's Hospital ethics committee (Human Research Ethics Committee no. 38236). Results will be disseminated through peer-reviewed journals, professional networks, conferences and social media.

Trial registration number ACTRN12618001852246

Strengths and limitations of this study

- This is the first study to investigate cannabidiol (CBD) for severe behavioural problem in children with intellectual disability and will contribute to the literature more broadly on the use of cannabinoids in children.
- Randomised, placebo-controlled study using online completion of outcome measures.
- This pilot study will inform the design of a full-scale randomised controlled trial of CBD for this indication, and will inform other CBD trials in children.
- The study is not powered to provide meaningful efficacy outcomes.

INTRODUCTION

Intellectual disability with severe behaviour problems and associated burden

Two per cent of children and adolescents have an intellectual disability (ID),[1] and approximately half of these individuals have mental health problems,[2] including many with challenging behaviours. These commonly include aggression, self-injury, agitation, mood changes, screaming and banging objects. We use the term severe behavioural problems (SBP) to describe this clinical phenotype.

SBPs in children with ID are a major contributor to morbidity, functional impairments, missed opportunities for learning and reduced quality of life. SBP also places an enormous burden on families and carers,[3] as well as health, education and disability sectors. Parents and siblings of youth with SBP often live in fear of them and are at increased risk of mental health problems.[4] Expensive long-term residential placement is often the only option.[5] ID is estimated to cost $A15 billion annually in Australia.[6] Much of this cost, including personal expenses, service use, government expenditure and opportunity cost for families, relates to SBP impacting on the health and care needs of these patients.[7] Patients with ID and SBP cause challenging demands for hospitals to

manage, with implications for staff training, ward design and safety of both staff and patients.

Problems with current treatment of SBP in youth with ID

Challenging behaviours are extremely difficult to treat in children with ID and SBP. Psychological interventions are often ineffective in patients with ID,[8] leaving environmental modification and medication as the main strategies available. Psychotropic medications are prescribed by Australian paediatricians for almost 50% of youth with ID.[9] The medications—antipsychotics, psychostimulants and antidepressants—carry a high risk of side effects for children and adolescents in general; however, patients with developmental disabilities are at particularly high risk,[10] and less able to report side effects. For example, adults with ID exposed to antipsychotic drugs have a higher incidence of treatment-emergent movement disorders compared with patients without ID.[11] Another common side effect of antipsychotics, weight gain, affects health in a patient group already at increased risk of chronic illness,[12] and is a risk factor for avoidable death.[13] Weight gain also brings practical problems in youth with ID, who are often dependent on carers for everyday activities such as dressing, bathing and toileting, as well as compounding the management of aggressive behaviour.

Current pharmacotherapy in children with ID and SBP is characterised by concerning practices, including polypharmacy and frequent changes to medication regimens[10]; adding drugs to treat side effects, such as use of metformin to control weight gain caused by antipsychotic medication[14] and long-term use of drugs 'off-label', for example, atypical antipsychotics. Innovative and safer interventions are urgently needed for children with ID and SBP.

Medicinal cannabis

The potential for medicinal cannabis products to treat a range of medical and psychiatric conditions is becoming increasingly understood.[15] There has recently been great interest in the potential therapeutic role of cannabinoids. The primary psychoactive compound in the cannabis plant is Δ^9-tetrahydrocannabinol (Δ^9-THC), which can cause serious side effects such as paranoia and hallucinations.[16] In contrast cannabidiol (CBD), another cannabis extract, does not have intoxicating properties and may provide benefits with minimal adverse psychological effects.

CBD pharmacology and safety

CBD has been delivered orally in an oil-based capsule or sublingual spray in human trials, in variable ratios with Δ^9-THC. The onset and duration of activity depends on the preparation and route of administration. The plasma half-life of CBD following oral administration is approximately 60 hours after two times per day dosing for 7 days in healthy adults.[17] It is highly lipophilic and accumulates in fat.[18] CBD is metabolised by cytochrome P450 enzymes 3A and 2C in the liver.

Both animal and human studies have indicated that CBD does not affect physiological parameters or psychological functions.[19] Studies in healthy adults have shown CBD to be well tolerated across a wide dose range, with no significant adverse effects on vital signs, cognition or mood in oral doses of up to 1500 mg per day.[18] In children with epilepsy up to 50 mg/kg/day of CBD has been prescribed.[20] Reported tolerance in trials has been generally good, with the most common adverse effects, somnolence, diarrhoea and decreased appetite, occurring in a minority of exposed patients.[21]

Indications for CBD

Medical cannabis is being advocated for an increasing range of indications. In children, the main indication for CBD is drug-resistant epilepsy, with supportive evidence emerging for its effectiveness as an adjuvant treatment to conventional antiepileptic medications for some specific epileptic syndromes.[21] In 2018, Epidiolex, a pure CBD oral solution manufactured by GW Pharmaceuticals, received approval from the US Food and Drug Administration for patients with Lennox-Gastaut syndrome and Dravet syndrome.[22] It is possible that reported improvements in 'overall condition' of children given CBD in epilepsy trials were due to more settled behaviour, although this has not specifically been reported.[23]

Biological plausibility of CBD to treat SBP in youth

Neural mechanisms by which CBD may influence mood and behaviour are only partially established, but include alterations in neurotransmission and calcium homeostasis, antioxidant activity and anti-inflammatory effects.[24] Thus, the endocannabinoid system is a novel target for pharmacological treatments of behavioural problems. Alterations in endocannabinoid signalling have been found in mice carrying a mutation related to autism,[25] and in a mouse model of Fragile-X syndrome,[26] so this system appears to play an important role in neurodevelopment and behaviour.[27] While THC has strong affinity for both cannabinoid receptors receptors (CB1 and CB2), CBD appears to exert its effects on the endocannabinoid system through indirect actions, and may also have activity on other neurotransmitter systems. Thus, CBD has biologically plausible potential therapeutic benefits for human behaviour, and there is emerging evidence of benefit from CBD in adult mental health disorders.[28] A recent review described the anticonvulsive, anxiolytic, antipsychotic, anti-inflammatory and neuroprotective properties of CBD, and suggested CBD may be a candidate for the treatment of autism spectrum disorder (ASD).[29] However, the lack of data showing efficacy and safety in this population was noted.

Evidence for cannabis products in treating SBP in youth

The use of medicinal cannabis to treat children and adolescents with behavioural problems has been discussed in the mainstream media (Ellison K. Medical Marijuana: No Longer Just for Adults. New York Times, 21 November

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2009), and parents have described 'the transformative power of medical cannabis' for their children with ID +SBP (eg, Mothers Advocating Medical Marijuana for Autism). Anecdotally, some parents have reported giving non-prescribed unregulated cannabis products to their children to help with their behaviour, and increasingly Australian parents of children with developmental disabilities and/or mental health disorders are asking their paediatricians if medicinal cannabis would be a useful treatment and whether they can assist them in obtaining it for their child.[23] Research to date suggests that CBD has substantially less side effects than antipsychotic medications,[21] however, there is currently insufficient evidence to inform its use in treating SBP. The American Academy of Pediatrics and the Royal Australasian College of Physicians[30] have highlighted the need for further research into the therapeutic uses of cannabinoids in youth.

A handful of reports in the literature suggest that there may be a legitimate role for medicinal cannabis to treat SBP in youth with developmental disabilities (table 1). Although promising, these uncontrolled reports provide only weak evidence in support of benefit.

There are currently four registered trials of medicinal cannabis products use for behavioural problems in youth (also summarised in table 1). In contrast to these, our study will include all children with ID and SBP, regardless of aetiology, and irrespective whether they have been diagnosed with ASD. Whereas one currently registered trial uses a Δ9-THC containing product, our study will use CBD alone, thus avoiding the potential risks associated with Δ9-THC. Two registered studies describe randomised controlled trials (RCTs) comparing cannabidivarin (a homolog of CBD) to placebo. CBD has a more established safety profile, is more commonly known and sought by consumers and more readily available commercially. Given the larger number of pharmaceutical companies manufacturing CBD, it would be expected that CBD is also more competitively priced—an important consideration for both research funding bodies and patients.

This pilot study will assess the feasibility of conducting a large scale, randomised, double-blind, placebo-controlled study of oral CBD in children with ID and SBP. We will also collect preliminary data on the safety and tolerance of CBD in children with ID and SBP.

METHODS AND ANALYSIS

Study objective

The primary objective of this pilot study is to evaluate all elements of the study design (recruitment strategy, tolerability of the study medication, study duration, study procedures and outcome measures) to assess if they are acceptable and feasible for the conduct of a full-scale RCT of CBD to reduce SBP in children with ID. The secondary objective is to collect preliminary data on the safety of oral administration of CBD in children aged 8–16 years with ID and SBP, by assessing adverse event signals. An exploratory aim of this study is to assess for a signal of behavioural change in participants treated with CBD, through completion of a parent-reported behavioural questionnaire pretreatment and post-treatment.

Patient and public involvement

Two clinician stakeholder forums have been held with groups of paediatricians and child and adolescent psychiatrists who manage children with ID. There was a strong and consistent expression of the need for evidence regarding the efficacy and safety of CBD in these patients, and a belief, based on the common experience of parents inquiring in consultations, that parents would be interested in participating in a trial.

Prior to development of this protocol, we conducted brief, semistructured telephone interviews with eight parents of children with ID and SBPs, in which they were asked whether they would be willing to enrol their child in an 8-week placebo-controlled trial of CBD. Responses were uniformly enthusiastic, with all parents indicating a willingness to participate if such a trial was conducted.

In this pilot study, parents will complete a brief questionnaire poststudy completion regarding their experience participating in the research study. Parents will be asked to rate their experience with recruitment, study visits, drug tolerability and questionnaires using Likert scales. They will also be invited to provide suggestions for improvements to the study design. This information will inform the design of the definitive trial.

Questionnaires to be piloted in this study include child-specific outcomes, as well as those assessing parent/carer quality of life and mental health.

Following completion of the study, participating families will be sent a summary of the study findings. Dissemination of findings will include distribution through community resources, including those accessed by carers such as support groups, and the Murdoch Children's Research Institute (MCRI) Facebook page.

Trial design

This is a single-site, double-blind, parallel-group, randomised, placebo-controlled pilot study of 10 participants comparing 98% CBD oil with placebo in reducing SBP in children aged 8–16 years with ID. Eligible participants will be randomised 1:1 to receive either CBD or placebo.

Investigational product

This study will use 98% CBD in grapeseed oil provided by Tilray, Canada as a 100 mg/mL CBD oral solution, and a placebo grapeseed oil matched for smell, taste and appearance.

Participants

Inclusion criteria

Each patient must meet all of the following criteria to be enrolled in this study:

1. Aged 8–16 years.
2. Diagnostic and Statistical Manual of Mental Disorders (DSM–5) diagnosis of ID.

Table 1 Completed and ongoing studies reporting behavioural outcomes of youth treated with medicinal cannabis products

Published studies

Sample size	Population	Study design	Product used	Findings
1	Child with ID+SBP	Case report	Dronabinol (Δ9-THC)	Improvements in hyperactivity, irritability and speech[38]
10	Adolescents with ID+SBP	Open-label case series	Dronabinol (Δ9-THC)	Reductions in self-injurious behaviour in 7 out of 10 participants[39]
75	Children with epilepsy (heterogeneous sample)	Retrospective chart review	'Oral cannabis '	Improvements in behaviour[40]
19	Children with epilepsy: Dravet syndrome (n=13), Doose syndrome (n=4), Lennox-Gastaut syndrome (n=1) and idiopathic epilepsy (n=1)	Facebook survey	'CBD-enriched cannabis'	Improvements in mood, sleep and self-stimulation[41]
53	Children with ASD	Open-label, symptoms graded as improvement, no change, worsening	CBD:Δ9-THC 20:1	Improvements in self-injury, rage-attacks, hyperactivity, sleep and anxiety.[42] Adverse events were mildQ
60	Children with ASD+SBP	Retrospective open label	'CBD-rich cannabis'	'Much improved' or 'very much improved' behaviour in 61% of patients.[43] Only one serious adverse event was noted, a transient psychotic event, which was considered to be related to an increase in Δ9-THC.
188	Children with ASD	Prospective open label	'CBD-enriched cannabis' (mostly 30% CBD and 1.5% Δ9-THC)	Significant or moderate improvements in anxiety, agitation and rage attacks for 79.8% of 119 participants assessed after 1 month.[44] The most common side effect was restlessness

Ongoing registered trials

Sample size	Population	Study design	Product used	ClinicalTrials.gov Identifier
150	Youth with ASD+SBP	Double-blind, cross-over RCT	Cannabis oil with a 20:1 ratio of CBD to Δ9-THC	NCT02956226
100	Children with ASD+SBP	Double-blind RCT	Cannabidivarin (CBDV; a homolog of CBD)	NCT03202303
26	Youth with Prader-Willi Syndrome +SBP	Double-blind RCT	CBDV	NCT03848481
204	Children with Fragile X Syndrome	Double-blind RCT	Synthetic CBD	NCT03614663

ASD, autism spectrum disorder; CBD, cannabidiol; ID, intellectual disability; RCT, randomised controlled trial; SBP, severe behavioural problem; Δ9-THC, Δ9-tetrahydrocannabinol.

a. Full scale IQ <70 on standardised cognitive assessment on verified records of testing performed within 2 years of enrolment. In the event that records of prior testing are unavailable or the assessment was more than 2 years prior, IQ will be estimated using the Wechsler Abbreviated Scale of Intelligence-II (WASI-II).
b. Deficit in adaptive function (basis for severity rating of ID in DSM-5) in at least one activity of life: Vineland Adaptive Behaviour Scales completed by interview with the parent or carer; derives scores in Communication, Daily Living Skills and Socialisation domains and a Global Adaptive score.

3. SBP: defined as:
   a. Scores of 18 or higher on the Aberrant Behaviour Checklist-Irritability subscale (ABC-I).[31]
   b. Moderate or higher on the Clinical Global Impressions-Severity scale.

4. Consistent pattern of frequent SBP symptoms for >3 months (parent interview).
5. No changes in either medication or other interventions in the 4 weeks prior to randomisation.
6. Has the ability to comply with the protocol requirements, in the opinion of the investigator.

Exclusion criteria

1. Non-English-speaking parents.
2. Psychosis, bipolar disorder, major depressive disorder, obsessive compulsive disorder.
3. Taking antiepileptic medications which interact with CBD (eg, clobazam, topiramate, zonisamide).
4. Current medicinal cannabis use or use within the 3 months prior to enrolment.

Procedure

Recruitment procedure

Participants will be recruited from the Royal Children's Hospital's (RCH) Paediatric Clinics and Child and Adolescent Mental Health Service, as well as paediatric private practices in Victoria. The study will be advertised to clinicians in relevant departments and private clinics with a request to consider whether they have eligible patients. Paediatricians and psychiatrists will send standard study-designed letters, signed by the doctor, to potentially eligible families that briefly outline the study and invite interested parents to contact the study coordinator for further information. Potential participants will then attend a screening visit to determine eligibility. The researchers will obtain written informed consent from parents at the screening assessment (refer to online supplementary material 1 for a sample consent form).

Randomisation, allocation concealment and double-blind conditions

A randomisation schedule will be generated by an independent statistician at the Clinical Epidemiology and Biostatistics Unit at the MCRI.

The randomisation schedule will be provided to the trials pharmacist at the RCH. Treatment allocation will be conducted by the pharmacy and will be blinded to all members of the study team and participants. Study medication codes will only be available once all data collected have been entered into the study database for every participant and the database has been finalised. In the event of a medical emergency, a pharmacist will be available to break the blind.

Study procedures

This study will be conducted at RCH, Melbourne. Study visits and assessments will be conducted as per table 2. To maximise protocol adherence and minimise treatment dropouts, a dedicated study coordinator will be available to respond to parent queries or concerns between study visits.

Further description of the assessments included in table 2 are as follows:

WASI-II. The WASI-II[32] is a general intelligence, or IQ test designed to assess specific and overall cognitive capabilities and is individually administered to children, adolescents and adults (ages 6–89). This will be administered to children who have not had an IQ test in the 2 years prior to screening.

Vineland-3. Vineland Adaptive Behaviour Scales V.3 will be completed by interview with the parent or carer of children who have not had an IQ test in the 2 years prior to screening. This instrument derives scores in Communication, Daily Living Skills and Socialisation domains, and a Global Adaptive score.

Autism-Tics attention deficit/hyperactivity disorder (ADHD) and Comorbidities (A-TAC). A-TAC[33 34] inventory is a comprehensive screening interview for ASD, attention deficit/hyperactivity disorder (ADHD), tic disorders, developmental coordination disorder, learning disorders and other childhood mental disorders. Modules screening for Motor skills, ADHD, Tics, Compulsions, Mood, Anxiety and Oppositional defiance will be administered with the participants' parent or carer by a study doctor.

Social Communication Questionnaire (SCQ). The 'current' version of the SCQ[35] will be used to screen for ASD symptoms. This will be administered online with the outcome measures.

ABC-I. The ABC[31] is an informant-rated questionnaire assessing severity of behavioural symptoms commonly seen in youth with ID that includes five subscales: Irritability, Social Withdrawal, Stereotypic Behaviour, Hyperactivity/Non-compliance and Inappropriate Speech. The Irritability subscale (ABC-I), which covers symptoms such as agitation, aggression, meltdowns and self-harm, will be used to determine eligibility.

Parent survey and Medical history. Demographic details will be collected from parents, along with details of the child's medical history, previous medications, allied health service utilisation and any non-pharmacological behaviour management strategies that have been tried.

Concomitant medications. At each visit, the investigators will ask about changes in participants' medications.

Physical examination. Physical examination including vital signs (temperature, heart rate, respiratory rate and blood pressure) and height and weight measurement will be conducted by a study doctor.

Haematology and Biochemistry. Blood will be collected by finger prick and tested for full blood count, electrolytes, creatinine, liver function tests and lipase. Participants with clinically significant abnormalities will be excluded from participating at the judgement of the investigators. Any abnormal results will be communicated to the families immediately, and to the paediatrician at the conclusion of the study (or immediately if considered clinically significant).

Study drug administration. Investigational product will be administered orally at a starting dose of 5 mg/kg/day in two divided doses. The dose will be increased in increments of 5 mg/kg every 3 days for 9 days up to

Table 2 Schedule of study visit procedures and assessments

			Double-blind evaluation				
	Screening	Baseline/ start of uptitration	Start of maintenance	Maintenance mid-point	Start of down-titration	End of down-titration	End of study (phone call)
Day	−14 to −1	1	Day 9–13	Day 36–40*	Day 66–70	Day 74*	Day 104
WASI-II	X						
Vineland-3	X						
A-TAC	X						
SCQ	X						
ABC-I	X						
Parent survey	X						
Medical history	X						
Concomitant medications	X	X	X		X		
Physical examination (including vital signs)	X	X	X		X		
Weight measurement	X	X	X		X		
Height measurement	X						
Haematology	X		X		X		
Biochemistry	X		X		X		
Randomisation		X					
Dispense study medication		X	X	X	X		
Study drug administration		X----------	----------	----------	----------X		
Dispense diary cards		X	X		X	X	
Collect diary cards			X		X	X	X
Evaluation measures		X			X		
Safety outcome measure (MOSES)		X	X		X		
Adverse events		X	X		X	X	X
Compliance check			X	X	X	X	
Pilot evaluation questionnaire							X

*Maintenance midpoint and end of down-titration visits require only the parent or carer to attend to return study medication.
ABC-1, Aberrant Behaviour Checklist-Irritability subscale; A-TAC, Autism Tics ADHD and Comorbidities; MOSES, Monitoring of Side Effects Scale; SCQ, Social Communication Questionnaire; WASI-II, Wechsler Abbreviated Scale of Intelligence-II.

the maintenance dose of 20 mg/kg/day (up titration phase). This dose was chosen to be consistent with a recent Dravet syndrome trial,[21] and because good human pharmacokinetic data are available for 20 mg/kg.[36] A ceiling dose of 1000 mg/day will be administered to all participants weighing 50 kg or greater. Participants will continue to receive investigational product at the maintenance dose for 8 weeks (maintenance phase). The treatment duration was chosen because the RCT of CBD in Dravet syndrome reported that 'the difference in favour of CBD was seen in the first month of the maintenance period'.[21] This was corroborated by personal correspondence with both researchers and clinicians experienced in prescribing CBD for youth with ASD. The 8-week maintenance period, therefore, will allow 4 weeks for treatment effects to emerge, followed by an additional 4 weeks, which corresponds with the period over which parents are required to reflect when completing the behavioural outcome questionnaire. On completion of the maintenance phase, the dose will be decreased in increments

Table 3 Evaluation measures

Construct	Measurement	Source
SBP	Summary score from the ABC-I[31] (15 items)	Parent report
Behaviour	Other subscales of the ABC[31] (4 outcomes)	Parent report
Overall clinical impression	Clinical Global Impressions[37]: 2-item clinician-rated summary measures of (a) severity of psychopathology and (b) improvement	Clinician-rating
Participation	Child and Adolescent Scale of Participation[45] (20 items). Participation in home, school and community activities	Parent report
Quality of life	Child Health Utility 9D[46 47] (9 items). Preference-weighted measure used to calculate quality adjusted life years for children.	Parent report
Sleep	Sleep Disturbance Scale for Children[48] (26 items)	Parent report
Parent quality of life	Assessment of Quality of Life 8D[49] (35 items). Health-related instrument used to calculate quality adjusted life years for parents.	Parent report
Family quality of life	Beach Centre Family Quality of Life[50] (25 items). Family interaction, parenting, emotional and material well-being, disability-related support	Parent report
Parent mental health	Depression Anxiety Stress Scale –21[51] (21 items). Report of symptoms over the past week.	Parent report
Parenting stress	Autism Parenting Stress Index[52] (13 items). Measures three categories of stress drivers: core social disability, difficult behaviour, physical issues	Parent report

ABC-1, Aberrant Behaviour Checklist-Irritability subscale; SBP, severe behavioural problems.

of 5 mg/kg for 9 days at which time administration will cease.

Diary cards. Diary cards will be provided to parents to record each administration of study medication, including administration time, dosage and any noteworthy comments such as incomplete administration of medication or possible side effects.

Evaluation measures. Parent-report questionnaires will be trialled for feasibility, burden and acceptability for this population, with a view to include these as outcome measures in a future full-scale randomised clinical trial of CBD to reduce SBP in children with ID. These will be administered online through Research Electronic Data Capture (REDCap). See table 3 for further details of these questionnaires.

Safety Outcome Measure. Safety outcomes will be collected using the Monitoring of Side Effects Scale (MOSES),[37] which will be completed by the parent or carer with the assistance of a study doctor. The MOSES is an 83-item measure that includes known side effects of psychotropic medications.

Assessment of adverse events. Adverse events will be evaluated at baseline (to exclude pre-existing problems) and throughout the study. Adverse events will be documented from physical examination findings, clinically significant lab results and diary cards. Documentation for all adverse events will include the specific event/condition, the dates and times of occurrence, the event severity, duration, likely relationship to CBD, action taken and date of resolution. In the event any participant (or their parent/carer) reports an intolerability to study medication, or there is a clinical or laboratory observation suggesting an intolerability to study medication, dose modification or cessation may be initiated in consultation with the Study Management Group.

In the event, any clinical observation suggests a severe intolerability of an individual participant to the study medication, study medication discontinuation will be considered. Any adverse event still ongoing at the time of study medication discontinuation will be monitored until it has returned to baseline status, stabilised, or, in the opinion of the Investigator and the Study Management Group agree that follow-up is no longer required.

Serious adverse events will be reported to the research governance office within 72 hours of becoming aware of the event and in accordance with local governance authorisation.

Compliance check. Parents will be instructed to return all medication bottles, empty or otherwise, for weighing by pharmacy staff to measure compliance. Compliance between 80% and 120% will be considered acceptable.

Pilot evaluation questionnaire. At the conclusion of the study, parents will complete a questionnaire specifically designed for this study to assess parent acceptability of study procedures (recruitment approach, number of study visits, questionnaire completion and blood tests) and medication tolerability. Refer to the online supplementary material 2 for a copy of this questionnaire.

Data collection and analysis

Data will be collected regarding the feasibility and acceptability of all study components, including recruitment, withdrawal rate, study visit attendance, protocol adherence and the time burden of parent questionnaires.

Data will be entered directly into an online database (REDCap) at the time of collection and cross-checked for

completion by the study coordinator. Only de-identified data will be entered into REDCap. Identifiable data (such as contact details) will be held in a separate, confidential, secure document accessible only to the investigators.

As this is a pilot study, all data will be reported using descriptive statistics. The recruitment rate will be presented as the percentage of eligible participants enrolled, and the reasons for not participating will be summarised. Study visit attendance and protocol adherence, medication compliance, study withdrawals, treatment discontinuations and protocol violations will be summarised by treatment arm. The acceptability of study visits and procedures, and tolerability of the study medication will be presented as mean scores with ranges and SD.

MOSES assessed safety outcomes and adverse events will also be summarised.

Scores from the evaluation measures listed in table 3 will be summarised as means and SD by treatment group.

ETHICS AND DISSEMINATION

Study-specific unique identifiers will to be used to identify trial subjects. Data will be deidentified and associated with study specific identification numbers. Data will be captured and stored directly in REDCap, Vanderbilt University, a secure, web-based application for building and managing online databases and surveys. REDCap is hosted on MCRI infrastructure. Data will be kept for at least 15 years after the completion of the trial in accordance with the requirements of the Therapeutic Goods Administration or until the 25th birthday of the youngest participant, whichever is the later date (Victorian Health Records Act 2001).

Research data for this project will be presented at conferences and published in peer-reviewed journals. Aggregated data only will be reported in publications and presentations, with individual identifying information removed. We will endeavour to make these research data/resources as widely available as possible, while safeguarding the privacy of participants, protecting confidential and proprietary data, and third-party intellectual property.

DISCUSSION

This pilot study aims to investigate the feasibility of conducting a double-blind RCT of CBD to reduce SBP in children with ID. This study is not sufficiently powered to evaluate the efficacy of CBD in this population, however, the findings of this pilot study will inform the design of a fully powered RCT of CBD for reducing SBP in ID. The secondary aim of collecting preliminary safety data of CBD in this population, and the exploratory aim of examining for a signal of behavioural change in those treated with CBD, may also be informative for future study design. The planned RCT will address an identified evidence-practice gap in the use of CBD to meet an important need for services, the community and families, the safe and effective treatment of SBP in children and adolescents with ID. If safe and effective the transition into medical practice will require dissemination of research findings, education and training of prescribers, and support material solutions such as evidence-based clinical practice guidelines.

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Funding This work was supported by an internal grant scheme available to employees of MCRI. This research received no specific grant from any external funding agency in the public, commercial or not-for-profit sectors.

Disclaimer Investigational product was supplied in kind from Tilray, who had no role in the conception or design of the study and will have no role in data collection, management, analysis, or interpretation, preparation, review, or approval of the manuscript; nor in thedecision to submit the manuscript for publication.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This project has ethics approval from the Human Research Ethics Committee of the Royal Children's Hospital, Melbourne (38236)

Provenance and peer review Not commissioned; externally peer reviewed.

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