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ORIGINAL ARTICLE

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A pilot randomised placebo-controlled trial of cannabidiol to reduce severe behavioural problems in children and adolescents with intellectual disability

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Aims: Severe behavioural problems (SBP) are a major contributor to morbidity in children with intellectual disability (ID). Medications used to treat SBP in ID are associated with a high risk of side effects. Cannabidiol has potential therapeutic effects in SBP. This pilot study aimed to investigate the feasibility of conducting a randomised placebo-controlled trial of cannabidiol to reduce SBP in children with ID.

Methods: This is a double-blind, placebo-controlled, two-armed, parallel-design, randomised controlled trial of cannabidiol in children aged 8–16 years with ID and SBP. Participants were randomised 1:1 to receive either 98% cannabidiol in oil (Tilray, Canada) or placebo orally for 8 weeks. The dose was up-titrated over 9 days to 20 mg/kg/day in two divided doses, with a maximum dose of 500 mg twice/day. The feasibility and acceptability of all study components were assessed.

Results: Eight children were randomised, and all completed the full study protocol. There were no serious adverse events or drop-outs. Protocol adherence for key study components was excellent: study visits 100%, medication adherence 100%, blood tests 92% and questionnaire completion 88%. Parents reported a high degree of acceptability with the study design. All parents reported they would recommend the study to other families with children with similar problems. There was an efficacy signal in favour of active drug.

Conclusions: The findings suggest that the study protocol is feasible and acceptable to patients with ID and SBP and their families.

KEYWORDS

cannabidiol, intellectual disability, irritability, medicinal cannabis, severe behaviour problems

1 | INTRODUCTION

Intellectual disability (ID) has a prevalence of 1–2%.[1] Approximately half of these individuals have psychopathology,[2] commonly manifesting as severe behavioural problems (SBP). SBP includes irritability, aggression, self-injury and elopement, which pose a threat to self and others. SBP in children with ID are very debilitating, and a major contributor to morbidity, functional impairments, missed opportunities for learning and reduced quality of life.[2]

SBP is extremely difficult to treat in youth with ID. Intensive behavioural interventions can be effective but are costly,

The authors confirm that the Principal Investigator for this paper is Daryl Efron and that he had direct clinical responsibility for patients.

resource-intensive and require specialised staff for delivery.[3] Comorbid conditions such as mood disorders often drive the SBP and require medication treatment. Management is often crisis-oriented, including calls to police and distressing emergency department presentations. Hospital admissions and respite care placements provide only short-term solutions.[4]

Psychotropic medications, including anti-psychotics, psychostimulants and anti-depressants, are prescribed by Australian paediatricians for almost 50% of youth with ID,[5] despite limited evidence for their efficacy.[6] These medications carry a high risk of side effects,[7] with patients with ID at particularly high risk,[8] while being less able to report side effects. Common side effects of antipsychotics, such as weight gain and metabolic syndrome, negatively affect health in a patient group already at increased risk of chronic illness,[9] and are risk factors for avoidable death.[10] Weight gain brings additional practical problems in youth with ID, who are often dependent on carers for activities such as dressing, bathing and toileting, as well as compounding the management of aggressive behaviour.

There has been little or no progress for decades in the development of medications to treat SBP in youth with ID. Current pharmacotherapy is characterised by concerning practices including polypharmacy and frequent changes to medications; adding drugs to treat side effects (e.g. metformin to control weight gain caused by antipsychotics)[11]; and the long-term use of drugs "off-label", e.g. atypical antipsychotics. Novel, safer interventions are needed to treat this highly vulnerable patient group.

The potential for medicinal cannabis to treat a range of psychiatric conditions is becoming increasingly understood,[12] and there is intense interest from parents and physicians in medical cannabis as a treatment for SBP in youth with ID. Parents of children with ID and SBP are asking paediatricians whether they can prescribe medical cannabis for their child,[13] and some parents have reported giving unregulated cannabis products to their children. However, there is a lack of evidence to support its use. Importantly, a recent systematic review has highlighted the need for research into therapeutic cannabis in youth.[14]

The primary psychoactive compound in the cannabis plant is Δ^9-tetrahydrocannabinol (THC), which has the potential to cause serious side effects, e.g. paranoia and hallucinations. In contrast, cannabidiol (CBD), another cannabis extract, does not have intoxicating properties,[15] and may provide benefits with tolerable adverse effects. CBD has anti-inflammatory and neuroprotective properties.[16] There is also evidence from both preclinical and human studies that CBD has anxiolytic effects,[17] and so it may be efficacious in youth with ID, as anxiety is commonly a prominent symptom and driver of SBP in these individuals.

The endocannabinoid system appears to play a role in neurodevelopment and behaviour. Neural mechanisms by which CBD may influence mood and behaviour are only partially established, but include alterations in neurotransmission and calcium homeostasis, anti-oxidant activity, and anti-inflammatory effects.[18] Alterations in endocannabinoid signalling have been found in mouse models of autism[19] and Fragile-X syndrome. While THC has strong affinity for both cannabinoid 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.[20] Thus CBD has biologically plausible potential for treating SBP in youth with ID, and is likely to cause fewer side effects than currently used medications.

What is already known about this subject

- Medications currently used to treat severe behavioural problems (SBP) in youth with intellectual disability (ID) commonly cause side effects.
- Cannabidiol is being used increasingly to treat a range of psychiatric conditions in adults, as well as paediatric epilepsy.
- Open-label studies suggest that cannabidiol may represent a novel therapy for patients with ID and associated SBP; however, evidence from randomised controlled trials is needed in order to inform prescribing practice.

What this study adds

- The protocol was feasible and acceptable to patients aged 8–16 years with ID and SBP and their families.
- Although not powered to address efficacy, there was a signal in favour of cannabidiol over placebo in this pilot study.

In children, the only strong evidence for the effectiveness of CBD is in the treatment of two specific epilepsy syndromes.[21,22] Somnolence, diarrhoea and decreased appetite are the most common adverse effects reported in trials of CBD in children. There has been very little research into the effect of CBD on SBP in children, beyond a few open-label observational studies in children with autism spectrum disorder (ASD). In one study, CBD was administered to 53 children with ASD and improvements in self-injury, rage attacks and hyperactivity were reported.[23] Adverse effects were described as mild. Another retrospective study assessed the tolerability and efficacy of CBD-rich cannabis in 60 children with ASD and SBP.[24] The investigators reported "much improved" or "very much improved" behaviour in 61% of patients. Only one serious adverse event was noted in the study, a transient psychotic event, which was considered related to the THC content. In a prospective open-label study, the parents of 84% of 93 children with ASD treated with 30% CBD/1.5% THC reported improvements in agitation and rage attacks after 6 months of treatment.[25] The most common side effect was restlessness. Although promising, these uncontrolled reports provide only weak evidence in support of benefit of CBD. Furthermore, there has been no investigation of CBD to treat SBP in children with ID (many but not all of whom have associated ASD).

This pilot study aimed to assess the feasibility of conducting a large-scale, randomised, double-blind, placebo-controlled study of oral CBD in children with ID and SBP. Preliminary data on the safety, tolerability and efficacy of CBD was also collected.

2 | METHODS

2.1 | Study objective

Details of the study design and methods have been described previously.[26] The primary objective of this pilot study was 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 randomised controlled trial of CBD to reduce SBP in children with ID. The secondary objective was 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 was to assess for a signal of behavioural change in participants treated with CBD, through completion of a parent-reported behavioural questionnaire pre- and post-intervention.

2.2 | Trial design

This was a single-site, phase I/II double-blind, parallel group, randomised, placebo-controlled pilot study of eight participants comparing 98% CBD oil with placebo in reducing SBP in children aged 8–16 years with ID.[26] Eligible participants were randomised 1:1 to receive either an oral solution of 98% CBD 100 mg/ml in grapeseed oil or a placebo matched for smell, taste and appearance. Both study drugs were provided by Tilray, Canada.

2.3 | Participants

2.3.1 | Inclusion criteria

Children were eligible if they were aged 8–16 years with:

1. Diagnostic and Statistical Manual of Mental Disorders (DSM–5) diagnosis of ID, based on: (a) Full scale IQ < 70 on standardised cognitive assessment on verified records of testing performed within two years of enrolment. If prior testing records were unavailable or the assessment was more than 2 years prior, IQ was estimated using the Wechsler Abbreviated Scale of Intelligence-II (WASI-II).[27] (b) Deficit in adaptive function in at least one activity of life as determined by the Vineland Adaptive Behavior Scales Version 3 (Vineland-3)[28] completed by interview with the parent or carer. Activity domains assessed by the Vineland-3 include Communication, Daily Living Skills and Socialization, as well as a Global Adaptive score.
2. SBP, defined as: a score of 18 or higher on the Aberrant Behavior Checklist-Irritability subscale (ABC-I)[29] and Moderate or higher on the Clinical Global Impressions-Severity scale, reported as being consistent for > 3 months via parent interview.
3. No changes in either medication or other interventions in the four weeks prior to randomisation.

2.3.2 | Exclusion criteria

Criteria for exclusion were if the child had: (1) non-English-speaking parents; (2) diagnoses of psychosis, bipolar disorder, major depressive disorder, obsessive compulsive disorder; (3) taken anti-epileptic medications which interact with CBD (e.g. clobazam, topiramate, zonisamide); (4) used medicinal cannabis within the 3 months prior to enrolment.

2.4 | Study procedures

2.4.1 | Recruitment

Participants were recruited from paediatric clinics at the Royal Children's Hospital, Melbourne, as well as private paediatric practices. The study was advertised to clinicians in relevant departments and private clinics with a request to consider whether they had eligible patients. Paediatricians sent letters to potentially eligible families briefly outlining the study and inviting interested parents to contact the study coordinator for further information. Potential participants then attended a screening visit to determine eligibility. Informed consent was obtained from parents at the screening assessment.

2.4.2 | Randomisation and double-blind conditions

A randomisation schedule was prepared by an independent statistician, and provided to the hospital trials pharmacist. Treatment allocation was conducted by the pharmacy who dispensed the study medication according to the randomisation schedule labelled with only the participant's study number. All members of the study team and participants remained blinded until the database was finalised.

2.4.3 | Study visits

Study visits and assessments occurred at the Royal Children's Hospital, Melbourne following the schedule outlined in Table 1.

Where children had not had an IQ test in the two years prior to screening, the *WASI-II* and *Vineland-3* were completed.

TABLE 1 Schedule of study visit procedures and assessments

			Double-blind evaluation				
	Screening	Baseline/start of up-titration	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[a]	Day 66–70	Day 74[a]	Day 104
WASI-II	X						
Vineland-3	X						
A-TAC	X						
SCQ	X						
ABC-I	X				X		
Parent survey	X						
Medical history	X						
Concomitant medications	X	X	X		X		
Physical examination	X	X	X		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		
Adverse events (MOSES)		X	X		X		
Compliance check			X	X	X	X	
Pilot evaluation questionnaire							X

[a]Maintenance mid-point and end of down-titration visits required only a parent to attend to return study medication.
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.

2.4.4 | A-TAC

Autism-Tics ADHD and Comorbidities (A-TAC)[30,31] inventory is a comprehensive screening interview for childhood developmental and/or mental disorders. Modules screening for ADHD, Tics, Compulsions, Mood, Anxiety & Oppositional defiance was administered with the participants' parent by a study doctor.

2.4.5 | SCQ

The "current" version of the Social Communication Questionnaire (SCQ)[32] was used to screen for ASD symptoms. This was administered online alongside the outcome measures.

ABC-I. The Aberrant Behaviour Checklist (ABC)[29] 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/Noncompliance and Inappropriate Speech. Study eligibility was assessed using the Irritability subscale (ABC-I), which covers symptoms such as agitation, aggression and self-harm.

2.4.6 | Parent survey and medical history

Parents provided details of the child's demographics, medical history, previous medications, allied health service utilisation, and any non-pharmacological behaviour management strategies that have been tried.

2.4.7 | Concomitant medications

At each visit the investigators asked about changes in participants' medications.

2.4.8 | Physical examination

Study doctors conducted physical examinations, which included vital signs (temperature, heart rate, respiratory rate and blood pressure) and measurement of height and weight.

2.4.9 | Haematology and biochemistry

Full blood count, electrolytes, urea, creatinine, liver function tests and lipase were all taken and recorded.

2.4.10 | Study drug administration

CBD was administered orally at a starting dose of 5 mg/kg/day in two divided doses, with matched dosing in the placebo group. The dose was increased in increments of 5 mg/kg every 3 days for 9 days up to 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.[33] Although lower doses have been reported to have been helpful for reducing SBP in some paediatric patients with ASD in open-label studies,[25] in the absence of clear data to inform optimal dosing we chose to use the higher dose demonstrated to be safe in children so as not to miss an effect due to insufficient dose. A ceiling dose of 1000 mg/day was administered to all participants weighing 50 kg or greater. Participants continued to receive investigational product at the maintenance dose for 8 weeks (maintenance phase). Study medication was then down-titrated over 9 days following the reverse of the up-titration schedule.

2.4.11 | Diary cards

Parents recorded each administration of study medication, including administration time, dosage, and any noteworthy comments such as incomplete administration of medication or possible side effects.

2.4.12 | Evaluation measures

Parent-report questionnaires were 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 were collected in an online database (REDCap, Vanderbilt University, TN).[34,35] See Table 2 for further details of these questionnaires. Higher scores on these measures reflect greater difficulties, with the exception of the quality of life and participation measures, where higher scores reflect better functioning. Permissions required for use of the ABC and Child Health Utility-9D were obtained prior to study commencement.

2.4.13 | Safety measures

Safety outcomes were collected using the Monitoring of Side Effects Scale (MOSES),[44] as completed by parents with the assistance of a study doctor. The MOSES is an 83-item measure that includes known side effects of psychotropic medications, each rated on a five-point scale from Not Present to Severe.

2.4.14 | Compliance check

Parents returned medication bottles, empty or otherwise, for weighing by pharmacy staff to measure compliance. Compliance of between 80–120% was considered acceptable.

2.4.15 | Pilot evaluation questionnaire

At the conclusion of their involvement in the study, parents completed a questionnaire to assess parent acceptability of study procedures (recruitment approach, number of study visits, questionnaire completion and blood tests), and medication tolerability.

TABLE 2 Evaluation measures

Construct	Measure
SBP	Summary score from the ABC-I[29] (15 items)
Behaviour	Other subscales of the ABC[29] (4 outcomes)
Participation	Child & Adolescent Scale of Participation[37] (20 items), which provides a measure of participation in home, school, and community activities
Quality of life	Child Health Utility 9D[38] (9 items). Preference-weighted measure used to calculate quality adjusted life years for children.
Sleep	Sleep Disturbance Scale for Children[39] (26 items)
Parent quality of life	Assessment of Quality of Life 8D[40] (35 items). Health-related instrument used to calculate quality adjusted life years for parents.
Family quality of life	Beach Center Family Quality of Life[41] (25 items), which provides measures of family interaction, parenting, emotional and material wellbeing, disability-related support
Parent mental health	Depression Anxiety Stress Scale –21[42] (21 items) provides an indication of parent mental health symptoms over the past week.
Parenting stress	Autism Parenting Stress Index[43] (13 items), which provides a measure of three categories of stress drivers: core social disability, difficult behaviour, physical issues

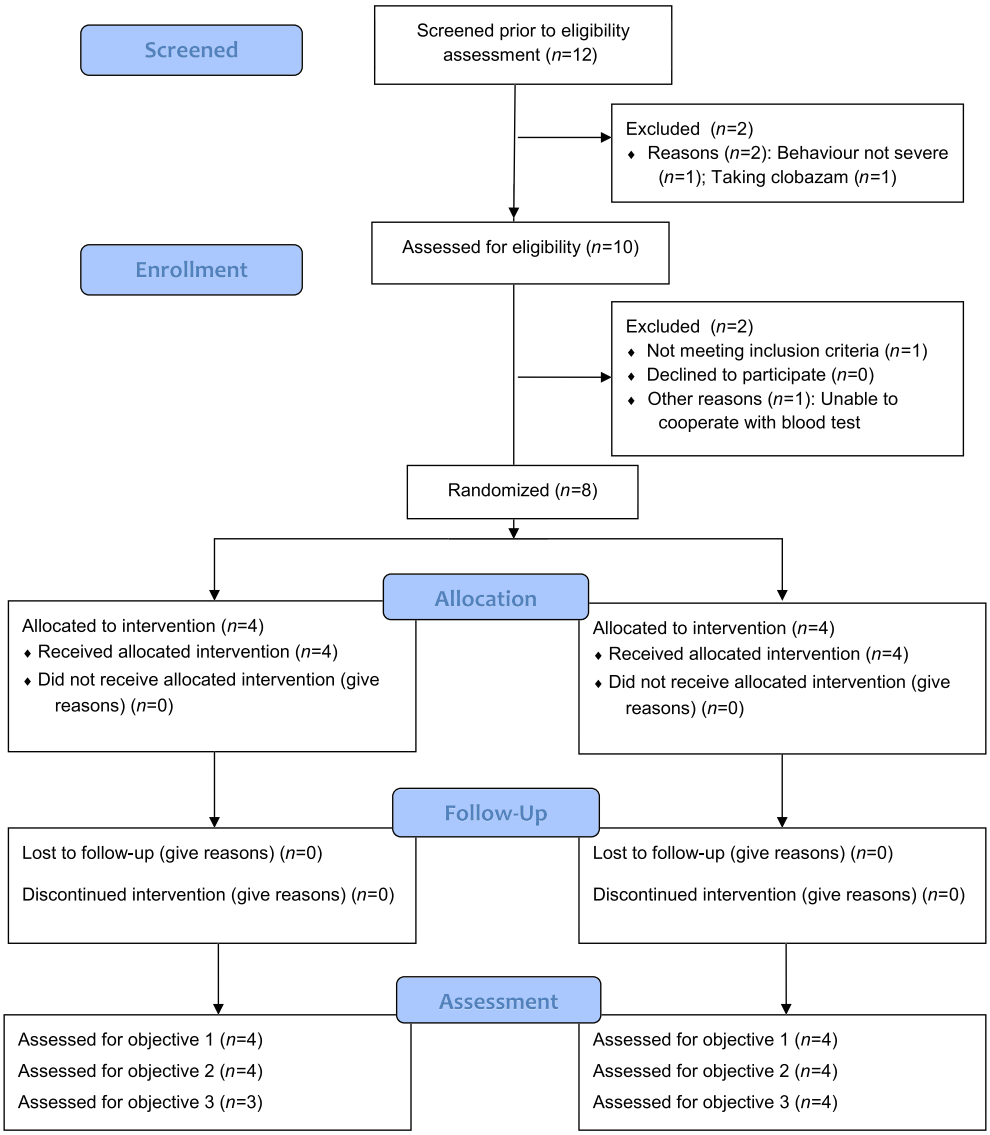

FIGURE 1 CONSORT flow diagram for pilot and feasibility trials[36]

2.5 | Data collection and analysis

Data were entered into a study-specific database in REDCap[34,35] at the time of collection and were cross-checked for completeness by the study coordinator.

Feasibility of the study design was assessed by ease of recruitment (adherence to study timeline and rate of recruitment) and percentage completion of study design elements. Safety of the study medication was assessed by number of adverse events, including serious adverse events. Parent responses to the MOSES were compared between baseline (pre-treatment) and day 66 (end of maintenance), in order to gauge treatment emergent symptoms. A two-point increase in symptoms on this measure was considered meaningful.

Acceptability of the study design was assessed using a purpose-built questionnaire completed by parents at the conclusion of their study involvement. Parents rated their experience with key elements of the study design and were given an opportunity to provide feedback.

Health economics analyses planned for a fully powered study rely on parent consent for the study team to access their child's Medicare and Pharmaceutical Benefits Scheme data. In order to gauge willingness to consent in the larger trial, parents were asked whether they would feel comfortable with sharing this information.

This pilot study was not powered to determine efficacy, hence no formal sample size calculation was conducted. The number recruited in this study was based on feasibility. Given the pilot nature

TABLE 3 Sample characteristics

	CBD (*n* = 4)	Placebo (*n* = 4)
Age: Years, mean (range)	13.5 (11.0–16.6)	14.4 (12.6–16.9)
Male, *n* (%)	2 (50%)	3 (75%)
Weight at baseline: kg, mean (SD)	63.6 (25.0)	58.3 (6.6)
Maintenance dose: mg/kg/bd, mean (SD)	7.8 (2.0)	9.0 (1.1)
Non-verbal	1 (25%)	1 (25%)
Aetiology of intellectual disability		
Known[a]	0	3
Unknown	4	1
Comorbidities, *n* (%)		
Autism spectrum disorder	4 (100%)	1 (25%)
Epilepsy	1 (25%)	1 (25%)
SCQ, *n* (%) above cut-off	3 (100%)[b]	1 (25%)
ATAC, cases above cut-off (%)		
ADHD	3 (75%)	4 (100%)
Obsessive compulsive	3 (75%)	3 (75%)
Oppositional defiant	2 (50%)	4 (100%)
Tics	2 (50%)	0 (0%)
Separation anxiety[c]	1 (25%)	0 (0%)
General anxiety[c]	2 (50%)	1 (25%)
Depression[c]	1 (25%)	0 (0%)
Concomitant medications, *n* (%)		
Risperidone	2 (50%)	1 (25%)
Fluoxetine	1 (25%)	2 (50%)
Methylphenidate	0 (0%)	1 (25%)
Clonidine	1 (25%)	1 (25%)
Guanfacine	1 (25%)	0 (0%)
Sodium valproate	0 (0%)	1 (25%)
Melatonin	1 (25%)	1 (25%)
Current supports, *n* (%)		
Psychology	2 (50%)	0 (0%)
Specific behavioural program	0 (0%)	2 (25%)
Allied health	4 (100%)	3 (75%)
Respite	3 (75%)	2 (50%)

[a]Neurofibromatosis type 1, FOXP1 mutation, periventricular leukomalacia.
[b]Data missing, *n* = 1.
[c]Cut-off scores unavailable—caseness reflects clinical decision informed by A-TAC responses.
SD = standard deviation.

of this study, all results are presented descriptively only. Feasibility outcomes are presented for all participants combined, and safety and efficacy outcomes are presented by treatment group as number and proportions, and means and standard deviations (SD) respectively. In order to assess for a signal of behavioural change, scores on the ABC-I were compared from baseline to end of maintenance (day 66).

This study received approval from the Human Research Ethics Committee of The Royal Children's Hospital, Melbourne, Australia (28 November 2018, HREC reference number 38236). This study was prospectively registered with ANZCTR on 14 November 14 2018: ACTRN12618001852246.

3 | RESULTS

Although the original recruitment target was ten participants, due to insufficient availability of investigational product within the timelines of the study, recruitment ceased after eight participants. Interest from parents in participating far exceeded the recruitment target

TABLE 4 Protocol adherence

Study design element	Completion rate
Full completion of medication protocol	100%
Study visit attendance (4 visits per participant)	100%
Acceptable medication adherence (>80% considered acceptable)	100%
Blood test completion (3 blood tests per participant)	92%
Online questionnaire completion	88%

(we accumulated a list of over 30 families who contacted the study team expressing interest in participating in the pilot or future trials), and so the recruitment strategy was adequately measured. Four children were randomised to each of the intervention and placebo groups (Figure 1). Three had not had recent cognitive testing and so required WASI-II and Vineland-3 assessments. Sample characteristics are described in Table 3.

3.1 | Feasibility

During the recruitment phase, participants were recruited at a rate of one participant per week, in line with the study targets.

Table 4 outlines protocol adherence for key elements of the study design.

3.2 | Safety

Symptoms for which parents reported a two-point increase on the MOSES from baseline to day 66 are presented in Table 5. The medication was generally well-tolerated, and no dose reduction adjustments for adverse events were necessary. There were no study withdrawals or serious adverse events, and no clinically significant abnormal laboratory test results.

3.3 | Acceptability

Seven parents completed the post-study evaluation questionnaire. Responses are outlined in Table 6.

Most (88%) parents reported being comfortable with Medicare (MBS) and Pharmaceutical Benefits Schedule (PBS) data linkage in relation to their child.

3.4 | Outcome measures

Although not powered for assessment of efficacy, there appeared to be a larger reduction in ABC-I score compared with baseline in the CBD group (mean reduction 12 points compared with 2.5 points). A clinically significant improvement, defined as a reduction of more than 1 standard deviation (7.9 points in the ABC-I

TABLE 5 Treatment emergent symptoms as reported on the MOSES

Item	CBD (n = 4)	Placebo (n = 4)
Eyes: Rolled up	1	0
Tics/grimace	1	0
Ear ringing	1	0
Headache	0	1
Drooling/pooling	1	0
Nose congestion/running nose	0	1
Abdominal pain	1	0
Appetite: Decreased	1	0
Appetite: Increased	1	1
Constipation	1	0
Weight: Decreased	1	0
Weight: Increased	1	3
Restlessness/pacing/can't sit still	1	0
Jitter/jumpiness/nervousness	1	0
Acne	1	0
Urination incontinence/nocturnal enuresis	1	0
Crying/feelings of sadness	1	1
Drowsiness/lethargy/sedation	1	0
Sleep: Excessive	1	0
Sleep: Insomnia	1	1

TABLE 6 Parent responses to the pilot evaluation questionnaire

Study design element	Rating/result (*n* = 7)
Experience of being approached for the study	All rated as very good or excellent
Child's tolerance of taking the medication	6 (86%) very good or excellent[a]
Number of hospital visits	5 (71%) acceptable, 2 (29%) too many
Completion of questionnaires	6 (86%) acceptable; 1 (14%) difficult
Child's experience of blood tests	6 (86%) acceptable
Overall quality of the study	1 excellent, 5 very good, 1 satisfactory
General comments	- Parents valued the ease of communication with study staff, and the structure provided by the medication diary and regular visits. - All seven parents reported that they would recommend the study to other families with children with similar problems.

[a]One child had difficulty with the mint flavouring.

normative sample),[29] was seen in all three participants in the CBD group (data missing for one participant), compared to none in the placebo group (Table 7).

4 | DISCUSSION

This pilot study aimed to evaluate the feasibility of conducting a large-scale, randomised, double-blind, placebo-controlled study of oral CBD in children with ID and SBP. Results indicate that the study design is feasible in this patient population. Importantly, parents reported high levels of acceptability regarding the study, all responding that they would recommend the study to families with children with similar clinical problems.

The efficacy data from this pilot study provides preliminary evidence in favour of the active treatment compared to the placebo, with all three participants with outcome data in the CBD group reporting a clinically significant change in behaviour in contrast to none of the four in the placebo group. Although the numbers were extremely small, these data are consistent with previous open-label observational studies of cannabinoids[23–25] and support the need for a properly powered RCT to test the efficacy of CBD in this patient population.

TABLE 7 Summary of pre- and post-intervention questionnaire data

	Pre mean (SD)		Post mean (SD)	
	CBD (*n* = 3)	Placebo (*n* = 4)	CBD (*n* = 3)	Placebo (*n* = 4)
Aberrant behaviour checklist subscales				
Irritability	26.3 (4.2)	21.3 (14.6)	14.3 (2.1)	18.8 (14.2)
Social withdrawal	14.0 (6.6)	6.0 (5.0)	5.3 (3.2)	5.3 (3.0)
Stereotypic behaviour	10.3 (8.1)	3.3 (4.6)	5.0 (1.0)	1.5 (1.3)
Hyperactivity/non-compliance	28.3 (4.0)	28.3 (15.2)	11.3 (5.7)	24.0 (12.8)
Inappropriate speech	3.0 (2.7)	2.3 (4.5)	1.7 (1.5)	0.8 (1.0)
The Child and Adolescent Scale of Participation	51.8 (12.9)	59.1 (17.2)	65.0 (15.3)	60.9 (13.8)
Sleep Disturbances Scale for Children Total score	47.7 (3.5)	44.3 (10.2)	39.0 (6.2)	44.0 (9.2)
Beach Family Quality of Life				
Family interaction	23.3 (4.2)	20.5 (3.4)	23.0 (3.6)	22.8 (2.6)
Parenting	24.7 (4.6)	22.0 (2.2)	23.0 (1.7)	22.8 (1.7)
Emotional well-being	12.0 (3.5)	12.3 (3.9)	12.0 (2.7)	12.8 (3.7)
Physical/material well-being	19.0 (2.0)	20.3 (3.4)	18.7 (5.0)	21.8 (2.2)
Disability-related support	15.7 (3.1)	14.8 (1.5)	15.7 (2.5)	15.3 (2.2)
Adult Quality of Life (AQoL) Total	61.5 (10.1)	68.1 (17.3)	52.01 (8.2)	71.3 (10.0)
Depression Anxiety Stress Scales				
Depression	7.0 (6.2)	4.0 (5.0)	10.3 (4.0)	2.3 (2.1)
Anxiety	6.3 (6.8)	1.8 (1.5)	5.3 (5.9)	0.8 (0.5)
Stress	6.3 (4.5)	8.0 (3.8)	7.3 (3.8)	7.0 (3.2)
Autism Parenting Stress Index	22.3 (5.0)	24.5 (10.7)	13.7 (3.1)	20.0 (9.1)
Child Health Utility 9D	0.63 (0.09)	0.60 (0.10)	0.77 (0.25)	0.66 (0.19)

SD = standard deviation.

To address minor concerns identified during the pilot study, the protocol for the formal RCT will be modified to: 1) reduce questionnaire content to information most relevant to this clinical population; 2) allow parents to complete baseline questionnaires on an iPad during the 1 hour observation period following the first dose of study medication; 3) reduce the number of blood tests and study visits required; and 4) allow parents to return empty medication bottles via post at the end of the study (rather than requiring a site visit).

This study had some limitations. Firstly, although the initial target was to recruit a sample size of ten,[26] the study concluded with eight participants. However, as mentioned above, this still provides much needed data on feasibility. Secondly, the chosen side effect monitoring scale (MOSES) was found to be suboptimal for this study, with many unnecessary items. A measure that more succinctly focuses on common adverse events seen with medicinal cannabis would be preferable, however none exists at present. Future research may consider developing a specific measure. Finally, as described in the Methods section, we elected to use a relatively high dose of CBD and so cannot comment on the effect of lower doses.

The findings suggest that our protocol is feasible and acceptable to patients with ID and SBP and their families. This study lays the foundations for a fully powered double-blind randomised placebo-controlled trial of CBD to treat SBP in youth with ID.

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COMPETING INTERESTS

There are no competing interests to declare. 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. Investigational product was supplied in kind from Tilray, who had no role in the conception or design of the study; data collection, management, analysis, or interpretation; preparation, review, or approval of the manuscript; nor in the decision to submit the manuscript for publication.

CONTRIBUTORS

All authors (D.E., J.L.F., N.C., J.M.P., M.M., C.P., K.J.L., K.T., K.W.):

- made substantial contributions to the design of this study and the writing of the protocol,
- made substantial contributions to the acquisition, analysis, or interpretation of data for the work;
- made substantial contributions to drafting the work and revising it critically for intellectual content;
- approved the final version submitted;
- agree to be accountable for the accuracy or integrity of the work.

DATA AVAILABILITY STATEMENT

The data from this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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