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Characteristics for Medical Cannabis Treatment Adherence among Autistic Children and Their Families: A Mixed-Methods Analysis

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Abstract
Introduction: Medical cannabis treatment for autistic children has recently become popular, and studies have focused on examining the treatment's effects on children's symptom presentation, reported side effects, and dropout rates. However, no previous study has investigated the factors influencing adherence and dropout rates in cannabis treatment. ***Method:*** This explanatory sequential mixed-methods study explored these factors by examining the characteristics of 87 autistic children and their families and deepening parents' perspectives and experiences of the 6-month CBD-rich cannabis treatment's benefits and barriers. ***Results:*** We found this treatment to have a high (75%) adherence rate, relatively mild side effects, and substantial reported benefits for the children and families. However, this treatment was not free of barriers; the intake regime, some side effects, and in some cases, unrealistic parental expectations made adherence difficult for some families. ***Conclusion:*** Our results highlight the importance of providing professional guidance and knowledge to parents of autistic children, enhancing their understanding of the impact of CBD-rich cannabis treatment on their children and expected related challenges, and coordinating realistic treatment expectations. We hope that addressing these important aspects will influence parents' ability to adhere to and enjoy the benefits of cannabis treatment for their autistic children.

Introduction

Autism spectrum disorder (ASD) is a pervasive, clinically and etiologically heterogeneous neurodevelopmental condition with a current prevalence of 1 in 36 children in the United States [1]. The diagnostic criteria for ASD include two primary areas of impairment: (1) social communication and interaction and (2) restricted and repetitive behaviors and interests (RRBIs) [2]. Additionally, children with ASD commonly display maladaptive behaviors like hyperactivity, impulsiveness, aggression, tantrums, noncompliance, and self-injurious behaviors (SIB) [3, 4], as well as mealtime challenges and sleep

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problems [5]. These behaviors and diagnoses are associated with decreased daily functioning and participation in autistic children [6–8].

Despite the prevalence of ASD, only a handful of medications have been found to effectively reduce its specific associated symptoms [9]. Instead, traditional pharmaceuticals effective for the treatment of attention-deficit/hyperactivity disorder (ADHD), such as antipsychotic medications (e.g., risperidone and aripiprazole), selective serotonin reuptake inhibitors, and other stimulant medications (e.g., methylphenidate), are commonly used to treat autism symptoms.

Matching pharmacological treatment to symptoms involves careful attention to the specific symptoms and needs, routine follow-up, and observation for efficacy and side effects [10]. However, adherence to this regime is challenging and relatively low among this population [11]. *Adherence to treatment* is "the extent to which a person's behavior, such as taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" [12], p. 3. Adherence is crucial to any effective intervention because poor adherence can reduce the treatment's effectiveness and compromise its benefits [13]. Poor adherence to medications has been associated with a risk for poorer health [14], unnecessary medications, and unnecessary healthcare costs [12].

The ecological model associates parental involvement with better adherence to interventions [15]. Therefore, interventions chosen for a child with disabilities should consider the child's targeted difficulties and their parents' ability to support adherence [16, 17]. However, intervention adherence among children with ASD has rarely been studied. Although adherence to medication treatments was reported to be significantly greater than adherence to behavioral, developmental, or alternative treatments [18], Logan et al.'s [11] study of 629 children with ASD on prescribed ADHD medications, antidepressants, or antipsychotics found that only 44%, 40%, and 52%, respectively, adhere to their treatments.

Kazdin et al. [19] proposed the barriers-to-treatment model as a basis for dropping out of treatment among children referred for outpatient therapy for oppositional, aggressive, and antisocial behavior. This model begins with the premise that many families are burdened by coming to treatment. Other adherence barriers are the treatment's perceived relevance, stressors, and obstacles that compete with treatment, problems within the therapeutic relationship, and treatment demands [19].

Unsurprisingly, the parents' perceptions of the treatment's burden on the family influence their adherence to ASD treatment [20], and perceived barriers to treatment participation significantly (negatively) predict treatment acceptability [17]. *Treatment acceptability* refers to the extent to which consumers (e.g., children, adolescents, parents, and mental health professionals) view the treatment as reasonable, fair, and palatable. Studies of families of children with oppositional behaviors [17, 21, 22] found that the perceived treatment relevance and demands were particularly prominent in predicting improved child outcomes. However, the ability to complete the treatment was associated more with how parents interpreted the progress during treatment, which relates to the treatment goals [23].

The challenges of finding and adhering to an adequate treatment to relieve ASD symptoms may lead parents and professionals to search extensively for alternate therapies and eventually try medical cannabis. The cannabis plant has been used medicinally since ancient times. However, in 1937, the United States outlawed its use due to its psychoactive effect. Only in the last decade has an in-depth understanding of the structure of cannabis enabled studies to show its advantages in many health situations [24].

Today, over 110 cannabinoids are known to exist in the cannabis plant. Previous research has primarily focused on distinguishing between the two main cannabinoids: THC and CBD. The THC cannabinoid activates the endocannabinoid system by binding to CB1 and CB2 receptors in the brain. It exhibits properties such as sensory differences, euphoria, sedation, and changes in appetite. However, in high doses, it may lead to anxiety and impair brain development and memory [25–29]. Conversely, the CBD cannabinoid possesses a variety of therapeutic properties, including sedative, anticonvulsant, sleep-inducing, anti-anxiety, antipsychotic, and anti-inflammatory effects. Additionally, it promotes neurogenesis and acts as an antioxidant [30–32]. Although both substances are neuroactive (i.e., acting on the brain), THC is mainly responsible for the psychoactive sensations [33].

The ability to isolate the main cannabinoids, THC and CBD, enabled the use of cannabis for medical treatment by adapting its doses and tailoring interventions to medical needs. In the past decade, cannabis has been tested as a treatment for common pediatric disorders. For instance, Dronabinol, a synthetic form of THC, has been used to treat Tourette syndrome and spasticity [34]. Additionally, the US Food and Drug Administration approved CBD-rich cannabis to treat specific types of refractory epilepsy in children [35].

Interestingly, parents of children with both epilepsy and ASD who were treated for epilepsy with CBD-rich cannabis noticed improvements in ASD symptoms [34]. Later, studies addressing CBD-rich cannabis treatment for autistic children reported improvements in communication and socialization skills [36–38], in co-occurring symptoms, including self-injury, tantrums, restlessness, and anxiety [36, 37, 39, 40], and in participation in daily routines like sleeping [37, 41]. Bar-Lev et al. [37] analyzed data prospectively collected from 188 ASD patients treated with medical cannabis oil containing 30.0% CBD and 1.5% THC as part of a treatment program. Following treatment, 82.4% of patients remained in active treatment, indicating the tolerability and safety of CBD-rich cannabis treatment for relieving ASD symptoms.

Common side effects of CBD-rich cannabis were reported to be mostly mild and transient adverse, such as somnolence, changes in appetite and gastrointestinal symptoms, irritability, psychoactive effects, and sleep disturbances [36–38, 41]. However, Fusar-Poli et al. [35] suggested that because many patients usually take concomitant medications, it is hard to determine which drug causes these effects. Dropout rates in CBD-rich cannabis studies ranged from 9% [40] to 27% [36]. Described dropout reasons included lack of improvement (from 28% [38] to 40% [40] and 70% [37]) and side effects (from 29% [37] to 100% [41]). Lower dropout rates were related to difficulty with cooperation of children/parents (from 19% [36] to 29% [37]).

Our review of the literature indicated that the use of medical cannabis in children with ASD is an increasing area of interest, and the use of CBD-rich cannabis, as in the studies described herein, was proven safe for children with ASD and epilepsy [41, 42]. Nevertheless, although the existing studies cited their dropout rates and reasons, no study deepened the understanding of or investigated factors that influence the adherence rate, such as child/family characteristics, the impact of parents' treatment goals, or parents' perspectives on CBD-rich cannabis treatment. Identifying and understanding the barriers to adherence to CBD-rich cannabis treatment may ultimately lead to improved treatment outcomes.

Hence, the main goals of this mixed-methods study are to:

1. Evaluate the adherence rate among parents of children with ASD to their children's CBD-rich cannabis treatment,
2. Explore characteristics of treatment goals set by parents who adhered to the treatment and those who dropped out,
3. Compare characteristics of children who completed a 6-month CBD-rich cannabis treatment with those unable to adhere to the treatment,
4. Explore the primary dropout reasons relative to the adherence period, and
5. Explore perspectives on the CBD-rich cannabis treatment, benefits, and barriers of parents of autistic children who adhered to the treatment and who dropped out.

Methods

Procedure and Participants

We used an explanatory, sequential, mixed-methods design model [43]. This methodology structured our quantitative data collection, focusing on parents' adherence to CBD-rich cannabis treatment for their autistic children. Specifically, we examined adherence rates, treatment goals, characteristics of children who adhered to the treatment, and primary reasons for dropout, as indicated in our first four study goals.

Subsequently, we conducted in-depth interviews to delve further into the parents' perspectives on the CBD-rich cannabis treatment, its benefits, and the barriers that affected adherence to the treatment from their viewpoints. This step aimed to explain and interpret the quantitative findings [44], aligning with our fifth study goal (as shown in Fig. 1).

Phase 1: Quantitative Study

The quantitative research was part of an open-label research at the Shamir Medical Center in Israel. Participants were recruited through social media advertisements and the Israeli Society for Autistic Children, ALUT. Inclusion criteria were parents of children aged 5–12 years with a medical diagnosis of ASD accepted by the Israeli Ministry of Health. The ASD diagnosis was confirmed in the present study using the Autism Diagnostic Observation Schedule™ 2nd edition (ADOS-2) [45]. Children with known genetic syndromes that cause autism symptoms or diagnosed metabolic disease and parents with severe mental health problems (e.g., psychosis or drug addiction) were excluded.

First, a pediatric neurologist specializing in ASD met with the parents, who provided the child's medical history, including the ASD diagnosis and concomitant medications. Parents of children who used medications before the study were instructed to avoid any changes during the study period. The cannabis treatment protocol was individualized for each child using a personalized medicine approach. The children received the Nitzan Spectrum®, a medical cannabis extract from Seach Medical Group, in medium-chain triglyceride oil with a CBD:THC ratio of 20:1 for 6 months. The Nitzan Spectrum® is a full spectrum extract (C20/T01) that was cleaned, winterized, and purified; 2% of the product volume are terpenes. All children started with one drop daily (each drop contained 5.7 mg CBD and 0.3 mg THC). The dosage was increased gradually until the parents reported improvement: first to two drops/day and then to three and four drops within 4 days. The timing of doses during the day was tailored to individual needs (e.g., higher doses at nighttime could be used to support sleep). The

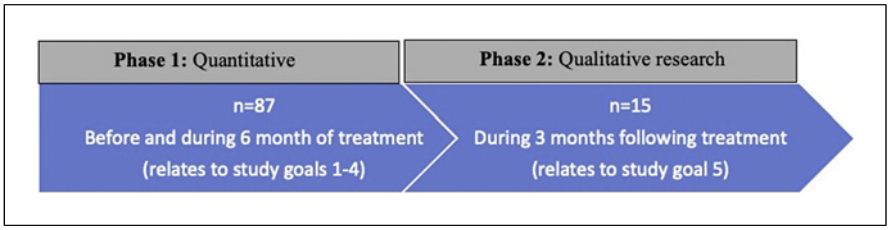

Fig. 1. Sequential mixed-methods research design.

final dose did not exceed 10 mg/kg/day (total 400 mg/day) CBD and 0.5 mg/kg/day (total 20 mg/day) THC.

Before the intervention, parents completed a medical-demographic questionnaire and were asked about their treatment goals for their autistic child. Information regarding co-morbid symptoms and safety was recorded biweekly during follow-up interviews during the 6-month study. Parents who stopped giving their child the medical cannabis treatment before the end of the 6-month treatment were asked to provide a reason for ceasing the treatment. We labeled parents of children who adhered to the study and completed the 6-month treatment the "adherent group"; those who dropped out before the end of the 6-month treatment were labeled the "dropout group." At the end of the trial, parents were offered a 1-year license to continue CBD-rich cannabis treatment. The clinical trial product is not registered, but similar products containing the same CBD:THC ratio (20:1) are available.

Phase 2: Qualitative Study

Over the course of 3 months following the CBD-rich cannabis treatment, an occupational therapist who specializes in working with parents of autistic children conducted semi-structured interviews with 15 parents selected through purposeful sampling of the full sample. Inclusion criteria were (1) participation in the former study, (2) completion of at least 3 months of CBD-rich cannabis treatment, and (3) language fluency. We further recommended that the interviewed parent be the one most involved in the child's daily activities (as a result, mothers were interviewed in all cases) and whose level of Hebrew-language fluency allowed them to participate in an in-depth interview.

Parents who consented to participate in the qualitative stage were interviewed online. The interviews, which lasted approximately 45 min, were audio recorded using the university's secure Zoom software and transcribed. Identifying details were deleted. Once the anonymized transcripts were saved, the recordings were deleted.

Measures

The medical-demographic questionnaire consisted of inquiries regarding gender, age, residence, and family status and medical queries about co-occurring diagnoses, medications, and complex medical conditions. Additionally, parents were asked to specify their primary treatment goal for their autistic child. Parents who stopped the intervention before it ended were asked to provide a reason.

Individual interviews were conducted using a qualitative phenomenological method based on a uniform interview guide. Parents were asked open-ended queries about (1) their overall experience with the treatment, (2) how they perceived the medical cannabis treatment, (3) its implications on their child, and (4) their ability to adhere to the treatment. They had opportunities to reveal treatment barriers and share their strategies for coping with them. The interviewer deepened and expanded the interviews, asking for examples, feelings, and dilemmas the parents experienced in the intervention process.

Data Analysis

The quantitative study data were processed with IBM SPSS (Version 27), and the demographic characteristics were described using descriptive statistics. The transcribed interviews were analyzed in a systematic, three-stage phenomenological approach [46]: (1) identifying meaningful text units into thematic codes, (2) grouping and mapping the codes into 10 categories that demonstrate commonalities and differences, and (3) merging the categories into three conceptualized major themes.

Initially, each author independently coded the first three interviews into the preliminary categories to map the remaining interviews. We stopped interviewing after the 15th participant due to content saturation – no new themes emerged from the data [47]. Data trustworthiness was achieved by presenting rich citations from the original text (with encrypted locations), documenting detailed descriptions of the process, and journaling reflective thoughts and feelings during the interviews to identify potential bias [48]. Additionally, we continually conducted open conceptual discussions alongside peer reviews of the data until agreement was achieved, supported by our familiarity with the phenomena and the literature.

Results

Quantitative Results

Descriptive and Demographic Characteristics

Participants comprised 87 parents of autistic children (5–12 years old; M = 7.39 years, SD = 2.02); 71 (81.6%) boys and 16 (18.4%) girls. Sixty-five (74.7%) children completed the 6-month treatment (adherent group), and 22 (25.3%) dropped out before it ended (dropout group). Independent sample *t* tests showed no significant group differences in the children's age, ASD severity (as indicated by the ADOS-2), living distance from the medical center providing the treatment, or final cannabis dosage. χ^2 tests showed no significant group differences for the child's gender or family status (Table 1).

Table 1. Demographic characteristics by group

Variable	Adherent group (n = 65), M (SD)	Dropout group (n = 22), M (SD)	t (85)
Age, years	7.37 (2.05)	7.22 (1.97)	0.290
Distance to medical center, km	34.20 (27.54)	24.23 (22.21)	1.530
ADOS standardized calibrated severity score	8.38 (1.61)	7.50 (2.68)	1.350
	Adherent group, n (%)	Dropout group, n (%)	χ^2
Gender			0.001
Boys	53 (81.5)	18 (81.8)	
Girls	12 (18.5)	4 (18.2)	
Family status			2.180
Married	57 (87.7)	17 (77.3)	
Unmarried	8 (12.3)	5 (22.7)	

Treatment Goals

The analysis of parents' intervention goal prevalence (Table 2) showed that the goals were divided into four categories. The goals were to improve (1) ASD core symptoms, such as RRBIs and communication skills; (2) the ability to calm down and reduce maladaptive behaviors, such as aggression toward others, SIB, and tantrums; (3) daily activities, such as sleeping and eating; and (4) executive functions, such as learning and attention.

Crosstabs between the primary dropout reasons and the study period showed "treatment did not work" as the most common reason, stated by nine (41%) parents with no further explanation. On average, these parents dropped out of treatment after 101 days (SD = 40.99). The second most common reason was the cluster of side effects, including worsened functioning (n = 2), violence (n = 3), abdominal pain (n = 1), weight gain (n = 1), and sleeping problems (n = 1). These eight (36%) participants dropped out of treatment after an average of 55 days (SD = 21.51).

The third and fourth most common dropout reasons were intake difficulty and parent-child cooperation; one parent cited both as the main reason. The three (14%) parents who cited intake difficulty as the main reason ceased the treatment after, on average, 138 days (SD = 12.42). Three (14%) other parents cited the parent-child cooperation cluster as their main reason for dropout. This cluster included the child's lack of cooperation in periodic follow-up examinations (two children), with dropout on average after 112.5 days (SD = 0.70), and the parents' lack of collaboration with the periodic follow-up (one family), with dropout at 37 days (this parent did not report any child-related reason for dropping out).

Qualitative Results

Of the 15 parents who participated in the interviews, 12 were in the "adherent group" and three were in the "dropout group," representing an adherent:dropout ratio similar to that in the quantitative phase. The phenomenological analysis of the in-depth interviews revealed three main themes affecting treatment adherence, as shown in Table 3: preintervention knowledge and perceptions of the treatment, treatment benefits, and treatment barriers.

Theme 1: Preintervention Knowledge/Perceptions

All parents described that their children had previously been unsuccessfully or only partially successfully treated with different medical or other interventions. They joined our study seeking a new treatment for their autistic child. R and D, mothers of 6-year-old autistic children, shared their previous unsuccessful experiences with prescribed psychiatric medicines. They described the extensive side effects and felt that it was not the right intervention for their child.

Parents shared their positive feelings and hopes from before the intervention because, at its inception, they had already been exposed to its advantages for their children. Specifically, they described searching for knowledge about medical cannabis treatments before enrolling in the study through lectures, Internet information, and conversations with people who experienced it. They explained that they understood this intervention was not about "smoking the plant" but about medical cannabis extract infused in oil, with individualized treatment protocols for each patient. Participation in a controlled study provided parents

Table 2. Prevalence of parents' treatment goals for their children by group

Adherent group (n = 65)		Dropout group (n = 22)	
parents' intervention goal (descending order)	n (%)	parents' intervention goal (descending order)	n (%)
Calming down	55 (84.61)	Restricted and repetitive behaviors and interests	15 (68.18)
Sleeping	21 (32.30)	Calming down	14 (63.63)
Restricted and repetitive behaviors and interests	20 (30.07)	Sleeping	8 (36.36)
Aggression toward others	16 (24.61)	Tantrums	6 (27.27)
Tantrums	9 (13.84)	Aggression toward others	5 (22.72)
Self-injurious behavior	7 (10.76)	Communication	3 (13.63)
Attention	6 (9.23)	Attention	3 (13.63)
Learning	5 (7.69)	Self-injurious behavior	3 (13.63)
Eating	4 (6.15)	Eating	2 (9.09)
Communication	4 (6.15)	Learning	0

with a further sense of safety. They described feeling confident trying this treatment as part of a hospital study.

Theme 2: Treatment Benefits

The benefits of the cannabis intervention were a significant component of the parents' ability to adhere to the treatment and overcome the barriers. Most (12/15) interviewees described this treatment as generally beneficial. The mothers addressed benefits in three main areas: (1) reduced maladaptive behaviors, (2) improved communication and social engagement, and (3) increased participation in daily activities, such as sleeping and eating, and within the school setting and family activities.

Most (13/15) mothers referred to changes in their children's communication abilities and RRBIs, core autism symptoms that are part of the diagnosis measures. H explained these changes as the essence of the intervention: "If you ask me what the main benefit, . . . it is communication." Improved RRBIs and other maladaptive behaviors arose from the interviews as pivotal factors enhancing participation. For instance, N, the mother of an 11-year-old, reported that a decrease in obsessions affected her son's ability to be "open to the world."

Moreover, 11 mothers mentioned their children's reduced anxiety and improved ability to deal with different situations following the treatment, stating that changes in communication abilities and maladaptive behaviors supported their children's ability to participate in different settings. Further, 12 mothers reported positive changes in school participation, which some attributed to their children's improved ability to be regulated and attentive. Others linked the changes to improvements in their children's learning abilities. As N said, "All of a sudden, he started to understand basic math!"

Parents also described positive changes in participation in daily activities, such as hygiene, bathing, dressing, and brushing teeth, and more independent routines compared to the past. Nine mothers also described positive changes in their children's sleep routines. L, the mother of a 12-year-old, reported this change in her son's sleep habits as the most significant: "He falls asleep and just doesn't get up. . . . This was the change."

Five mothers reported some improvements in eating habits; however, parents inconsistently perceived these changes as positive or negative according to their child's previous eating and weight challenges. Whereas some perceived it as a problematic side effect, others saw it as an advantage for their "picky eaters." Overall, most mothers enjoyed the benefits and adhered to the treatment, However, two reported dropping out due to their children's severe side effects, and one due to the child's difficulty taking the oil drops.

Theme 3: Treatment Barriers

In the interviews, parents brought up challenges to adhering to this treatment, including intake difficulties due to the cannabis oil's bitter taste, the study's strict protocol, and the severe side effects. The mothers noted that administering cannabis drops to autistic children is not trivial, especially because the children's sensory-processing differences often manifest in taste and texture sensitivity. The mothers reported that the oil tasted bitter, and some children refused or found it difficult to take. D shared how challenging it was for her 6-year-old

Table 3. Summary of manual coding categories and example quotations

Theme	Coding category	Example quote
1. Preintervention knowledge/ perceptions	• Hopes for new and safe treatment after previous unsuccessful experiences with prescribed psychiatric medicines	• We tried risperidone, which is a chemical medicine. . . . It affected his brain, and he had bad side effects and severe withdrawal. (R, mother of 6-year-old) • We used psychiatric medicine and homeopathy supplements, and they did not help. . . . It wasn't the right intervention!" (D, mother of 6-year-old)
	• Information from different sources about the positive effects of this treatment	• I've learned about it, I've heard lectures, and I've heard that it helped many, many children." (T, mother of 7-year-old)
	• Distinguishing between cannabis used for its psychoactive effects and medical cannabis used for treatment purposes	• I realized it's not this cannabis we're actually getting high from. (M, mother of 8-year-old) • I was excited about the idea that it's not chemical and it's not addictive. (T, mother of 7-year-old)
	• Safe and controlled environment within a study to experiment with a new treatment	• It reassured me to know it was studied in a hospital, and there are doctors and professors. . . Yes, it provided me the safest place to do it. (H, mother of 7-year-old)
2. Treatment benefits	• Reduced maladaptive behaviors	• His repetitive sounds did not vanish completely but decreased upon receiving cannabis. (R. mother of 6-year-old) • He no longer gets angry; he no longer slams the door. (L. mother of 12-year-old)
	• Improved communication and social engagement	• If you ask me what the main benefit (is), . . . it is communication, as if this ability had suddenly been discovered in my child (following the cannabis intervention). (H, mother of 7-year-old)
	• Increased participation in daily activities	• I'll show you a record from the teacher that he sits and he listens and he cooperates and he takes part in classroom activities. Never happened before! (L, mother of 12-year-old) • She takes a few drops (of the cannabis oil) before bedtime, . . . and then it takes her 15–20 min, and she falls asleep alone! (B, mother of 12-year-old) • Come now, . . . we're going to take a shower, . . . and he goes to the bath and does what I asked. . . He is functioning at a much higher level. (G, mother of 7-year-old) • Today he [her son] joins the eating table – looking, smelling, being interested. He shows new interest in various foods. (R, mother of 6-year-old)
3. Treatment barriers	• Intake difficulties due to the cannabis oil's bitter taste	• You cannot tell him, "Come, let's taste something new." He wasn't ready to taste it; it did not work! (A, mother of 11-year-old) • At first, he agreed to take it, and it seemed he could have seen the change for himself. . . . After a while, he just refused. It was a war. . . . My husband said, "Come on, I'm putting it in ice cream; he'll forget it exists." My son noticed it right away. He went wild and said he knew we added the drops. He had a big tantrum. (Z, mother of 11-year-old)

Table 3 (continued)

Theme	Coding category	Example quote
	• Following strict treatment protocol	• Don't forget, be careful as the dosage is very, very important. Find the exact amount that does good for the child, the exact hours. . . . Constantly being on it, constantly paying attention to changes. (Y, mother of 9-year-old)
	• Side effects	• I thought the cannabis would actually help him, . . . but. . . it was going entirely somewhere else. He became nervous, very aggressive. (D, mother of 6-year-old) • His behavior regressed following treatment – to the point of talking about suicide. (S, mother of 10-year-old)

son: "He almost vomited every morning when he took it."

The mothers also described their "creative solutions" to the intake challenges, ranging from explanations and persuasions to hiding the oil in other foods to obscure its taste. These strategies worked only in some cases, as described by Z, the mother of an 11-year-old who dropped out due to major intake difficulties.

Another major challenge was the burdensome need to follow the strict treatment protocol. The protocol included participating in periodic examinations and strict adherence to times and doses when administering the cannabis drops. Parents also described side effects as a major factor influencing treatment adherence. Although most mothers described the side effects as minor, two reported significant deterioration in their children's behavior, four described weight gain following the treatment, and two reported weight loss. Notably, all mothers who described changes in their children's weight adhered to the treatment, whereas those who described behavior deterioration ceased their child's participation in the study. Overall, although some parents reported significant barriers to this treatment in the interviews, most indicated they could adhere to the treatment, explaining that the benefits outweighed the feeling of burden.

Discussion

This study aimed to explore factors that influence the characteristics of parental adherence to CBD-rich cannabis treatment for children with ASD. The findings reveal that the following factors support adherence to CBD-rich cannabis: providing (1) treatment in a safe and knowledgeable medical framework that accompanies the process, (2) parents with accurate knowledge of potential results and side effects, (3) realistic goals for this treatment, coordinated with the parents, and (4) visible and prominent benefits of treatment for the child and their family. On the other hand, the treatment's strict protocol, intake difficulties, and some side effects decreased the parents' ability to adhere to treatment. Our results support the effectiveness of CBD-rich cannabis treatment alongside the importance of professional guidance to inform parents of the treatment's expected benefits and barriers.

Adherence

Of the 87 parents of autistic children in the study, 65 (74.7%) adhered to the intervention and completed the 6-month cannabis treatment. This adherence rate is consistent with an earlier study regarding CBD-rich cannabis treatment for autistic children, which identified a 73% adherence rate [36]. Further, we found no significant differences in demographic factors between the adherent and dropout groups. Similarly, Logan et al. [11] who investigated adherence rates to prescribed antidepressant or antipsychotic medications among children with ASD found that neither demographic factors nor ASD severity significantly predicted adherence.

We conducted our study at a hospital with follow-up by physicians. As the parents' interviews revealed, these factors were critical to their adherence. Specifically, parents said acquiring knowledge about the cannabis intervention's benefits and the sense of safety they felt as part of a controlled study accompanied by professionals contributed to their adherence. Similarly, the literature noted that acquiring relevant knowledge and understanding potential benefits contributed to this population's adherence to psychiatric medicine interventions

[15]. These results indicate that these factors are crucial for adherence to any medical intervention.

The parents revealed that a major reason for joining this study was their motivation to try a new treatment with fewer side effects than the psychiatric medications they had previously tried. Indeed, most side effects reported in the current study were mild, manageable, and supported the parents' expectations and ability to adhere to the treatment. These results are in line with previous studies, which reported that medical cannabis treatment is safe and has mostly mild side effects [36–38, 40, 41].

Examining the treatment goals, parents stated before the intervention revealed different attitudes toward the treatment's potential benefits for their children's autistic characteristics. Interestingly, while social communication problems are an ASD characteristic by definition [2], parents rarely mentioned improving them as a primary goal. Only 6% of the adherent group and 13% of the dropout group identified communication as an important goal. However, following treatment, the parents described their children's improved communication with family and friends as a primary advantage of this treatment.

In contrast, 30% of the adherent group noted improved RRBIs as an important goal, and 68% of parents in the dropout group set improved RRBIs as their first goal in order of importance. Possibly, setting goals to improve RRBIs – a second ASD diagnostic criterion [2] – suggests that parents' hidden expectations for a "cure" proved unrealistic and prone to disappointment, resulting in a lack of adherence.

The adherent group was characterized by setting goals other than only those related to disability characteristics. For example, the first goal in importance order for 84% of parents was "calming down." This finding may indicate that parents experience mental restlessness or stress in their autistic children. Indeed, the literature describes stress and restlessness as common among children with ASD [3, 4]. Specifically, ADHD was found to be the most common condition comorbid to ASD [49]. Parents described associating cannabis intervention with calming effects, perceiving it as a potential answer to their children's restlessness. The prevalence of aggression toward self (SIB) and others among children and adolescents with ASD is high; 68% of parents reported aggression toward caregivers [50]. In our study, over 20% of parents in both groups declared reduced aggression in general and reduced violence in SIB as important goals for their children.

Our interviews described positive changes in the children's maladaptive behaviors, aggression, obsessive behaviors, and anxiety following the CBD-rich cannabis treatment, consistent with other recent studies [36, 37, 39, 40, 42]. Maladaptive behaviors in children with ASD negatively affect their daily functioning and participation [51, 52]; eating [53] and sleeping [54] have been caregivers' major concerns. Children with ASD have a higher prevalence of sleep problems than typically developing children [55].

Unsurprisingly, improved sleeping was the main goal for both groups in our study. During the in-depth interviews, the mothers noted that improved sleep habits following the cannabis treatment greatly affected the children's and the parents' quality of life. The literature also noted this positive change in sleep habits following cannabis treatment [37, 40, 41].

Interestingly, although the literature described eating problems as prevalent among autistic children [56], only a small percentage of parents in our study set reduced eating difficulties as a main goal before treatment. The changes in eating habits and their results during the study were inconclusive and inconsistent. Although some parents interpreted changes in their children's appetites during treatment as an advantage, others considered them a disadvantage. Recent studies reported appetite changes as a treatment side effect rather than an advantage [36–38, 40, 41]. A recent systematic review investigating the effect of cannabis treatment on appetite and body weight suggested this treatment has an anorexigenic effect correlating with decreased body weight [57]. However, in our study, parents reported both increases and decreases in body weight and appetite.

Except for one case study [58], the recent literature does not indicate participation in school settings and learning abilities as ancillary advantages of cannabis intervention for autistic children. Thus, it was unsurprising that few parents from either group considered these as goals before the intervention. However, the parents who both adhered to the treatment and participated in the qualitative study mentioned an astonishing improvement in their children's attention and learning abilities. This change also received the attention of the children's teachers. Although unexpected, some parents eventually perceived it as a major benefit of medical cannabis treatment. This result is significant because atypical attention [59] and learning difficulties [60] are considered ASD's comorbidities.

Our results indicate that it is worthwhile to examine in more depth the effects of CBD-rich cannabis treatment on the diagnostic characteristics and possibly specific comorbidities of autism. These results may point to the importance of further investigating the

influence of CBD-rich cannabis, specifically on attention and learning among children with primary disorders in these areas.

Dropout

Approximately 25% of the cases in our study ceased the treatment. The most common reason for dropping out was "the treatment did not work," with no further details or explanations. It is important to note that dosage adjustments were made for children whose parents expressed a lack of treatment effect, yet the parents still chose to cease the treatment. The barriers-to-treatment model [21] proposes that adherence to treatment relates to the parents' perceptions of the treatment and the ability to understand its benefits and relevance to the child's difficulties [23]. Thus, the "didn't work" reason could relate to unrealistic expectations stemming from a lack of knowledge or understanding or how parents perceived the treatment and interpreted its benefits. Another barrier proposed by this model is difficulty perceiving that such treatment is demanding, and parents feeling the treatment was more work than expected. Indeed, nonadherent parents in the current study expressed the intense demands of the treatment on not only the child but also themselves.

The second most common dropout reason in our study is the side effect cluster, including worsened functioning, violence, abdominal pain, weight gain, and sleeping problems. Previous studies on the effects of CBD-rich treatment in autism reported most of these side effects as mild and manageable [36, 37, 40, 41]. Side effects of psychiatric drugs are sometimes severe and may include sedation, appetite changes, weight gain, potential extrapyramidal symptoms, irritability, hyperactivity, and insomnia [10]. Thus, prior knowledge of the nature of the side effects led parents in the current study to choose CBD-rich treatment over psychiatric drugs, such as risperidone, with which they described having unsuccessful experiences.

However, although most parents reported only mild side effects, eight (9%) participants experienced the side effects as severe and eventually dropped out of the study. Two mothers shared their experiences of extreme behavioral deterioration in their children, including increased violence and, in one child, anxiety to the point of suicidal ideas. These severe side effects, specifically described by two mothers in our interviews, were not mentioned in previous studies in the context of CBD-rich cannabis treatment.

The third most common reason for ceasing treatment relates to the medication regimen complexity [21]. This reason includes the parent-child cooperation cluster, comprising the child's or parents' lack of cooperation with periodic follow-up examinations and intake difficulties with the cannabis drops. Although most parents did not drop out due to intake difficulties and adhered to this treatment for the longest duration, they revealed that intake difficulty was a main concern. Most coped with this difficulty and shared their techniques and thoughts.

The parents' significant adherence efforts accompany this treatment's substantial benefits. Therefore, when the treatment does not fulfill their expectations, their disappointment often leads them to cease treatment. Parents play a key role in this treatment's success. It is essential to provide them with knowledge about the treatment benefits and barriers and support them in setting realistic expectations and adhering to the treatment's strict protocol.

Limitations

This study's limitations should be acknowledged. First, this was an open-label study, likely to create a positive bias in parent reports, given known placebo effects [61, 62], which were not controlled. Second, the interpretation of factors influencing the adherence and dropout rates includes the described cannabis benefits and barriers based on subjective parental reports rather than objective child measurements or subjective child's reports. However, despite its limitations, this study contributed significantly to understanding adherence characteristics for CBD-rich cannabis treatment and identifying its barriers to better treatment results among autistic children and their families.

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Statement of Ethics

Ethical approval was obtained from the Institutional Review Board of the University of Haifa (no. 274/21) and the Shamir Medical Center Helsinki Committee (ASF-0056-21). All parents signed informed consent forms and were told they could discontinue their participation at any point. Written informed consent was obtained from the parents for the anonymous use of their quotes in this research.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

A.D.: conceptualization, methodology, data curation, writing-original draft preparation, and formal analysis. O.S.: conceptualization, methodology, formal analysis, resources, writing-review and editing, supervision, and project administration. M.B. and E.K.: resources, data curation, and software. MWN: methodology and formal analysis. I.H.: data curation and project administration. E.G.: conceptualization, methodology, formal analysis, writing-review and editing, visualization, and supervision. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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