

Article

Retrospective Observations from a Pilot Study on the Feasibility and Safety of Medication Reduction or Withdrawal in Children with Autism Spectrum Disorder Taking Cannabidiol-Rich Oil

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Abstract: Background: Due to the limited efficacy of current treatments for Autism Spectrum Disorder (ASD), a high proportion of families turn to alternative or unregulated interventions, including medicinal *Cannabis*-derived products. Interest has grown in exploring the potential of cannabidiol (CBD)-based preparations as adjunctive or alternative treatments for managing core and associated symptoms of ASD. **Purpose:** To explore whether a CBD-rich oil provided by a Brazilian civil association for therapeutic cannabis access might be used safely alone or as adjunct, and could allow for the reduction of other medications in children with ASD. **Study design:** Retrospective analysis of an open-label pilot study. **Methods:** Thirty children with ASD aged 2–15 years old were enrolled. The feasibility, safety, and preliminary effects of medication reduction or withdrawal alongside a 24-week administration of a CBD-rich oil (CBD: delta-9-tetrahydrocannabinol -THC- ratio 14.5:1) was assessed. **Results:** Twenty-seven participants completed the study. Sixteen participants reduced or withdrew medications under supervision; fourteen remained on or off medication. Mild side effects like increased appetite and nervousness occurred without clear differences between groups. Two participants with epilepsy experienced seizure recurrence following the tapering of valproic acid and risperidone, respectively. Exploratory observations suggested potential improvements in ASD symptoms, parenting stress, and neuropsychiatric evaluations across participants. **Conclusions:** The use of CBD-rich oil alongside supervised medication tapering may be tolerated in some children with ASD. However, the study is limited by the retrospective design, small sample size, and lack of a placebo control. Careful clinical monitoring remains essential, particularly in children with epilepsy. Further randomized controlled trials are needed to investigate potential therapeutic roles, optimal dosing strategies, and long-term safety of CBD as an adjunctive or alternative treatment in ASD.



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1. Introduction

Autism Spectrum Disorder (ASD) is a persistent deficit in social communication and interaction, along with restricted and repetitive behaviors, interests, or activities, beginning in early development and causing significant functional impairment [1]. Despite not being fully understood, the pathogenesis of ASD includes genetic and environmental factors that alter brain development, mainly synaptic plasticity [2,3], neural connectivity [4,5], and the excitatory/inhibitory neurotransmitter balance [6,7].

Brain and behavioral changes in ASD are related to alterations in neural apoptosis, synaptic pruning, and neurotransmission in the prenatal period, when many ASD risk genes have maximal expression levels [2,8–11]. Neuroimmune alterations are observed in ASD and preclinical ASD models [12], leading to a reactive phenotype of microglial-astrocytic interaction, heightened inflammation and oxidative stress, altered endocannabinoid system (ECS) [13] and endocannabinoidome (eCBome, the ensemble of endocannabinoids, their receptors, metabolic enzymes, and functionally related mediators and targets that together form an extended signaling system beyond the classical ECS) [14], and altered gut microbiome composition [15,16], leading to the exacerbation of ASD and comorbid neuropsychiatric symptoms.

To date, no pharmacological options are available to resolve the core symptoms of ASD, and the efficacy of psychotropic drugs used for adjuvant symptoms is limited and often accompanied by adverse effects [17,18]. Compounds from the *Cannabis sativa* plant have shown positive preliminary results in improving ASD symptoms and comorbid neuropsychiatric and systemic ailments, putatively through anti-inflammatory [19], antioxidant, and anti-epileptic [20,21] activities, offering hope as a potential novel intervention for the treatment of ASD. Globally, a high proportion of families affected by ASD turn to alternative or unregulated interventions, often with limited scientific evidence, in search of symptom relief [22]. In Brazil, this includes access to medical cannabis sometimes mediated by civil society associations, some operating without formal regulatory authorization [23].

In this retrospective analysis of an open-label pilot study, the preliminary feasibility, safety, and effects on ASD and neuropsychiatric symptoms of a CBD-rich oil (CBD:THC ratio 14:1) administered over 6 months, with or without concurrent medication reduction or withdrawal, were explored.

2. Materials and Methods

2.1. Ethics Approval and Patient Consents

The study was approved by the Ethics Committee in Research with Human Beings of the Federal University of Santa Catarina (consent No. 5.533.605, date of approval 18/07/2022). Prior to any trial procedures, written consent was obtained from the parent, caregiver, or legal representative.

2.2. Study Design

The open-label pilot study was designed to evaluate the feasibility and safety of administering a cannabidiol (CBD)-rich oil (CBD/THC ratio of 14:1) from the Brazilian Association for Access to Therapeutic Cannabis (ABRAFLOR, Florianópolis, Santa Catarina) for 6 months, alongside the medically supervised, yet voluntary withdrawal or reduction of other pharmacological treatments in children with ASD. The primary outcomes were the feasibility and safety of this approach. The secondary outcomes were the effects on core ASD symptoms, on comorbid neuropsychiatric conditions, and on parental stress.

2.3. Study Site

The study was carried out in a single center, the Bittencourt Neurological Clinic in Florianópolis, SC, Brazil.

2.4. Participants

Thirty children diagnosed with Autism Spectrum Disorder (ASD), residing in the metropolitan region of Grande Florianópolis, Santa Catarina, Brazil, were enrolled in the study. Recruitment was conducted through social media posts, primarily on pages affiliated with the Federal University of Santa Catarina (UFSC). A total of 301 individuals expressed interest in participating. Of these, 185 did not meet the inclusion criteria. From the remaining eligible candidates, 30 participants were randomly selected using an online randomization tool. The

sample size was limited by the amount of CBD-rich oil available, which was sufficient to support treatment for only 30 children.

2.5. Inclusion Criteria

Eligible participants were (i) children and adolescents (2–15 years old); (ii) resident in the metropolitan region of Grande Florianópolis; (iii) diagnosed with ASD according to Diagnostic and Statistical Manual (DSM)-5 criteria and confirmed by the Childhood Autism Rating Scale (First Edition; CARS) (Table 1).

2.6. Exclusion Criteria

The following exclusion criteria were applied: (i) a medical history of intolerance to cannabinoid-based compounds; (ii) treatment with any cannabinoid in the 4 weeks prior to the beginning of the study; and (iii) clinical conditions that could interfere with study participation or behavioral assessment—such as debilitating cerebral palsy, serious non-neurological diseases requiring recurrent hospitalization (e.g., acute lymphoid leukemia), or poorly compensated chronic conditions (e.g., type 1 diabetes)—which may either hinder data collection or increase susceptibility to adverse effects. Intellectual disability was not an exclusion criterion. Participants with comorbid intellectual disability were eligible and included in the study, reflecting the heterogeneous clinical presentation of children with ASD (Table 1).

Table 1. Inclusion/exclusion criteria for study participation.

Inclusion Criteria	
1.	Male or female outpatients aged 2–15 years old
2.	Diagnosis of ASD according to Diagnostic and Statistical Manual of Mental Disorders (5th Edition; DSM-5)
3.	Score greater than 30 on the Childhood Autism Rating Scale (First Edition; CARS) *
4.	Commitment of a caregiver capable of performing the assessments consistently throughout the study
5.	Residence in the metropolitan region of Grande Florianópolis, Santa Catarina, Brazil
Exclusion criteria	
1.	Medical history of intolerance to cannabinoid compounds
2.	Treatment with cannabinoids in the 4 weeks prior to the beginning of the study
3.	Clinical condition that interferes with the patient's ability to participate in the study or that makes the patient susceptible to adverse effects.

* Two participants had previous CARS assessments with scores >30, and the assessment was not repeated for the study.

2.7. DSM-V and CARS Assessment (T-1)

Eligibility criteria according to the DSM-5 were applied by the neurologist during the first meeting. The Childhood Autism Rating Scale (First Edition; CARS) [24,25] was employed to assess the eligibility of participants in the study and to assess the severity of ASD symptoms. During this initial visit, participants and their parent/legal guardian received information about the protocol followed by signing the informed consent form.

2.8. Study Duration and Evaluation Sessions

The study duration was 24 weeks. Five evaluations were performed at the medical center (assessed by a neurologist) and online (assessed by the neuropsychologist and the parents). Here, we report the data collected at: initial evaluation (T0), 8-weeks (T1), and 24 weeks (T2) (see timeline of experimental design, Figure 1).

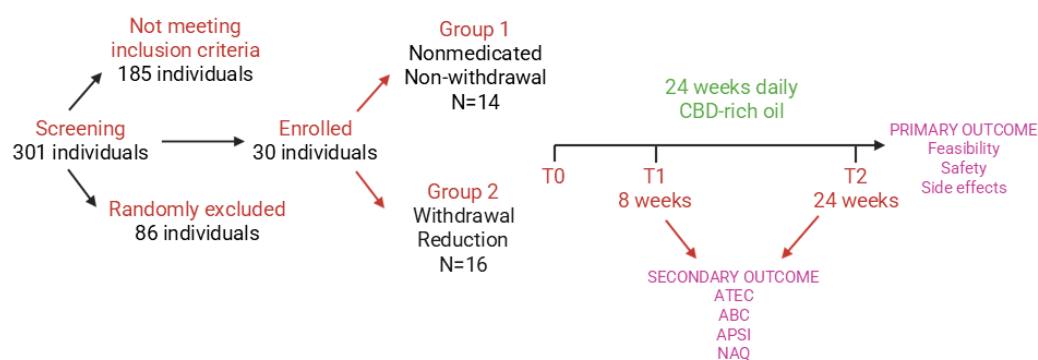


Figure 1. Timeline of experimental design.

2.9. Baseline Assessment (T0)

At T0, participants were administered the Aberrant Behavior Checklist (ABC) [26,27] a tool used to assess behavioral responses to pharmacological interventions in individuals with intellectual disabilities and behavioral disorders. Participants were also administered the Neuropsychiatric Assessment Questionnaire (NAQ; neurologist-administered), a scale developed by our team based on DSM-5 criteria to evaluate clinical impressions of common comorbidities in individuals with ASD, including Avoidant/Restrictive Food Intake Disorder (ARFID), Attention-Deficit/Hyperactivity Disorder (ADHD), Generalized Anxiety Disorder (GAD), Major Depressive Disorder (MDD), and Insomnia Disorder.

Parents/legal guardians were administered the Autism Treatment Evaluation Checklist (ATEC) [28], a caregiver-completed instrument designed to track changes in ASD symptoms over time. Caregivers were also administered the Autism Parenting Stress Index (APSI ages 3–6, parent form) [29], a tool designed to identify specific manifestations of ASD that contribute to parental stress, as well as to evaluate changes in stress levels over the course of clinical interventions. As no validated Portuguese version was available at the time of the study, the questionnaire [29] was translated by the research team (see Supplementary Material for the Portuguese translation).

2.10. CBD Administration

The intervention consisted of daily administration of an oral solution of a CBD-rich oil with a CBD:THC ratio of approximately 14.5:1, over a 24-week period. The oil was supplied by the Brazilian Association for Access to Therapeutic Cannabis (ABRAFLOR, Florianópolis, Santa Catarina), and was extracted from organically grown plants cultivated without chemical pesticides. The final product, containing a 10% CBD-rich oil, was diluted in 90% organic extra virgin olive oil. Treatment began with a fixed dose of 18.8 mg/day of CBD and 1.3 mg/day of THC, divided into two or three daily administrations. Doses were gradually titrated in consultation with the neurologist, based on parental reports of individual clinical response and tolerability, continuing until therapeutic benefits were achieved without unacceptable adverse effects. Dose escalation was halted if patients demonstrated meaningful clinical improvement.

2.11. Reduction/Withdrawal of Concomitant Medication (T0)

At the start of the study and throughout its duration, parents or guardians were given the option to reduce or discontinue the administration of other psychotropic medications under medical direction, yet on a voluntary basis. When deemed appropriate, these medications were tapered slowly and gradually, sometimes partially, sometimes fully. Although no fixed withdrawal schedule was established, dose reductions typically involved decreasing approximately 25% of the initial dose at each follow-up visit, with adjustments individualized according to patient response and tolerability.

To retrospectively compare the outcomes in participants in which any other psychotropic medication was reduced or withdrawn, the sample was a posteriori divided into two groups: Group 1 (Nonmedicated/No withdrawal), which includes participants who were unmedicated or participants whose medication was not reduced or withdrawn, and Group 2 (medication Reduction/Withdrawal), which included participants whose one or more medications were reduced or withdrawn at any point during the 24-weeks administration period.

After the study period, some participants who demonstrated clinical improvement continued using the CBD-rich oil under the neurologist's supervision. Conversely, participants who did not experience meaningful benefits or reported insufficient improvement opted to discontinue its use.

2.12. Visit T1

At T1 (8 weeks after the initiation of CBD treatment), participants were assessed using the ABC and NAQ questionnaires, while parents or guardians completed the ATEC and APSI questionnaires.

2.13. Visit T2

At T2 (24 weeks after the initiation of CBD treatment), participants were assessed using the ABC and NAQ questionnaires, while parents or guardians completed the ATEC and APSI questionnaires.

2.14. Outcome Measures

2.14.1. Primary Outcome Measures

The primary outcome was to obtain preliminary observations regarding the feasibility and safety of a 24-week daily administration of CBD-rich oil provided as an alternative medication in children with ASD who were already receiving medication and had one or more medications reduced or withdrawn, compared to children with ASD who were either unmedicated or whose medication regimen remained unchanged.

Feasibility

Feasibility was measured by recruitment, retention, attrition, and drop-out rates.

Safety

Safety was assessed through the monitoring and documentation of adverse events and side effects in the two groups, which were recorded throughout the study. The Liverpool Adverse Event Profile (LAEP, Neurologist Form) [30,31] was employed, a systematic measure assessing the frequency of adverse effects from antiepileptic drug use. We employed a modified version of the LAEP, which included the criterion of intensity of side effects 0 (none), 1 (Mild, symptom present but not problematic); 2 (Moderate, problematic symptom, requiring change in oil posology) and 3 (Severe, problem that requires removal of the patient from the research due to its harmful potential). Additional 10 possible adverse effects related to cannabis use were included in the questionnaire. Parents were also allowed to report effects that were not in the study script [30,31]. The following side effects from the LAEP were assessed: unsteadiness, tiredness, restlessness, nervousness, aggression, headache, hair loss, problems with skin, double or blurred vision, upset stomach, difficulty in concentrating, trouble with mouth or gums, shaky hands, dizziness, sleepiness, memory problems, eye redness, unexplained laughter, loss of appetite, increased appetite, diarrhea, dry mouth, hallucinations, constipation, tachycardia. Participants' weight was assessed at the three timepoints.

2.14.2. Secondary Outcome Measures

The secondary outcomes were preliminary effects data at T1 and T2 in the following questionnaires: ATEC, ABC, NAQ, APSI, and weight gain.

2.15. Statistical Analyses

Statistical analyses were conducted using GraphPad Prism® 10 (version 10.3.1, GraphPad Software Inc., San Diego, CA, USA). All analyses were conducted using a modified intention-to-treat approach, including all available data from participants even in the case of drop-outs. Descriptive statistics were used to summarize participant demographics, treatment adherence, and reported side effects. Fisher's exact test was employed to compare the frequency and incidence of side effects between the two groups. For the analysis of ATEC, ABC, APSI, and NAQ scores, a mixed-model ANOVA with Greenhouse–Geisser correction was performed, incorporating the within-subject factor Time (T0, T1, T2), the between-subject factor Group (all participants vs. nonmedicated/no withdrawal vs. withdrawal/reduction), and their interaction (Time × Group). When the mixed-model ANOVA yielded significant results, post hoc comparisons were conducted using Bonferroni multiple comparison test with adjusted P-values. Side effects frequency between group 1 and group 2 was compared with Fisher's exact test. Statistical significance was set at $p < 0.05$.

2.16. Data Availability

The datasets and statistical analyses are available upon request to the corresponding author.

3. Results

3.1. Primary Outcome Measures

3.1.1. Enrollment

Feasibility was evaluated by tracking recruitment, retention, attrition, and drop-out rates. Of the 301 individuals initially screened, 185 did not meet the inclusion criteria. To manage study logistics and maintain a

manageable cohort size for close clinical observation, 86 of the remaining eligible participants were randomly excluded using a sweepstakes-style random drawing method, in which each participant was assigned a number and selections were made at random. This process resulted in a final sample of 30 participants enrolled in the study. All participants received follow-up assessments at baseline, midpoint (12 weeks), and endpoint (24 weeks), with a study completion rate of 90% (27/30).

3.1.2. Demographics and Comorbid Neuropsychiatric Symptoms

Of the 30 participants enrolled in the study, 27 (90%) were boys. The average age was 7.3 ± 3.1 (SD) years old. The average CARS score at enrollment was 43.9 ± 10.1 (SD), indicating that most participants had severe autism. ADHD was the most common neuropsychiatric comorbid symptom, occurring in 26/30 participants (86.7%) followed by insomnia disorder in 23 (76.7%) participants, avoidant/restrictive food intake disorder in 14 (46.7%) participants, generalized anxiety disorder in 5 (16.7%) participants, and Major Depressive Disorder in 3 (10%) participants (Table 2).

Table 2. Descriptive characteristics of participants.

<i>n</i>	Groups		
	All 30	(1) Nonmedicated/Nonreduction 14	(2) Medication Withdrawal/Reduction 16
Sex: Boys <i>n</i> (%)	27 (90%)	14 (100%)	13 (81%)
Age: Mean $\pm$ SD	7.3 ± 3.1	7.2 ± 4.0	7.4 ± 2.4
CARS Score: Mean $\pm$ SD	43.9 ± 10.1	44.4 ± 9.2	43.5 ± 11.1
Retention	27 (90%)	13 (92.9%)	14 (87.5%)
Drop-outs	3 (10%)	1 (7.1%)	2 (12.5%)
Attention Deficit Hyperactivity Disorder: <i>n</i> (%)	26 (86.7%)	13 (92.9%)	13 (81.3%)
Insomnia Disorder: <i>n</i> (%)	23 (76.7%)	11 (78.6%)	12 (75%)
Avoidant/Restrictive Food Intake Disorder: <i>n</i> (%)	14 (46.7%)	7 (50%)	7 (43.8%)
Generalized Anxiety Disorder: <i>n</i> (%)	5 (16.7%)	2 (14.3%)	3 (18.8%)
Major Depressive Disorder: <i>n</i> (%)	3 (10%)	1 (7.1%)	2 (12.5%)
Concomitant Medications (<i>N</i> = 20)			
Antipsychotics: <i>n</i> (%)	18 (90%)	3 (15%)	14 (70%)
Melatonin: <i>n</i> (%)	5 (25%)	2 (10%)	3 (15%)
Antiepileptics: <i>n</i> (%)	3 (15%)	1 (5%)	2 (10%)
Stimulants: <i>n</i> (%)	3 (15%)	-	3 (15%)
Antianxiety Agent: <i>n</i> (%)	2 (10%)	-	2 (10%)
SSRIs: <i>n</i> (%)	2 (10%)	-	2 (10%)

3.1.3. Retention and Drop-Out

The retention was 90% (27/30 participants), slightly higher in group 1 (nonmedicated/no withdrawal) (92.5%, 13/14 participants in the group) compared to group 2 (87.5%, 14/16 participants in the medication reduction/withdrawal group). The drop-out rate was 10% (*N* = 3). One participant was from group 1 (drop-out rate 7.1%) and dropped out due to a perceived lack of effect from the CBD-rich oil. Two participants were from Group 2 (drop-out rate 12.5%): one due to the recurrence of atonic epileptic seizures following the tapering of the antiepileptic valproic acid, and the second due to agitation, nervousness, and aggression associated with the reduction of the antipsychotic aripiprazole. A total of 27 participants (13/14 in group 1 and 14/16 in group 2) completed the full 24-week study, yielding a retention rate of 90% (92.9% in group 1 and 87.5% in group 2) (Table 2).

3.1.4. CBD Dosage

Participants received a CBD-rich oil with a CBD:THC ratio of 14.5:1, administered in two or three daily doses. All participants began with an initial total daily dose of 18.8 mg of CBD and 1.3 mg of THC. Doses were individually titrated throughout the study period based on clinical response and tolerability. Participants who showed satisfactory improvement at lower doses had their titration halted accordingly. By the end of the 24-week treatment period, the average final CBD dose was 1.12 mg/kg/day (range: 0.38–2.9 mg/kg/day), while the average final THC dose was 0.08 mg/kg/day (range: 0.03–0.15 mg/kg/day). These values remained well below the pre-established safety ceiling of 0.5 mg/kg/day for THC to avoid adverse events due to the relatively higher THC

content in the preparation (compared to previous studies such as Aran et al., which used ~5.7 mg/kg/day of CBD with lower THC ratios).

3.1.5. Concomitant Medications

Supplementary Materials Table S1 shows a list of the medications taken by each participant at the start of the study and at each of the study visits. Of the 30 participants enrolled, 20 (66.7%) were taking concomitant medications at enrollment. Among these, eight (40%) were taking 1 medication, six (30%) were taking 2 medications, five (25%) were taking 3 medications, and one (5%) was taking 4 medications. The most used prescription medications were antipsychotics, taken by 18 out of 20 (90%) children. Risperidone was taken by 12 (60%) and Aripiprazole by 6 (30%) medicated participants. Although melatonin is usually considered a supplement rather than a prescription medicine, it was still considered as a “medication” in this study, being part of the therapeutic plan of five participants.

3.1.6. Reduction or Withdrawal of Concomitant Medications

Group 1: Nonmedicated/no withdrawal. Participants who were not medicated (10, 33.3%), for which medications were not withdrawn or reduced (3, 10%), or that had their medication changed (1, 3.3%) during the study were included retrospectively in Group 1 (nonmedicated/no withdrawal, $N = 14$).

Group 2: We considered as “reduction” if the dosage of at least one of the medications taken at the start of the study was decreased (8 participants, 26.7%) “withdrawal” if any of the prescription drugs taken was completely stopped during the 6 months of the study (8 participants, 26.7%). Participants who had at least one medication reduced or withdrawn were included retrospectively in Group 2 ($N = 16$).

3.1.7. Continuation of CBD Oil Intake After the End of the Study

Of the 27 patients who completed the study, the majority ($N = 22$, 81.5%) continued using the CBD oil (which can be prescribed by medical doctors in Brazil). Of the five who did not continue two were in group 1, and three were in group two. The reasons for discontinuation were as follows: fear of psychotic effects from long-term use (1), no significant improvement in symptoms (3), and symptoms worsened with the intervention (1).

3.1.8. Safety

Adverse Events

The seven most commonly reported mild adverse events are presented in Figure 2. Restlessness was the most frequently reported, observed in 19 participants (63.3%)—6 from Group 1 and 13 from Group 2. Increased appetite was reported by 17 participants (56.7%)—8 from Group 1 and 9 from Group 2. Nervousness occurred in 14 participants (46.7%)—5 from Group 1 and 9 from Group 2. Unexplained laughter was reported in 13 participants (43.3%)—5 from Group 1 and 8 from Group 2. Dry mouth was noted by 10 participants (33.3%)—3 from Group 1 and 7 from Group 2. Aggression was also reported in 10 participants (33.3%)—4 from Group 1 and 6 from Group 2. Difficulty concentrating occurred in 8 participants (26.7%)—5 from Group 1 and 3 from Group 2. Less frequent mild adverse events are listed in Supplementary Materials Figure S1, and reported intensity levels are shown in Supplementary Materials Figure S2. Overall, no serious treatment-emergent adverse events directly related to CBD were reported in either group.

We did not detect statistically significant differences in the frequency and intensity of side effects when comparing nonmedicated/no withdrawal participants to participants whose medication was reduced/withdrawn (Fisher’s exact test, all $p > 0.05$). Two severe adverse events were recorded in group 2. One female child with epilepsy experienced the return of epileptic seizures following the tapering and eventual withdrawal of valproic acid between week 16 and week 24. Following this event, low dose valproic acid therapy was reinstated and the participant/parent decided to continue the study and CBD oil therapy. No further episodes of seizures were recorded, and the participant completed the 24-week treatment period. A male child with epilepsy from group 2 experienced atonic epileptic seizures even though the antiepileptic medication regimen had been left unchanged, following the tapering and eventual withdrawal of the antipsychotic risperidone. The participant/parent chose to drop-out of the study. No statistically significant changes were observed concerning the participants’ body weight throughout the study (Supplementary Materials Figure S3).



Figure 2. The seven most common mild adverse events experienced by study participants. The white color indicates an adverse effect that never occurred; the pink color indicates an adverse effect that occurred rarely; the orange color indicates an adverse effect that occurred sometimes; the red color indicates an adverse effect that occurred always or often. All participants $N = 30$; Nonmedicated/No withdrawal $N = 14$; Medication Reduction/Withdrawal $N = 16$.

3.2. Secondary Outcome Measures

3.2.1. Autism Treatment Evaluation Checklist (ATEC)

Regarding the *Speech, Language and Communication* category of the ATEC (Figure 3A), mixed-model ANOVA identified a significant effect of *Time* ($F(1.921, 101.8) = 32.12, p < 0.0001$), but no effect of *Group* or *Time x Group* interaction. When considering all participants, decreases were observed at T1 and T2 compared to T0 (post-hoc respectively $p = 0.0156$ and $p < 0.0001$). Additionally, a decrease was observed from T1 to T2 ($p = 0.0213$). In nonmedicated/no withdrawal participants, a decrease was observed at T2 compared to T0 ($p = 0.0018$), and at T2 compared to T1 ($p = 0.0098$). In participants whose medication was reduced/withdrawn, a decrease was detectable at T2 compared to T0 ($p = 0.0055$). No differences were present at any of the timepoints between groups (post-hoc $p > 0.05$).

Regarding *Sociability* (Figure 3B) there was a significant effect of *Time* ($F(1.567, 81.47) = 34.61, p < 0.0001$), but no effects of *Group* or *Time x Group* interaction (post-hoc $p > 0.05$). When considering all participants, decreases were observed at T1 and T2 compared to T0 (post-hoc test respectively $p = 0.0022$ and $p = 0.0001$), and at T2 compared to T1 ($p = 0.0010$). No statistically significant differences were observed in nonmedicated/no withdrawal participants. A decrease was observed in participants whose medication was reduced/withdrawn from T0 to T1 ($p = 0.0019$) and from T1 to T2 ($p = 0.0087$). No differences were present at any of the timepoints between groups (post-hoc $p > 0.05$).

Regarding *Sensory and cognitive awareness* (Figure 3C), there was a significant effect of *Time* ($F(1.507, 79.88) = 36.04, p < 0.0001$), but no effect of *Group* or *Time x Group* interaction (post-hoc $p > 0.05$). When considering all participants, decreases were observed at T1 and T2 compared to T0 (respectively $p = 0.0124$ and p

< 0.0001). Additionally, a decrease was observed from T1 to T2 ($p = 0.0008$). In nonmedicated/no withdrawal participants, a decrease was observed at T2 compared to T0 ($p = 0.0172$), and from T1 to T2 ($p = 0.0071$). In participants whose medication was reduced/withdrawn, a decrease was detectable at T2 compared to T0 ($p = 0.0080$). No differences were present at any of the timepoints between groups (Bonferroni post-hoc $p > 0.05$).

Concerning *Health, physical and behavior* (Figure 3D), there was a significant effect of *Time* ($F(1.778, 94.22) = 44.31$, $p < 0.0001$), but no effect of *Group* or *Time x Group* interaction (post-hoc $p > 0.05$). When considering all participants, decreases were observed at T1 and T2 compared to T0 (post-hoc respectively $p = 0.0007$ and $p < 0.0001$), and from T1 to T2 ($p = 0.0080$). In nonmedicated/no withdrawal participants, a decrease was observed at T1 and T2 compared to T0 (respectively $p = 0.0147$ and $p = 0.0151$). In participants whose medication was reduced/withdrawn, a decrease was detected at T1 and T2 compared to T0 (respectively $p = 0.0472$ and $p = 0.0004$). No differences were present at any of the timepoints between groups (post-hoc $p > 0.05$).

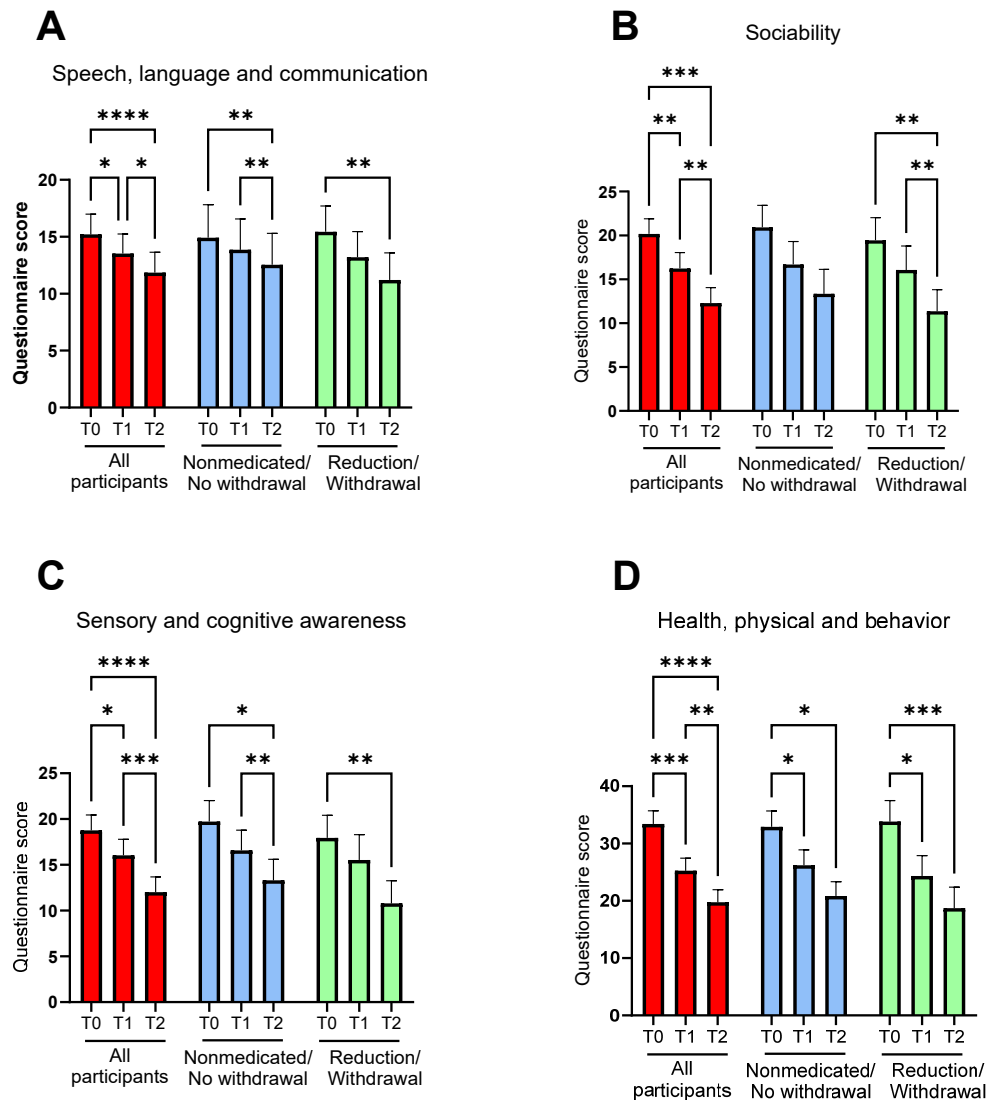


Figure 3. Results of the Autism Treatment Evaluation Checklist (ATEC) questionnaires. The graphs illustrate the observed apparent improvement in Autism Spectrum Disorder (ASD) core symptoms (the lower the score, the lower the symptom); these include (A) speech, language and communication; (B) sociability; (C) sensory and cognitive awareness, and (D) overall physical and behavioral health. (X axis) T0: baseline assessment; T1: 8-weeks of CBD oil administration; T2: 24-weeks of CBD oil administration. (Y axis) questionnaire score (the lower, the better the outcome). All participants ($N = 30$); Nonmedicated/No withdrawal: participants who were unmedicated, or whose medication was not withdrawn/reduced ($N = 14$); Reduction/Withdrawal: medicated participants whose medication was reduced or withdrawn during the study ($N = 16$). Mixed model ANOVA followed by Bonferroni post-hoc test. * indicates Bonferroni post-hoc p value < 0.05 ; ** p value < 0.01 ; *** p value < 0.001 ; **** p value < 0.0001 .

3.2.2. Aberrant Behavior Checklist (ABC)

Concerning the *stereotyped behavior* category of the ABC (Figure 4A), mixed-model ANOVA identified an effect of Time ($F(1.518, 80.47) = 54.15, p < 0.0001$), but no effect of *Group* or *Time x Group* interaction (Bonferroni post-hoc $p > 0.05$). When considering all participants, decreases were observed at T1 and T2 compared to T0 (post-hoc respectively $p = 0.0006$ and $p < 0.0001$). Additionally, a decrease was observed from T1 to T2 ($p = 0.0012$). In nonmedicated/no withdrawal participants, a decrease was observed at T2 compared to T0 ($p = 0.0009$) and from T1 to T2 ($p = 0.0290$). In participants whose medication was reduced/withdrawn, a decrease was detectable at T1 and T2 compared to T0 (respectively $p = 0.0090$ and $p = 0.0011$). No differences were present at any of the timepoints between groups (post-hoc $p > 0.05$).

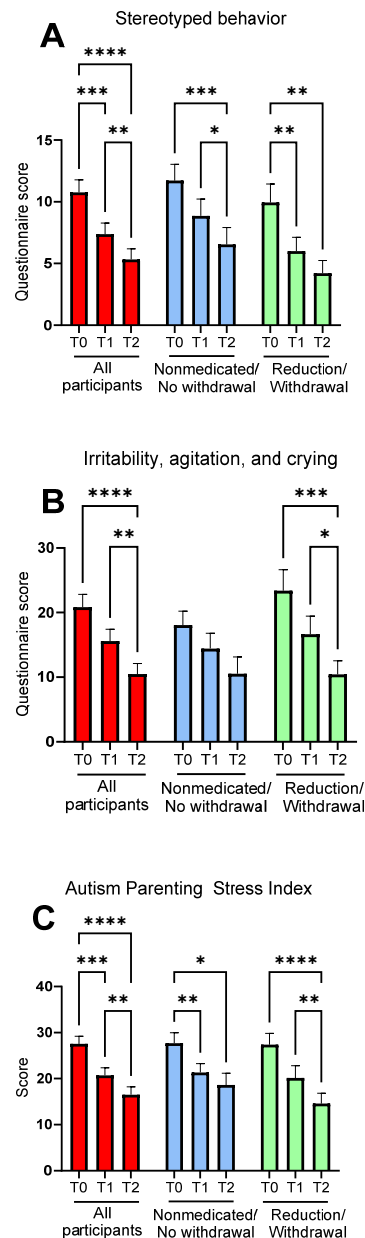


Figure 4. Results of the Aberrant Behavior Checklist (ABC) and Autism Parenting Stress Index (APSI) questionnaires. The graphs illustrate the decrease in (A) stereotyped behavior and (B) irritability, agitation, and crying in the ABC; and (C) in the APSI index. (X axis) T0: baseline assessment; T1: 8-weeks assessment; T2: 24-weeks assessment. (Y axis) questionnaire score (the lower, the better the outcome). All participants ($N = 30$); Nonmedicated/No Withdrawal: participants who were unmedicated, or whose medication was not withdrawn/reduced ($N = 14$); Reduction/Withdrawal: participants who were medicated, and whose medication was reduced or withdrawn during the study ($N = 16$). Mixed effect ANOVA followed by Bonferroni post-hoc test. * indicates Bonferroni post-hoc p value < 0.05 ; ** p value < 0.01 ; *** p value < 0.001 ; **** p value < 0.0001 .

Concerning *Irritability, agitation, and crying* (Figure 4B), there was a significant main effect of Time ($F(1.732, 90.07) = 25.91, p < 0.0001$), but no effect of *Group* or *Time x Group* interaction (post-hoc $p > 0.05$). When considering all participants, a decrease was observed at T2 compared to T0 ($p < 0.0001$). Additionally, a decrease was observed from T1 to T2 ($p = 0.0014$). No differences were observed in nonmedicated/no withdrawal participants. In participants whose medication was reduced/withdrawn, a decrease was detectable at T2 compared to T0 ($p = 0.0008$). Additionally, a decrease was observed from T1 to T2 ($p = 0.0320$). No differences were present at any of the timepoints between groups (Bonferroni post-hoc $p > 0.05$).

3.2.3. Autism Parenting Stress Index

Concerning the APSI index (Figure 4C), there was an effect of Time ($F(1.683, 89.21) = 52.17, p < 0.0001$), but no effect of *Group* or *Time x Group* interaction (post-hoc $p > 0.05$). When considering all participants, decreases were observed at T1 and T2 compared to T0 (respectively $p = 0.0004$ and $p < 0.0001$). Additionally, a decrease was observed from T1 to T2 ($p = 0.0022$). In nonmedicated/no withdrawal participants, decreases were observed at T1 and T2 compared to T0 (post-hoc respectively $p = 0.0021$ and $p = 0.0156$). In participants whose medication was reduced/withdrawn, a decrease was detectable at T2 compared to T0 ($p < 0.0001$). Additionally, a decrease was observed from T1 to T2 ($p = 0.0021$). No differences were present at any of the timepoints between groups (Bonferroni post-hoc $p > 0.05$).

3.2.4. Comorbid Neuropsychiatric Symptoms

Concerning co-morbid Attention-Deficit/Hyperactivity Disorder (ADHD) symptoms, mixed-model ANOVA identified an effect of Time ($F(1.686, 79.23) = 88.36, p < 0.0001$), but no effect of *Group* or *Time x Group* interaction (post-hoc $p > 0.05$). When considering all participants, score increases (meaning decreased symptom intensity) were observed at T1 and T2 compared to T0 (both $p < 0.0001$). Additionally, a decrease was observed from T1 to T2 ($p = 0.0006$). In nonmedicated/no withdrawal participants, a decrease was observed at T1 and T2 compared to T0 (respectively $p = 0.0066$ and $p = 0.0006$). Similarly, in participants whose medication was reduced/withdrawn, a decrease was detectable at both T1 and T2 compared to T0 (respectively $p = 0.0022$ and $p < 0.0001$). Additionally, a decrease was observed from T1 to T2 ($p = 0.0052$). No differences were present at any of the timepoints between groups (Bonferroni post-hoc $p > 0.05$) (Figure 5A).

Concerning co-morbid Avoidant/Restrictive Food Intake Disorder (ARFID) symptoms, mixed-model ANOVA identified an effect of Time ($F(1.493, 32.84) = 14.21, p = 0.0001$), but no effect of *Group* or *Time x Group* interaction ($p > 0.05$). When considering all participants, score increases were observed at T2 compared to T0 ($p = 0.0141$). Considering the post-hoc comparison between nonmedicated/no withdrawal participants and participants whose medication was reduced/withdrawn, no differences emerged. No differences were present at any of the timepoints between groups ($p > 0.05$) (Figure 5B).

Concerning co-morbid Generalized Anxiety Disorder (GAD) symptoms, mixed-model ANOVA identified an effect of Time ($F(1.766, 12.36) = 27.76$), but no effect of *Group* or *Time x Group* interaction ($p > 0.05$). When considering all participants, score increases were observed at T2 compared to T0 ($p = 0.0064$). In nonmedicated/no withdrawal participants, a decrease was observed at T2 compared to T1 ($p < 0.0001$). No differences were observed in participants whose medication was reduced/withdrawn ($p > 0.05$). No differences were present at any of the timepoints between groups ($p > 0.05$) (Figure 5C).

Concerning co-morbid Insomnia Disorder (ID) symptoms, mixed-model ANOVA identified an effect of Time ($F(1.838, 71.66) = 27.37$) but no effect of *Group* or *Time x Group* interaction. When considering all participants, score increases were observed at T2 compared to T0 ($p < 0.0001$). Additionally, a decrease was observed from T1 to T2 ($p = 0.0068$). In nonmedicated/no withdrawal participants, a decrease was observed at T2 compared to T0 ($p = 0.0075$). In participants whose medication was reduced/withdrawn, a decrease was observed at T2 compared to T0 ($p = 0.0202$). No differences were present at any of the timepoints between groups ($p > 0.05$) (Figure 5D).

Concerning co-morbid Major Depressive Disorder (MDD) symptoms, mixed-model ANOVA identified an effect of Time ($F(1.095, 3.286) = 16.15$) but no effect of *Group* or *Time x Group* interaction ($p > 0.05$). Post-hoc testing was not performed due to the few participants displaying this comorbidity (Figure 5E).

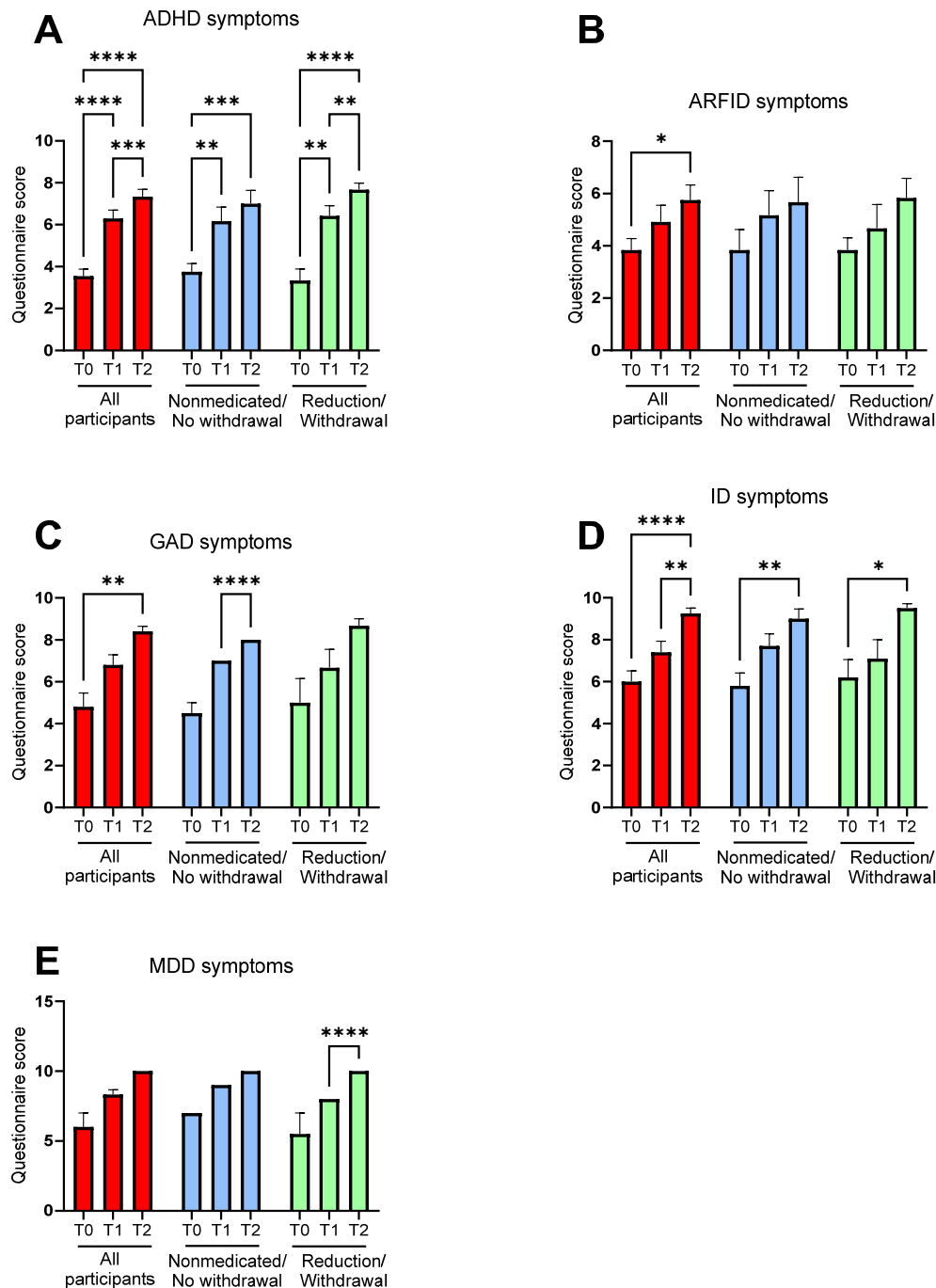


Figure 5. Neuropsychiatric symptoms (the higher the score, the milder the symptoms). The graphs illustrate the significant attenuation of (A) Attention Deficit/Hyperactivity Disorder (ADHD) symptoms; (B) Avoidant Restrictive Food Intake Disorder (ARFID) symptoms; (C) Generalized Anxiety Disorder (GAD) symptoms; (D) Insomnia Disorder (ID) symptoms; (E) Major Depressive Disorder (MDD) symptoms. Mixed effect ANOVA followed by Bonferroni post-hoc test. * indicates Bonferroni post-hoc p value < 0.05 ; ** p value < 0.01 ; *** p value < 0.001 ; **** p value < 0.0001 .

4. Discussion

This retrospective analysis of an open-label pilot study assessed the preliminary feasibility, safety, and effects of administering a CBD-rich oil as an adjunct or alternative medication over a 24-week period to children with ASD. The reduction or withdrawal of standard medications was medically supervised and conducted on a voluntary basis. The treatment was generally well tolerated. The most commonly observed mild adverse effects were restlessness, increased appetite, and nervousness or aggression, most observed during the initial introduction

of the CBD-rich oil or following dose adjustments. While most participants experienced mild side effects, one participant discontinued due to more pronounced restlessness and aggression. Of note, after 16-weeks, adverse effects seemed to have largely subsided, raising the possibility that some individuals may develop tolerance to early side effects over time. This is consistent with the findings of previous studies, where mild and transient side effects were common during the initial stages of cannabinoid therapy [32].

Two participants experienced a recurrence of seizures—one following valproic acid tapering and another after risperidone withdrawal, despite stable antiepileptic therapy. These events are clinically notable given the small sample size and underscore the limitations of the current safety assessment. While no statistically significant differences in the frequency or intensity of side effects were observed between groups, the retrospective nature of the design and overlapping interventions limit causal interpretations. Nonetheless, the findings reinforce the need for close clinical monitoring during medication changes, particularly in children with epilepsy receiving CBD.

Among participants on antipsychotics, for 12 out of 18 individuals the dosage was reduced by 70% or more. Reductions or discontinuations also concerned antiepileptics, SSRIs, and stimulants. However, the simultaneous implementation of two interventions—CBD introduction and medication changes—means that no causal conclusions can be drawn about the safety of CBD or medication tapering alone. The outcomes, while preliminary and descriptive, underscore the need for prospective, controlled trials that can more clearly isolate and assess the respective roles of CBD and concomitant medication reduction. This observation aligns with prior literature showing that reducing psychotropic medications in ASD is both clinically valuable and challenging. Withdrawal, especially without structured tapering protocols, can trigger symptom recurrence [33–35].

The secondary goal of this study was to explore the effects of CBD-rich oil on core symptoms of ASD of voluntary medication withdrawal or reduction in children with ASD. The ATEC and ABC scales showed preliminary signs of improvement in several areas. Participants demonstrated apparent improvements in the Speech, Language, and Communication category, with some reductions in communication difficulties over time, though previous findings have been inconsistent [36–40]. Similarly, the Sociability category also showed suggestive improvements, in agreement with the findings of two previous clinical trials [36,41], particularly among those who reduced their medication doses. The present pilot study adds to this literature by being one of the few investigations exploring the intersection of CBD use and psychotropic medication reduction [42–44]. Across the full cohort of participants, significant decreases were observed across various domains of the ATEC and ABC, including stereotyped behaviors, irritability, and aggression, though the interpretation is limited by the non-randomized, observational design. The observed improvements in sociability and communication may relate to the potential role of CBD in modulating the ECS. Preclinical studies suggest that CBD increases anandamide (AEA) levels by inhibiting fatty acid amide hydrolase (FAAH), the enzyme responsible for AEA degradation [45]. Elevated AEA has been associated with enhanced social behavior via CB1R activation in key brain regions such as the nucleus accumbens and hippocampus [46]. However, these mechanisms are speculative and are yet to be directly validated in clinical ASD populations [16,47–49]. While preclinical evidence provides a plausible biological rationale, the findings in our cohort are hypothesis-generating and not conclusive.

Apparent improvements in comorbid neuropsychiatric scores were observed, with possible signals of benefit in ADHD symptoms. These patterns are broadly consistent with the hypothesized role of CBD in enhancing attention and reducing hyperactivity in children with ADHD, potentially through modulation of dopaminergic neurotransmission [50] and are in line with growing evidence of CBD's effects on executive function [38,50–53]. Yet again, these potential mechanisms remain hypothetical and largely extrapolated from animal models or small-scale studies in other populations. Similarly, some indications of improvements were noted in symptoms associated with ARFID and ID, including reported gains in food selectivity and intake diversity, which may relate to hypothesized effects of cannabinoids on reward pathways and sensory processing. Such mechanisms are also speculative and not yet supported by robust clinical evidence in ASD. While these exploratory observations are encouraging, the study's design limitations preclude causal interpretation. These findings highlight the importance of future controlled research to better characterize the potential role of CBD in managing comorbid neuropsychiatric symptoms in children with ASD.

Caregivers of autistic children—particularly women—often face disproportionate emotional and logistical strain [54]. Interventions that reduce behavioral difficulties and psychotropic medication use may contribute to improved family functioning and mental health. The decreased APSI scores suggest a potential reduction in caregiver stress, suggesting that improvements in the child's behavior and the reduction of psychotropic medication use positively affected the caregivers' mental health. While the retrospective design limits causal interpretation, this pattern aligns with previous findings suggesting that clinical improvements in children with ASD may be associated with better caregiver mental health and family functioning [39,55]. Other studies have

similarly found that reduced medication burden and behavioral symptom improvement are associated with decreased caregiver stress and improved family dynamics [56–58].

While both groups—those who underwent supervised medication reduction or withdrawal and those who remained nonmedicated or on stable regimens—showed signs of improvements over time across various outcome measures, no statistically significant differences emerged between the groups. These results should be interpreted cautiously, as this was an exploratory, retrospective study not designed to test efficacy or causality.

Several factors may help explain the lack of observed group differences. First, the small sample size, lack of randomization, and naturalistic grouping reduced statistical power and increased the risk of confounding. Participants were not assigned to groups *a priori* but categorized based on real-world clinical decisions, which may have introduced variability in baseline characteristics or response tendencies. Second, all participants received the same CBD-rich oil preparation, which may have led to general improvements across the sample, thereby reducing between-group contrast.

Moreover, while improvements were noted in core ASD symptoms, comorbid neuropsychiatric symptoms, and caregiver stress, these changes were detected through caregiver-reported instruments, which may be subject to bias or placebo effects, especially in an open-label design. The absence of a control group further limits the interpretability of these findings. Overall, the lack of group differences does not imply equivalence or lack of effect, but rather underscores the need for caution in interpreting preliminary observational data. These findings are best understood as hypothesis-generating and support the rationale for future controlled studies to examine whether CBD-rich preparations can safely support medication tapering and contribute to symptom management in ASD.

While data on psychotropic medication tapering in ASD are limited, existing evidence suggests that withdrawal is feasible but must be approached with structured planning due to the risk of symptom exacerbation or recurrence. This observation aligns with existing literature highlighting both the challenges and clinical value of psychotropic medication reduction in ASD, where withdrawal can be associated with symptom recurrence, particularly in the absence of structured tapering protocols.

One potentially notable clinical implication is that observed improvements appeared to occur regardless of whether psychotropic medications were reduced or maintained. Our study contributes a preliminary signal that a CBD-rich oil may serve as a supportive adjunct in this context. This suggests that CBD-based interventions may be well-tolerated and potentially beneficial both as an aid to medication reduction and as a broader therapeutic adjunct in ASD management. However, given the retrospective design, lack of a control group, and small sample size, these findings should be viewed as preliminary and hypothesis-generating. Controlled trials are needed to clarify the potential role, mechanisms, and safety of CBD products in ASD care, both with and without concurrent pharmacotherapy.

4.1. Limitations

This study presents important limitations. As a retrospective, open-label analysis without randomization or placebo control, it is not possible to isolate the effects of CBD administration from those of medication tapering or other confounding variables. The post-hoc division of participants into medicated and nonmedicated groups after data collection limits internal validity and prevents causal inferences regarding the effects of medication withdrawal or CBD. The absence of additional control groups—such as children receiving CBD without medication changes, undergoing tapering without CBD, or receiving placebo—further restricts the ability to draw clear conclusions about either intervention. The wide dosing range and individualized titration make results difficult to generalize, despite mirroring real-world usage. Outcome measures were based on parent-reported instruments, which are susceptible to expectancy and reporting bias, particularly in unblinded studies involving novel treatments. The open-label design likely amplified placebo effects, as families may have had strong expectations about the benefits of cannabis-based interventions [59]. Clinical assessments were conducted by trained clinicians using standardized protocols, but inter-rater reliability was not formally assessed, the study's sample size was small (30 enrolled, 27 completed), and the two resulting groups ($N = 16$ vs. $N = 14$) were unequal, further limiting statistical power. A formal power calculation was not performed, which limits the ability to determine whether the sample size was sufficient to detect differences. The sample was heavily skewed toward males (90%), limiting the generalizability of findings to female populations. The CBD oil was provided by a patient association operating at the time without standardized manufacturing practices or third-party testing. While this reflects common real-world usage in Brazil, it introduces significant variability in product quality, cannabinoid content, and dosing accuracy. Although most adverse events were mild, two participants experienced seizure recurrence—one of whom discontinued due to atonic seizures following risperidone tapering. While these events were not definitively linked to CBD, they represent 3–7% of the sample and underscore safety concerns,

particularly for children with epilepsy. In a small cohort, even isolated serious events have substantial impact and warrant careful monitoring. Finally, no laboratory or physiological assessments were conducted.

4.2. Future Directions

Building on these preliminary observations, future research should prioritize prospective RCTs to evaluate both the efficacy and safety of different formulations of CBD in children with ASD. Early-phase studies will be important to determine optimal dosing strategies using standardized cannabinoid preparations. Dose-finding trials should explore not only therapeutic windows but also tolerability in subgroups with heightened vulnerability, such as children with ASD and comorbid epilepsy. In populations often exposed to polypharmacy, it will also be essential to monitor potential pharmacokinetic and pharmacodynamic interactions between CBD and commonly prescribed psychotropic drugs. These future studies should incorporate structured tapering protocols, seizure surveillance, and laboratory monitoring (e.g., liver function, metabolic panels) to build a clearer safety profile. The observation that CBD may support or enhance medication reduction is a promising hypothesis that warrants direct testing in randomized clinical trials.

5. Conclusions

This retrospective analysis of an open-label study offers initial observations on the potential feasibility and short-term safety of CBD-rich oil as an adjunct or under supervised medication reduction or withdrawal, in children with ASD, and potential greater risk of symptom recurrence following medication reduction or withdrawal in children with ASD and comorbid epilepsy. These observations are in line with the existing literature but should be interpreted with caution given the study's limitations. Further randomized clinical trials are needed to more clearly assess safety, potential benefits, and the role of CBD as an adjunct or alternative therapy in ASD.

Supplementary Materials

The additional data and information can be downloaded at: <https://media.scilit.com/articles/others/2510291416173540/CNA-25090013-Supplementary-Materials-FC.pdf>. Figure S1: The frequency of mild adverse events experienced by study participants at any of the study visits. Figure S2: The intensity of mild adverse events experienced by study participants at any of the study visits. Figure S3: Body weight of study participants throughout the study (X axis). Table S1: Medication reduction-withdrawal.

Author Contributions

A.M.d.L.: conceptualization, methodology, formal analysis, investigation, data curation, writing—original draft, writing—review and editing, visualization, and project administration; L.R.d.N.J., R.A. and D.A.G. investigation, data curation, and writing—review and editing; K.d.S.K. formal analysis; R.M.d.B. and P.C.T.B. conceptualization, investigation, data curation, writing—review and editing, visualization, supervision, and project administration; A.I. and A.C. formal analysis and writing—review and editing. All authors reviewed and approved the final version of the manuscript.

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Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee in Research with Human Beings of the Federal University of Santa Catarina (consent No. 5.533.605, date of approval 18/07/2022).

Informed Consent Statement

Prior to any trial procedures, written consent was obtained from the parent, caregiver, or legal representative.

Data Availability Statement

The datasets and statistical analyses are available upon request to the corresponding authors.

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Conflicts of Interest

The authors declare that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest. RA is affiliated with a patient advocacy organization (SouCannabis Therapeutic Association). This affiliation is independent of the Brazilian Association for Access to Therapeutic Cannabis (ABRAFLOR), which supplied the CBD-rich oil used in the present study.

Use of AI and AI-Assisted Technologies

During the preparation of this work, the authors used ChatGPT to improve the language and correct typos and grammatical errors. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Abbreviations

ABC	Aberrant Behavior Checklist
ADHD	Attention-Deficit/Hyperactivity Disorder
AEA	Anandamide
APSI	Autism Parenting Stress Index
ARFID	Avoidant/Restrictive Food Intake Disorder
ASD	Autism Spectrum Disorder
ATEC	Autism Treatment Evaluation Checklist
CBD	Cannabidiol
CB1R	Cannabinoid receptor type 1
CARS	Childhood Autism Rating Scale
ECS	Endocannabinoid System
FAAH	Fatty Acid Amide Hydrolase
GAD	Generalized Anxiety Disorder
ID	Insomnia Disorder
LAEP	Liverpool Adverse Events Profile
MDD	Major Depressive Disorder
NAQ	Nutrition and Appetite Questionnaire
SD	Standard Deviation
SSRI	Selective Serotonin Reuptake Inhibitor
THC	Δ^9 -tetrahydrocannabinol
<i>n</i>	number of participants

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