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# A natural history study of medical cannabis consumption in pediatric autism in the United States

Mary Ann DiLiberto [a,1], Athena F. Zuppa [a,b,1], Amanda Cornetta [a], Walter Faig [c], Tryce Scully [c], Amanda Bennett [d,e], Meghan Thomas [e], Elizabeth Ward [a], Stephen Barr [a], Benjamin E. Yerys [f,g,*]

[a] Center for Clinical Pharmacology, Children's Hospital of Philadelphia, Philadelphia, PA, USA
[b] Anesthesiology and Critical Care, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
[c] Biostatistics and Data Management Core, Children's Hospital of Philadelphia, Philadelphia, PA, USA
[d] Division of Developmental and Behavioral Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA, USA
[e] Zelira Therapeutics Limited, Perth, Australia
[f] Center for Autism Research, Children's Hospital of Philadelphia, 2716 South Street 5th Floor, Philadelphia, PA 19146, USA
[g] Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

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ABSTRACT

*Background:* Autism spectrum disorder is specifically approved for medical cannabis consumption in 20 U.S. states, the District of Columbia, and the Territory of Puerto Rico. Despite increased access, there is limited knowledge about who consumes medical cannabis, what they consume, and perceived effectiveness. We addressed these gaps by conducting a natural history study of medical cannabis consumption.

*Method:* Children and their families engaged with a large pediatric care system were recruited to complete a telephonic study regarding their medical cannabis consumption. All children had to be consuming approved medical cannabis products issued from a state that had legalized medical cannabis for the treatment of ASD or related behaviors (irritability, hyperactivity, anxiety) ($N$ = 89).

*Results:* The sample's 'level of support' and gender-ratio reflected the general autism population (~33 % requiring 'Very Substantial Support' and ~80 % male). The most common treatment targets were ASD behaviors (repetitive behaviors) and irritability. More children consumed compounds with high cannabidiol (CBD) and low or no tetrahydrocannabinol (THC). While dose did not affect overall perceived effectiveness, compounds with high-levels of CBD and low-levels of THC (CBD-dominant) were perceived as more effective than CBD-only.

*Conclusions:* This "real world" study revealed that medical cannabis is being used to treat a wide range of behaviors. Our study also suggests that children consume CBD-rich products, and the effectiveness of CBD-dosing may be tied to the inclusion of THC in the compound. Future research should evaluate optimal dosing with a particular focus on the CBD-to-THC ratio.

* Correspondence to: Center for Autism Research, 2716 South Street, 5th Floor, Philadelphia, PA 19146, USA.
*E-mail address:* yerysb@chop.edu (B.E. Yerys).
[1] *Co-first authorship

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## 1. Introduction

Although autism spectrum disorder (hereafter 'autism') is specifically approved for medical cannabis consumption in 20 states, the District of Columbia, and the territory of Puerto Rico in the U.S., there is scant information about who consumes it, what product(s) are consumed, what behaviors are targeted, and its effectiveness. Developing this knowledge base is critical as the increased access to medical cannabis in the U.S. paired with reports of positive outcomes and limited side effects in other countries elevate the profile of medical cannabis as a treatment accessed by autistic people. Due to Federal restrictions surrounding marijuana in the United States, at present, it is extremely difficult to perform a gold standard randomized placebo-controlled trial examining the efficacy of medical marijuana as a treatment for autistic children.

To date, four published studies outside of the U.S. have either demonstrated safety and tolerability of medical cannabis or reported data on initial efficacy across a range of behaviors and functional impairments. Studies have focused on tetrahydrocannabinol (THC) and cannabidiol (CBD) because they are the most understood of the 100 + active endocannabinoids in medical cannabis; however, the endocannabinoid system has a demonstrated "entourage effect" in which a combination of cannabinoids (and active metabolites) contribute to an overall pharmacological effect. (Russo, 2019) Two studies demonstrated both safety and tolerability of compounds that had a 20:1 CBD-to-THC ratio in samples of moderate size (N = 60–188). (Aran et al., 2018; Barchel et al., 2019) With a variety of CBD-to-THC ratios, approximately 66 % of participants showed an improvement in behaviors related to ASD (communication) across all studies, along with improvements for most people in other related domains (e.g., disruptive behaviors, sleep, seizures) (Aran et al., 2018; Barchel et al., 2019; Bar-Lev et al., 2019; Kuester et al., 2017) Unfortunately, none of the above studies included a placebo arm, so it is not possible to comparatively evaluate the efficacy and tolerability of medical cannabis.

Conducting medical cannabis research in the U.S. presents a unique set of challenges. Medical cannabis regulation occurs at the state-level, which leads to variability in the process to obtain medical cannabis as well as oversight of product recommendation and distribution practices. These state-level differences result in inconsistency of the products available to and consumed by patients and generates a disconnect between the treating physician and the product recommended to the patient. Also, there remains variability in those products provided over the counter and outside of a state-licensed and regulated medical marijuana dispensary compared to those products regulated by a licensed medical marijuana dispensary. Differences in state-level regulation and variability in products from various sources present a barrier to patient care and management of medical cannabis treatments. These barriers limit the medical field's ability to ensure best practices and outcomes for an already vulnerable and medically complex patient population. Indeed, this problem led to the creation of a Standard THC Unit (5 milligrams of THC) by the National Institute of Health in May of 2021 (Volkow & Weiss, 2020), which was established after the present study completed data collection and was not available for distributors or vendors to use for product labeling. Further, no clear guidelines exist for follow-up care after starting medical cannabis treatment, and individuals can switch, remove, or add products without the recommendation or guidance from a medical professional. This differs greatly from other pharmacological treatments for autistic children. The lack of regulation in the U.S. may result in autistic individuals and their family members taking more ownership of finding an optimal dose on their own than what may occur with a traditional pharmacological intervention. However, the limited regulation also provides an opportunity to observe which autistic children consume medical cannabis and why (i.e., target behaviors), what CBD-to-THC ratios and doses are used, and how effective is medical cannabis at treating target behaviors.

It is critical to address these knowledge gaps to improve the scientific foundation of medical cannabis consumption as a potential intervention for autism. We conducted a natural history study of medical cannabis consumption in a large pediatric healthcare system in the U.S. We addressed three overarching questions from this natural history study:

1. *Who consumes medical cannabis?* This includes both child characteristics and behaviors targeted for treatment.
2. *What medical cannabis is consumed and how much?* This includes drug characteristics, such as number of products, CBD-to-THC ratio, and dose (total and weight-adjusted).
3. *How do caregivers rate the effectiveness of medical cannabis and do they report adverse events?* This is based on caregiver report for target behaviors. This includes evaluating effectiveness across CBD-to-THC ratio, dose (total and weight-adjusted), and interactions between CBD-to-THC ratio and weight-adjusted dose.

## 2. Method

### 2.1. Recruitment

This study received Institutional Review Board approval at our institution and was conducted in accordance with all applicable Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46, and the HIPAA Privacy Rule. Overall, we contacted over 10,000 individuals on our autism research mailing list, and 4330 individuals in our electronic medical records with an ASD diagnosis. Recruitment flyers were placed in medical cannabis dispensaries and on social media within autism support groups. Potential participants contacted the study team, were informed of the inclusion/exclusion criteria and then invited to participate. If they wished to participate, a member of the study team consented/assented the participant telephonically and then screened the participant to confirm inclusion criteria. Participants were eligible for enrollment if they were currently consuming approved medical cannabis product(s) issued from a state-sanctioned dispensary for ASD or its related behaviors (e.g., anxiety) as a qualifying condition, had a diagnosis of ASD from a qualified medical or mental health provider, had a Social Communication Questionnaire (Rutter et al., 2003) total raw score > 11, were under the age of 21 and were English-speaking. Exclusion criteria

included consumption of any cannabis products that were not obtained from a state-sanctioned dispensary. Participants were withdrawn from the study if they were no longer taking medical cannabis products, were no longer obtaining the products from a state-sanctioned dispensary or elected to no longer participate.

### 2.2. Caregiver questionnaires and ratings

After consent/assent were obtained, an initial intake telephone call was conducted with the caregivers of the participants to obtain information on demographics, medical history, details of medical cannabis products use and dosing regimen. A medical record review was done for enrolled participants who were also patients at our institution to confirm diagnosis and medication regimens. Parents were asked to rate the level of support needed for their child. The levels of support were based on the DSM-5 criteria and the study team provided the examples from the criteria so that parents could provide their best estimate. The specific ASD-related behaviors that the medical cannabis was used to alleviate were identified. The perceived effectiveness of medical cannabis, as reported by the caregivers, to treat the ASD and related behaviors was determined by asking the caregiver how effective on a scale from 1 to 10 (1 being least effective and 10 being most effective) the medical cannabis was in treating each target behavior. Targeted behaviors are listed in Table 1 and concomitant medications in Table 2.

The Social Communication Questionnaire - Lifetime (SCQ) (Rutter et al., 2003) was administered to all participants to confirm an ASD diagnosis. The SCQ is a 40-item yes/no questionnaire used to evaluate the presence of ASD behaviors. Based on recent work, a raw score $> 12$ confirmed the ASD diagnosis (Lee et al., 2010).

### 2.3. Calculation of clinician-rated "level of support" scores

To determine the level of support needed by children enrolled in the study and to create a single score of overall functioning, one of two qualified clinical professionals with extensive expertise in ASD diagnostics and treatment (BEY psychologist, ABP – developmental behavioral pediatrician) reviewed each participant's data. The clinicians reviewed each child's available data, and assigned a level of support rating for social reciprocity and communication support, restricted, repetitive, behaviors and interests support, and an overall level of support. The rating matched the DSM-5′s levels of support: needs support, needs substantial support, needs very substantial support. The clinicians cross-checked 100 % of all cases with independent reviews and found disagreements on less than 10 %; disagreements were resolved with consensus coding.

**Table 1**
Participant characteristics (N = 89).

| **Characteristics** | |
|---|---|
| Age, mean years (range) | 9.9 (3.5, 19.0) |
| Sex, N ( %) | |
| Male | 71 (79.8) |
| Female | 18 (20.2) |
| Weight, mean kg (SD) | 40.3 (19.6) |
| **Overall Levels of Support (Clinician Rated) N ( %)** | |
| Needs Support | 31 (34.8) |
| Needs Substantial Support | 25 (28.1) |
| Needs Very Substantial Support | 33 (37.1) |
| **Overall Levels of Support, (Caregiver Rated) N ( %)** | |
| Needs Support | 7 (7.9) |
| Needs Substantial Support | 19 (21.3) |
| Needs Very Substantial Support | 32 (36.0) |
| Missing | 31 (34.8) |
| **Social Communication Support, (Caregiver Rated) N ( %)** | |
| Requires support | 8 (9.0) |
| Requires substantial support | 18 (20.2) |
| Requires very substantial support | 31 (34.8) |
| Missing | 32 (36.0) |
| **Repetitive Behavior Support, (Caregiver Rated) N ( %)** | |
| Requires support | 11 (12.4) |
| Requires substantial support | 27 (30.3) |
| Requires very substantial support | 20 (22.5) |
| Missing | 31 (34.8) |
| **Targeted behaviors, N ( %)** | |
| Autistic behaviors | 84 (94.4) |
| Nausea/vomiting | 16 (18.0) |
| Increase appetite | 5 (5.6) |
| Pain relief | 24 (27.0) |
| Inattention, Hyperactivity/Impulsivity | 64 (71.9) |
| Irritability/Emotional dysregulation | 72 (80.9) |
| Sleep problems | 48 (53.9) |
| Anxiety/worry | 66 (74.2) |

**Table 2**
Number of medical cannabis products consumed.

| Number of Cannabis Products Used | N ( %) |
|---|---|
| 1 | 50 (56.2) |
| 2 | 26 (29.2) |
| 3 | 7 (7.9) |
| 4 | 5 (5.6) |
| Not Reported | 1 (1.1) |

### *2.4. Determination of cannabinoid dose*

Information regarding the medical cannabis product(s) consumed included: 1) cannabinoid content based on product label, 2) ratio of CBD to THC, 3) formulation, and 4) the dispensary from which the product was obtained. When possible, photographs of medical cannabis packaging and labels were obtained, and cannabinoid content of the specific products were confirmed. Product content was determined based on the information provided on the label, confirmation with the dispensary and parental/guardian report. Products included: 1) tinctures/oils with reported concentrations (mg/ml); 2) tincture/oils that reported percentages but not concentration on the label (the product content was converted to mg/ml); and 3) pills/capsules. If a participant was taking multiple medical marijuana medications, each compound was converted to mg/ml and all of the THC doses added together, and likewise all CBD doses added together to get total mg for THC and CBD, respectively, and ultimately into mg/kg/day. All doses were calculated as mg and mg/kg consumed per day for both CBD and THC.

### *2.5. Statistical analysis plan*

To answer the question of who takes medical cannabis and why, demographics (age, weight, gender) and clinical characteristics (patient functioning, support needs by parent and clinician rating, target behaviors) of the cohort were summarized with frequency tables and summary statistics (mean, standard deviation, range).

To answer the question of what medical cannabis is consumed and how much, the number of cannabis products consumed were summarized in a frequency table, and individuals were assigned to one of five treatment groups based on the ratio of the weight-adjusted daily dose of CBD to that of THC (CBD-to-THC): Group 1) THC Only; Group 2) THC Dominant (Ratio: 0 – 0.5); 3) Mixed (Ratio: 0.5 – 1.25); Group 4) CBD Dominant (Ratio: 1.25 – 800); and Group 5) CBD Only. This grouping was determined through clinical understanding of product use and natural break points in the ratio distribution. Frequency differences were evaluated with a chi-square goodness-of-fit test for one-sample with Cohen's w as a measure of effect size. Differences in the combined total weight-adjusted daily dose across the CBD-to-THC ratio grouping was first assessed overall via the Kruskal-Wallis test, and the Wilcoxon signed rank test was used for post-hoc analyses. Significance was determined by the effect sizes, eta$^2$ and r,(Tomczak & Tomczak, 2014) respectively, and an alpha of 0.05.

To answer the question of how effective is medical cannabis, the overall treatment perceived effectiveness across all outcomes (ASD behaviors, ADHD behaviors, anxiety, irritability, sleep) were examined across CBD-to-THC ratio groupings with a Kruskal-Wallis test and Wilcoxon signed rank tests for the pairwise difference. We probed for perceived treatment effectiveness differences by CBD-to-THC grouping within each outcome using Kruskal-Wallis tests and Wilcoxon signed rank test. Pain, nausea and appetite were excluded due to their low base rates as target behaviors. Effect sizes were reported as eta$^2$, and all tests used an alpha of 0.05. We also probed for weight-adjusted dose by CBD-to-THC grouping interactions to see if there was a combination of a specific CBD-to-THC compound and a specific weight-adjusted dose range of CBD-to-THC, CBD-only or THC-only associated that was particularly effective for treating a target behavior. Linear regression was used for all target behaviors. Significance of the interaction terms was assessed by the effect sizes and the coefficients' p-values with an alpha of 0.05. For significant interactions, follow-up regressions within each CBD-to-THC ratio grouping was used to evaluate how changes in the weight-adjusted daily dose associated with the perceived effectiveness of the treatment on the target behavior. To address adverse events, we summarized caregiver-reported adverse events with descriptive statistics.

We withheld corrections for multiple comparisons across all analyses, because this natural history study's goal is to be hypothesis-generating and we prefer to explore leads that may be proven wrong in future studies rather than to miss possibly important findings (Michels & Rosner, 1996; Rothman, 1990).

## 3. Results

In total, 124 participants enrolled in the study from 386 screened (32 %), and 89 included in the final analysis. Caregivers of potential participants contacted the study from information that they received in a mailing from CHOP, a post within autism parental support groups or a flyer at a dispensary. Participants were excluded (n = 35) due to either incomplete information or the doses reported were not measurable. These included doses that were reported to be a qualitative measure, such as the size of a grain of rice, or those that were of an inconsistent size, such as several drops of an oil or puffs of a vaporized oil.

### 3.1. Who consumes medical cannabis and why?

Table 1 shows that the mean age, gender-ratio and weight of autistic individuals who were consuming medical cannabis. The mean age and range of ages is consistent with an institution that serves pediatric populations, and the gender composition of approximately 1 female to 4 males is similar to the rates seen in the autism population (Christensen, 2018). Further, nearly 4 out of 5 caregivers indicated that they chose medical cannabis because it was a natural remedy; this is not a surprising caregiver belief given the significant side effects of FDA-approved pharmacological treatments for autistic people (Wink et al., 2010). The most common treatment targets were ASD behaviors, with a particular emphasis on restricted and repetitive behaviors, interests, and sensory sensitivities, irritability and emotional dysregulation, anxiety or worry, and ADHD behaviors (hyperactivity and impulsivity). Per clinician ratings of overall support needs, the sample was roughly evenly split across the three support groupings; however, few caregivers identified their children in the 'needs support' grouping. This lower number of children rated as requiring the least supports may be due to missing data from caregivers.

### 3.2. What medical cannabis is consumed and how much?

As shown in Table 2**,** most children (85 %) were consuming either one or two distinct medical cannabis products to treat targeted behaviors. As shown in Table 3, most autistic children were consuming either a CBD-dominant medication or a CBD-only medication and there was a medium-to-large effect size on this choice, chi-square= 21.06, $p < 0.001$, w= 0.49.

Total weight-adjusted daily dose (THC and CBD combined) differs across ratio grouping with a large effect size (Kruskal-Wallis p-value=0.003, $eta^2$ =0.146). In pairwise comparisons, the CBD Dominant grouping had a larger weight-adjusted daily dose than both the THC Dominant group (W=86, p-value=0.021, r = 0.33) and the Mixed group (W=63, p-value=0.001, r = 0.35); these effect sizes were medium-to-large in each comparison. All other comparisons showed small effect sizes between groups that were not significant. See Table 3 for mean weight-adjusted dose overall and for CBD and THC individually.

### 3.3. How effective is medical cannabis and are there adverse events?

As shown in Table 4, mean caregiver ratings were all above 5 on the 1–10 scale for effectiveness, indicating that caregivers reported medical cannabis as moderately effective in treating target behaviors. However, no specific CBD-to-THC ratio was rated as more effective over another—effect sizes were small and not statistically significant within each target symptom (two right columns of Table 4). Linear regressions showed that effectiveness between the CBD-to-THC ratio groupings were not moderated by CBD-to-THC weight-adjusted daily dose for any target behaviors (all partial $eta^2$ <0.10, p-value >0.05).

As a follow-up, we explored whether a higher CBD dose by itself or THC dose by itself changed the effectiveness of medical cannabis. Increases in CBD but not THC dosages improved effectiveness for ASD behaviors ($\beta = 0.39$, partial $eta^2$ =0.09, $p = 0.02$) and irritability ($\beta = 0.38$, partial $eta^2$ =0.07, $p = 0.04$) when there was a small amount of THC (CBD-dominant) compared to no THC (CBD-only). This means that higher doses of CBD were associated with better effectiveness ratings when the compound included some THC, but this relationship was not present true for children taking CBD-only compounds. Follow-up regressions within each treatment group showed a large effect of CBD weight-adjusted daily dose on effectiveness ratings in the CBD-dominant group (ASD behaviors: $\beta = 0.51$, $eta^2$ =0.26, $p = 0.006$; Irritability: ($\beta = 0.53$, $eta^2 = 0.28$, $p = 0.008$). A small effect size was observed within the CBD-only group (ASD behaviors: $\beta = -0.02$, $eta^2$ =0.00, $p = 0.92$; Irritability: $\beta = 0.02$, $eta^2 = 0.00$, $p = 0.93$). All other analyses revealed small-to-medium effects (all partial $eta^2$ <0.09, p-value >0.07).

Adverse events were observed in 34 participants (38 %). A 'mental status change' was the most common adverse event (n = 21), these included: appearing 'high' (n = 12), drowsy (n = 4), increase in OCD symptoms (n = 2) or a change in aggression (n = 6). The second most common adverse event experienced was 'GI changes' (n = 11), these include: changes in appetite (n = 7), stomach issues (n = 3), and constipation (n = 1). Four children experienced both mental status and GI changes. Other rare adverse events included: headaches (n = 2) and sexual arousal (n = 1). It is unclear whether these adverse events are due to drug-to-drug interactions resulting from a combination of medical cannabis, prescriptions medications, and over-the-counter medications or from the medical cannabis independently.

**Table 3**
The number of participants in each CBD-to-THC grouping, total weight-adjusted daily dose, and dose of CBD and THC milligrams per kilogram per day.

| | N | Dose (mg/kg/day) **Mean (SD)** | CBD (mg/kg/day) Mean (SD) | THC (mg/kg/day) Mean (SD) |
|---|---|---|---|---|
| 1. THC Only | 7 | 0.71 (0.46) | 0.00 (0.00) | 0.71 (0.46) |
| 2. THC Dominant (0 – 0.5) | 14 | 0.46 (0.47) | 0.07 (0.09) | 0.39 (0.44) |
| 3. Mixed (0.5–1.25) | 12 | 0.36 (0.28) | 0.15 (0.11) | 0.22 (0.18) |
| 4. CBD Dominant (1.25–800) | 29 | 3.72 (5.62) | 3.01 (4.35) | 0.71 (1.64) |
| 5. CBD Only | 27 | 2.06 (4.96) | 2.06 (4.96) | 0.00 (0.00) |
| Total | **89** | **2.01 (4.38)** | **1.64 (3.85)** | **0.38 (1.00)** |

**Table 4**
Caregiver-reported effectiveness by target behavior.

| Target Symptom | Sample Size | Overall Effectiveness Mean (SD) | Effect size for CBD:THC | p-value for CBD:THC |
|---|---|---|---|---|
| Autism Behaviors | 82 | 6.59 (2.59) | 0.028 | 0.78 |
| ADHD Behaviors | 60 | 6.25 (2.47) | 0.031 | 0.68 |
| Anxiety Behaviors | 65 | 5.20 (2.82) | 0.015 | 0.54 |
| Irritability Behaviors | 69 | 6.58 (2.64) | 0.037 | 0.80 |
| Sleep | 46 | 6.74 (3.17) | 0.025 | 0.29 |

Effect size for all target behaviors are reported as eta2 for comparing across the CBD:THC ratio groupings where values of 0.01, 0.05, and 0.14 are considered small, medium, and large. (Cohen, 1992).
ADHD = Attention Deficit/Hyperactivity Disorder

### *3.4. What concomitant medications were being taken?*

As expected, ASD participants were taking a variety of medications concomitantly with medical cannabis (Table 5). Eighteen children were concomitantly taking anti-adrenergic agents, the most common of which were clonidine (n = 9) and guanfacine (n = 8). Of these 18 children, 7 experienced side effects when starting medical cannabis, most commonly GI changes (n = 2), mental status changes (n = 4) or a combination of mental status and GI changes (n = 3). Eleven children in this group were not reported to experience side effects. Thirteen children were taking various anti-psychotics concomitantly with medical cannabis, the two most common being Aripiprazole (n = 5) and Risperidone (n = 6). Eight caregivers reported no side effects. The only side effects reported when starting medical cannabis within this group were mental status changes (n = 4), GI changes (n = 1) and a decrease in appetite (n = 1). Seven children in this group were not reported to experience side effects. Ten children were taking anti-convulsants concomitantly with medical cannabis, the most common being oxcarbazepine (n = 3) and lorazepam (n = 3). In this group, caregivers reported that two children have decreased appetites and one had a change in mental status. Seven children in this group were not reported to experience side effects. Ten participants were not prescribed any medications.

## 4. Discussion

In this natural history study, we examined medical cannabis consumption in autistic children recruited through a large pediatric care system in the U.S. Our results replicate and extend prior findings by showing that autistic children consuming medical cannabis in the U.S. reflect the broader autism population in terms of gender-ratio and those who require Very Substantial Support (Christensen, 2018). Prior studies reported similar gender-ratios; (Aran et al., 2018; Barchel et al., 2019; Bar-Lev Schleider et al., 2019) however the only study to report on cognitive functioning had an overrepresentation of children with intellectual disability/require Very Substantial Support (Aran et al., 2018). Thus, our sample may provide a better reflection of the broader autism population. Finally, consistent with all prior studies the top two treatment targets are ASD behaviors and irritability/aggression.(Aran et al., 2018; Barchel et al., 2019; Bar-Lev Schleider et al., 2019; Kuester et al., 2017).

Regarding medical cannabis consumption, prior studies were clinical trials that controlled compound and dosing of medical cannabis consumption in countries other than the United States (Aran et al., 2018; Barchel et al., 2019; Bar-Lev Schleider et al., 2019; Kuester et al., 2017), whereas our natural history study was positioned to observe how medical cannabis is being used in a country that has no consensus for dosing or compound mixtures to treat autistic youth. The present study offered a unique opportunity to observe what compounds, doses, and administration methods families naturally gravitated toward. As such, families gravitated toward lower doses than what are used in controlled clinical trials or recommended by providers in countries where systematic dosing studies are

**Table 5**
Frequency of children taking various concomitant medications and supplements.

| Drug Type | n |
|---|---|
| Supplements | 45 |
| Anti-convulsant | 10 |
| Anti-histamine | 19 |
| Anti-adrenergic agent | 18 |
| Anti-psychotic | 13 |
| Anti-depressant | 17 |
| Bronchodilator | 2 |
| Proton pump inhibitor | 7 |
| Antibiotic | 5 |
| NSAID | 3 |
| Mucolytics | 2 |
| CNS stimulant | 4 |
| GI support | 3 |
| Anxiolytic | 4 |

carried out (Aran et al., 2018; Barchel et al., 2019; Bar-Lev Schleider et al., 2019; Kuester et al., 2017). Furthermore, we observed that a substantial portion of the sample consumed multiple medical cannabis products (43.8 %), and that they skewed toward CBD-rich products. It is possible that this skew towards CBD-rich products was an attempt to mitigate potential euphoric effects related to THC, or because of perceived effectiveness. One hypothesis to explore in a future study is whether CBD-rich products, particularly those products that still contain some amount of THC, provide optimal efficacy over CBD-only products.

Regarding effectiveness, our natural history study was the first to collect data from caregivers administering a variety of medical cannabis products. Across all CBD-to-THC ratio groups and target behaviors, caregivers endorsed moderate scores of effectiveness (mean scores in the 5–6 range on a 0–10 scale). There were no meaningful differences across effectiveness by ratio grouping or interactions with weight-adjusted daily dose for the CBD-to-THC ratio. However, further exploration of the effectiveness of CBD and THC separately revealed that the effectiveness ratings for ASD behaviors and irritability between the CBD-dominant and CBD-only groups were moderated by the CBD weight-adjusted dose. Specifically, the larger doses of CBD weight-adjusted dose had a large effect on effectiveness ratings for the CBD dominant group but a small effect on the ratings for the CBD-only group. While these findings are preliminary, they suggest that the effectiveness of medical cannabis could be optimized through dose ranging studies in CBD-Dominant products in comparison to a placebo control. Finally, the adverse event rate (38 %) was similar to what has been observed in prior studies (Aran et al., 2018; Barchel et al., 2019; Bar-Lev Schleider et al., 2019; Kuester et al., 2017). The effectiveness findings reported here should be interpreted cautiously as this natural history study has no 'placebo' control and caregivers were unblinded to their child's treatment, thus the effectiveness score is likely weighted positive to some degree by expectancy effects.

The present study is limited by factors that are inherent to a natural history study for a treatment that cannot be handled directly by the investigative team. Specifically, our use of a clinician-rated "level of support" measure cannot be validated against gold standard diagnostic measures, but this validation study can happen in future work. Also, the sample may have been biased by the current out-of-pocket costs and resources needed to obtain medical cannabis legally, the potential stigma associated with medical cannabis treatment, families continuing treatment may have a biased view toward the efficacy of medical cannabis, and families who discontinued treatment due to a lack of perceived efficacy would not qualify for the present study. We did not collect additional information on family demographics (race/ethnicity family income, neighborhood median income, caregiver education). This was a missed opportunity to better characterize which families are opting for medical cannabis treatment. We excluded children if they were initially enrolled but discontinued treatment during the study period. These sample biases likely enhance the potential effectiveness ratings, as does the use of unblinded caregivers' ratings as the primary outcome measure. Product labeling is not always consistent with the actual product (Oldfield et al., 2020). The variability in labeling and actual product can be addressed in future studies using standardized THC units and standardized testing with specific products that will be given to participants. While concomitant medications were tracked, the present study was not positioned to determine specific drug-drug interactions. Future studies can address these concerns of sampling bias through a controlled clinical trial with direct observation as primary outcome and include detailed information regarding non-responders, adverse effects, concomitant medications and multiple weight-adjusted daily dose levels to identify optimal response. Treatments other than concomitant medications should be tracked and evaluated for possible medical cannabis-behavior treatment interactions that may influence primary and secondary outcomes in future clinical trials.

## 5. Conclusion

Caregivers of autistic children in the U.S. are turning to medical cannabis as a treatment for their children. However, there is heterogeneity in the number and type of products administered by caregivers. Overall medical cannabis had a moderate effect on target behaviors. There is a potential new lead that the perceived effectiveness of CBD may increase with a higher dose, but only in cases where the compound includes THC. This lead should be evaluated in a future randomized double-blin d controlled trial where dosing of CBD-to-THC and adverse events can be rigorously evaluated.

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## CRediT authorship contribution statement

**Mary Ann DeLiberto:** Data curation, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing, preparation, **Athena F. Zuppa:** Conceptualization, Funding acquisition, Methodology, Supervision, Resources, Writing – original draft, Writing – review & editing. **Amanda Cornetta:** Data curation, Writing – review & editing. **Walter Faig:** Formal analysis, Writing – original draft, Writing – review & editing. **Tryce Scully:** Formal analysis, Writing – original draft, Writing – review & editing. **Amanda Bennett:** Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **Meghan Thomas:** Writing – review & editing. **Elizabeth Ward:** Data curation, Writing – review & editing. **Stephen Barr:** Data curation, Writing – review & edit. **Benjamin E. Yerys:** Conceptualization, Formal analysis, Methodology, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing.

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Meghan Thomas of Zelira Therapeutics Limited, Australia contributed to data interpretation and contributed as a co-author on this manuscript.

*Clinical trial registration (if any)*

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