

Non-Seizure Impact of Cannabidiol Treatment in Patients With Seizures Associated With Tuberous Sclerosis Complex: Analysis from a Global, Longitudinal, Observational, Mixed Methods Study

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Introduction

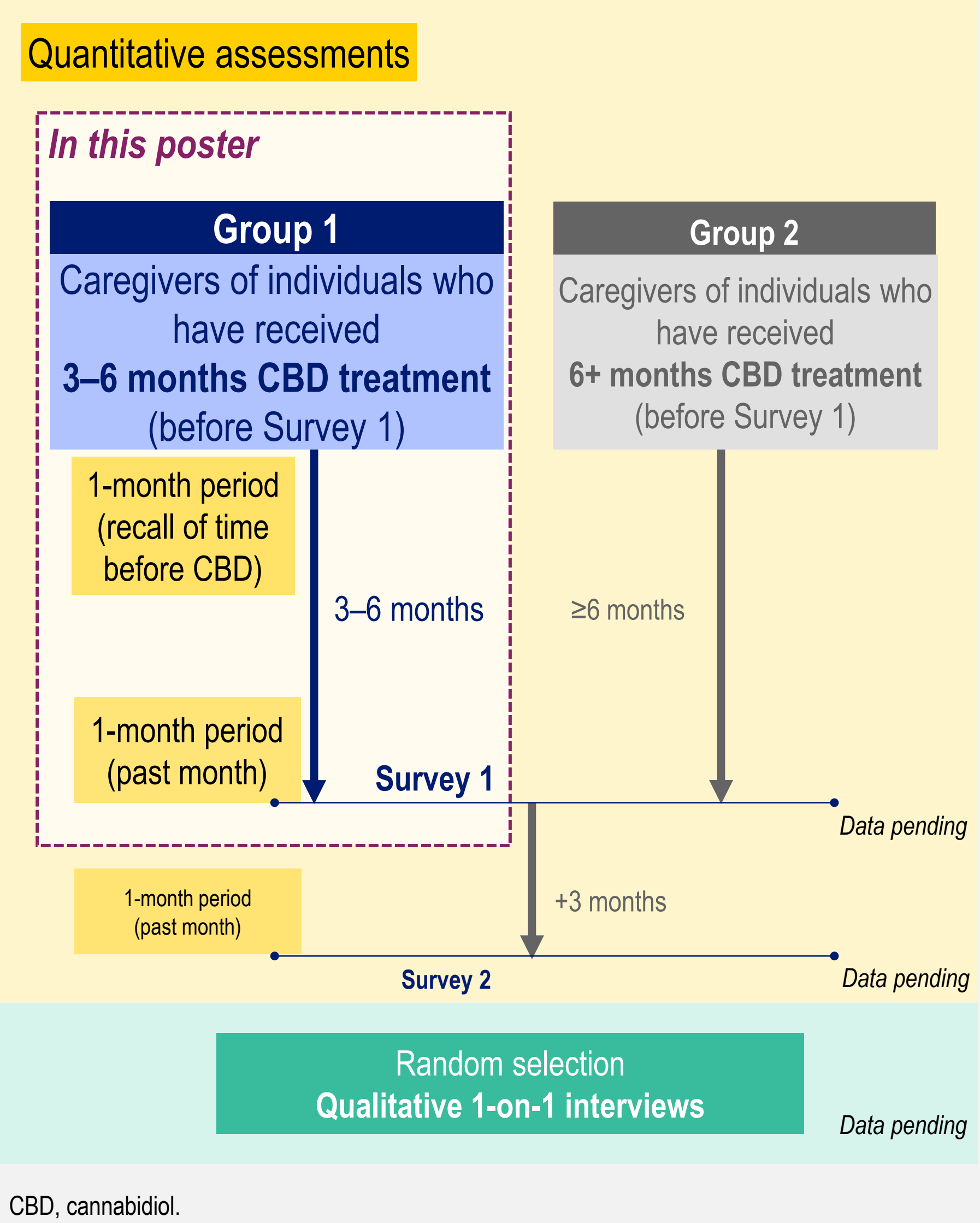
- Tuberous sclerosis complex (TSC) is a rare genetic disorder; epilepsy impacts 80–90% of patients with TSC, which often manifests in the first year of life¹
- Highly purified cannabidiol (CBD; Epidyolex® [EU]/Epidiolex® [US], 100 mg/mL oral solution) is approved as an adjunctive treatment for patients with seizures associated with TSC^{2–4}
- TSC is also linked to a range of neurodevelopmental and neuropsychiatric conditions, such as learning difficulties, anxiety, and depression, termed TSC-associated neuropsychiatric disorders (TAND)^{5–7}
- TAND can have a profound impact on the quality of life (QoL) of both patients and their caregivers; it is important to assess non-seizure outcomes to fully understand treatment effects^{5–7}
- This international, longitudinal, observational, mixed methods study aimed to assess the non-seizure impact of CBD, as reported by caregivers, in patients with TSC-associated seizures

Objectives

- To describe non-seizure related outcomes, such as cognitive function, behaviour, and communication, among patients with TSC receiving CBD, as reported by their caregivers
- To explore short-term non-seizure effects of CBD, defined as occurring between 3 to 6 months from start of treatment

Methods

Figure 1. Overall study design



Study participants

- Caregivers (informal, unpaid), ≥18 years old, self-reported as the main or one of the main caregivers of a patient ≥2 years old with TSC receiving CBD for ≥12 weeks prior to Survey 1, in France, Germany, Israel, Italy, Spain, the UK, or the US
 - Participants had to provide written informed consent, and understand, read, and speak the local language to complete the questionnaires and interview discussion
 - Data reported here are from **Survey 1 of Group 1** (caregivers of individuals who were already receiving CBD for 3–6 months prior to completing Survey 1) (**Figure 1**)

Survey 1

- A ~45-minute, quantitative survey was completed upon study entry
- Questions related to demographics, symptoms, and health-related QoL impact of TSC experienced by the person being cared for
 - Questions about TSC impacts were repeated to cover the month prior to initiating CBD treatment, and the past month
 - Level of functioning aspects were measured on 2- to 5-point categorical scales with response choices varying by question
 - Behavioural issues, academic skills, and neuropsychologic problems were rated on a Numeric Rating Scale from 0 (not at all) to 10 (very much)
 - Intellectual ability (IA)** was assessed based on caregiver responses to the question “*how would you describe their IA?*” (normal IA: “above-average” or “normal” IA; impaired IA: “mild-moderate” or “severe-profound” intellectual disability)

Results

- Of 88 caregivers recruited to the study overall, **32 were in Group 1** (caring for someone who had received 3–6 months CBD treatment)
 - The mean age of the patients cared for (n=32) was 20.7 years, 50% were male, and 56% had impaired IA
 - Among caregivers, 69% were female and 44% were full-time homemakers
- Detailed characteristics of patients and caregivers can be viewed in the **Supplementary Material** via the QR code (**Tables S1** and **S2**)

Impacts on levels of functioning, normal activities, skills, and behavioural issues

Figure 2. Summarised changes in reports from caregivers of patients receiving CBD for 3–6 months, as assessed for the past month (on treatment) and compared with their recall of the month before treatment began

Categorical domains: Change in number of caregivers pre- and post-CBD			
Level of mobility		Level of ability to talk	
Able to walk independently (without assistance or walking aids) (no change)		Use of complete sentences (increase)	
Able to walk only with assistance or the use of walking aids (no change)		Use of only 2- or 3-word phrases (decrease)	
Not able to walk but able to stand (no change)		Use of only single words and no phrases (no change)	
Not able to walk or stand (no change)		Unable to use recognisable words but may make some sounds (no change)	
Level of motor skills		Statements best describing speech	
Able to use their hands without difficulty (increase)		Has age-appropriate speech (increase)	
Able to use their hands but has difficulty with tasks such as using a fork, spoon, or pencil (no change)		Does not have age-appropriate speech (decrease)	
Unable to use their hands for tasks such as using a fork, spoon, or pencil (decrease)			
Level of ability for independent care		Prevented from taking part in normal activities ^a	
Able to dress and undress without assistance (no change)		Always (no change)	
Able to dress and undress with some assistance (no change)		Often (decrease)	
Able to dress and undress with a lot of assistance (increase)		Sometimes/rarely (decrease)	
Unable to dress or undress themselves with or without assistance (decrease)		Never (increase)	
Numerical domains: How much were the following a problem for the person you care for pre- and post-CBD?			
Items scored by caregivers from 0 (not at all) to 10 (very much)			
Neuropsychologic skills		Academic skills ^b	
Balance, coordination or gait		Reading	
Understanding spoken language		Writing	
Attention		Spelling	
Dual-tasking/multi-tasking ^b		Mathematics	
Memory ^b			
Visuospatial tasks			
Executive skills ^b			
Being disorientated			
Processing speed/slower thinking ^b			
		Behavioural issues and psychosocial functioning	
		Anxiety	Very rigid or inflexible behaviour
		Depressed mood	Sensory sensitivities
		Extreme shyness	Over-/hyper-activity
		Mood swings	Paying attention or concentrating
		Aggressive outbursts	Restlessness or fidgetiness
		Temper tantrums	Impulsivity
		Self-injury	Eating and/or drinking
		Repeating words or phrases	Sleep
		Poor eye contact	Relationship difficulties
		Getting on with people of a similar age	
		Repetitive behaviours	

Green = this may be an increase or decrease in the number of caregivers reporting a change, green signifies the change is considered positive beneficial for the patient. Only values where the change (categorical domains) or both the mean and SD (numerical domains) were wholly above/below neutral have been marked in green; Black = neutral, that is score or number of reports unchanged i.e. 0; Red = change is not considered beneficial for the patient

Changes are all between answers given with respect to the past month compared with respect to the month before treatment began. Changes for categoric domains are in the number of caregivers endorsing an item. Changes for numeric domains are in mean score, including SD. Details of changes can be viewed in the **Supplementary Material** via the QR code.

^aIncludes going to school or work, playing, seeing friends and relatives, and doing chores; ^bReported for caregivers of individuals aged ≥5 years at the time of taking Survey 1 (Overall, N=29; Normal IA, N=14; Impaired IA, N=15). Caregivers of those aged <5 years were not shown this question. CBD, cannabidiol; IA, intellectual ability; SD, standard deviation.

- Caregivers' responses indicated that some individuals with TSC had better functioning for the month prior to Survey 1 (following 3–6 months of CBD treatment) compared with the month before they had started taking CBD (**Figure 2**; details in **Table S3** via the QR code)
 - Improvements were all reported for patients with impaired IA (most of those with normal IA did not have functional difficulties prior to treatment), and included +2 reports of being able to dress and undress with a lot of assistance (previously unable to do so), +2 reports of using complete sentences, and +3 reports of never being prevented from taking part in normal activities
- Among numeric domains, neuropsychologic and academic skills remained largely unchanged in this 3–6-month timeframe (**Figure 2**, details in **Figure S1** and **Table S4** via the QR code), although there was a potential signal of improvement in attention (**Figure S1**)
- For behavioural issues, improvements were noted in **anxiety** and **sleep**, in both the normal IA and impaired IA groups (**Figure S2** via the QR code)

Conclusions

- These initial findings, reported by caregivers looking after individuals who were already receiving CBD for 3 to 6 months, are encouraging
 - Non-seizure outcomes did not worsen with CBD, and there is an indication that treatment with CBD may positively impact some of them, including level of functioning in patients with impaired intellectual ability, as well as anxiety and sleep in patients irrespective of intellectual ability
- These preliminary results are based on a small sample size and should be interpreted with caution
 - The findings accord with early reports from another ongoing study of caregivers of patients with TSC, suggesting non-seizure benefits of CBD⁸
- Analyses of longer-term quantitative data (Group 1, Survey 2; Group 2, Surveys 1 and 2) and qualitative assessments are ongoing

References: 1. Specchio N, et al. *Eur J Paediatr Neurol*. 2023;47:25–34. 2. European Medicines Agency, Epidyolex® 100 mg/ml oral solution: summary of product characteristics. 2024. Available from: https://www.ema.europa.eu/en/documents/product-information/epidyolex-epar-product-information_en.pdf (Accessed 21 May 2025). 3. Electronic Medicines Compendium (eMC). Epidyolex® 100 mg/ml oral solution: summary of product characteristics. 2025. Available from: <https://www.medicines.org.uk/emc/product/10781/smpc/print> (Accessed 21 May 2025). 4. US Food and Drug Administration. Epidiolex® Prescribing Information. 2024. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/210365s021bl.pdf (Accessed 21 May 2025). 5. Zöllner JP, et al. *Orphanet J Rare Dis*. 2020;15:23. 6. de Vries P, et al. *Am J Med Genet C Semin Med Genet*. 2018;178(3):309–320; 7. Tye C, et al. *Dev Med Child Neurol*. 2020;62(3):322–329; 8. Wheless JM, et al. Poster presented at the American Epilepsy Society Congress 2024 (Poster P1.433). **Acknowledgements:** The authors would like to thank all of the study investigators, study staff, patients, and caregivers for their participation in this research. Writing and editorial assistance were provided to the authors by Vijay Kadasi, M.Sc. ISMPP-CMPP, and Chiara Lee, PhD, of Syneos Health, UK, and funded by Jazz Pharmaceuticals, Inc., in accordance with Good Publication Practice (GPP) 2022 guidelines. **Support:** This study was sponsored by Jazz Pharmaceuticals, Inc. **Disclosures:** All authors met the ICMJE authorship criteria and had full access to relevant data. Neither honoraria nor payments were made for authorship. **SA** and **MT** have consulted for, conducted studies funded by, or received honoraria for services provided to Jazz Pharmaceuticals, Inc.; **MH**, **SB**, **JS**, **FA**, and **KV** are employees of Jazz Pharmaceuticals, UK Ltd., with stock and/or hold options in the company; **NB**, **CC**, and **LK** are employees of PPD Evidera Patient Centered Research, Thermo Fisher Scientific. Epidyolex® is approved in the EU and UK for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome, in conjunction with clobazam, in patients ≥2 years of age; it is additionally approved in the EU and UK for the adjunctive treatment of seizures associated with tuberous sclerosis complex in patients ≥2 years of age.



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Supplementary Material

Table S1. Demographics and characteristics of patients

	Total Group 1 (N=32)	Adult (N=14)	Paediatric (N=18)	Normal IA (N=14)	Impaired IA (N=18)
Age of Individual with TSC at baseline, mean (SD)	20.7 (14.40)	32.2 (14.47)	11.7 (4.87)	30.4 (16.12)	13.2 (6.53)
Sex of Individual with TSC, n (%) ^a					
Male	16 (50.0%)	9 (64.3%)	7 (38.9%)	9 (64.3%)	7 (38.9%)
Female	15 (46.9%)	4 (28.6%)	11 (61.1%)	4 (28.6%)	11 (61.1%)
Age when first had signs/symptoms of TSC, Mean (SD) ^b	1.4 (2.04)	1.7 (1.88)	1.3 (2.13)	2.2 (2.09)	1.0 (1.97)
Age when first diagnosed with TSC, mean (SD) ^b	2.1 (2.30)	2.7 (2.53)	1.9 (2.26)	3.4 (2.17)	1.5 (2.17)
Age when first experienced epileptic seizures, mean (SD) ^c	2.8 (4.66)	4.3 (7.82)	2.1 (2.31)	7.5 (8.50)	1.5 (2.07)
Co-occurring neuropsychiatric diagnoses, n (%)					
ASD, including autism and Asperger's	11 (34.4%)	2 (14.3%)	9 (50.0%)	0 (0.0%)	11 (61.1%)
ADHD	8 (25.0%)	3 (21.4%)	5 (27.8%)	3 (21.4%)	5 (27.8%)
Anxiety disorder ^d	10 (31.3%)	7 (50.0%)	3 (16.7%)	7 (50.0%)	3 (16.7%)
Depressive Disorder	5 (15.6%)	5 (35.7%)	0 (0.0%)	3 (21.4%)	2 (11.1%)
OCD	5 (15.6%)	2 (14.3%)	3 (16.7%)	3 (21.4%)	2 (11.1%)
Psychotic disorder, including schizophrenia	1 (3.1%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
Other psychiatric disorder(s)	2 (6.3%)	1 (7.1%)	1 (5.6%)	0 (0.0%)	2 (11.1%)
Do not have any of the diagnoses	4 (12.5%)	1 (7.1%)	3 (16.7%)	1 (7.1%)	3 (16.7%)
Perceived intellectual ability, n (%)					
Above-average intellectual ability	2 (6.3%)	2 (14.3%)	0 (0.0%)	2 (14.3%)	0 (0.0%)
Normal intellectual ability	12 (37.5%)	7 (50.0%)	5 (27.8%)	12 (85.7%)	0 (0.0%)
Mild-moderate intellectual disability	13 (40.6%)	4 (28.6%)	9 (50.0%)	0 (0.0%)	13 (72.2%)
Severe-profound intellectual disability	5 (15.6%)	1 (7.1%)	4 (22.2%)	0 (0.0%)	5 (27.8%)

^aPreferred not to answer: caregiver of 1 adult with normal IA; ^bNine caregivers (caring for 8 adults, 1 paediatric patient; 7 with normal IA, 2 with impaired IA) answered "don't know/can't remember"; ^c13 caregivers (caring for 13 adults, 8 paediatric patients; 10 with normal IA, 3 with impaired IA) answered "don't know/can't remember"; ^dIncludes panic, phobia, and separation anxiety disorder; 1 caregiver (of an adult with impaired IA) answered "I don't know".
ADHD, attention deficit hyperactivity disorder; ADS, autism spectrum disorder; IA, intellectual ability; OCD, obsessive compulsive disorder; SD, standard deviation; TSC, tuberous sclerosis complex.

Table S2. Demographics and characteristics of caregivers

	Total Group 1 (N=32)	Adult (n=14)	Paediatric (n=18)	Normal IA ^a (n=14)	Impaired IA (n=18) ^a
Sex of caregiver, n (%)					
Male	7 (21.9%)	3 (21.4%)	4 (22.2%)	1 (7.1%)	6 (33.3%)
Female	22 (68.8%)	10 (71.4%)	12 (66.7%)	10 (71.4%)	12 (66.7%)
Prefer not to answer	3 (9.4%)	1 (7.1%)	2 (11.1%)	3 (21.4%)	0 (0.0%)
Employment status ^b , n (%)					
Self-employed full-time	8 (25.0%)	5 (35.7%)	3 (16.7%)	2 (14.3%)	6 (33.3%)
Self-employed part-time	4 (12.5%)	1 (7.1%)	3 (16.7%)	0 (0.0%)	4 (22.2%)
Full-time homemaker/caregiver	14 (43.8%)	6 (42.9%)	8 (44.4%)	8 (57.1%)	6 (33.3%)
Retired	2 (6.3%)	1 (7.1%)	1 (5.6%)	1 (7.1%)	1 (5.6%)
Other	1 (3.1%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	1 (5.6%)
Prefer not to answer	3 (9.4%)	1 (7.1%)	2 (11.1%)	3 (21.4%)	0 (0.0%)
Caregiver household composition ^c , n (%)					
Lives with partner/spouse	27 (84.4%)	13 (92.9%)	14 (77.8%)	11 (78.6%)	16 (88.9%)
Lives with children	26 (81.3%)	11 (78.6%)	15 (83.3%)	10 (71.4%)	16 (88.9%)
Lives with other relatives	1 (3.1%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	1 (5.6%)
Other	1 (3.1%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
Preferred not to answer	3 (9.4%)	1 (7.1%)	2 (11.1%)	3 (21.4%)	0 (0.0%)

^aIntellectual ability assessed by questionnaire 'how would you describe their intellectual ability?' (normal IA: response options "above-average intellectual ability" or "normal Intellectual ability"; impaired IA: response options "mild-moderate intellectual disability" or "severe-profound intellectual disability"); ^bNo caregiver answered seeking work/unemployed, on long-term sick leave, or in education or training; ^cNo caregiver lives with parents or siblings.
IA, intellectual ability.

Table S3. Level of functioning and impact on normal activities

Change in number of caregivers pre- and post-CBD	Change from pre-treatment to past month, +/- N (%) change		
	Overall (N=32)	Normal IA (N=14)	Impaired IA (N=18)
Level of mobility			
They were able to walk independently, without assistance or the use of walking aids	0 (0.0%)	0 (0.0%)	0 (0.0%)
They were able to walk only with assistance or the use of walking aids	0 (0.0%)	0 (0.0%)	0 (0.0%)
They could not walk with or without assistance or walking aids, but they could stand	0 (0.0%)	0 (0.0%)	0 (0.0%)
They could not walk with or without assistance and could not stand	0 (0.0%)	0 (0.0%)	0 (0.0%)
Level of motor skills			
They were able to use their hands without difficulty	+1 (+3.1%)	0 (0.0%)	+1 (+5.5%)
They were able to use their hands but had difficulty with tasks such as using a fork, spoon, or pencil	0 (0.0%)	0 (0.0%)	0 (0.0%)
They were unable to use their hands for tasks such as using a fork, spoon, or pencil	-1 (-3.2%)	0 (0.0%)	-1 (-5.5%)
Level of ability to care for self independently			
They were able to dress and undress themselves without assistance	0 (0.0%)	0 (0.0%)	0 (0.0%)
They were able to dress and undress themselves with some assistance	0 (0.0%)	0 (0.0%)	0 (0.0%)
They were able to dress and undress themselves with a lot of assistance	+2 (+6.2%)	0 (0.0%)	+2 (+11.1%)
They were unable to dress or undress themselves with or without assistance	-2 (-6.2%)	0 (0.0%)	-2 (-11.1%)
Level of ability to talk			
They had age-appropriate speech	+1 (+3.1%)	0 (0.0%)	+1 (+5.6%)
They did not have age-appropriate speech	-1 (-3.1%)	0 (0.0%)	-1 (-5.6%)
Which of the following statements best describes their speech?			
They used complete sentences	+2 (+6.2%)	0 (0.0%)	+2 (+11.1%)
They used only 2- or 3-word phrases	-2 (-6.2%)	0 (0.0%)	-2 (-11.1%)
They used only single words and no phrases	0 (0.0%)	0 (0.0%)	0 (0.0%)
They were unable to use recognisable words but may make some sounds	0 (0.0%)	0 (0.0%)	0 (0.0%)
Prevented from taking part in normal activities			
Always	0 (0.0%)	0 (0.0%)	0 (0.0%)
Often	-2 (-6.3%)	0 (0.0%)	-2 (-11.1%)
Sometimes/rarely	-1 (-3.1%)	0 (0.0%)	-1 (-5.5%)
Never	+3 (+9.3%)	0 (0.0%)	+3 (+16.6%)
I don't know	0 (0.0%)	0 (0.0%)	0 (0.0%)

Level of functioning was measured on 2- to 5-point categorical scales with response choices varying by question. Change is in number (%) of caregivers endorsing an item. Green text denotes a positive signal versus neutral (black) where no change is observed.
IA, intellectual ability.

Table S4. Change in academic skills from the month before starting CBD to the month prior to Survey 1 (after 3–6 months of CBD treatment)

	Mean change (SD)		
	Overall (N=29)	Normal IA (N=14)	Impaired IA (N=15 ^a)
How much was reading a problem?	-0.2 (1.00)	0.0 (0.00)	-0.5 (1.51)
How much was writing a problem?	-0.1 (0.60)	0.0 (0.00)	-0.3 (0.90)
How much was spelling a problem?	-0.1 (0.83)	0.0 (0.00)	-0.3 (1.27)
How much was mathematics a problem?	-0.4 (1.32)	-0.2 (0.80)	-0.5 (1.81)

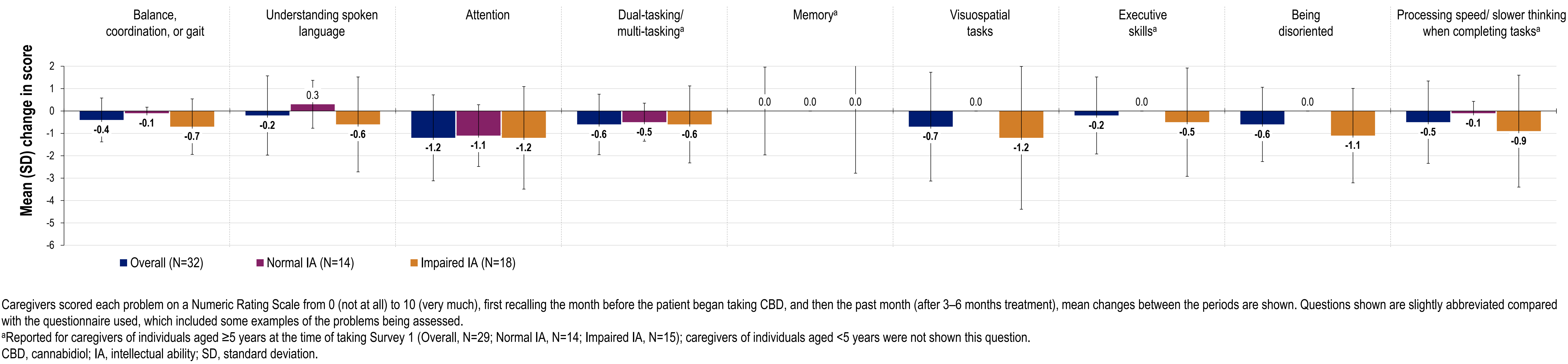
Caregivers reported scores using a Numeric Rating Scale, from 0 (not at all) to 10 (very much); mean changes between scores for the month before the patient started taking CBD and the past month (prior to survey 1) are shown. Only caregivers of individuals aged ≥5 years (N=29) were shown these questions. Green text denotes a positive signal versus neutral (black) where no change is observed. ^aFour caregivers of individuals with impaired IA answered "not able to observe" and their answers were excluded from the calculation.
CBD, cannabidiol; IA, intellectual ability; SD, standard deviation; TSC, tuberous sclerosis complex.

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Supplementary Material

Neuropsychologic skills

Figure S1. How much were the following a problem for the person you care for during the month before they started taking CBD and in the past month (following 3–6 months of CBD treatment)?



Behavioural issues and psychosocial functioning

Figure S2. How much were the following a problem for the person you care for during the month before they started taking CBD and in the past month (following 3–6 months of CBD treatment)?

