

Clinical outcome analysis of patients with autism spectrum disorder: analysis from the UK Medical Cannabis Registry

Simon Erridge^{ID}, Jess Kerr-Gaffney, Carl Holvey, Ross Coomber, Daniela A. Riano Barros, Urmila Bhoskar, Gracia Mwimba, Kavita Praveen, Chris Symeon, Simmi Sachdeva-Mohan, Mikael H. Sodergren and James J. Rucker

Abstract

Introduction: Cannabis-based medicinal products (CBMPs) have been identified as a promising novel therapeutic for symptoms and comorbidities related to autism spectrum disorder (ASD). However, there is a paucity of clinical evidence of their efficacy and safety.

Objective: This case series aims to assess changes to health-related quality of life and the incidence of adverse events in patients treated with CBMPs for associated symptoms of ASD enrolled on the UK Medical Cannabis Registry (UKMCR).

Methods: Patients treated with CBMPs for ASD-related symptoms for a minimum of 1 month were identified from the UKMCR. Primary outcomes were changes in validated patient-reported outcome measures [Generalised Anxiety Disorder-7 (GAD-7), Single-Item Sleep Quality Scale (SQS), 5-level version of the EQ-5D (EQ-5D-5L) index values] at 1, 3 and 6 months compared with baseline. Adverse events were recorded and analysed. Statistical significance was determined by $p < 0.050$.

Results: Seventy-four patients with ASD were included in the analysis. The mean age of participants was 32.7 (± 11.6) years. There were significant improvements in general health-related quality of life and sleep as assessed by the EQ-5D-5L, SQS and GAD-7 at 1 and 3 months, with sustained changes in EQ-5D-5L and SQS at 6 months ($p < 0.010$). There were 180 (243.2%) adverse events reported by 14 (18.9%) participants. If present, adverse events were commonly mild ($n = 58$; 78.4%) or moderate ($n = 81$; 109.5%), rather than severe ($n = 41$; 55.4%).

Conclusion: This study demonstrated an associated improvement in general health-related quality of life, and anxiety- and sleep-specific symptoms following initiation of treatment with CBMPs in patients with ASD. These findings, while promising, are limited by the confines of the study which lacks a control arm and is subject to attrition bias. Therefore, further evaluation is required with randomised controlled trials.

Keywords: autism spectrum disorder, cannabidiol, cannabis, psychiatry, tetrahydrocannabinol

Received: 4 May 2022; revised manuscript accepted: 11 July 2022.

Introduction

Autism spectrum disorder (ASD) is a heterogeneous pervasive developmental disorder defined according to deficits in social communication and interaction, in addition to the presence of restricted, repetitive behaviours.¹ ASD is estimated to affect 1 in 132 individuals globally, and

its incidence is increasing.² Individuals with ASD are affected by a higher incidence of comorbid irritability, challenging behaviours, self-injury and psychiatric conditions.^{3,4} Challenging behaviours, such as irritability, destructiveness, aggression and hyperactivity, are estimated to affect anywhere between 56% and 94% of children with

Ther Adv Psychopharmacol

2022, Vol. 12: 1–12

DOI: 10.1177/
20451253221116240

© The Author(s), 2022.

Article reuse guidelines:
sagepub.com/journals-
permissions

Correspondence to:

James J. Rucker
Sapphire Medical Clinics,
London, UK.

Bethlem Royal Hospital,
South London and
Maudsley NHS Foundation
Trust, London, UK.

Department of
Psychological
Medicine, Institute of
Psychiatry, Psychology
& Neuroscience, King's
College London, 16 De
Crespigny Park, London
SE5 8AF, UK.

james.rucker@kcl.ac.uk

Simon Erridge
Mikael H. Sodergren
Imperial College Medical
Cannabis Research Group,
Department of Surgery
and Cancer, Imperial
College London, London,
UK; Sapphire Medical
Clinics, London, UK

Jess Kerr-Gaffney
Department of
Psychological
Medicine, Institute of
Psychiatry, Psychology
& Neuroscience, King's
College London, London,
UK

Carl Holvey
Urmila Bhoskar
Gracia Mwimba
Kavita Praveen
Simmi Sachdeva-Mohan
Sapphire Medical Clinics,
London, UK

Ross Coomber
Sapphire Medical Clinics,
London, UK; St George's
Hospital NHS Trust,
London, UK

Daniela A. Riano
Barros Chris Symeon
Sapphire Medical Clinics,
London, UK; Bethlem
Royal Hospital, South
London and Maudsley
NHS Foundation Trust,
London, UK

a diagnosis of ASD.³ These behaviours, except for hyperactivity, have been observed as persisting into adulthood.³ ASD is also associated with a higher incidence of physical comorbidities and sleep disturbance in adults.⁵⁻⁷ Consequently, ASD has been associated with reduced quality of life for both adult and paediatric patients.^{4,8}

Management of the core symptoms of ASD is predominantly via a psychological approach.⁹ However, there is paucity of high-quality research to delineate the effectiveness of different psychological approaches.⁴ At present, there are no established pharmacological treatments for the core symptoms of ASD. Medications, such as monoamine reuptake inhibitors, have been used in the treatment of comorbid psychiatric illnesses, although the efficacy in people with ASD compared with the general population is not well-known.⁴ Atypical neuroleptics, such as risperidone and aripiprazole, have demonstrated efficacy in treating irritability and aggression in children and adolescents.¹⁰ However, these medications are poorly tolerated due to their side effect profile,¹⁰ and their efficacy in an adult population with ASD is again unknown. Consequently, there is an unmet clinical need to identify novel therapeutics for the core symptoms of ASD, other associated symptoms or comorbid diagnoses.

The endocannabinoid system has been implicated in the pathophysiology of ASD, as well as is a potential pharmaceutical target. Cannabinoid type 1 receptors (CB1Rs) are predominantly located in the central nervous system and at increased density within the basal ganglia, hippocampus and cerebellum.¹¹ Moreover, CB1Rs are principally expressed at pre-synaptic terminals of γ -aminobutyric acid (GABA)ergic and glutamatergic neurons.¹² Endogenous agonists of CB1Rs, such as anandamide, cause inhibition of either GABA or glutamate synaptic release.¹² Subsequently, the endocannabinoid system has been implicated in the regulation of anxiety, mood, motor coordination and social behaviour.¹¹⁻¹³ Children with ASD have been found to have lower circulating levels of anandamide compared with the general population.¹⁴

Cannabidiol (CBD), a major phytocannabinoid, is an inhibitor of anandamide reuptake and breakdown, a negative allosteric modulator of CB1Rs and is an agonist of 5-HT_{1A} serotonin receptors.¹² (–)-trans- Δ^9 -tetrahydrocannabinol (Δ^9 -THC), another active pharmaceutical ingredient of the

cannabis plant, is an agonist of CB1Rs.¹² Cannabis-based medicinal products (CBMPs), containing these phytocannabinoids, have therefore been highlighted as a potential class of medications for utilisation across the broad potential symptom profile of ASD. In the United Kingdom, CBMPs may be considered for these symptoms if licensed treatments have failed to produce a sufficient clinical response or are not tolerated.¹⁵ In 2019, Schleider *et al.*¹⁶ published a series of outcomes from 188 children and adolescents treated with CBMPs. In this study they demonstrated an improvement in quality of life, mood, sleep and challenging behaviours. However, they did not utilise any validated measures to assess for symptom prevalence and change over time.¹⁶ At present, there is a paucity of randomised controlled trials and other high-quality evidence on the efficacy and safety of CBMPs in the treatment of ASD-associated symptoms. Importantly, there are no published clinical studies of the outcomes of adult patients treated with CBMPs. Herein, the primary aim of this study is to report the general health-related quality of life outcomes and adverse event incidence of patients prescribed CBMPs for ASD enrolled on the UK Medical Cannabis Registry.

Methods

Study design and database

Extraction of an uncontrolled case series of patients from the UK Medical Cannabis Registry of patients treated with CBMPs for ASD was performed. The UK Medical Cannabis Registry is a bespoke prospective registry, which has collected outcomes on patients prescribed CBMPs in the United Kingdom and Channel Islands since 2019.¹⁷ It is the largest registry of its kind in the United Kingdom, with data on more than 3500 pseudonymised patients treated with CBMPs. Participants are recruited from Sapphire Medical Clinics, a specialist private clinic. All patients completed formal, written consent prior to enrolment in the registry.

The study was reported in line with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement for reporting observational studies.¹⁸

Patient and data selection

Inclusion criteria for this study were patients who were receiving treatment with CBMPs where

ASD was the primary condition for which treatment was commenced. Patients treated for other conditions, where ASD was not the primary indication, were excluded. Participants who had not completed baseline patient-reported outcome measures (PROMs) or who had received treatment for less than 1 month were also excluded from analysis.

The clinicopathological characteristics of study participants were recorded by clinicians and extracted at baseline, including age, gender, body mass index (BMI) and comorbidities. The Charlson Comorbidity Index was calculated to allow comparison of comorbidity against other epidemiological studies.¹⁹ This is calculated using baseline age, and the presence or absence of the following comorbidities: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident/transient ischaemic attack, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, diabetes mellitus, hemiplegia, chronic kidney disease, solid tumour, leukaemia, lymphoma and acquired immune deficiency syndrome.¹⁹ A higher index score is associated with an increased incidence of mortality at 1 and 10 years.¹⁹

Drug and alcohol data were collated in line with previously published research from our group.^{20–22} Concurrent medications taken at baseline by a patient and any changes to medications were self-recorded by patients via a remote data collection platform or by clinicians during routine follow-up. These were mapped to SNOMED CT codes to improve the accuracy of reporting and identification.

CBMPs were recorded throughout treatment. All prescriptions were for CBMPs that adhered to Good Manufacturing Practice. Patients could be prescribed sublingual/oral or vapourised preparations according to clinical requirements. In accordance with UK guidance, CBMPs were only initiated by consultant physicians in their clinical area of interest.¹⁵ The doses of major cannabinoids, CBD and Δ^9 -THC, prescribed at the time of data extraction in milligrams (mg) per day were extracted, in addition to specific CBMP prescribed.

The primary outcomes were changes in the Generalised Anxiety Disorder Scale (GAD-7), 5-level version of the EQ-5D (EQ-5D-5L) index value and Sleep Quality Scale (SQS) from

baseline to 1, 3 and 6 months. These were assessed in line with previously described methodology from our group.^{17,20,21} The GAD-7 is a validated scale to assess the severity of generalised anxiety symptoms. Scores of ≥ 5 , ≥ 10 and ≥ 15 represent mild, moderate and severe anxiety levels, respectively.²³ The EQ-5D-5L index value is a measure of health-related quality of life where a score of 1 represents an ideal health state, while a score less than 0 is equivalent to being worse than death.²⁴ The SQS is a single-item scale from 0 to 10 of sleep quality whereby 0 is ‘terrible’ sleep quality and 10 is ‘excellent’.²⁵ The Patient Global Impression of Change (PGIC) was also reported at 1, 3 and 6 months. The PGIC is a 7-point numerical rating scale where participants self-rate the change in activity limitations, symptoms, emotions and overall quality of life since starting treatment. A score of 1 represents ‘no change’, while a score of 7 represents ‘a considerable improvement’.²⁶

Secondary outcome measures were the incidence of adverse events recorded utilising the Common Terminology Criteria for Adverse Events v4.0.²⁷ Adverse events were self-reported by patients when completing PROMs or completed by clinicians during routine follow-up.

Statistical analysis

Data about patient clinicopathological characteristics, drug and alcohol consumption, CBMP prescriptions and adverse events were analysed using descriptive statistics. The Shapiro–Wilk test was used to assess the distribution of studied data. Unless otherwise stated, parametric data were presented as mean \pm standard deviation (SD), while non-parametric data were presented as median [interquartile range (IQR)]. Frequencies were presented as n (%). Analysis of PROMs was performed using a paired t -test for parametric data or the Wilcoxon signed-rank test for non-parametric data. Due to the number of analyses performed on the PROMs, a Benjamini–Hochberg procedure was performed to control for the false discovery rate. Statistical significance was defined as p -value < 0.050 . All analyses were performed in Statistical Package for Social Sciences (SPSS) (IBM Statistics version 27.0.0.0 SPSS Inc).

Results

Seventy-four patients were included in the analysis. The median follow-up was 204.0 (range:

Table 1. Clinicopathological characteristics of study participants at baseline.

| Baseline characteristics | n (%) / Mean \pm SD / Median [IQR] |
|---|--------------------------------------|
| Gender | |
| Female | 21 (28.4%) |
| Male | 53 (71.6%) |
| Age | 32.7 \pm 11.6 |
| Body mass index (kg/m ²) | 26.3 \pm 6.4 |
| Occupation | |
| Unemployed | 46 (62.2%) |
| Undisclosed | 8 (10.8%) |
| Professional | 7 (9.5%) |
| Service and sales workers | 5 (6.8%) |
| Elementary occupations | 3 (4.1%) |
| Other occupations | 2 (2.7%) |
| Clerical support workers | 1 (1.4%) |
| Managers | 1 (1.4%) |
| Technicians and associate professionals | 1 (1.4%) |
| Charlson Comorbidity Index | 0.0 [0.0–0.0] |
| Anxiety/depression | 51 (68.9%) |
| Arthritis | 0 (0.0%) |
| Endocrine dysfunction | 2 (2.7%) |
| Epilepsy | 3 (4.1%) |
| Hypertension | 1 (1.4%) |
| Venous thromboembolism | 0 (0.0%) |
| IQR, interquartile range. | |

34.0–557.0) days. Completion of PROMs varied at 1 ($n=60$; 81.1%), 3 ($n=49$; 66.2%) and 6 ($n=31$; 41.9%) months. The mean age of the participants was 32.7 (± 11.6) years. Fifty-three (71.6%) participants were male. The mean BMI was 26.3 (± 6.4) kg/m². Table 1 details the full clinicopathological characteristics of study participants at baseline.

The majority of patients were regular cannabis consumers at baseline ($n=50$; 67.6%) (Table 2).

The median lifetime exposure to cannabis was 8.0 [IQR: 2.0–20.0] gram years. The median weekly alcohol consumption of the cohort was 0.0 [IQR: 0.0–1.5] units.

Cannabis-based medicinal product dosing

Thirty-six (48.6%) participants were prescribed dried flower CBMPs only, 16 (21.6%) participants were prescribed oral/sublingual preparations and 22 (29.7%) were prescribed both CBMPs. The median prescribed CBD dose per day at the date of extraction was 10.0 [IQR: 4.0–100.0] mg, while the median Δ^9 -THC dose was 112.5 [IQR: 91.3–202.5] mg per day.

Patient-reported outcome measures

Table 3 outlines in full paired baseline and follow-up results of PROMs up to 6 months. There were significant improvements in general health-related quality of life and sleep, as assessed by the EQ-5D-5L and SQS, respectively, at 1, 3 and 6 months ($p < 0.010$). There were reductions in anxiety severity, as measured by the GAD-7 scale, at 1 and 3 months ($p < 0.001$). However, there was no change at 6 months ($p = 0.102$). The median PGIC value was 6.0 at 1, 3 and 6 months.

Co-administered medications

The most commonly co-administered class of medications were antidepressants ($n=45$; 60.8%), antiepileptics ($n=7$; 9.5%), benzodiazepines ($n=12$; 16.2%), neuroleptics ($n=12$; 16.2%) and stimulants ($n=6$; 8.1%) (Table 4). In all, 33.3% ($n=4$) and 25.0% ($n=3$) of patients stopped taking benzodiazepines and neuroleptics, respectively, during treatment with CBMPs (Table 4).

Adverse events

Fourteen (18.9%) participants reported 180 (243.2%) total adverse events. If present, adverse events were commonly mild ($n=58$; 78.4%) or moderate ($n=81$; 109.5%), rather than severe ($n=41$; 55.4%). There were no (0.0%) life-threatening or disabling adverse events in this group (Table 5).

Discussion

The results of this study are the first published observational data of CBMP therapy focused on adult participants with ASD. They demonstrate

an associated improvement in general health-related quality of life, sleep and anxiety in patients with ASD after commencement of therapy with CBMPs. There was also a 33.3% and 25.0% reduction in the concomitant prescribing of benzodiazepines and neuroleptics, respectively, within this cohort. Adverse events were experienced by 18.9% of the cohort with a total adverse event incidence of 243.2%. However, the findings must be interpreted cautiously due to the limitations of study design.

Improvements in health-related quality of life are supported by previous evaluations of CBMPs in the setting of ASD. A systematic review by Fusar-Poli *et al.*²⁸ identified that the majority of studies have found improvements in problem behaviours, hyperactivity, parental stress and other studied outcomes. However, the present study is the first to report these findings in an adult population. Previous studies have only reported outcomes for patients aged up to 22 years, while the mean age of the present case series was 32.7 years. However, adult patients with ASD have reported using medical cannabis and illicitly obtained cannabis for mental health symptoms or challenging behaviours.^{29,30} The finding of improved health-related quality of life is, however, supported by findings from other studies of UK patients treated with CBMPs. A study of 312 patients with all conditions from the UK Medical Cannabis Registry published by our group, similarly, demonstrated improved health-related quality of life as measured by the EQ-5D-5L index value.²² Moreover, similar results were published in a cohort of patients with generalised anxiety disorder.³¹

Adults with ASD have a higher prevalence of comorbid sleep disorders.⁵ The present study found an associated improvement in self-reported sleep quality among participants at up to 6 months. The effect of CBMPs on sleep is disputed; however, the endocannabinoid system has been implicated in the regulation of the sleep-wake cycle.³² A recent randomised controlled trial of a CBMP containing CBD, Δ^9 -THC and cannabigerol found improvements in reducing sleep-onset latency and waking after sleep onset.³³ However, this study only lasted 2 weeks and was limited to a small sample size. Other studies have raised concerns with respect to developing tolerance to the sleep-promoting effects of CBMPs with longitudinal use.³⁴ In addition, insomnia was the most frequently reported adverse event in this

Table 2. Tobacco, alcohol and cannabis exposure of patients at baseline.

| Tobacco, alcohol and cannabis status | n (%)/ median [IQR] |
|--------------------------------------|---------------------|
| Cannabis status | |
| Cannabis naïve | 14 (19.9%) |
| Ex-user | 10 (13.5%) |
| Current user | 50 (67.6%) |
| Cannabis use, gram years | 8.0 [2.0–20.0] |
| Tobacco status | |
| Non-smoker | 26 (35.1%) |
| Ex-smoker | 24 (32.4%) |
| Current smoker | 24 (32.4%) |
| Tobacco pack years | 5.0 [2.0–15.0] |
| Weekly alcohol consumption, units | 0.0 [0.0–1.5] |
| IQR, interquartile range. | |

study, highlighting that the benefits of CBMPs on sleep may also be negative in certain patients. A long-term pharmacovigilance strategy, such as the UK Medical Cannabis Registry, shall be necessary for continued evaluation of the benefits and risks of long-term prescribing of CBMPs.

The present study demonstrated statistically significant improvements in generalised anxiety symptoms at 1 and 3 months; however, the same findings were not present at 6 months. This divergence at 6 months appears to be secondary to a limitation in study design, whereby there is a reduction in the number of patients followed up to 6 months. Therefore, there is a reduction in sample size, such that despite a trend towards improved generalised anxiety symptoms at 6 months, the finding is not significant. In addition, the baseline values indicate a lower severity of anxiety. The reason for incomplete follow-up is not recorded in the UK Medical Cannabis Registry; however, this may be secondary to those patients with the most severe anxiety symptoms at baseline not continuing treatment up to 6 months due to being unable to tolerate therapy, insufficient clinical response or a non-clinical reason such as cost of treatment. Previous evaluations of the children and young adult patients with ASD have similarly found associated improvements in anxiety outcomes.²⁸

Table 3. Paired baseline and follow-up patient-reported outcome measures.

| | <i>n</i> | Baseline score | Follow-up score | <i>p</i> -value |
|---------------------------------|----------|-----------------|-----------------|-----------------|
| GAD-7 | | | | |
| 1 month | 59 | 15.0 [8.0–18.0] | 7.0 [5.0–12.8] | <0.001 |
| 3 months | 48 | 13.0 [6.8–18.0] | 6.0 [4.0–12.5] | <0.001 |
| 6 months | 30 | 11.5 [5.0–18.0] | 7.0 [5.0–13.0] | 0.102 |
| SQS | | | | |
| 1 month | 59 | 3.0 [2.0–6.0] | 6.0 [3.0–8.0] | <0.001 |
| 3 months | 48 | 4.0 [2.0–6.0] | 6.0 [4.0–8.0] | <0.001 |
| 6 months | 30 | 4.0 [1.8–7.0] | 5.5 [3.8–8.0] | 0.005 |
| EQ-5D-5L Mobility | | | | |
| 1 month | 60 | 1.0 [1.0–2.8] | 1.0 [1.0–2.0] | 0.581 |
| 3 months | 49 | 1.0 [1.0–3.0] | 1.0 [1.0–2.0] | 0.027 |
| 6 months | 31 | 1.0 [1.0–3.0] | 1.0 [1.0–2.0] | 0.183 |
| EQ-5D-5L Self-Care | | | | |
| 1 month | 60 | 2.0 [1.0–3.0] | 1.5 [1.0–2.8] | 0.131 |
| 3 months | 49 | 2.0 [1.0–3.0] | 1.0 [1.0–2.5] | 0.125 |
| 6 months | 31 | 1.0 [1.0–2.0] | 1.0 [1.0–2.0] | 0.441 |
| EQ-5D-5L Usual Activities | | | | |
| 1 month | 60 | 3.0 [2.0–4.0] | 2.0 [1.0–3.0] | 0.002 |
| 3 months | 49 | 3.0 [2.0–4.0] | 2.0 [1.0–3.0] | 0.002 |
| 6 months | 31 | 3.0 [2.0–3.0] | 2.0 [1.0–3.0] | 0.029 |
| EQ-5D-5L Pain and Discomfort | | | | |
| 1 month | 60 | 2.0 [1.0–3.0] | 2.0 [1.0–3.0] | 0.005 |
| 3 months | 49 | 2.0 [1.0–3.0] | 2.0 [1.0–3.0] | 0.003 |
| 6 months | 31 | 2.0 [1.0–3.0] | 2.0 [1.0–3.0] | 0.124 |
| EQ-5D-5L Anxiety and Depression | | | | |
| 1 month | 60 | 3.5 [2.0–4.0] | 3.0 [2.0–4.0] | <0.001 |
| 3 months | 49 | 3.0 [2.0–4.0] | 3.0 [2.0–3.0] | 0.003 |
| 6 months | 31 | 3.0 [2.0–4.0] | 3.0 [2.0–3.0] | 0.425 |
| EQ-5D-5L Index Value | | | | |
| 1 month | 60 | 0.44 ± 0.31 | 0.59 ± 0.29 | <0.001 |
| 3 months | 49 | 0.49 ± 0.30 | 0.66 ± 0.24 | <0.001 |

(Continued)

Table 3. (Continued)

| | <i>n</i> | Baseline score | Follow-up score | <i>p</i> -value |
|---|----------|----------------|-----------------|-----------------|
| 6 months | 31 | 0.54 ± 0.26 | 0.63 ± 0.23 | 0.008 |
| PGIC | | | | |
| 1 month | 60 | – | 6.0 [5.0–6.0] | – |
| 3 months | 46 | – | 6.0 [5.0–7.0] | – |
| 6 months | 30 | – | 6.0 [5.0–6.0] | – |
| GAD-7, Generalised Anxiety Disorder Scale; PGIC, Patient Global Impression of Change; SQS, Sleep Quality Scale. | | | | |

Table 4. Changes in co-administered medications throughout treatment with cannabis-based medicinal products to end of follow-up.

| Medication | Total | Stopped taking | Reduced dose | No change | Increased dose | New medication |
|-------------------------------|-------|----------------|--------------|-----------|----------------|----------------|
| Antidepressants, <i>n</i> (%) | 45 | 5 (11.1) | 0 (0.0) | 37 (82.2) | 0 (0.0) | 3 (6.7) |
| Antiepileptics, <i>n</i> (%) | 7 | 1 (14.3) | 0 (0.0) | 6 (85.7) | 0 (0.0) | 0 (0.0) |
| Benzodiazepines, <i>n</i> (%) | 12 | 4 (33.3) | 0 (0.0) | 8 (66.7) | 0 (0.0) | 0 (0.0) |
| Neuroleptics, <i>n</i> (%) | 12 | 3 (25.0) | 0 (0.0) | 9 (75.0) | 0 (0.0) | 0 (0.0) |
| Stimulants, <i>n</i> (%) | 6 | 0 (0.0) | 0 (0.0) | 6 (100.0) | 0 (0.0) | 0 (0.0) |

Table 5. Adverse events reported by participants.

| Adverse event | Mild | Moderate | Severe | Total |
|--------------------------|------|----------|--------|------------|
| Abdominal pain (upper) | 1 | 1 | 1 | 3 (4.1%) |
| Agitation | – | 1 | 2 | 3 (4.1%) |
| Amnesia | 1 | 3 | 1 | 5 (6.8%) |
| Anorexia | – | 3 | 3 | 6 (8.1%) |
| Anxiety | – | – | 1 | 1 (1.4%) |
| Ataxia | 3 | 1 | 1 | 5 (6.8%) |
| Blurred vision | 1 | 3 | 2 | 6 (8.1%) |
| Cognitive disturbance | 1 | 2 | 2 | 5 (6.8%) |
| Concentration impairment | 5 | 4 | 1 | 10 (13.5%) |
| Confusion | – | – | 2 | 2 (2.7%) |
| Constipation | – | 1 | – | 1 (1.4%) |
| Delirium | 1 | – | 1 | 2 (2.7%) |
| Depression | – | – | 4 | 4 (5.4%) |
| Diarrhoea | – | 1 | – | 1 (1.4%) |

(Continued)

Table 5. (Continued)

| Adverse event | Mild | Moderate | Severe | Total |
|-----------------------------------|------------|-------------|------------|--------------|
| Dizziness | 2 | 2 | 1 | 5 (6.8%) |
| Dry mouth | 10 | 1 | – | 11 (14.9%) |
| Dysgeusia | 1 | 1 | 2 | 4 (5.4%) |
| Dyspepsia | 4 | 2 | – | 6 (8.1%) |
| Fall | – | 2 | – | 2 (2.7%) |
| Fatigue | 3 | 3 | 4 | 10 (13.5%) |
| Fasciculations | – | 1 | – | 1 (1.4%) |
| Generalised muscle weakness | 2 | 2 | 1 | 5 (6.8%) |
| Headache | – | 7 | 1 | 8 (10.8%) |
| Increased seizure frequency | – | 1 | 2 | 3 (4.1%) |
| Insomnia | 2 | 7 | 4 | 13 (17.6%) |
| Lethargy | 3 | 7 | 1 | 11 (14.9%) |
| Nausea | 4 | 2 | – | 6 (8.1%) |
| Pharyngitis | – | 3 | – | 3 (4.1%) |
| Pyrexia | – | 1 | – | 1 (1.4%) |
| Rash | 2 | – | – | 2 (2.7%) |
| Somnolence | – | 9 | – | 9 (12.2%) |
| Spasticity | 2 | 3 | 1 | 6 (8.1%) |
| Tremor | 5 | – | 2 | 7 (9.5%) |
| Vertigo | 2 | 1 | 1 | 4 (5.4%) |
| Vomiting | 2 | – | – | 2 (2.7%) |
| Weight loss | 1 | 3 | – | 4 (5.4%) |
| Upper respiratory tract infection | – | 3 | – | 3 (4.1%) |
| Total | 58 (78.4%) | 81 (109.5%) | 41 (55.4%) | 180 (243.2%) |

There was a reduction in concomitant medication use during treatment. Benzodiazepines are not recommended for the long-term treatment of aggression or irritability in ASD as they can induce tolerance and are associated with a high incidence of adverse events.³⁵ In all, 33.3% of participants stopped taking benzodiazepines during treatment. Atypical neuroleptics risperidone and aripiprazole are licensed for the treatment of irritability associated with ASD.³⁵ However, long-term use is associated with metabolic syndrome. In this study,

there were reductions in neuroleptic (25.0%) prescribing. Observational studies in children have also shown that administration of CBMPs can lead to a reduction in other medications.²⁸ The long-term efficacy and safety of this approach, however, need evaluation in long-term observational series and randomised controlled trials.

Adverse events were reported by 18.9% of participants, with a total incidence of 243.2%. This incidence is higher than reported in previous

observational series.^{36–38} The reason for this is likely due to the methodology for collecting adverse events. First, patients are prompted to report adverse events remotely alongside PROMs at 1, 3 and 6 months. In addition, they may report adverse events during a clinical encounter. This methodology therefore represents one of the most sophisticated pharmacovigilance strategies for CBMPs globally at present. Similar to other studies, CBMPs were well tolerated by most patients as 81.1% of patients did not experience any adverse events.^{36–38} Moreover, there were no life-threatening or disabling adverse events, while most adverse events were mild (78.4%) or moderate (109.5%).

Despite being the first published experience of clinical outcomes for adult patients with ASD prescribed CBMPs, there are limitations to the present study design. There is no control group for comparison, and therefore, it is not possible to determine whether the associated changes are caused by CBMPs and not due to another cause, such as regression to the mean. The study participants are all recruited from a private medical clinic and therefore may not be representative of the general population. However, 62.2% of participants were unemployed, indicating that the cost of treatment was not wholly prohibitive to starting treatment. Moreover, paying for treatment may enhance the placebo effect, which is already enhanced in CBMPs due to the associated aroma, and psychoactive and vasoactive effects.³⁹ Finally, attrition bias is likely due to loss to follow-up, which subsequently reduces the internal validity of the study. To ensure that changes in individuals were measured accurately, changes were compared with baseline rather than previous follow-up period.

Conclusion

In this first published experience of clinical outcomes in adult patients with ASD treated with CBMPs, there were associated improvements in general health-related quality of life, in addition to sleep- and anxiety-specific outcomes. Moreover, there was a reduction in the administration of concomitant medications, some of which are associated with serious adverse events with long-term use. CBMPs were well tolerated by the majority (81.1%) of patients. These results must be interpreted within the context of the limitations of study design, and causation cannot be determined. However, it provides scientific justification for further evaluation within the context of

randomised controlled trials while also providing guidance for clinical practice in the interim.

Declarations

Ethics approval and consent to participate

As a registry study, and as advised by the NHS Health Research Authority and Research Ethics Committee, formal ethical approval was not required. Informed consent was provided by all participants prior to enrolment in the registry.

Consent for publication

Not applicable.

Author contributions

Simon Erridge: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Validation; Visualization; Writing – original draft; Writing – review & editing.

Jess Kerr-Gaffney: Conceptualization; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Carl Holvey: Conceptualization; Data curation; Investigation; Methodology; Project administration; Writing – review & editing.

Ross Coomber: Conceptualization; Data curation; Methodology; Project administration; Writing – review & editing.

Daniela A. Riano Barros: Methodology; Project administration; Writing – review & editing.

Urmila Bhoskar: Methodology; Project administration; Writing – review & editing.

Gracia Mwimba: Methodology; Project administration; Writing – review & editing.

Kavita Praveen: Methodology; Project administration; Writing – review & editing.

Chris Symeon: Methodology; Project administration; Writing – review & editing.

Simmi Sachdeva-Mohan: Methodology; Project administration; Writing – review & editing.

Mikael H. Sodergren: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

James J. Rucker: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualisation; Writing – original draft; Writing – review & editing.

Acknowledgements

The authors acknowledge support of the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

Funding

The authors received no financial support for the research, authorship and/or publication of this article.

Competing interests

The authors declared the following potential conflicts of interest with respect to the research, authorship and/or publication of this article: Simon Erridge is a junior doctor and undertakes paid consultancy work at Sapphire Medical Clinics. Simon Erridge is an honorary clinical research fellow at Imperial College London. The views expressed are those of the author(s) and not necessarily those of the NHS. Simon Erridge has no shareholdings in pharmaceutical companies. Jess Kerr-Gaffney is a post-doctoral researcher at King's College London. Jess Kerr-Gaffney has no shareholdings in pharmaceutical companies. Carl Holvey is chief clinical pharmacist at Sapphire Medical Clinics. Carl Holvey has no shareholdings in pharmaceutical companies. Ross Coomber is a consultant orthopaedic surgeon, a director at Sapphire Medical Clinics and a consultant at St George's Hospital, London. The views expressed are those of the author(s) and not necessarily those of the NHS. Ross Coomber has no shareholdings in pharmaceutical companies. Daniela A. Riano Barros is a consultant psychiatrist at Sapphire Medical Clinics and at The South London and Maudsley NHS Foundation Trust. The views expressed are those of the author(s) and not necessarily those of the NHS. Daniela A. Riano Barros has no shareholdings in pharmaceutical companies. Urmila Bhoskar is a consultant psychiatrist at Sapphire Medical Clinics. Urmila Bhoskar has no shareholdings in pharmaceutical companies. Gracia Mwimba is a consultant psychiatrist at Sapphire Medical Clinics and Lead Clinician at the National Inpatient Unit for Under 12s in Scotland. She is also consultant

psychiatrist in the Paediatric Liaison team for Greater Glasgow and Clyde NHS Board. The views expressed are those of the author(s) and not necessarily those of the NHS. Gracia Mwimba has no shareholdings in pharmaceutical companies. Kavita Praveen is a consultant psychiatrist at Sapphire Medical Clinics. The views expressed are those of the author(s). Kavita Praveen has no shareholdings in pharmaceutical companies. Chris Symeon is a consultant psychiatrist at Sapphire Medical Clinics (London) and at St George's University Hospitals NHS Foundation Trust. The views expressed are those of the author(s) and not necessarily those of the NHS. Chris Symeon has no shareholdings in pharmaceutical companies. Simmi Sachdeva-Mohan is a consultant psychiatrist at Sapphire Medical Clinics. The views expressed are those of the author(s). Simmi Sachdeva-Mohan has no shareholdings in pharmaceutical companies. Mikael H. Sodergren is a consultant hepatopancreatobiliary surgeon, a director at Sapphire Medical Clinics and a consultant at Imperial College NHS Trust, London. He is senior clinical lecturer at Imperial College London and Chief Medical Officer at Curaleaf International. The views expressed are those of the author(s) and not necessarily those of the NHS. James J. Rucker is a consultant psychiatrist, a former director at Sapphire Medical Clinics (London). James J. Rucker is an honorary consultant psychiatrist at The South London & Maudsley NHS Foundation Trust and an NIHR Clinician Scientist Fellow at the Centre for Affective Disorders at King's College London. James J. Rucker is funded by a fellowship (CS-2017-17-007) from the National Institute for Health Research (NIHR). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. James J. Rucker has no shareholdings in pharmaceutical companies. James Rucker reviewed this article and made comments.

Availability of data and material

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. The raw data that belonged to the present study cannot be made publicly available because the disclosure of personal data, albeit pseudonymised, was not included in the research protocol of the present study.

ORCID iD

Simon Erridge  <https://orcid.org/0000-0001-5871-6501>

References

1. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing, 2013.
2. Baxter AJ, Brugha TS, Erskine HE, *et al.* The epidemiology and global burden of autism spectrum disorders. *Psychol Med* 2015; 45: 601–613.
3. Rattaz C, Michelon C, Munir K, *et al.* Challenging behaviours at early adulthood in autism spectrum disorders: topography, risk factors and evolution. *J Intellect Disabil Res* 2018; 62: 637–649.
4. Lord C, Brugha TS, Charman T, *et al.* Autism spectrum disorder. *Nat Rev Dis Primers* 2020; 6: 1–23.
5. Croen LA, Zerbo O, Qian Y, *et al.* The health status of adults on the autism spectrum. *Autism* 2015; 19: 814–823.
6. Weir E, Allison C, Ong KK, *et al.* An investigation of the diet, exercise, sleep, BMI, and health outcomes of autistic adults. *Mol Autism* 2021; 12: 1–14.
7. Brondino N, Fusar-Poli L, Miceli E, *et al.* Prevalence of medical comorbidities in adults with autism spectrum disorder. *J Gen Intern Med* 2019; 34: 1992–1994.
8. Fusar-Poli L, Brondino N, Rocchetti M, *et al.* Prevalence and predictors of psychotropic medication use in adolescents and adults with autism spectrum disorder in Italy: a cross-sectional study. *Psychiatry Res* 2019; 276: 203–209.
9. Schreibman L, Dawson G, Stahmer AC, *et al.* Naturalistic developmental behavioral interventions: empirically validated treatments for autism spectrum disorder. *J Autism Dev Disord* 2015; 45: 2411–2428.
10. McPheeters ML, Warren Z, Sathe N, *et al.* A systematic review of medical treatments for children with autism spectrum disorders. *Pediatrics* 2011; 127: e1312–e1321.
11. Zou S and Kumar U. Cannabinoid receptors and the endocannabinoid system: signaling and function in the central nervous system. *Int J Mol Sci* 2018; 19: 833.
12. Di Marzo V. The endocannabinoidome as a substrate for noneuphoric phytocannabinoid action and gut microbiome dysfunction in neuropsychiatric disorders. *Dial Clin Neurosci* 2022; 22: 259–269.
13. Kerr DM, Downey L, Conboy M, *et al.* Alterations in the endocannabinoid system in the rat valproic acid model of autism. *Behav Brain Res* 2013; 249: 124–132.
14. Aran A, Eylon M, Harel M, *et al.* Lower circulating endocannabinoid levels in children with autism spectrum disorder. *Mol Autism* 2019; 10: 2–11.
15. Case P. The NICE guideline on medicinal Cannabis: keeping Pandora’s box shut tight? *Med Law Rev* 2020; 28: 401–411.
16. Bar-Lev Schleider L, Mechoulam R, Saban N, *et al.* Real life experience of medical cannabis treatment in autism: analysis of safety and efficacy. *Sci Rep* 2019; 9: 1–7.
17. Erridge S, Salazar O, Kawka M, *et al.* An initial analysis of the UK Medical Cannabis Registry: outcomes analysis of first 129 patients. *Neuropsychopharmacol Rep* 2021; 41: 362–370.
18. Von Elm E, Altman DG, Egger M, *et al.* The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Bull World Heal Org* 2007; 85: 867–872.
19. Brusselaers N and Lagergren J. The Charlson comorbidity index in registry-based research. *Methods Inf Med* 2017; 56: 401–406.
20. Ergisi M, Erridge S, Harris M, *et al.* UK Medical Cannabis Registry: an analysis of clinical outcomes of medicinal cannabis therapy for generalized anxiety disorder. *Exp Rev Clin Pharmacol*. Epub ahead of print 18 January 2022. DOI: 10.1080/17512433.2022.2020640.
21. Harris M, Erridge S, Ergisi M, *et al.* UK Medical Cannabis registry: an analysis of clinical outcomes of medicinal cannabis therapy for chronic pain conditions. *Exp Rev Clin Pharmacol*. Epub ahead of print 31 December 2021. DOI: 10.1080/17512433.2022.2017771.
22. Ergisi M, Erridge S, Harris M, *et al.* An updated analysis of clinical outcome measures across patients from the UK Medical Cannabis Registry. *Cannabis Cannabinoid Res*. Epub ahead of print 24 January 2022. DOI: 10.1089/can.2021.0145.
23. Löwe B, Decker O, Müller S, *et al.* Validation and standardization of the Generalized Anxiety Disorder Screener (GAD-7) in the general population. *Med Care* 2008; 46: 266–274.
24. van Hout B, Janssen MF, Feng YS, *et al.* Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health* 2012; 15: 708–715.

25. Snyder E, Cai B, DeMuro C, *et al.* A new single-item sleep quality scale: results of psychometric evaluation in patients with chronic primary insomnia and depression. *J Clin Sleep Med* 2018; 14: 1849–1857.
26. Hurst H and Bolton J. Assessing the clinical significance of change scores recorded on subjective outcome measures. *J Manipulative Physiol Ther* 2004; 27: 26–35.
27. National Cancer Institute. Common terminology criteria for adverse events v4. 0. NIH publication number 09-7473, 2009. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm
28. Fusar-Poli L, Cavone V, Tinacci S, *et al.* Cannabinoids for people with ASD: a systematic review of published and ongoing studies. *Brain Sciences* 2020; 10: 572.
29. Lintzeris N, Mills L, Suraev A, *et al.* Medical cannabis use in the Australian community following introduction of legal access: the 2018–2019 Online Cross-Sectional Cannabis as Medicine Survey (CAMS-18). *Harm Reduc J* 2020; 17: 1–12.
30. Weir E, Allison C and Baron-Cohen S. Understanding the substance use of autistic adolescents and adults: a mixed-methods approach. *Lancet Psych* 2021; 8: 673–685.
31. Ergisi M, Erridge S, Harris M, *et al.* UK Medical Cannabis Registry: an analysis of clinical outcomes of medicinal cannabis therapy for generalized anxiety disorder. *Expert Rev Clin Pharmacol*. Epub ahead of print 18 January 2022. DOI: 10.1080/17512433.2022.2020640.
32. Murillo-Rodríguez E. The role of the CB1 receptor in the regulation of sleep. *Prog Neuropsychopharmacol Biol Psychiatry* 2008; 32: 1420–1427.
33. Walsh JH, Maddison KJ, Rankin T, *et al.* Treating insomnia symptoms with medicinal cannabis: a randomized, crossover trial of the efficacy of a cannabinoid medicine compared with placebo. *Sleep* 2021; 44: zsab149.
34. Sznitman SR, Vulfovics S, Meiri D, *et al.* Medical cannabis and insomnia in older adults with chronic pain: a cross-sectional study. *BMJ Support Palliat Care* 2020; 10: 415–420.
35. Santosh PJ and Singh J. Drug treatment of autism spectrum disorder and its comorbidities in children and adolescents. *BjPsych Advances* 2016; 22: 151–161.
36. Moreno-Sanz G, Madiedo A, Hernandez P, *et al.* Sex-dependent prescription patterns and clinical outcomes associated with the use of two oral cannabis formulations in the multimodal management of chronic pain patients in Colombia. *Front Pain Res (Lausanne)* 2022; 3: 854795.
37. Gulbransen G, Xu W and Arroll B. Cannabidiol prescription in clinical practice: an audit on the first 400 patients in New Zealand. *BjGP Open* 2020; 4: bjgpopen20X101010.
38. Cahill SP, Lunn SE, Diaz P, *et al.* Evaluation of patient reported safety and efficacy of cannabis from a survey of medical cannabis patients in Canada. *Front Public Health* 2021; 9: 626853.
39. Gertsch J. The intricate influence of the placebo effect on medical cannabis and cannabinoids. *Med Cannabis Cannabinoids* 2018; 1: 60–64.