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Use of Medical Cannabis in Patients with Gilles de la Tourette's Syndrome in a Real-World Setting

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Abstract

Objective: Tourette's syndrome (TS) is a neurodevelopmental disorder characterized by vocal and motor tics and other comorbidities. Clinical recommendations for the use of medical cannabis are established, yet further guidance is needed. The aim of this study was to describe the experience of patients with TS with medical cannabis.

Materials and Methods: TS patients were recruited from a registry of patients ("Tikun Olam" company). Questionnaires were answered before and after 6 months of treatment. Patients were divided into two groups: (A) patients who responded and (B) patients who did not respond to the follow-up questionnaire. In group A, an analysis was made to evaluate the presence and frequency of motor and vocal tics. The patients' general mood, employment status, quality of life, and comorbidities were also included in the analysis.

Results: Seventy patients were identified. The tetrahydrocannabinol and cannabidiol mean daily dose was 123 and 50.5 mg, respectively. In group A, a statistically significant improvement was identified in quality of life ($p < 0.005$), employment status ($p = 0.027$), and in the reduction of the number of medications ($p < 0.005$). Sixty-seven percent and 89% of patients with obsessive-compulsive disorder and anxiety comorbidities, respectively, reported an improvement. No statistically significant improvement was identified in motor tics ($p = 0.375$), vocal tics ($p > 0.999$), tics frequency ($p = 0.062$), or general mood ($p = 0.129$). The most frequent adverse effects were dizziness ($n = 4$) and increased appetite ($n = 3$).

Conclusion: Subjective reports from TS patients suggest that medical cannabis may improve their quality of life and comorbidities. More studies are needed to evaluate the efficacy and safety of medical cannabis.
Registry in the MOH: https://www.moh.gov.sg/ (Trial number: 0185-19-ASF)

Keywords: Tourette's syndrome; medical cannabis; quality of life; obsessive compulsive disorder; motor and vocal tics

Introduction

Gilles de la Tourette's syndrome (Tourette's syndrome [TS]) is a neurodevelopmental disorder characterized by vocal and motor tics that cause distress and functional impairment.[1] Based upon the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), TS can be diagnosed by the presence of two or more motor tics and at least one vocal tic, occurring multiple times a day, nearly every day, for longer than a year, with onset before the age of 18.[2] Tics are described as sudden movements or vocalizations, which are repetitive and stereotypical, and may include eye blinking, jerks of the head, shoulders and torso, facial grimaces, humming noises, throat clearing, sniffing, grunting or

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squealing and calling out a word or phrase.[1] Dysfunctional neurobiological and psychological processes contribute to the development and continuance of tics; however, emotional status (i.e., anxiety, frustration) and behavioral principles play a role in tic exacerbation.[3]

Tics can be associated with a poorer quality of life and up to 88% of patients reported that tics have a negative effect on their social skills, relationships and difficulties at school.[4] Comorbid disorders, in particular obsessive–compulsive disorder (OCD), attention deficit and hyperactivity disorder (ADHD), and depression and anxiety disorders are reported in most patients.[5] These comorbidities compound to worsen social difficulties and quality of life measures in TS patients.[5]

The pathophysiology of TS is still incompletely understood. Studies demonstrated a loss of inhibition resulting from abnormalities in brain, specifically the GABA and dopaminergic pathways.[6] Based on the fact that the endocannabinoid system plays a paramount role in basal ganglia function by modulating the activity of key neurotransmitters, including dopamine, glutamate, and GABA and thereby, influences different motor responses,[7] a "cannabinoid hypothesis" has been suggested in TS.[8]

Dopamine plays an important role in TS. Dopamine-blocking drugs are used to reduce tics, dopamine agonists are known to enhance tics, and the level of the dopamine metabolite, homovanillic acid, has been found to be reduced in the cerebrospinal fluid of TS patients.[8] Neuroimaging studies using various methods of single-photon emission computed tomography (SPECT) have demonstrated increased dopamine transporter binding and different dopamine D receptor binding in monozygotic twins discordant for TS.[9,10] Specific binding of [123I]AM281 to CB1 receptors using SPECT was also detected in TS patients when evaluating the treatment of tetrahydrocannabinol (THC).[11] Berding et al conducted a pilot [123I]AM281 SPECT study of CB1 receptor binding in TS patients before and during 9-THC therapy, imaging the central cannabinoid CB1 receptors *in vivo*, but found no significant difference in tracer binding to CB1 receptor values.[11]

On the other hand, in a recent study, elevated endocannabinoid levels in TS patients were found, possibly reflecting secondary changes to compensate for alterations in other neurotransmitter systems such as the dopaminergic system or possibly representing the primary cause of TS.[12]

The treatment of TS includes both behavioral interventions and pharmacological treatments. Some of the conventional drugs, including nondopaminergic agents and typical and atypical antipsychotics, are associated with intolerable adverse effects.[13] Clinical recommendations were published in 2019, which included treatment with cannabis-based medication in otherwise treatment-resistant adults with TS as an official recommendation.[14] In 2021, the treatment guidelines of the European Society for the Study of Tourette's syndrome were updated with similar recommendations.[15]

As of today, the experiences with medical cannabis in TS patients is limited and further research is needed.[14,15] In a literature review we found that the first reports of the beneficial effects of cannabis for TS were published in the late 80s and 90s and described TS patients who reported previous use of marijuana with improvements in TS symptoms.[13,16] Treatment of TS patients with THC was first described by Müller-Vahl et al in the late 90s, followed by two studies: a randomized crossover trial and a 6-week randomized trial, demonstrating a reduction in both tics and OCD behaviors.[17–19] More recent publications include a case report of a successful treatment with vaporized cannabis[20] and two publications of a single center's experience with TS patients that describe results from a telephone interview[21] and an online survey.[22]

The use of medical cannabis in children is rapidly growing. The current knowledge on the longterm side-effects of cannabinoids is based mainly on follow-up data from cannabis users.[23] Exposing children and young adults to medical cannabis early in life is inadvisable, because it may cause chronic adverse effects on brain development that increases the risk of psychosis.[24] There are case reports in children with TS who were treated successfully with medical cannabis as a last-resort therapy in which no adverse events were reported.[20,25,26] Hasan et al described a 15-year-old boy with refractory TS and ADHD that was successfully treated with D9-THC.[23,25] Szejko et al published a case report of a 7-year-old boy diagnosed with TS and ADHD who failed on conventional treatment but had significant improvements in tic reduction, ADHD symptoms, mood, stress, and quality of life when treatment was augmented with oral THC.[26] In another publication, Szejko et al describe a case of a 12-year-old boy diagnosed with TS who was successfully treated with a combination of vaporized medicinal cannabis and oral pure THC.[20]

In this study, we aimed to describe the real-life experiences and to assess the long-term effects of patients with TS using medical cannabis by collecting data from reports from a single medical center.

Materials and Methods

TS patients were identified from a medical cannabis clinic's patient registry. Diagnosis was made by a neurologist, according to the DSM-5 criteria.[2] Patients received a license for the use of medical cannabis under the indication of TS from the Israeli Ministry of Health. Before dispensing cannabis to patients, they were instructed by an experienced nurse practitioner on proper administration. The cannabis preparation (oil solution or inflorescence) was made by an approved supplier in Israel (Tikun Olam, Inc., Israel). Each patient completed a questionnaire before treatment and 6 months after treatment according to the standard treatment process at the clinic. Inclusion criteria included patients diagnosed with TS who were treated with medical cannabis for the TS indication.

Patients under 9 years of age were excluded. In most studies, TS starts at a mean age of around 6.7 years (range 1–17), beginning first with motor tics, followed by vocal tics at around age 9. This is why the age threshold chosen in our study was 9 years old.[27] Patients were divided in two groups: group A patients answered the questionnaire before treatment and after 6 months of active treatment and group B patients answered the questionnaire before treatment but did not respond to the 6-month follow-up questionnaire.

We analyzed and compared the baseline characteristics of patients with and without the follow-up questionnaire, the presence of vocal and motor tics, tics frequency, quality of life, general mood, employment status, and number of medications of conventional treatment. The number of medications was analyzed as a continuous variable. All other variables were categorical. Information about the types of conventional drugs used and the drugs that were discontinued was not fully reported and, therefore, was not included in the analysis. Vocal and motor tics were categorized as either present or absent based on the reports of participants. Tic frequency was scaled as daily or weekly. Quality of life was measured on a 5-point Likert scale from very low to very high. This was rated by the patient as part of a self-assessment.[28] General mood was categorized as positive, neutral, or negative.

In group A, a subanalysis of the changes after 6 months was made for all seven parameters and the comorbidities, OCD and ADHD. Reports of adverse events were recorded from the questionnaires and coded using the Medical Dictionary for Regulatory Activities.[29] The study was approved by the local Research Ethics Committee. The need for informed consent form was removed, due to the retrospective nature of the data analysis.

Statistical analysis

Categorical variables were described as frequency and percentage. Continuous variables were evaluated for normal distributions using histogram and Q-Q plot. They were reported as median and interquartile range. Chi-square test and Fishers' exact test or Mann–Whitney tests were applied to compare categorical and continuous variables, respectively, between those who continued the treatment at 6 months and those who stopped and between those who participated in the follow-up study and those who did not. The McNemar and Wilcoxon signed-rank tests were used to compare categorical and continuous variables between the two time points. All statistical tests were two sided and $p < 0.05$ was considered statistically significant. SPSS (IBM SPSS Statistics for Windows, version 25; IBM corp., Armonk, NY, USA, 2017).

Results

Eighty patients with the diagnosis of TS were included in the study. Of them, 70 patients met inclusion criteria. Ten patients did not meet inclusion criteria due to medical cannabis treatment for other indications and were excluded from the study. Out of 70 patients, 57 were males (81.4%) and 13 were females (18.6%). Median age was 31 years (range 9–64); seven patients were under 18 years of age. The use of conventional drug therapies for TS was reported by 28 patients. The most common drug groups were selective serotonin reuptake inhibitors (SSRI's), atypical antipsychotics, and monoamine depletors. Group A included 57 patients who completed the 6-month questionnaire, three of which were under 18 years of age (two patients were 16 and one patient was 15). Group B included 13 patients who did not complete the 6-month questionnaire. In the comparison of baseline characteristics and categorical variables between groups A and B, no significant differences were found (Table 1).

In group A ($n = 57$) there were 47 males (82%) and 10 females (18%). Of them, 46 patients answered the sections on cannabis consumption, product type, and daily dose. THC and cannabidiol average daily doses were 123 and 50.5 mg, respectively. Sixty-nine percent of participants used products with a high THC dose (Table 2). Forty patients (70%) used more than one cannabis product.

Table 1. A Comparison of Baseline Characteristics Between Groups A (Responded to Follow-Up) and B (Lost to Follow-Up)

Baseline characteristics at time zero	Group A ($n=57$)	Group B ($n=13$)	p-Value
Gender (male), *n* (%)	47 (82.5)	10 (77)	0.697
Median age (years)	31	30.5	
Presence of motor tics (%)	51 (96.2)	12 (92.3)	0.740
Presence of vocal tics (%)	37 (67)	10 (77)	0.634
Tics frequency (daily)	49	12	0.488
General mood (positive, %)	22 (42.3)	4 (33.3)	0.195
Employment status (employed, %)	27 (48.2)	8 (61.5)	0.236
On current medication (%)	38 (69)	6 (46.2)	>0.999

Six months after initiation of the medical cannabis treatment, patients responded to the same questionnaire again (group A; Table 3).

Vocal tics

Information on 48 (84%) patients who had vocal tics was available. Twenty-six (54.2%) patients reported no change after 6 months of treatment. Five (10.4%) patients reported an improvement, and four (8.3%) patients reported worsening. Thirteen (27%) patients reported no presence of vocal tics before or after treatment. The improvements were not statistically significant ($p>0.999$).

Motor tics

Information on 49 (86%) patients who had motor tics was available. Forty-four (89.8%) patients reported no change after 6 months of treatment. Four (8.7%) patients reported an improvement and one (2.2%) reported worsening. The improvements were not statistically significant ($p=0.375$).

Table 2. List of Medical Cannabis Products Used and Description of THC and Cannabidiol Concentrations for Each Product

Product name	No. of patients	Daily average consumption (in grams)	Daily average mg of THC	Daily average mg of CBD
Erez flowers	35	0.41	74.52	–
Alaska flowers	23	0.47	84.26	–
Midnight flowers	14	0.54	65.25	58.50
Avidekel flowers	4	0.41	4.13	74.25
Avidekel oil 15% CBD	12	0.32	3.16	47.45
Erez oil 15% THC	11	0.37	55.64	–

CBD, cannabidiol; THC, delta-9 tetrahydrocannabinol.

Table 3. The *p* Values for 6 Months Improvement Evaluation of Group A (Patients in Follow-Up)

Categorical variables	p-Value
Quality of life	<0.005
General mood (positive)	0.129
Employment status	0.027
Presence of motor tics	0.375
Presence of vocal tics	0.999
Tics frequency (daily)	0.062

Tics frequency

Information on 45 (79%) patients was available. Thirty-seven (82%) patients reported no change after 6 months of treatment. Six (13.3%) patients reported an improvement and two (4.4%) patients reported worsening. The improvement was not statistically significant ($p=0.062$).

OCD and anxiety disorder in group A

Of the 57 patients, 9 (15.7%) patients reported OCD as a comorbidity. Of those nine, six (67%) patients reported an improvement, two (22%) patients reported no change, and one (11%) patient reported worsening of OCD. Nineteen of 57 (33.3%) patients reported an anxiety disorder. Of those 19, 17 (89%) patients reported an improvement, and 2 (11%) patients reported no change.

Quality of life

Information on 43 patients was available. Thirty (69.8%) patients reported an improvement, 11 (25.6%) patients reported no change, and 2 (4.6%) patients reported worsening. The improvement was statistically significant ($p<0.005$).

General mood

Information on 44 patients was available. Twenty-five (56.8%) patients reported no change. Thirteen (29.3%) patients reported an improvement, and six (13.7%) patients reported worsening. The improvement was not statistically significant ($p=0.129$).

Employment status

Information on 43 patients was available. Twenty-nine (67.5%) reported no change. Eight (18.6%) patients reported a change of status, from unemployed to employed or student. The change was statistically significant ($p<0.05$).

Table 4. Adverse Events Reported in the Study

Adverse events	Number of reports
Dizziness	4
Increased appetite	3
Fatigue	3
Dry mouth	3
Decreased memory and concentration	2
Fear	2
Illuminations	1
Headache	1
Lightheadedness	1
Restlessness	1
Nausea	1
Itching	1

Dizziness, increased appetite, fatigue, and dry mouth were the most frequently reported.

Number of medications

Twenty-eight patients reported the use of conventional drugs for TS during the study period, using medical cannabis as a supplemental treatment. The average number of medications was 2 (range 0–7) before treatment and 0.5 (0–1) after 6 months of treatment. The decrease in medications was statistically significant ($p < 0.005$).

Adverse events were relatively minor. The most frequent adverse events reported (Table 4) were dizziness ($n = 4$), increased appetite ($n = 3$), fatigue ($n = 3$), and dry mouth ($n = 3$).

Discussion

A statistically significant improvement in quality of life ($p < 0.005$), employment status ($p = 0.027$), and reduction in the number of medications ($p < 0.005$) was found, with a statistically significant number of patients reporting improvements in OCD and anxiety symptoms after 6 months of treatment (group A). No statistically significant improvement was observed in motor ($p = 0.375$) and vocal ($p > 0.999$) tics.

The majority of TS patients experience poor quality of life and social and relationship difficulties. School performance and employment status are also reported to be affected by TS.[5] In 2008, Cavanna et al published a health-related measure specifically for TS cohorts, called the Gilles de la Tourette Syndrome-Quality of Life Scale.[30] In 2013, Cavanna et al conducted a survey to evaluate TS patients' quality of life, reviewing 13 studies that investigated health-related quality of life in adults and/or young people with TS.[31] They concluded that the severity of tics and the presence of comorbidities, particularly OCD and anxiety disorder, are associated with a poorer quality of life[31,32]; however, conventional treatment typically only slightly reduces these TS symptoms.[25]

Our study showed a statistically significant improvement in patients' quality of life ($p < 0.005$), measured from 1 to 5 on a 5-point Likert scale (very low to very high) reported by the patient. These findings coincide with the improvements in OCD and anxiety disorder comorbidities.

A statistically significant reduction in the number of conventional medications used was observed in our study ($p < 0.005$). Patients reported that this reduction was made in consultation with their primary care physician. This may suggest that medical cannabis contributes to an overall improvement in TS symptoms with less potential side effects.

Müller-Vahl et al studied the efficacy of THC treatment for TS patients, focusing on how the treatment improved motor and vocal tics.[18,19] Tic severity was measured according to the Shapiro Tourette's Syndrome Severity Scale, The Tourette's Syndrome Global Scale, and the Yale Global Tic Severity Scale (YGTSS).[33] OCD was assessed using a self-rating scale (Tourette's syndrome symptom list [TSSL]). Patients reported improvements in OCD; however, TSSL scores were only collected after administration of a daily single dose of THC for 2 days, at the first 24 h postadministration.[18] In a follow-up 6-week randomized study, Müller-Vahl et al found an improvement in motor and vocal tics.[19] In that study, TS patients were treated for over 6 weeks with up to 10 mg/day of THC and tics were rated at six visits according to the same scales.

Results showed an improvement in motor and vocal tic severity.[19] Our study did not find a statistically significant improvement in motor or vocal tics or in tic frequency; however, these results are limited in that the method of evaluation we utilized lacks the sensitivity of the scales used in other literature (i.e., YGTSS).[34] In other scales, the assessment is performed by rating tic severity according to number, frequency, intensity, complexity, and interference of tics.

The information collected from this cohort of patients sheds light on the impact of prolonged cannabis treatment's role in improving TS comorbidities, quality of life, social integration, and employment status of TS patients. Our study has some limitations. The sample size was small with no control group, the tics assessments were not performed using objective measures, and the information on conventional medications used or stopped was missing.

While the use of medical cannabis for the TS indication is increasing, the effect of medical cannabis on TS patients needs to be further studied. Most TS patient's reports on quality-of-life improvements are documented in social media networks and were not able to be appropriately quantified in this study. We did show that quality of life was improved in two-thirds of participants, likely due to the reduced anxiety and OCD symptoms. Our findings suggest that medical cannabis may be an effective and safe option to improve comorbidities and quality of life in TS patients. Medical cannabis effectiveness should be further evaluated in large-scale randomized clinical trials.

Authors' Contributions

D.B.: conceptualization and investigation, data acquisition, formal analysis, and writing original draft (lead); O.S.: writing—review and editing (equal); T.Z.-B.: formal analysis (lead); M.B.: supervision, and writing—review and editing (equal); I.G.: supervision (supporting); E.K.: conceptualization, and data acquisition (equal); L.B.-L.S.: conceptualization, and review and editing (equal). All authors have contributed to the article.

Author Disclosure Statement

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Abbreviations Used

ADHD = attention deficit and hyperactivity disorder
DSM-5 = Diagnostic and Statistical Manual of Mental Disorders
OCD = obsessive compulsive disorder
SPECT = single photon emission computed tomography
THC = tetrahydrocannabinol
TS = Tourette's syndrome
TSSL = Tourette's syndrome symptom list
YGTSS = Yale Global Tic Severity Scale