

# Preliminary Evidence on Cannabis Effectiveness and Tolerability for Adults With Tourette Syndrome

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The authors retrospectively evaluated effectiveness and tolerability of cannabis in 19 adults with Tourette syndrome. Tics scores decreased by 60%, and 18 of the 19 participants were at least “much improved.” Cannabis was generally well tolerated, although most participants reported side effects.

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Tourette syndrome (TS) is an inherited neuropsychiatric disorder characterized by motor tics and at least one vocal tic with childhood onset that has persisted for more than 1 year.<sup>1</sup> TS has a high comorbidity with other neuropsychiatric disorders, including obsessive-compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), and rage attacks. When active treatment of tics is required, comprehensive behavioral intervention for tics based on habit reversal training is the first-line treatment.<sup>2</sup> Mainstay pharmacological agents are high-potency antipsychotics and the alpha-2 receptor agonists. These drugs are limited by significant side effects. Other pharmacological treatments have only limited evidence.

Cannabinoids have been explored as a treatment for TS since the 1980s.<sup>3–5</sup> Delta-9-tetrahydrocannabinol (THC), a major psychoactive ingredient of cannabis, is thought to account for many of the pharmacological actions of cannabis. In recent years, there has also been interest in cannabidiol (CBD), a primary cannabinoid in cannabis, which has been found to have antiemetic, anticonvulsant, neuroprotective, and anti-inflammatory properties.<sup>6</sup> The earliest case series reported on inhaled cannabis resulting in improvement in tics and comorbid symptoms in three patients with TS.<sup>3</sup>

Subsequently, a survey of TS patients found that 17 out of 64 consecutive respondents had used cannabis, and the majority of these (82%) reported that cannabis was effective in reducing tics, premonitory urges, and comorbidities.<sup>7</sup> Later, several open uncontrolled studies with THC showed similar results.<sup>5</sup> Two controlled trials have been reported to date, both of which investigated the effect of oral THC in TS patients. In a randomized double-blind placebo-controlled crossover single-dose trial with 12 adult patients, a significant global tic improvement was observed with the self-

rating Tourette Syndrome Symptom List (TSSL) after treatment with oral THC compared with placebo.<sup>8</sup> In another randomized double-blind, parallel group placebo-controlled study over 6 weeks with 24 adult patients, a significant difference was found in the TSSL between the THC and placebo groups after 10 treatment days.<sup>9</sup> No serious side effects occurred during the study. These two studies are limited by small sample sizes and short treatment duration. It is noteworthy that the improvements seen in THC trials were not as large as those described in the case series with cannabis. Given this limited evidence, several systematic reviews have concluded that there is currently insufficient evidence to support the use of cannabinoids for tics.<sup>10–13</sup>

The goal of the present retrospective study was to evaluate the effectiveness and tolerability of cannabis treatment in adult patients with TS. We hypothesized that cannabis would be effective and well tolerated in the treatment of tics and comorbid symptoms. We add to the emerging literature on the topic by reporting the findings from semistructured assessments of 19 adult patients with TS treated with inhaled cannabis to help control their tics.

## METHODS

We identified 22 patients who had been using cannabis for TS in our Tourette Syndrome Neurodevelopmental Clinic at the Toronto Western Hospital (Toronto, Ontario, Canada). Our inclusion criteria were diagnosis of TS according to DSM-5 criteria and using cannabis regularly for 6 months or longer. Exclusion criteria were significant cognitive delay, current polysubstance abuse, or current alcohol abuse. Of the 22 patients we identified, one was excluded because the patient had been using cannabis for less than 6 months. Twenty-one patients met our inclusion criteria and were

TABLE 1. Demographic and Clinical Characteristics and Cannabis Use in the Study Participants (N=19)<sup>a</sup>

ID	Age (Years)/ Gender	Comorbidities	Current and Past Medications	How Participant Learned About Cannabis for Tics	Pharmaceutical Cannabinoid	Cannabis			Duration of Single Dose Effect on Tics (Hours)
						Current Source	Dosing	Route	
1	19/M	OCD, ADHD, restless leg syndrome, nocturnal myoclonus	Past: clonidine, risperidone, sertraline, amphetamine/dextroamphetamine, atomoxetine, clonazepam, desmopressin	Mother found information online	None	Approved supplier	0.5 g four times daily	Smoked	2–3
2	40/F	OCD, depression	Current: citalopram, clonazepam; Past: clonidine, risperidone, pimozone, aripiprazole, quetiapine, tetrabenazine, paroxetine, fluoxetine	Family friend with TS	Past: nabiximols, nabilone	Approved supplier	0.125–0.5 g in food every night; 0.5 g smoked/day	Smoked, ingested with food	6
3	21/M	OCD, anxiety	Past: olanzapine, quetiapine, methylphenidate, atomoxetine, fluoxetine, bupropion	Personal experience	None	Unapproved supplier	1 g three times daily	Vaporized, ingested with food	3–4
4	32/M	ADHD, ASD, hypertension	Past: clonidine, risperidone, haloperidol, pimozone, fluoxetine	TS clinic	Past: nabiximols	Approved supplier	0.5 g every night for 1 week, then discontinued for 3 weeks	Vaporized	24
5	34/M	OCD, social phobia	Current: venlafaxine Past: clonidine, pimozone	Friend	Past: dronabinol	Compassion clinic	0.25 g daily	Vaporized	Uncertain
6	51/M	OCD	Current: clonazepam Past: clonidine, mirtazapine, amitriptyline, lorazepam, valerian	Read research by Muller-Vahl and colleagues online	none	compassion clinic	3 g in food, twice weekly	ingested with food	5
7	28/M	OCD, ADHD, platelet abnormality	Past: risperidone	Personal experience	None	Unapproved supplier	<3 g spread over entire day	Smoked	Uncertain
8	27/M	HIV positive	Current: elvitegravir/cobicistat/ emtricitabine/tenofovir, guanfacine, clonazepam Past: clonidine	Personal experience	None	Compassion clinic	0.1 g three times daily	Smoked	2–3
9	18/M	OCD, ADHD, panic disorder	Current: sertraline Past: clonidine, methylphenidate	Online	None	Unapproved supplier	0.3 g spread over entire day	Smoked	1.5–2
10	22/M	ADHD	Past: clonidine, risperidone, pimozone, quetiapine, methylphenidate, atomoxetine, bupropion, fluoxetine, clonazepam	Online	Past: nabilone	Unapproved supplier	1.5 g spread over entire day	Smoked, ingested with food	2
11	27/M	OCD, ADHD	Past: clonidine, methylphenidate, fluoxetine, clobazam, prindolol	Personal experience	None	Approved supplier	1.5–2 g 4–5×/daily	Smoked, ingested with food	1–2

continued

TABLE 1, continued

ID	Age (Years)/ Gender	Comorbidities	Current and Past Medications	How Participant Learned About Cannabis for Tics	Cannabis			
					Pharmaceutical Cannabinoid	Current Source	Dosing	Route
12	64/M	OCD, ADHD, COPD, type 2 diabetes	Current: citalopram, acetylsalicylic acid, clopidogrel, metformin, bisoprolol, amlodipine, atorvastatin, hydrochlorothiazide, omeprazole; Past: clonidine, amitriptyline, bupropion	Personal experience	Past: nabiximols	Approved supplier	10 g/day	Smoked, ingested with food
13	24/M	OCD, ADHD, depression	Past: clonidine, risperidone, haloperidol, methylphenidate, atomoxetine, valproate, topiramate, fluoxetine, fluvoxamine, bupropion, zopiclone, clonazepam, lorazepam, diphenhydramine	Magazine	Past: nabiximols, nabilone	Unapproved supplier	1 g/day smoked, 2 g/day vaporized	Smoked, vaporized
14	30/F	Anxiety	Current: ziprasidone, clonazepam, sertraline, pimozone Past: risperidone, lurasidone, quetiapine, tetrabenazine, pramipexole, clomipramine, trazodone, zopiclone, lorazepam, melatonin, tetracycline, isotretinoin	Personal experience	None	Approved supplier	0.2–0.4 g 1–2 times/week	Smoked
15	24/M	ADHD, anxiety, depression	Current: fluoxetine Past: haloperidol, risperidone, olanzapine, quetiapine, clonidine, topiramate, fluoxetine, fluvoxamine, citalopram, methylphenidate, dextroamphetamine, atomoxetine, clonazepam, diazepam	Friend	Past: nabiximols, nabilone	Unapproved supplier	0.6 g 4–5 times/day	Vaporized
16	42/F	OCD, ADHD, PTSD, hepatitis C	Current: clonidine, aripiprazole, lisdexamfetamine, paroxetine, trazodone, clonazepam Past: ziprasidone, topiramate, bupropion	Personal experience	Past: nabilone	Approved supplier	0.25 g 4–6 times/day	Smoked

continued

TABLE 1, continued

ID	Age (Years)/ Gender	Comorbidities	Current and Past Medications	How Participant Learned About Cannabis for Tics	Cannabis			
					Pharmaceutical Cannabinoid	Current Source	Dosing	Route
17	25/M	OCD	Current: haloperidol, fluoxetine, acetaminophen/dextromethorphan/ doxylamine Past: aripiprazole, lorazepam	Personal experience	None	Unapproved supplier	1 g three times daily	Smoked
18	32/M	OCD, ADHD, specific phobia (needle)	Past: clomipramine, imipramine, methylphenidate, sertraline, fluoxetine, paroxetine	TV: news report	None	Approved supplier	1 g/day total: small amount ingested every few hours, vaporizer in PM	Vaporized, ingested with food
19	49/M	none	Current: sildenafil Past: clonidine, pimo- zide, tetrabenazine, clonazepam, nortriptyline, gabapentin, naproxen	TS clinic	Past: dronabinol, nabiximols, nabilone	Approved supplier	0.5 g twice daily	Vaporized
								8–12

<sup>a</sup> ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; COPD, chronic obstructive pulmonary disease; F, female; g, grams; HIV, human immunodeficiency virus; M, male; OCD, obsessive-compulsive disorder; PTSD, posttraumatic stress disorder; TS, Tourette syndrome.

invited to take part in the study. Of these, 19 were willing to participate (a response rate of 90%) and were recruited into the study after signing informed consent forms. The study was approved by the institutional research ethics board.

Clinical charts for all participants were reviewed for demographic, medical and medication history, psychiatric history, and symptomatology of tics and comorbidities. All 19 participants were invited to the clinic for semistructured interviews, which were carried out by two clinic psychiatrists who have extensive experience with TS (EA-J and PS). The following standardized questionnaires (current and prior to cannabis use) were administered: the Yale Global Tic Severity Scale (YGTSS)<sup>14</sup>; PUTS [Premonitory Urges for Tics Scale]<sup>15</sup>; Y-BOCS [Yale-Brown Obsessive Compulsive Scale]<sup>16</sup>; the Adult ADHD Self-Report Scale, version 1.1<sup>17</sup> (ASRS); the Structured Clinical Interview for DSM-IV Axis I Disorders, with psychotic screen, Patient Edition<sup>18</sup> (SCID-I/P); and the short version of the Marijuana Effect Expectancy Questionnaire (MEEQ),<sup>19</sup> a structured list of specific effects previously reported with the use of cannabis or THC. Assessment for adverse effects associated with cannabis was based on open-ended questions, as well as the SCID-I/P psychosis interview and the MEEQ. Finally, clinicians completed the Clinical Global Impressions Improvement (CGI-I) and Clinical Global Impressions Severity (CGI-S) scales.

YGTSS questionnaires were completed by the study psychiatrists retrospectively to assess tic severity prior to treatment with cannabis and for current symptom severity during cannabis treatment. The retrospective YGTSS questionnaires were based on clinical information in the patient's chart supplemented by patient recollection. The primary efficacy endpoints were the mean change from baseline in YGTSS-total tic score (YGTSS-TTS) and the percentage of patients rated as "much improved" or "very much improved" on the CGI-I. Tolerability endpoints included spontaneous and structured adverse effects reporting via the MEEQ and the SCID-I/P psychosis interview. In addition, the percentage of patients experiencing side effects leading to discontinuation of treatment was noted.

Data analysis was conducted with SPSS 22 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, N.Y., IBM Corp.). Continuous variables were compared with paired sample two-tailed *t* tests, and categorical variables were compared using chi-square tests. A threshold value of *p* < 0.05 was used for statistical significance.

## RESULTS

### Clinical Characteristics and Cannabis Use

Out of the 21 patients who were contacted, 19 took part in the study, for a response rate of 90%. The demographic and clinical characteristics, as well as cannabis history for each participant, are shown in Table 1. The sample consisted of 16 males and three females. The mean age of the participants was 32 years ( $\pm 12.3$  years). Most participants had

TABLE 2. Cannabis Effectiveness in Individual Patients<sup>a</sup>

ID	YGTS Total Tic Score			YGTS Impairment			Y-BOCS Total			ASRS Criteria for ADHD			CGI-S Score			Cannabis Impact on Comorbid Conditions
	Before Cannabis Use	During Cannabis Use		Before Cannabis Use	During Cannabis Use		Before Cannabis Use	During Cannabis Use		Before Cannabis Use	During Cannabis Use		Before Cannabis Use	During Cannabis Use		
1	26	0		40	0		17	0		Yes	No		5	1		Decreased OCS, ADHD and rage
2	46	20		50	40		27	16		Yes	No		7	4		Decreased OCS and rage
3	26	10		30	10		22	11		Yes	No		3	1		Improved attention; decreased restlessness, impulsivity and rage
4	44	18		50	0		12	12		Yes	No		4	2		Improved attention and communication skills
5	36	11		20	10		28	16		Yes	Yes		4	3		Decreased OCD and anxiety; improved attention
6	26	17		30	20		21	19		Yes	No		4	3		Decreased OCD, anxiety, and rage; improved sleep
7	21	8		20	0		0	0		No	No		4	2		Reduced rage and irritability
8	26	13		30	10		20	14		Yes	No		4	3		Decreased ADHD and rage; improved sleep
9	23	6		0	20		23	19		No	No		4	2		Reduced rage
10	30	18		30	10		0	0		Yes	No		5	3		Reduced restlessness and anxiety; improved attention
11	37	24		40	20		23	20		No	No		5	3		Reduced OCD and ADHD; improved concentration and organization
12	26	28		40	30		26	18		No	No		4	4		Reduced OCD and restlessness; improved concentration and organization
13	31	0		50	0		25	0		Yes	No		5	1		Decreased OCD, ADHD and rage
14	24	0		40	0		0	0		Yes	No		5	3		Reduced rage
15	35	0		50	0		35	0		Yes	No		6	1		Decreased OCD, ADHD, and rage
16	33	15		40	20		38	12		Yes	No		5	2		Decreased symptoms of OCD and rage

continued

TABLE 2, continued

ID	YGTSS Total Tic Score			YGTSS Impairment			Y-BOCS Total			ASRS Criteria for ADHD			CGI-S Score		CGI-I Score	Cannabis Impact on Comorbid Conditions
	Before Cannabis Use	During Cannabis Use		Before Cannabis Use	During Cannabis Use		Before Cannabis Use	During Cannabis Use		Before Cannabis Use	During Cannabis Use		Before Cannabis Use	During Cannabis Use		
17	25	7		40	10		0	6		No	No		6	2	1	Decreased anxiety and rage
18	39	15		40	10		25	13		Yes	No		5	3	1	Reduced anxiety and improved productivity
19	26	21		30	10		14	3		No	No		4	3	1	Decreased OCS

<sup>a</sup> ADHD, attention deficit hyperactivity disorder; ASRS, Adult ADHD Self-Report Scale v1.1; CGI-I, Clinical Global Impression Severity scale; CGI-S, Clinical Global Impression Severity scale; OCD, obsessive-compulsive disorder; OCS, obsessive-compulsive symptoms; Y-BOCS, Yale-Brown Obsessive Compulsive Scale; YGTSS, Yale Global Tic Severity Scale.

comorbidities; in particular, 13 patients had a diagnosis of OCD, and 11 had a diagnosis of ADHD.

Except for one patient, all had previously been treated with medications for tics, including 14 with clonidine, 13 with at least one antipsychotic, and nine with both. Nine patients had previously participated in trials with one or more pharmaceutical cannabinoid. While pharmaceutical cannabinoids had been helpful for tics, the patients reported that these were not nearly as effective as cannabis.

All study patients had been using cannabis regularly for at least 2 years. Eight of the patients serendipitously discovered the use of cannabis for tics after personally experiencing notable reductions in their tics following the use of cannabis recreationally. Given the varied sources of medical cannabis among patients, many of which used numerous and idiosyncratic names to refer to their different cannabis products, we were unable to obtain reliable information with regard to cannabis strain or THC/CBD content.

The frequency of use varied significantly, from frequent usage of small doses throughout the day, to twice weekly in the case of two patients, and one participant reporting daily use for 1 week followed by 3 weeks off. The estimated average total daily dose also varied substantially, from less than 0.1 g to 10 g, for a median of 1 g daily. The tic-reducing effects of each cannabis dose lasted a median of 3 hours; there were two notable outliers who reported effects lasting 10 and 24 hours, respectively.

### Effect of Cannabis on Tics and Related Symptoms

All study participants experienced clinically significant symptom relief. Eighteen out of 19 patients experienced a decrease in YGTSS total tic severity and impairment scores (Table 2). Fifteen patients reported obsessive-compulsive symptoms at baseline, and among all of these, YBOCS total scores improved after starting cannabis (Table 2). Of the 13 patients who met criteria for ADHD according to the ASRS, only one continued to do so while using cannabis ( $p < 0.001$ ) (Table 3). All patients reported improvement in comorbid symptoms with cannabis, including obsessive-compulsive symptoms, attention, impulsivity, anxiety, irritability, rage outbursts, and sleep (Table 2). Group average YGTSS baseline scores prior to cannabis use all decreased substantially during cannabis use (Table 3), including total tic severity score (from  $30.5 \pm 7.2$  to  $12.2 \pm 8.6$  [60% reduction],  $p < 0.001$ ) (Figure 1) and impairment score (from  $35.0 \pm 12.9$  to  $11.7 \pm 11.5$  [67.1% reduction],  $p < 0.001$ ). Based on the CGI-I, 18 out of 19 patients (94.7%) were rated as being “very much improved” or “much improved” (Table 3).

### Cannabis Tolerability

The MEEQ short version is comprised of 48 items rated on a 5-point Likert scale, from disagree strongly to agree strongly, covering 6 areas. The ratings for each area on the MEEQ for each individual participant are shown in Table 4. Average ratings across individuals for each scale were as follows: cognitive and behavioral impairment,  $2.4 \pm 0.9$ ; relaxation



**TABLE 3. Cannabis Effectiveness Group Averages<sup>a</sup>**

Instrument and Symptoms		Baseline (Mean±SD)	During Cannabis Treatment (Mean±SD)	Percentage Reduction From Baseline (%)	p
YGTSS	Motor tic severity	16.7±3.3	7.3±5.2	56.3	<0.001
	Vocal tic severity	13.8±4.4	4.8±4.4	65.2	<0.001
	Impairment	35.3±12.6	11.6±11.2	67.1	<0.001
	Total tic severity	30.5±7.2	12.2±8.6	60	<0.001
	Total severity scale	65.8±17.7	23.7±18.1	64	<0.001
Y-BOCS	Obsession subtotal	9.5±6.0	5.0±4.5	47.4	0.001
	Compulsion subtotal	9.2±5.8	4.5±3.7	51.1	0.003
	Total	18.7±11.7	9.4±7.8	49.7	0.001
PUTS		26.2±4.9	18.6±4.6	29	<0.001
		Baseline (Number of Participants)	During Cannabis Treatment (Number of Participants)	Percentage Reduction From Baseline (%)	
ASRS: Symptoms highly consistent with ADHD		13	1	92.3	<0.001
CGI-I: Much improved or very much improved		N/A	18	N/A	N/A
CGI-S: Moderately to extremely ill		18	2	88.9	<0.001

<sup>a</sup> ASRS, Adult ADHD Self-Report Scale v1.1; CGI-I, Clinical Global Impression Improvement scale; CGI-S, Clinical Global Impression Severity scale; PUTS, premonitory urges for tics scale; SD=standard deviation; Y-BOCS, Yale-Brown Obsessive Compulsive Scale; YGTSS, Yale Global Tic Severity Scale.

and tension reduction,  $3.9 \pm 0.5$ ; social and sexual facilitation,  $3.0 \pm 0.7$ ; perceptual and cognitive enhancement,  $3.0 \pm 0.7$ ; global negative effects,  $1.5 \pm 0.6$ ; and craving and physical effects,  $3.3 \pm 1.0$ . The maximum rating reported by an individual patient for the cognitive and behavioral impairment was 3.8 (i.e., between “uncertain” and “agree somewhat”), and the maximum rating for the global negative effects was 2.8 (i.e., between “disagree somewhat” and “uncertain”).

In response to open-ended questions, the following adverse effects were reported: feeling of a “high” (N=3), decreased concentration (N=3), decreased short-term memory (N=2), increased social anxiety (N=2), increased appetite (N=2), confusion with higher doses (N=1), sedation (N=1), irritability (N=1), dry mouth (N=1), dry eyes (N=1), decreased motivation (N=1), increased tics with higher doses (N=1), and wheezing (N=1). Eight of the 19 participants did not report any adverse effects in response to open-ended questions (Table 4). One patient out of the 19 had previously discontinued cannabis due to experiencing severe irritability. However, he subsequently noted that by using cannabis for only 1 week at a time, he avoided the problem of irritability while still getting a tic suppressant effect lasting up to 3 weeks after the last dose. Finally, none of the patients met criteria for a psychotic disorder based on the SCID-I/P.

## DISCUSSION

We conducted a retrospective study of cannabis effectiveness and tolerability in adult patients with TS by interviewing eligible patients in our clinic. Of the 21 patients who were contacted, 19 participated in the study, for a response rate of 90%. These patients had moderate to severe symptoms overall, based on the baseline severity scores of their tic and comorbid symptoms, their baseline CGI-S ratings, and their complex medication histories (Table 1). Based on our two primary outcome measures, the patients appear to have

had striking improvements in symptoms, with an average 60% reduction in YGTSS-TTS scores (from  $30.5 \pm 7.2$  to  $12.2 \pm 8.6$ ,  $p < 0.001$ ) (Table 3, Figure 1) and 18 of the 19 participants (94.7%) being rated as “very much improved” or “much improved” on the CGI-I (Table 3). In addition, there were substantial improvements in comorbid symptomatology (Tables 2 and 3).

It appears that medical cannabis has been generally well tolerated by this group of patients, all of whom had been using cannabis for at least 2 years. The MEEQ did not suggest ongoing adverse effects overall, and the SCID-I/P was

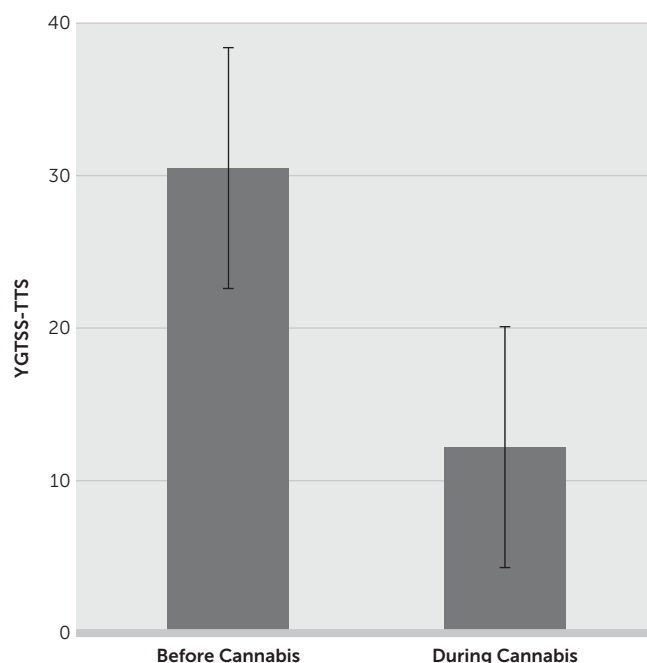
**FIGURE 1. Effect of Cannabis on the Yale Global Tic Severity Scale Total Tic Score (YGTSS-TTS)**

TABLE 4. Cannabis Tolerability

ID	Marijuana Effect Expectancy Questionnaire						Adverse Effects Based on Open-Ended Questions
	Cognitive and Behavioral Impairment	Relaxation and Tension Reduction	Social and Sexual Facilitation	Perceptual and Cognitive Enhancement	Global Negative Effects	Craving and Physical Effects	
1	2.6	2.3	2.3	2.3	1.0	2.5	None reported
2	3.3	3.1	3.0	3.3	2.7	4.2	Increased sleepiness and reduced concentration
3	2.4	2.4	1.7	2.1	1.3	3.0	None reported
4	3.2	3.3	3.0	3.3	2.8	3.3	Increased irritability and appetite
5	2.6	3.8	2.8	3.3	2.3	3.3	Dry mouth and eyes
6	2.4	3.3	2.4	2.4	1.4	2.7	None reported
7	1.7	3.1	2.0	2.8	1.1	2.5	Less motivated, reduced short-term memory
8	3.3	3.0	2.9	2.9	2.1	3.7	Higher doses cause increased social anxiety and appetite
9	3.3	2.9	1.9	2.8	1.3	3.0	Decreased concentration and worsening of symptoms at higher doses
10	3.8	3.9	2.2	2.8	1.4	3.0	May impair attention, short-term memory, information processing
11	1.9	2.9	1.9	1.8	1.1	2.3	None reported
12	2.7	3.1	2.1	2.9	1.7	3.2	None reported
13	1.7	1.4	1.9	2.0	1.3	2.0	None reported
14	3.5	3.4	2.2	3.4	1.4	3.5	Increased anxiety if around others
15	2.7	2.3	1.7	2.0	1.1	2.5	None reported
16	2.2	3.0	1.7	1.5	1.0	2.3	None reported
17	3.0	3.0	2.0	2.5	1.2	2.8	Higher doses cause wheezing and the sensation of being "high"
18	3.2	3.4	2.1	2.0	1.1	3.5	Higher doses cause sleep problems, confusion, and "high" sensation
19	2.6	2.6	2.3	2.4	1.3	2.8	Feels "high" sometimes

negative for psychotic disorders. Nevertheless, on open-ended questioning, most patients did report one or more adverse effect, including feeling "high," cognitive effects, and anxiety. One patient had to temporarily discontinue treatment due to difficulties with irritability.

Overall, these study participants experienced substantial improvements in their symptoms. This is particularly striking given that almost all participants had failed at least one anti-tic medication trial. Our findings are consistent with those of Müller-Vahl and colleagues, who found that most patients in their case series had reported at least a moderate improvement in tic symptoms.<sup>7</sup> It is noteworthy that the improvements reported in that study, as well as those described in ours, are much larger than what was seen in the trials with oral THC.<sup>8,9</sup> This may be due to the uncontrolled

nature of the observational studies. Nevertheless, it is interesting that our patients appear to have had much greater improvement in their symptoms using inhaled cannabis compared with pure oral THC, THC/CBD oromucosal spray, or the oral cannabinoid nabilone. Thus, one might wonder whether inhaled medical cannabis is more effective for tics, possibly as a result of the impact of one or more of the various different compounds that it contains in addition to THC and CBD, and perhaps enhanced by a route that avoids first-pass hepatic metabolism. It is also worth considering the issue of dosing. There is little information on comparing oral and inhaled doses of cannabinoids, and the limited information available is specific to THC. If one accepts various assumptions, a conversion factor of 2.5 can be used to estimate an oral THC equivalent of a certain quantity



of inhaled cannabis.<sup>20,21</sup> If we further assume that the average percentage of THC in the cannabis used by our participants to be 10%, their median total daily amount of 1 g of cannabis would entail 100 mg of THC. Multiplying 100 mg by the conversion factor of 2.5 would yield 250 mg equivalent of oral THC. This would be much higher than the up to 10 mg used in the previous trials with oral THC.

Nevertheless, it is important to highlight the limitations of our retrospective observational study. There is likely a selection bias, as patients who would have tried cannabis and found it to be ineffective or intolerable would be unlikely to remain on it for long or may not be receptive to it as a treatment option. Such patients would not have been eligible for our study. On the other hand, according to the case series of consecutively interviewed patients by Müller-Vahl and colleagues, 82% of patients who had tried cannabis had experienced improvement in symptoms.<sup>7</sup> Another limitation to our study is the potential for recall bias given the retrospective nature of the baseline assessments. These assessments included reviewing the patient charts for supporting clinical notes, including objective clinical examinations at various clinical visits. Still, this cannot completely eliminate the effect of recall bias in the assessments for the present study. An additional limitation of an observational study is the lack of a control. Therefore, it is possible that some of the improvement, perhaps in our younger adult patients, is related to the natural history of tics, which typically improves by early adulthood for most patients. However, this is unlikely to account for the improvements seen in older patients, most of whom had tried multiple other treatments with limited benefit. Still, there could be a regression to the mean effect, especially given the known waxing and waning nature of tics. In addition, there could be an enhanced placebo effect at play with inhaled cannabis, especially given the sociocultural issues surrounding the use of medical cannabis, the administrative process to obtain it, and the ritualized procedure to utilize it. It is noteworthy, however, that eight of our patients had discovered the use of cannabis for tics only serendipitously when they personally experienced notable reduction in their tics after using cannabis recreationally. Nevertheless, to adequately address this issue and other limitations raised here, one would need to conduct a randomized trial that is properly controlled and blinded for inhaled cannabis.

In conclusion, cannabis seems to be a promising treatment option for tics and associated symptoms. However, despite the substantial improvements reported here, some patients continued to take other medications in addition to cannabis. Moreover, while cannabis appears to be generally well tolerated, side effects were common. Importantly, the strength of our conclusions is limited by the retrospective nature of our study. Therefore, to better characterize the benefits and risks of medical cannabis in TS, including the roles of various cannabinoid compounds, there is a need for well-designed prospective, well-controlled studies.

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