

Chronic Vocal or Motor Tic Disorder Issue Brief

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Introduction

Briefings such as this one are prepared in response to petitions to add new conditions to the list of qualifying conditions for the Minnesota medical cannabis program. The intention of these briefings is to present to the Commissioner of Health, to members of the Medical Cannabis Review Panel, and to interested members of the public scientific studies of cannabis products as therapy for the petitioned condition. Brief information on the condition and its current treatment is provided to help give context to the studies. The primary focus is on clinical trials and observational studies, but for many conditions there are few of these. A selection of articles on pre-clinical studies (typically laboratory and animal model studies) will be included, especially if there are few clinical trials or observational studies. Though interpretation of surveys is usually difficult because it is unclear whether responders represent the population of interest and because of unknown validity of responses, when published in peer-reviewed journals surveys will be included for completeness. When found, published recommendations or opinions of national medical organizations will be included.

Searches for published clinical trials and observational studies of cannabis therapy are performed using the National Library of Medicine's MEDLINE database, using key words appropriate for the petitioned condition. Articles that appeared to be results of clinical trials, observational studies, or review articles of such studies, were accessed for examination. References in the articles were studied to identify additional articles that were not found on the initial search. This continued in an iterative fashion until no additional relevant articles were found. Though the Minnesota medical cannabis program does not allow smoked or vaporized dried cannabis, studies using these forms of cannabis administration were allowed for insight they could provide. Finally, the federal government-maintained website of clinical trials, clinicaltrials.gov, was searched to learn about trials currently under way or under development and to check whether additional articles on completed trials could be found.

Definition

Tics are sudden and repetitive twitches, movements, or sounds, which a person cannot stop themselves from doing. Persistent (chronic) vocal or motor tic disorder is defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) as the presence of one or more motor tics (examples include blinking or shrugging shoulders) or vocal tics (examples include humming or clearing the throat), but not both motor and vocal tics (American Psychiatric Association 2013). Tics vary in complexity and are often preceded by

premonitory sensations, often localized to the site of the tic; patients report that performing the tic relieves these sensations (Kurlan 2011 NEJM). To meet DSM-5 diagnostic criteria for chronic vocal or motor tic disorder, a person must have tics that occur many times a day, starting before the age of 18 and lasting over a year. These symptoms must not be caused by medication or another medical condition (Centers for Disease Control and Prevention). Chronic vocal or motor tic disorder is distinct from Tourette Syndrome in that patients experience *only* vocal or motor tics, whereas Tourette Syndrome patients experience *both* vocal and motor tics. Much of the research included in this issue brief refers to studies conducted on the impact of medical cannabis on tics in patients with Tourette Syndrome.

Tics are often preceded by premonitory sensations, often localized to the site of the tic; patients report that performing the tic relieves these sensations. Children with tic disorders often suppress tics in certain social settings, such as school, but this suppression can lead to mental fatigue. Frequency and severity of tics fluctuate over time; intensity of tics can be exacerbated by stress (Kurlan 2011).

Tic onset usually occurs before the age of 10; simple motor tics have a median onset at 5 to 6 years of age; vocal tics typically appear later, usually between ages 8-15. Tics usually worsen during early adolescence, and most patients reach their worst-ever tic severity between ages 7 and 15, followed by a lessening in severity over time. Studies have generally found that some symptoms persist into adulthood, but are associated with less psychological distress, although the physiologic reasons for these changes are not fully understood (Leckman 2003). Of note, a minority of adult patients experience severe tics (Artukoglu 2019). Other neuropsychiatric conditions, most notably Attention Deficit Hyperactivity Disorder (ADHD) and obsessive-compulsive disorder (OCD), are often present in patients with tic disorders (Bloch Sept. 2009, Bloch Dec. 2009).

Prevalence

Chronic vocal or motor tic disorder occurs in both children and adults but is more commonly found among children; estimated prevalence has been reported as high as 6% among school-aged children, with males experience greater risk (Snider 2002).

Current Therapies

The pathophysiology of tic disorders is not fully understood; however, behavioral and pharmacotherapy interventions have been found to be effective in some patients. Generally, evidence supports the efficacy of medication in managing tics, with a typical reduction of 25-50% of tics (Quezada 2018), but available pharmaceuticals hold risk of adverse events (Pringsheim 2012). The first-line treatment for chronic vocal or motor tic disorders in children over the age of 9 is behavioral therapy, and pharmacotherapy with alpha-2 agonists (most commonly clonidine and guanfacine). Behavioral therapy consists of Comprehensive Behavioral Intervention for Tics (CBIT), which has three elements: training the patient to increase awareness of tics; to perform a competing behavior when they feel the urge to tic; and making changes to daily activities to reduce tics (Woods 2016). Behavioral interventions have shown strong evidence of efficacy in reducing tics (Pringsheim 2012). In adults, botulinum toxin

injection is also considered first-line therapy. Second-line treatments include antipsychotics (risperidone and aripiprazole), which have the greatest evidence of efficacy in clinical trials, reporting up to 70% tic reduction (Quezada 2018), but are associated with more severe adverse effects, such as sedation, metabolic side effects, and drug-induced movement disorders (Artukoglu 2019). In milder cases of tic disorders, clinical observation and psychoeducation serves as adequate clinical management (Cothros 2020).

Pre-Clinical Research

The endocannabinoid system, which includes the endogenous cannabinoids (endocannabinoids) as well as the cannabinoid receptors (CB1 and CB2) to which cannabinoids bind, is still a relatively new field of scientific inquiry. Preclinical data investigating the impact of cannabis on tic-based behaviors are extremely limited. Artukoglu et al. included a brief discussion of preclinical findings in their 2019 review paper, which is summarized below. Also included in this section is a paper from Ceci et al. who conducted a mouse study with indirect cannabinoid agonist URB597 to treat tic-like behavior.

Artukoglu BB, Bloch MH. The Potential of Cannabinoid-Based Treatments in Tourette Syndrome. *CNS Drugs*. 2019; 33:417-430.

In a 2019 review of current evidence for the use of cannabinoids in treatment of tics, Artukoglu et al. summarize preclinical findings by stating, “CB1 receptors are located in CNS regions that are thought to be impaired in [Tourette Syndrome]. The endocannabinoid system may regulate the direct and indirect pathways and have an inhibitory effect on the striatal dopaminergic system, which is likely overactive in [Tourette Syndrome].” They conclude that these findings hold therapeutic promise but that additional genetic, neurochemical, and neuroimaging studies are needed to understand the role of cannabinoids in modulating tics (Artukoglu 2019).

Ceci C, Onori P, Macri S, Laviola G. Interaction Between the Endocannabinoid and Serotonergic System in the Exhibition of Head Twitch Response in Four Mouse Strains. *Neuroto Res* 2015; 27:275-283.

This study examines the use of URB597, an indirect cannabinoid agonist that enhances endogenous anandamide levels, in reducing pharmacologically-induced tics in a mouse model. Four strains were selected to represent a broad spectrum of genetic variability; 16 adult male mice were injected with either vehicle solution or URB597 and recorded for 10 minutes. The mice were then injected with DOI, a pharmaceutical agent producing tic-like behavior, and recorded for another 10 minutes. The recordings were scored by a trained observer for head twitch response, skin jerk, bar holding, digging, immobility, grooming and movement, and exploratory behaviors. The authors found there were differences across strains in baseline movements. Once the cannabinoid agonist URB597 was administered, one of the four strains reduced sniffing behavior and one increased its sniffing behavior; no other changes were observed. Following DOI administration, all four strains of mice began to show head twitch and skin jerk behavior and URB597 administration significantly reduced frequency and duration of head twitch behavior in all four mouse strains. No effect was observed in regard to skin jerk behavior or other observed behaviors. The authors suggest that their findings support the idea that the endocannabinoid system may be a therapeutic target for tic behaviors in humans.

Clinical Trials

Clinical trial data on patients with chronic vocal or motor tic disorders including Tourette Syndrome are also limited; a few recent review papers discuss two main randomized trials published by Muller-Vahl in 2002 and 2003 and provide useful interpretation; these reviews are summarized along with the two relevant trials. One ongoing but unpublished study listed registered on ClinicalTrials.gov is briefly described.

Artukoglu BB, Bloch MH. The Potential of Cannabinoid-Based Treatments in Tourette Syndrome. *CNS Drugs*. 2019; 33:417-430.

The authors reviewed evidence for cannabinoid-based treatment of Tourette Syndrome and related tics. They found only two randomized placebo-controlled trials, one using THC as monotherapy and the other using THC as adjuvant therapy. The first trial was a double-blind crossover, single-dose trial in 12 adults with Tourette Syndrome (Müller-Vahl 2002); five of these patients were already taking psychotropic medication and maintained their previous dosages during the study. The patients were given either 5 mg, 7.5 mg or 10 mg THC according to body weight, sex, and prior marijuana use. Using the Tourette's Syndrome Symptom List (TSSL), this study found a significant reduction in tics and obsessive-compulsive disorder, which is often correlated with tic behaviors with THC treatment compared to placebo. Subjective global tic severity scores, as rated by an examiner, were lower with THC treatment but did not reach statistical significance. Five patients experienced mild side effects.

The second trial was a six-week double-blind parallel group trial with a maximum THC dosage of 10 mg in 24 adults with Tourette Syndrome (Müller-Vahl 2003). In the THC treatment group, there were five drop-outs, of which one was attributed to adverse effects. This study found that the THC treatment group showed significant improvement on the Yale Global Tic Severity Scale and Tourette's Syndrome Clinical Global Impressions scale after the study duration of one month, with statistically significant benefit observed at two weeks and dissipating within one day of ceasing treatment. Five subjects in the THC group experienced mild adverse effects.

The authors also describe two unpublished trials of pharmaceuticals that act on the endocannabinoid system. The first is an uncontrolled trial of palmitoylethanolamide (PEA), an agent which mimics properties of cannabis, in 16 adults with Tourette Syndrome, which suggested benefit when combined with THC. The second is a single-dose, placebo-controlled trial of monoacylglycerol lipase inhibitor (ABX-1431), which amplifies cannabinoid signaling in the endocannabinoid system. This study showed an improvement in tic severity eight hours after treatment.

The review authors conclude that clinical trial data on the efficacy of cannabinoids in treating tics is limited, and "considering the current evidence, it is premature to prescribe cannabinoid-based treatments in children given the risks for developmental adverse effects. They are also not the ideal medications to use in adults, due to the significant effects they have on driving and urine toxicology test positivity."

Koppel BS, Brust JC, Fife T. et al. Systematic review efficacy and safety of medical marijuana in selected neurologic disorders: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2013; 82(17):1556-63.

This report is a systematic review of literature on medical marijuana for treatment of symptoms of multiple sclerosis, epilepsy, and movement disorders. This review graded 34 studies which met inclusion criteria according to the American Academy of Neurology classification scheme for therapeutic articles. Only two articles were included in the discussion of Tourette Syndrome: Müller-Vahl 2002 was found to lack statistical power to enable reliable conclusions to be drawn and Müller-Vahl 2003 was found to have no significant differences between the treatment and placebo group after Bonferroni correction was applied to the results. The authors concluded: "For patients with Tourette Syndrome, data are insufficient to support or refute efficacy of THC for reducing tic severity."

Müller-Vahl KR, Schneider U, Koblenz A, Jöbges M, Kolbe H, Daldrup T, Emrich HM. Treatment of Tourette's syndrome with Delta 9-tetrahydrocannabinol (THC): a randomized crossover trial. *Pharmacopsychiatry*. 2002 Mar; 35(2):57-61.

In this randomized crossover trial with 12 patients (11 men, mean age was 34 ± 13 years) with Tourette Syndrome were recruited from a clinic who were on stable medication for at least two months; exclusion included significant illness or psychiatric comorbidity. Five patients were being medicated for Tourette Syndrome. Additionally, seven patients had previously used marijuana, among whom four were regular users but were asked to stop use at least a week prior to beginning the study. The study was double-blind and placebo controlled, and patients were randomly assigned a single dose of 2.5 mg or 5 mg THC oral capsule (depending on weight, sex, and marijuana use history) or a placebo, with a four-week washout period between treatments. Blood samples were taken at six intervals in the 24 hours following treatment to collect plasma concentrations of THC and its metabolites. Patients completed self-rating scales for tic severity using the Tourette's Syndrome Symptom List (TSSL) before and three-four hours after treatment; an examiner completed the Shapiro Tourette's Syndrome Severity Scale (STSS), Yale Global Tic Severity Scale (YGTSS), and Tourette's Syndrome Global Scale (TSGS) as well as a subjective improvement rating. Treatment versus placebo TSSL scores showed a significant improvement in motor and vocal tics after THC treatment as well as in obsessive compulsive behaviors. The authors analyzed data a second time, including only patients who received 7.5 mg THC or 10 mg THC and found significant improvements measured by the TSSL and motor tics measured by the YGTSS. No subjects experienced serious adverse events; five reported mild transient adverse reactions lasting less than six hours and two patients reported mild side effects after placebo treatment. Simple linear regression showed a significant correlation between tic improvement, as measured by STSS, TSGS, and YGTSS, and maximum plasma concentration of THC metabolite 11-OH-THC. The authors note that the study's small sample size is a major limitation and its results should be considered preliminary and should be confirmed with larger placebo-controlled studies with a longer treatment period.

Muhler-Vahl KR, Schneider U, Prevedel H. Delta 9-tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome: a 6-week randomized trial. J Clin Psychiatry. 2003;64(4)459-465.

This study was a small randomized, double-blind, placebo controlled six-week trial of the effectiveness of THC at controlling Tourette syndrome symptoms. The 24 subjects had an average age of 33 (range=18-68 years). Fifteen patients were unmedicated for at least six months prior to the study and nine were taking tic-related medications. Patients were randomly assigned to the THC group (n=12) or placebo group (n=12) and THC was administered via oral capsules with a starting dose of 2.5 mg/day. The dosage was increased by 2.5 mg/day every four days, with a target maximum dose of 10 mg/day. If a subject could not tolerate the maximum dose, an adjustment could be made by decreasing study medications up to 5.0 mg until a tolerated dose was achieved. The same dosing schedule was used to reduce medication at the end of the treatment period. Patients were examined at baseline and days nine, 20-22, 30-31, one or two days after medication stopped, and six weeks after medication stopped. At each visit, tic severity was measured using multiple clinician-rated measurement tools. Seven patients dropped out of the study or had to be excluded afterward, but only one of these did so because of side effects (anxiety and restlessness). Most rating scales demonstrated marked tic reduction at visits two, three, and four. However, Bonferroni correction (statistical adjustment for multiple measures) eliminated the statistically significant observations, except for those at day 30-31 of the study. No serious adverse reactions occurred. Five of the patients in the THC group reported mild side effects (tiredness, dry mouth, dizziness), however none of these patients reduced study medication below 7.5 mg due to these side effects because none felt seriously impaired.

Ongoing Clinical Trials

The Hannover Medical School has posted a multi-center randomized controlled trial of nabiximols, a cannabis plant extract, in the treatment of patients with Tourette Syndrome and chronic vocal or motor tic disorders. The study design is double-blind and placebo-controlled and will enroll 96 adult patients to be randomized to the placebo arm (1-12 puffs placebo oromucosal spray per day) or experimental arm (1-12 puffs of oromucosal nabiximols spray per day) over a course of 13 weeks. The primary outcome measure is tic severity, measured by the Total Tic Score of the Yale Global Tic Severity Scale. As of October 2020, the study is recruiting participants and the principal investigator is Dr. Kirsten Müller-Vahl, who has authored the two completed clinical trials reported earlier in this section. More information can be found at *CANNAbinoids in the Treatment of TICS (CANNA_TICS)*:

<https://clinicaltrials.gov/ct2/show/study/NCT03087201?term=tic+cannabis&draw=2&rank=2>

Observational Studies

Two published observational studies on Tourette Syndrome patients using cannabis are included in this section, along with reported data on Tourette Syndrome patients enrolled in Minnesota's Medical Cannabis Program from 2015-2017.

Abi-Jaoude E, Chen L, Cheung P, Bhikram T, Sandor P. Preliminary evidence on cannabis effectiveness and tolerability for adults with Tourette Syndrome. *J Neuropsychiatry Clin Neurosci* 2017; 29:391-400.

This retrospective observational study recruited 19 adult patients at a Toronto Tourette Syndrome clinic who had been using inhaled cannabis regularly for at least six months. On reviewing records of their adult patients, they found 22 that were currently using cannabis. One was excluded due to use less than six months and two declined to participate. In addition to medical record review, patients were brought into the office for a semi-structured interview and multiple standardized questionnaires (current and prior to cannabis use) administered by two psychiatrists. Main outcomes were mean change from baseline in the Yale Global Tic Severity Scale – Total Tic Score (YGTSS-TTS) and the percentage of patients rated as “much improved” or “very much improved” on the Clinical Global Impressions Improvement (CGI-I). Mean age of the 19 patients was 32 years (± 12.3 years), 16 were male, and three female. All but one had previously been treated with medications for tics, including 14 with clonidine, 13 with at least one antipsychotic, and nine with both. The patients were found to have had 60% improvement in YGTSS-TSS (from 30.5 ± 7.2 to 12.2 ± 8.6 , $p < 0.001$) and 18 of the 19 being rated as “very much improved” or “much improved” on the CGI-I. Investigators were unable to obtain reliable information regarding cannabis strain or THC/CBD content. Using reported cannabis usage amounts, estimates of THC content, and approximated conversion of inhaled to oral THC dosing, the authors produced an estimated median dose of 250 mg equivalent of oral THC, notably, this is significantly higher than the doses used in the two extant clinical trials (which used maximum dosages of 10 mg THC). The authors note that this study is limited by likely presence of selection bias. Patients who tried cannabis and quit due to ineffectiveness or intolerable side effects would have been excluded from the study.

Thaler A, Arad S, Schleider LB, Knaani J, Taichman T, Giladi N, Gurevich T. Single center experience with medical cannabis in Gilles de la Tourette syndrome. *Parkinsonism and Related Disorders* 2019; 61:211-213.

This retrospective observational study identified Tourette Syndrome patients who were approved to use medical cannabis in Tel-Aviv, Israel. Sixty-three patients were initially identified; of these, 42 patients were included in the study (exclusion criteria were the presence of other movement disorders and use of medical cannabis for less than one year). Participants answered a structured phone questionnaire assessing subjective overall impression of efficacy of cannabis treatment (1-5 Likert scale). The subjects were mostly male ($n=33$) and mean age was 34.45. Mean global impression of medical cannabis efficacy was 3.85 out of 5 points; subjects reported reduction in tic severity, better sleep, and improved mood as positive therapeutic effects. Of 42 participants, all had tried at least one tic-related therapy and 17 were taking other tic-related medication along with cannabis (atypical antipsychotics ($n=2$), typical antipsychotics ($n=1$), SSRIs ($n=8$), benzodiazepines ($n=5$), methylphenidate ($n=3$), antidepressants ($n=1$) and tetrabenazine ($n=2$)). Four patients administered cannabis orally; 28 used inhalation, and 10 used both methods. Ten patients chose to stop medical cannabis after less than a year of treatment; four reported they stopped because they experienced no benefit on symptoms; the remaining six reported various reasons including side effects. Among all participants, side effects reported included hallucinations ($n=4$), irritability and confusion ($n=6$), subjective cognitive decline ($n=7$), and acute psychotic episode ($n=1$). This study is limited in

interpretation because THC and CBD dosage are unknown and participants were asked to report subjective global impressions; the authors note that some effects can be attributed to placebo.

Office of Medical Cannabis, Minnesota Department of Health. (2019) *Benefits Reported on the Patient Self-Evaluation: Patients With First Enrollment July 2015-June 2017.*

https://www.health.state.mn.us/people/cannabis/docs/about/cohort/c2015_2017_benefits_pse.pdf

Minnesota's medical program began in July 2015 and includes Tourette Syndrome as a qualifying condition. From July 2015-June 2017, 58 patients were certified by a health care practitioner as having Tourette Syndrome, and made at least two purchases of medical cannabis. These patients reported their weekly tic frequency each time they purchased medical cannabis. Their first reported weekly tic frequency was used as a baseline, and subsequent reports were compared to the baseline to assess degree of benefit. Among 58 patients included in this report, 30 (52%) achieved a 30% reduction in weekly tic frequency within four months of their first medical cannabis purchase. Additionally, 19 patients (33%) maintained this 30% reduction for four months after achieving it. This observational data lacks placebo control or dosage information, and relies on self-reported data from patients.

National Medical Organization Recommendations

Pringsheim T, Okun MS, Müller-Vahl K, Martino D, Jankovic J, Cavanna AE, Woods DW, Robinson M, Jarvie E, Roessner V, Oskoui M, Holler-Managan Y, Piacentini J. Practice guideline recommendations summary: Treatment of tics in people with Tourette syndrome and chronic tic disorders. *Neurology*. May 2019; 92(19): 896-906

The American Academy of Neurology *Practice Guideline Recommendations Summary: Treatment of Tics in People with Tourette Syndrome and Chronic Tic Disorders* states: "There is limited evidence that delta-9-tetrahydrocannabinol (THC), dronabinol, is possibly more likely than placebo to reduce tic severity in adults with [Tourette Syndrome]." The guidelines recommend that where regional legislation allows, physicians may consider treatment with cannabis-based medicine for adult patients with otherwise treatment-resistant tics or adult patients who already use cannabis as self-medication to control tics. Additionally, they recommend that physicians who prescribe cannabis-based medicine should prescribe the lowest possible dose to minimize adverse effects and should inform patients of the risks of impairment. Finally, they indicate periodically reevaluating the need for ongoing treatment (Pringsheim 2019).

National Academies of Sciences, Engineering and Medicine. 2017. *The health effects of cannabis and cannabinoids: Current state of evidence and recommendations for research.* Washington, DC: The National Academies Press.

The National Academies of Sciences, Engineering and Medicine produced a report on the health effects of cannabis in 2017, and the committee found limited evidence that THC capsules are an effective treatment for improving the symptoms of Tourette Syndrome (Conclusion 4-8).

Pringsheim T, Doja A, Gorman D, et al. Canadian guidelines for the evidence-based treatment of tic disorders: pharmacotherapy. *Can J Psychiatry*. 2012; 57(3):133-143.

The Canadian Guidelines for the Evidence-Based Treatment of Tic Disorders: Pharmacotherapy states: “There is no evidence to support the use of cannabinoids for the treatment of tics in children or adolescents. Given this lack of evidence, as well as concerns about potential misuse, we do not recommend that cannabinoids be used for treating tics in youth. However, there is low-quality evidence that cannabinoids have modest benefits in the treatment of tics in adults.”

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Müller-Vahl KR, Schneider U, Prevedel H, Theloe K, Kolbe H, Daldrup T, Emrich HM. Delta 9-tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome: a 6-week randomized trial. *J Clin Psychiatry*. 2003 Apr;64(4):459-65.

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