Cannabinoids reduce symptoms of Tourette’s syndrome

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Currently, the treatment of Tourette’s syndrome (TS) is unsatisfactory. Therefore, there is expanding interest in new therapeutical strategies. Anecdotal reports suggested that the use of cannabis might improve not only tics, but also behavioural problems in patients with TS. A single-dose, cross-over study in 12 patients, as well as a 6-week, randomised trial in 24 patients, demonstrated that Δ9-tetrahydrocannabinol (THC), the most psychoactive ingredient of cannabis, reduces tics in TS patients. No serious adverse effects occurred and no impairment on neuropsychological performance was observed. If well-established drugs either fail to improve tics or cause significant adverse effects, in adult patients, therapy with Δ9-THC should be tried. At present, it remains unclear whether herbal cannabis, different natural or synthetic cannabinoid CB1-receptor agonists or agents that interfere with the inactivation of endocannabinoids, may have the best adverse effect profile in TS.

Keywords: cannabinoids, cannabis, Δ9-tetrahydrocannabinol, marijuana, tics, Tourette’s syndrome


1. Introduction

Tourette’s syndrome (TS) is a chronic neuropsychiatric disorder. According to the Tourette’s syndrome Classification Study Group (1), TS is characterised as: multiple motor and one or more vocal tics that must change over time; a duration of > 1 year; and an onset occurring at an age of < 21 years. There is general agreement that TS is often associated with behavioural problems, such as obsessive compulsive behaviour (O CB), attention deficit hyperactivity disorder (ADHD), depression, anxiety, auto-aggression, rage, learning disorders, conduct disorder and oppositional deficit disorder (2). Although the cause of the disease still remains unclear, there is evidence for an involvement of frontal-subcortical pathways. Pathophysiologically, the dopaminergic system seems to play a role (3).

The treatment of TS is unsatisfactory. Currently, no drug reduces the whole spectrum of symptoms: tics and all possible behavioural problems. Treatment of TS is symptomatic and must be individualised. In the treatment of tics, dopamine-receptor blocking drugs (neuroleptics; NL) such as pimozide, haloperidol, sulpiride and risperidone, are considered the most effective agents. Alternatively, clonidine, an α-adrenergic-receptor agonist, can be used for tic suppression. Recent studies provided evidence that dopamine-receptor agonists such as pergolide, are also effective in the treatment of tics. However, the aim of the therapy is to reduce, but not to eliminate, motor and vocal tics. Some patients do not have any benefit from these drugs. In addition, all available drugs are associated with potential adverse effects such as sedation, drowsiness, impaired motivation, weight gain, depression, akathisia and acute dystonic reactions. Behavioural problems require comedication (e.g., selective serotonin re-uptake inhibitors [SSRIs] and psychostimulants), if clinically relevant (4).
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Because therapy of TS is often unsatisfactory, there is expanding interest in new therapeutic strategies that are more effective, cause less side effects and in addition, in ideal circumstances, improve behavioural problems. Preliminary data suggest that Cannabis sativa L. as well as ∆9-tetrahydrocannabinol (THC; dronabinol), the most psychoactive ingredient of cannabis, ameliorates symptoms in TS. In this review, historical aspects, current medical use of cannabinoids, available studies investigating the effect of ∆9-THC in patients with TS and its possible mode of action, are summarised.

2. History

Cannabis has been used medically for thousands of years in oriental and Middle Eastern countries. Since the eleventh century, cannabis was mentioned in most medicinal books in central Europe. In English herbaria of the sixteenth and seventeenth century, cannabis was recommended for easing pain, for the treatment of jaundice, inflammations, tumours or knots of joints. A comprehensive study of Indian hemp by Dr W. O’Shaughnessy in 1839 reintroduced cannabis into European medicine. In the second-half of the nineteenth century, cannabis was widely used for a variety of ailments, including muscle spasms, menstrual cramps, rheumatism, convulsions of tetanus, rhabies and epilepsy, to promote uterine contractions in childbirth and as a sedative to induce sleep. At the beginning of the twentieth century, many chemically oriented studies of cannabis appeared. However, during the mid-twentieth century, cannabis substances almost completely disappeared because of the development of more potent and reliable drugs, the pharmaceutical instability of cannabis, difficulties in its standardisation and legal restrictions.

During the 1960s and 1970s, there was a large increase in the use of smoked cannabis as an intoxicant in the USA and in Europe; today it is the most widely used of all illegal intoxicants. During the 1970s and once again during the 1990s, there has been renewed interest in the potential medical uses of cannabis and its derivatives: first due to the stereochemical definition and synthesis of ∆9-THC, followed by the characterisation of the cannabinoid receptor-system and its endogenous ligands. Today, substantial numbers of patients suffering from various conditions are illegally self-medicating with cannabis [5,101].

3. Current medical use of cannabis/∆9-tetrahydrocannabinol

Cannabinoids can be used in different preparations (e.g., herbal cannabis, cannabis extract, different cannabinoids such as ∆9-THC and cannabidiol, alone or in combination). The route of administration (oral, inhalation, rectal, sublingual) strongly influences the clinical pharmacology; after oral intake, absorption is slow and erratic but the effect may last for as long as 4 – 6 h (maximal up to 12 h); after inhalation, absorption is fast but the action is shorter. ∆9-THC has antinausea effects and, therefore, is used to suppress the nausea and vomiting associated with chemotherapy in cancer patients. In addition, ∆9-THC is known to stimulate the appetite and increases weight in AIDS patients. Furthermore, there is evidence that ∆9-THC is effective in reducing spasticity, ataxia and tremor and improves urinary control in patients suffering from multiple sclerosis (MS). It is suggested that ∆9-THC can be used to control a variety of acute and chronic pain conditions (including migraine). There is also some evidence for its effectiveness in epilepsy, glaucoma, asthma and movement disorders such as dystonia and levodopa-induced dyskinesia in Parkinson’s disease (PD). From experimental models, it is suggested that cannabinoids have neuroprotective effects, for example, in ischaemia and closed head trauma. Other clinical effects of ∆9-THC are reduction of anxiety, enhanced well-being, induction of sleep and general relaxation (reviewed in [6]).

4. Anecdotal reports of cannabis in Tourette’s syndrome

In 1988 [7] and 1993 [8], anecdotal reports suggested that marijuana (C. sativa L.) smoking improves tics and associated behavioural disorders in TS. Sandyk et al. [7] reported on three 15 – 39-year-old male patients who experienced an improvement of tic severity, urge to tic, self-mutilatory behaviour, attention span, hypersexuality and a generalised relaxation when smoking 0.5 – 2 marijuana cigarettes/day. Hemming et al. [8] described a single case of a 36-year-old man who reported that he had been symptom free for > 1 year when taking one ‘cone’ of marijuana per night.

These initial reports were supported by a retrospective survey using a standardised interview in 64 consecutive TS patients attending the Tourette Clinic of the Medical School of Hannover, Germany [9]. Of the 17 patients reporting prior use of marijuana, 14 (82%) experienced a reduction or complete remission of motor and vocal tics and an amelioration of premonitory urges (experienced by a large number of patients immediately before the occurrence of tics), OCB and ADHD. N one of these patients reported serious side effects or a deterioration of symptoms when smoking marijuana. Beneficial effects were noted by both patients without medication and patients treated with NL and/or SSRIs.

Once becoming interested in the clinical effects of cannabinoids in the treatment of TS, an increasing number of patients attending a TS clinic reported an improvement of their symptoms, or even a complete remission of motor and vocal tics when using marijuana illegally. Some of these patients felt that regular use of marijuana was superior to treatment with NL. Some used marijuana in combination with NL, whilst other patients used marijuana only occasionally, when their tics deteriorated or significantly interfered with activities of daily living. Most of these patients used smoked marijuana and reported an improvement of tics lasting ~ 3 – 4 h, starting during, or some minutes after
beginning smoking. One might argue that these beneficial effects of marijuana might be due to unspecific effects such as sedation, relaxation, reduction of anxiety, the fact of using an illegal drug, set and setting. Furthermore, tics in TS are characterised by spontaneous fluctuation, the possibility of voluntarily suppression and are largely influenced by environmental factors. Therefore, controlled studies had to be performed to further establish the effects of cannabinoids in the treatment of tics.

5. Treatment of Tourette's syndrome with $\Delta^9$-tetrahydrocannabinol: results from clinical trials

5.1 Uncontrolled, single case studies

In many countries, including Germany, the use of marijuana is illegal and the cannabis herb is not licensed for clinical use. To investigate the therapeutic effect of cannabinoids in the treatment of TS, further uncontrolled and controlled studies, therefore, were performed using $\Delta^9$-THC, the most psychoactive ingredient of Cannabis sativa L.

In an uncontrolled, single case study, for the first time, $\Delta^9$-THC was found to be effective in the treatment of TS [10]. The 25-year-old male patient suffered from TS associated with ADHD, OCB, anxiety, lack of impulse control and self-injurious behaviour. When using marijuana 2 – 3 mg/day (illegally), he noted a marked improvement of both vocal and motor tics and associated behavioural disorders. This patient was treated once with $\Delta^9$-THC 10 mg. At that time, he was unmedicated and had stopped smoking marijuana 3 days before. Using the section on tic symptoms of the Tourette Syndrome Global Scale (TSGS) [11], the total tic severity score was 41 before treatment and was reduced to 7, 2 h after treatment. Both motor and vocal tics improved and coprolalia disappeared. The improvement began 30 min after treatment and lasted for 7 h, no adverse effects occurred. Measuring cognitive functions neuropsychological tests showed improved signal detection, sustained attention and reaction time after treatment. The patient himself noted an improvement of motor and vocal tics, combined therapy with $\Delta^9$-THC, the most psychoactive ingredient of C. sativa L.

In a 24-year-old female suffering from TS with extreme tics, combined therapy with $\Delta^9$-THC and the atypical NL amisulpride was found to be superior to $\Delta^9$-THC or NL alone [12]. Amisulpride was most effective at a high dose of 1200 mg/day, and $\Delta^9$-THC at a low dose of 10 mg/day. The only side effect the patient complained of was minimal galactorrhea. From these preliminary results, it is therefore suggested that $\Delta^9$-THC may augment the antitonic effect of atypical NL such as amisulpride. In rats, it has been demonstrated that hypokinesia, induced by the dopamine-receptor antagonist, haloperidol, significantly increases after co-administration of $\Delta^9$-THC [13]. It has therefore been suggested that cannabinoids in combination with NL might be of therapeutic value in hyperkinetic movement disorders such as TS [14].

5.2 Controlled, single-dose trial

These preliminary results were confirmed by a randomised, double-blind, placebo-controlled crossover single-dose trial of $\Delta^9$-THC in 12 adult TS patients [15]. Patients were treated once with $\Delta^9$-THC 5, 7.5 or 10 mg according to their body weight, sex, age and prior use of marijuana. Using a self rating scale (Tourette's Syndrome Symptom List; TSSL) [11], there was a significant improvement of tics ($p = 0.015$) and OCB ($p = 0.041$) after treatment with $\Delta^9$-THC compared to placebo. Examiner ratings (Shapiro Tourette-Symdrome Severity Scale [STSS] [16], Yale Global Tic Severity Scale [YGTTSS] [17] and TSGS) demonstrated a trend towards a significant improvement ($p < 0.1$) or a significant improvement using different subscores for motor and vocal tics ($p < 0.05$). On the $\Delta^9$-THC treatment day, 10 of 12 patients experienced a global improvement (mean of $+35\% \pm 28\%$; range: 20 – 90%). In contrast, on the placebo day, only three patients reported a global improvement (mean of $+7\% \pm 13.7\%$; range: 10 – 40%). No serious adverse reactions occurred. Blood pressure and pulse did not change. A total of five patients experienced transient mild side effects after treatment with $\Delta^9$-THC lasting for 1 – 6 h. Adverse effects such as headache, nausea, dizziness, hot flush, tiredness, poor powers of concentration and cheerfulness were reported by four. One patient experienced (for $\sim$ 30 min) dizziness, anxiety, tremble, sensitivity to noise and light, dry mouth and ataxia. This patient was treated with $\Delta^9$-THC 10 mg and had never used cannabis before, therefore, it can be assumed that these adverse reactions were due to the relatively high dose, particularly since no dose titration was done.

In addition, a variety of neuropsychological tests were performed to investigate the influence of a single-dose treatment of $\Delta^9$-THC on neuropsychological performance [18]. After treatment with $\Delta^9$-THC compared to placebo, no significant differences were found in verbal and visual memory, reaction time, intelligence, sustained attention, divided attention, vigilance and mood. Using the Symptom Checklist 90-R (SCL-90-R) [19], data provided evidence for a deterioration of OCB and a trend towards an increase in phobic anxiety. However, limitations of the SCL-90-R on measuring OCB are known. The increase in phobic anxiety is probably mainly due to the fact that a single-dose treatment rules out the possibility of administering the dose slowly.

5.3 A 6-week, randomised trial

Results obtained from this pilot study were confirmed by a randomised, double-blind, placebo-controlled study in 24 patients with TS. Patients were treated over a period of 6 weeks with $\Delta^9$-THC 5 – 10 mg [20]. The dose was titrated to the target dose of $\Delta^9$-THC 10 mg. Starting at 2.5 mg/day, the dose was increased by increments of 2.5 mg/day every 4 days. The study consisted of six visits: visit 1 = baseline, visit 2 – 4 = during treatment period, visit 5 and 6 = immediately and 5 – 6 weeks after withdrawal.

Using the Global Clinical Impression Scale (GCIS) [11] at visit 3 and 4 there was a statistically significant difference
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between the Δ⁹-THC and placebo group (p < 0.05). Using examiner ratings such as STSS, YGTSS and a video-based rating scale [21], there was a significant difference (p < 0.05) or a trend towards a significant difference (p < 0.1) between both groups at visit 2, 3 and 4, respectively, in either global scores or subscores (‘motor global scale’, ‘frequency/intensity of motor tics’). Using a self-rating scale (TSSL), at 10 treatment days (between day 16 and 41), there was a significant difference between both groups and at further 13 days, a trend towards a significant difference. ANOVA tests demonstrated a significant difference (p = 0.037).

Seven patients dropped out of the study or had to be excluded but only one due to side effects. No serious adverse effects occurred. Blood pressure and pulse did not change. Five patients in the Δ⁹-THC group reported mild side effects such as tiredness, dry mouth, dizziness and muzziness. Three patients in the placebo group reported adverse effects such as tiredness, dizziness, anxiety and depression. One patient in the Δ⁹-THC group stopped medication at day 4 (first day at dose 5 mg) due to side effects of anxiety and restlessness.

In addition, the influence of a 6-week Δ⁹-THC treatment on neuropsychological performance was investigated [22]. During medication, immediately after medication was stopped and 5 – 6 weeks after withdrawal, no detrimental effects were seen on learning curve, interference, recall and recognition of word lists, immediate visual memory span and divided attention. On measuring immediate verbal memory span, there was even a trend towards a significant improvement during and after treatment. Furthermore, no significant influence on OCB, anxiety, depression and ‘the current emotional state’ was found [unpublished data].

6. Adverse effects of Δ⁹-tetrahydrocannabinol

In the report of the US Institute of Medicine of 1999 on the medical use of marijuana, it is said: ‘Marijuana is not a completely benign substance. It is a powerful drug with a variety of effects. However, except for the harms associated with smoking, the adverse effects of marijuana use are within the range of effects tolerated for other medications’ [23].

The acute effects of Δ⁹-THC are well-established. The acute toxicity is low. Death caused by Δ⁹-THC (and cannabis) has not been reported. The median lethal dose (LD₅₀) in humans is unknown [24]. Acute effects of Δ⁹-THC are dose-dependent and mainly pertain to psyche, cognition, psychomotor performance and circulation. A common side effect is fatigue, less common side effects are euphoria and dysphoria, anxiety, panic, alteration in time perception, fragmented thinking, disturbed memory, attention and reaction time, dizziness, unsteady gait, ataxia, slurred speech, deterioration or amelioration of motor coordination, irritability and lack of impulse. Rarely, depersonalisation, hallucinations and aggravation of psychotic states were observed (reviewed in [25]).

Other side effects of Δ⁹-THC are dry mouth, injected (red) conjunctivae, reduced tear flow, tachycardia, enhanced heart activity, vasodilation, orthostatic hypotension and hypertension (in horizontal position). The following less common side effects have also been reported: headache, vomiting, reduced bowel movements, delayed gastric emptying, muscle pain and weakness, nightmares and diarrhoea [25].

Δ⁹-THC influences numerous hormones including luteinising hormone, follicle-stimulating hormone, testosterone, prolactin, somatotropin, thyroid stimulating hormone and the glucose metabolism. However, mostly these effects are relatively small and tolerance develops to hormonal effects. Δ⁹-THC exerts complex effects on immunity, including impairment of cell-mediated and humoral immunity, immune stimulation, anti-inflammatory and anti-allergic effects. However, currently it is unknown whether these effects are of clinical relevance [25]. There is some evidence that Δ⁹-THC causes impairment of fetal development such as malformations, growths retardation and impairment of cognitive functions. However, there is only a limited number of studies available investigating the effects of Δ⁹-THC/cannabis use in pregnancy. Most of these investigations suggest that the consequences of prenatal exposure to cannabis are subtle [26].

It is controversial whether heavy, regular use of cannabis may impair cognition [27-29]. Long-term medical use of cannabis (> 15 years) has been reported to be well-tolerated without significant physical or cognitive impairment [27,30].

Cannabinoids are contraindicated in patients suffering from a psychotic illness as Δ⁹-THC can induce a schizophrenic psychosis in vulnerable persons. However, at the moment, it is controversial whether there exists a causative relationship between cannabis use and long-term schizophrenic psychosis [31]. Furthermore, the medicinal use of cannabinoids should be restricted to patients without significant cardiac disorder as Δ⁹-THC induces tachycardia, increases cardiac output and, by this, increases cardiac oxygen demand [32]. In pregnant and breast-feeding women Δ⁹-THC should not be used because there is evidence that cannabis may cause subtle disturbances of cerebral development [26]. In children, use of cannabinoids should be restricted to severe and otherwise untreatable diseases (e.g., severe and refractory epilepsy or severe vomiting during antineoplastic treatment) because there is evidence that frequent cannabis use in young people is associated with increased rates of psychotic symptoms, depression and anxiety [33,34]. However, in a small study in eight children (3 – 13 years of age) with haematological cancers, Δ⁹-THC was found not only to completely prevent vomiting during antineoplastic treatment but also to be well-tolerated [35]. The authors suggest that the side effects observed were negligible, because in children the central cannabinoid CB₁ receptor system is not fully developed. Δ⁹-THC should be used with caution in patients with a history of substance
abuse and concomitant therapy with sedatives, hypnotics and other psychoactive drugs. Patients receiving treatment with ∆9-THC should be warned not to drive or operate machinery until it is established that they are able to tolerate the drug.

7. Tolerance, withdrawal and dependency

Tolerance to the effects of ∆9-THC has been demonstrated in most of the behavioural and physiological effects, for example, behavioural actions, cardiovascular effects, analgesia and the disruption of the hypothalamic–hypophyseal axis. There is evidence that tolerance is caused by pharmacodynamic changes such as receptor downregulation and desensitisation [32,36].

Withdrawal has been observed during ‘wash-out’ periods in subjects who had received high doses of oral ∆9-THC or smoked cannabis (∆9-THC 210 mg/day), respectively [37,38]. Most common reported withdrawal symptoms were decreased appetite, inner unrest, increased activity, irritability, insomnia, restlessness, ‘hot flushes’, sweating, rhinorrhea, loose stools, hiccups and anorexia. In general, withdrawal symptoms are mild and there are no obvious physical withdrawal symptoms [31].

A substantial number of long-term, heavy cannabis users meets the criteria for cannabis dependence [36]. The general risk of developing dependence among those who had ever tried cannabis has been estimated at ~ 1 in 10 chance [39]. However, it is unclear whether the risk of dependence in regular recreational users can be applied to patients using cannabinoids for therapeutic reasons. There is evidence that the risk of dependence is low when cannabinoids are used to treat symptoms of chronic diseases such as neurological disorders [36,40]. There is general agreement that the risk for physical and psychological dependency is low compared to that of opiates, benzodiazepines, alcohol and even tobacco [41,42].

8. Central cannabinoid CB1 receptor system

Cannabinoids are highly lipophilic. They act through central (CB1), peripheral (CB2) and probably other, so far unknown, receptors. In 1990, the CB1 receptor was identified as the first cannabinoid receptor [43]. In the CNS, the highest densities of CB1 receptors were found in the basal ganglia, cerebellum and hippocampus [44,45]. Within the basal ganglia, CB1 receptors are particularly prominent in the globus pallidus (GP) and substantia nigra pars reticulata – the indirect and direct output pathways [44]. This accounts for the effects of cannabinoids on motor coordination. CB1 receptors are predominantly localised presynaptically. Since 1992, five endogenous fatty-acid ligands (endocannabinoids) have been identified: anandamide (arachidonoylthanolamide), 2-arachidonoyl glycerol (2-AG), noladin ether, virodhamine (O-arachidonoylethanolamine) and N-arachidonoyldopamine (NADA). There is evidence that endocannabinoids are synthesised and released on demand. After release, they are rapidly deactivated by uptake into cells and enzymatic hydrolysis [46].

Cannabinoids act as regulators of synaptic neurotransmission. There is substantial evidence that they affect the activity of both excitatory neurotransmitters such as glutamate and inhibitory transmitters such as GABA and glycine, as well as several monoamines such as dopamine, serotonin, noradrenaline, acetylcholine and neuropeptides [47].

It can be speculated that the CB1 receptor system might play a causative role in the pathophysiology of TS. However, there is no evidence that TS is caused by mutations in the central cannabinoid receptor (CNR1) gene [48]. Studies using single photon emission tomography (SPECT) and [123I] AM 281 to investigate central CB1 receptors have already been performed in humans, but are not yet suitable to clarify the functional role of CB1 receptors in TS [49].

9. Possible explanations for the beneficial effects of ∆9-tetrahydrocannabinol in Tourette’s syndrome

In TS, positive effects of ∆9-THC in the treatment of tics might be explained by different mechanisms. The neurochemical basis of the disease is still unknown. However, there is evidence that tics are caused by a hyperactive dopaminergic system, based on the observation of the beneficial effect of dopamine blocking agents on tics. From neuroimaging studies, it is suggested that presynaptic dopamine transporter abnormalities are involved in the pathophysiology of TS [50,51]. In addition, decreased levels of homovanillic acid, a metabolite of dopamine, have been reported in the CSF of TS patients [52,53]. There is substantial evidence for a complex functional interaction between the dopaminergic and the cannabinoid receptor system [54]. Dopamine acting at D2-like receptors stimulates anandamide release in the dorsal striatum suggesting that the endocannabinoid system participates in dopaminergic regulation of striatal function [55]. In the reserpine-treated rat, a model for PD, a sevenfold increase in the levels of the 2-AG was observed in the GP. Administration of a dopamine D2-receptor agonist increased locomotion accompanied by reduced 2-AG and anandamide levels in the GP [54]. In humans, it has been shown that nabilone, a classical synthetic THC analogue, ameliorates levodopa-induced dyskinesia in PD [56]. Therefore, it can be speculated that ∆9-THC inhibits dopaminergic activity in motor-control centres and, by this, reduces tics in TS.

On the other hand, several other neurotransmitters involved in frontal-subcortical circuits have been suggested to play a role in the pathobiology of TS, including the GABAergic, glutamatergic, cholinergic, serotonergic, noradrenergic, opioid and secondary-messenger systems [57]. There is experimental evidence that the activity of most of these transmitters is affected by cannabinoids. Therefore, beneficial effects of ∆9-THC in TS might also be explained by an interaction between THC and one of these neurotransmitter systems. It has been suggested that tics might be caused by a hyperactivity of the excitatory amino acid, glutamate. There is evidence that cannabinoids inhibit abnormal glutamate production,
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that might result in tic improvement after ∆²-THC treatment [47]. In addition, it has been hypothesised that a decrease in striatal GABAergic projections resulting in increased glutamatergic cortical excitation might cause tics [57]. Cannabinoid receptors are located at high concentrations on GABAergic terminals projecting from the striatum to the globus pallidus lateralis and, by this, enhance inhibitory motor effects [58]. This might result in a reduction of tics as well.

10. Cannabis, ∆⁹-tetrahydrocannabinol and other compounds

Although it is clear that agents interacting with the central cannabinoid receptor system have a great therapeutic potential, it is completely unknown which of the different agents may have the best adverse effect profile. So far, there are only two small studies available suggesting no relevant difference in the use of either ∆²-THC or C. sativa L. plant extract and marijuana, respectively, in the treatment of spasticity in MS (n = 16) [59] and the effect of antiretroviral agents in AIDS (n = 62) [60]. Results of a first Phase III trial comparing the efficacy of oral cannabis extract and ∆²-THC in MS spasticity (n = 660) are expected in the Autumn of 2003 [47]. Several other CB1 agonists have been used in animal studies (but not in humans) and might be more effective and better tolerated than ∆²-THC because the window of ∆²-THC is narrow between clinical and unwanted psychic effects. Furthermore, several other experimental agents stimulating the CB1 receptor system have been used in vitro. Endocannabinoid release can be stimulated through inhibition of its degradation through inhibition either of the re-uptake mechanisms or enzymes that cause degradation [46]. The therapeutic potential of both CB1 antagonists (SR141716A) and non-psychoactive cannabinoids such as dexanabinol and ajulemic acid (CT3) (not binding to CB1 receptors) is under investigation.

11. Expert opinion

The treatment of TS must be individualised. If tics are marked and/or cause psychosocial problems, pharmacotherapy is indicated. Treatment of tics should be started with an antidopaminergic agent such as sulphiride or pimozide. If classical NL as well as more recently developed atypical antidopaminergic drugs (e.g., risperidone) fail to improve tics or cause significant adverse effects, alternatively clonidine, dopamine agonists such as pergolide and augmentation with clonazepam or an SSRI can be tried.

However, if all these attempts fail to improve tic severity in our opinion treatment with ∆²-THC should be tried. To avoid relevant adverse effects the starting dose should be low (1 – 2 mg/day) and the dose should be increased slowly by increments of 1 – 2 mg/day every 3 – 5 days. ∆²-THC should be taken twice-daily. So far there is no optimal or maximal dose known for the treatment of TS. However, in our experience, clinical effects will start at a daily dose of 2.5 – 5 mg in these group of patients. If no effect occurs (neither beneficial effects nor adverse reactions), the dose should be increased up to 15 – 20 mg/day. The most common side effects are tiredness, dizziness and dry mouth and, albeit rarely, anxiety and panic.

∆²-THC should not be used in patients suffering from a psychotic illness. In children, ∆²-THC should be tried only when tics are extreme and otherwise untreatable. It should be used with caution in patients with a history of substance abuse and cardiac disorder. In older patients, adverse effects seem to occur more often. Although there is some evidence that combined treatment with ∆²-THC and NL might be superior to ∆²-THC or NL alone, concomitant treatment with other psychoactive drugs should be used with caution. Before therapy is started, patients have to be informed about possible impairments of memory and concentration after long-term treatment and possible mild withdrawal symptoms. They should be instructed not to drive until ∆²-THC is well-tolerated.

At present ∆³-THC is available as Marinol® capsules (Unimed Pharmaceuticals) in 2.5, 5 and 10 mg containing synthetic ∆³-THC (dronabinol). Marinol® is the only FDA-approved cannabinoid. It is approved for the treatment of anorexia and weight loss in patients with AIDS and for the treatment of refractory nausea and cancer chemotherapy-induced vomiting. In 1999, the Drug Enforcement Agency (DEA) reclassified Marinol® from a Schedule II to a Schedule III medication, indicating lower abuse and addiction potential and facilitating the prescription refill process. In Germany, two pharmaceutical companies (∆³-THC PHARM GmbH The Health Concept and ∆³-Pharma GmbH) manufacture ∆³-THC from hemp fibre. It is delivered as a resin and has to be dissolved in oil (e.g., sesame or neutral oil). It can be prescribed as capsules or drops. In Germany, ∆³-THC is not licensed for the treatment of TS and, therefore, health insurances often refuse to cover the costs.

Available results on therapeutic effects of ∆³-THC in the treatment of TS has to be considered as preliminary. However, these data strongly suggest that there is at least a group of patients that clearly benefit from oral ∆³-THC treatment. Available controlled studies suggest that ∆³-THC improves motor and vocal tics. However, from case reports, there is also some evidence that ∆³-THC might improve associated behavioural problems such as OCB, autoagression, attention span and impulse control. Further controlled trials including a larger number of patients are needed to further investigate the effects of ∆³-THC in TS. At present, it remains unclear whether herbal cannabis, different natural or synthetic CB1 receptor agonists or agents that interfere with the inactivation of endocannabinoids, may have the best adverse effect profile in TS. However, even today, it is clear that agents that enhance the function of endocannabinoids have a therapeutic potential in hyperkinetic movement disorders.
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Bibliography
Papers of special note have been highlighted as either of interest (+) or of considerable interest (+++) to readers.


• An excellent and very detailed summary, particularly of clinical characteristics and the treatment of TS.


• A good overall review of the phenomenology, pathology, and treatment of TS.


• A comprehensive review of the therapeutic effects of cannabinoids.


• This is the first longer-term controlled study of ∆9-THC in TS suggesting beneficial effects on motor and vocal tics.


• A well-designed study in 63 current and 45 former heavy cannabis users and...
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72 control subjects demonstrating that in heavy cannabis use, cognitive deficits appear reversible and related to recent cannabis exposure.


Websites


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