

Combined Treatment of Tourette Syndrome with Δ^9 -THC and Dopamine Receptor Antagonists

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SUMMARY. Animal studies suggest that cannabinoid receptor agonists might enhance the effect of dopamine receptor antagonists (neuroleptics, NL) in hyperkinetic movement disorders. In Tourette syndrome, NL are the most effective drugs for the treatment of tics. Recent clinical trials demonstrated that delta-9-tetrahydrocannabinol (Δ^9 -THC) also produces a tic-suppressing effect. In this single case study in a 24 years old female suffering from TS with extreme tics, it is suggested for the first time that Δ^9 -THC may be useful in augmenting the pharmacological response to atypical NL such as amisulpride and risperidone in TS patients. No serious adverse reactions occurred. Controlled studies are necessary to confirm this initial report. [Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <getinfo@haworthpressinc.com> Website: <<http://www.HaworthPress.com>> 2002 by The Haworth Press, Inc. All rights reserved.]

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INTRODUCTION

Tourette syndrome (TS) is a chronic neuropsychiatric spectrum disorder characterized by multiple motor and one or more vocal tics. The pathology is still unknown but there is evidence for an involvement of the dopaminergic system (Singer 1997). Dopamine blocking drugs (neuroleptics, NL) are considered the first-line pharmacotherapy for tics. However, these drugs are not effective in all patients, and their usage is limited due to dose dependent side effects such as sedation, weight gain, depression, and irritability (Kurlan 2001).

From animal studies carried out over many years, it is well known that cannabinoids influence motor behavior. It has been demonstrated that acute administration of cannabinoid receptor agonists induces catalepsy and immobility and attenuates turning behavior (Pertwee and Wickens 1991, Souilhac et al. 1995). Central CB₁ cannabinoid receptors are found at very high density in neurons of the basal ganglia. Therefore, there is considerable evidence that cannabinoids modulate the outflow of information from the basal ganglia.

To date the physiological role of the central cannabinoid receptor system is not well understood. However, there is evidence that cannabinoids might be of therapeutic value in different neurological movement disorders. Single case studies and an open uncontrolled trial in five patients suffering from focal and generalized dystonia suggested that cannabidiol (CBD), a non-psychoactive ingredient of *Cannabis sativa*, might be effective in the treatment of different forms of dystonia (Snider and Consroe 1984, Sandyk et al. 1986, Consroe et al. 1986). A pilot study in seven patients suffering from Parkinson's disease (PD) demonstrated that the cannabinoid receptor agonist nabilone reduces levodopa-induced dyskinesia (Sieradzan et al. 2001). In patients suffering from multiple sclerosis (MS) there is evidence that both smoked cannabis and oral delta-9-tetrahydrocannabinol (Δ^9 -THC), the major psychoactive ingredient of cannabis sativa, improves tremor (Consroe et al. 1997, Clifford 1983, Meinck et al. 1989).

In TS, anecdotal reports as well as two randomized double-blind placebo-controlled clinical trials in 12 and 24 patients, respectively, demonstrated that cannabis and Δ^9 -THC reduce motor and vocal tics (Sandyk and Awerbuch 1988, Hemming and Yellowlees 1993, Müller-Vahl et al. 1998, Müller-Vahl et al. 1999, Müller-Vahl et al. 2001, Müller-Vahl et al. in press). Several years ago, Moss et al. (1989) suggested that in TS, cannabinoid receptor agonists might enhance the effect of NL in the treatment of tics because animal studies had demonstrated that cannabinoids like Δ^9 -THC increase NL-induced hypokinesia (Moss et al. 1984).

In this open uncontrolled single case study in a 24 years old female with TS, we report a successful treatment of motor and vocal tics with a combination of oral Δ^9 -THC and amisulpride, an atypical dopamine receptor antagonist.

CASE STUDY

Ms. R. is a 24-year-old female suffering from TS. Motor and vocal tics started at age 9. At the age of 16 years, her clinical status deteriorated and medical treatment was initiated. Between age 16 and 21 several drugs had been prescribed, but either failed to improve tics or could not be tolerated due to significant side effects. The following drugs were used in monotherapy or combination: tiapride, pimozide, sulphiride, olanzapine, clonazepam, fluvoxamine, and clomipramine. At age 21, treatment with risperidone was started and tics improved. Although she complained of side effects such as acute dyskinesia (that required long-term treatment with biperiden), galactorrhea, and amenorrhea, she continued medication. However, by age of 23 years tics worsened again, and could no longer be controlled by risperidone even after the dosage was increased up to 8 mg/d.

At that time, she participated in a randomized double-blind placebo-controlled clinical trial investigating the effect of Δ^9 -THC in TS over a 6-week period at our clinic. During the treatment period her tics clearly improved, and then deteriorated after study medication was stopped. During the course of the study, her treatment with risperidone remained unchanged. After completion of the study it turned out that she had received Δ^9 -THC (10 mg/d). Therefore, she asked for a prescription of Δ^9 -THC for long-term treatment. Unfortunately, her health insurance refused to cover the costs because in Germany Δ^9 -THC is not approved for the treatment of TS.

This open uncontrolled study was carried out to reexamine the effect of oral Δ^9 -THC in combination with an atypical NL. Tics were rated using examiner rating scales (Global Clinical Impression Scale (GCIS) (Leckman et al. 1988), Shapiro Tourette-Syndrome Severity Scale (STSS) (Shapiro et al. 1988), Yale Global Tic Severity Scale (YGTSS) (Harcherik et al. 1984) and a self-rating (Tourette-Syndrome Symptom List) (TSSL) (Leckman et al. 1988). Using the TSSL the patient was asked to rate not only tics, but also “premonitory experiences” prior to the occurrence of tics.

Baseline visit 1 was performed on monotherapy with 8 mg risperidone. At that time, she suffered from extreme vocal tics, including very loud and frequent yelling and severe coprolalia (compulsive swearing). In addition, she had moderate to severe motor tics with facial grimacing, head jerking, arm extension, jumping, and stamping feet. (For tic rating at visit 1 see Table 1 and Figure 1.)

In the first part of the study, combined treatment with risperidone (8 mg/d) and Δ^9 -THC (up to 17.5 mg/d) was started. At a dose of 10 mg Δ^9 -THC, tics clearly

improved. Further dose increases, however, did not cause an additional improvement. Tic rating at visit 2 (week 6) was performed at a dose of 17.5 mg/d Δ^9 -THC in combination with 8 mg/d risperidone (Table 1, Figure 1). The only reported adverse effect was a mild “high-feeling.” Two weeks later, the patient herself reduced the dosage of risperidone at home, but felt that tics deteriorated and, therefore, resumed taking 8 mg/d.

After a treatment period of about 2 months with a combination of risperidone (8 mg/d) and Δ^9 -THC (10 mg/d), tics slightly increased. Tic rating at visit 3 (week 12) documented that tics worsened, but did not reach the severity measured at baseline visit 1 (Table 1, Figure 1).

Therefore, treatment with risperidone was stopped and therapy with amisulpride, an atypical neuroleptic drug, was started. Treatment with Δ^9 -THC (10 mg/d) was continued. The dose of amisulpride was slowly increased up to 600 mg twice a day. Tics improved in frequency and intensity (visit 4, week 17, for tic rating see Table 1 and Figure 1). The only side effect that occurred was minimal galactorrhea.

To exclude that this improvement was attributable only to the treatment with amisulpride and not to the combination of both drugs, treatment with Δ^9 -THC was reduced and discontinued. Tics deteriorated after withdrawal from Δ^9 -THC (visit 5, week 19, Table 1, Figure 1) and improved again after resumption of Δ^9 -THC (10 mg/d) (visit 6, week 20, Table 1, Figure 1).

One month later a final visit (visit 7, week 24, Table 1, Figure 1) was performed. The patient reported mild tic deterioration compared to visit 6, but still

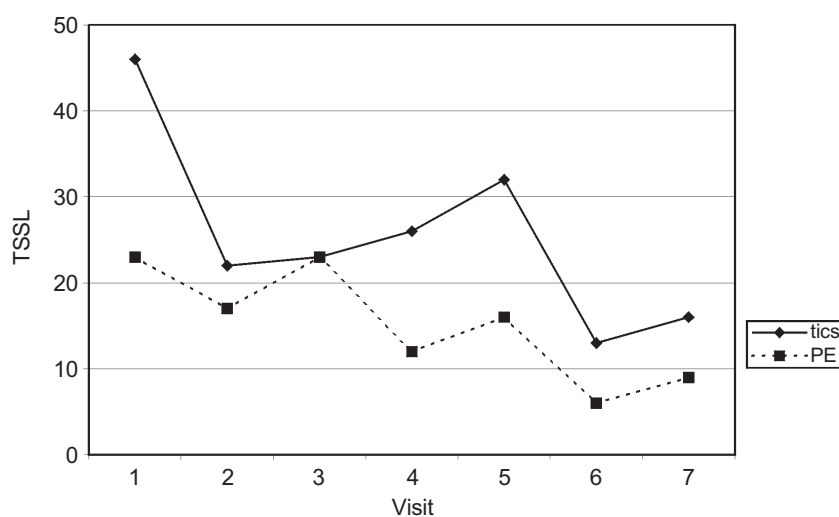
TABLE 1. Tic Rating at Visits 1-7

	visit 1	visit 2	visit 3	visit 4	visit 5	visit 6	visit 7
GCIS	5	4	5	4	4	4	4
STSS	5	4	5	4	4	3	4
YGTSS	81	67	74	64	70	46	59
TSSL	46	22	23	26	32	13	16
PE	23	17	23	12	16	6	9

GCIS = Global Clinical Impression Scale, STSS = Shapiro Tourette-Syndrome Severity Scale, YGTSS = Yale Global Tic Severity Scale, TSSL = Tourette-Syndrome Symptom List, PE = premonitory experiences (measured by the TSSL).

Visit 1: risperidone (8 mg) monotherapy, visit 2: combination of risperidone (8 mg) and Δ^9 -THC (17.5 mg), visit 3: combination of risperidone (8 mg) and Δ^9 -THC (10 mg), visit 4: combination of amisulpride (800 mg) and Δ^9 -THC (10 mg), visit 5: amisulpride (1200 mg) monotherapy, visit 6: combination of amisulpride (1200 mg) and Δ^9 -THC (10 mg), visit 7: combination of amisulpride (1200 mg) and Δ^9 -THC (10 mg).

FIGURE 1. Self rating of tics and premonitory experiences (PE) using the Tourette-Syndrome Symptom List (TSSL). Visit 1: risperidone (8 mg) monotherapy, visit 2: combination of risperidone (8 mg) and Δ^9 -THC (17.5 mg), visit 3: combination of risperidone (8 mg) and Δ^9 -THC (10 mg), visit 4: combination of amisulpride (800 mg) and Δ^9 -THC (10 mg), visit 5: amisulpride (1200 mg) monotherapy, visit 6: combination of amisulpride (1200 mg) and Δ^9 -THC (10 mg), visit 7: combination of amisulpride (1200 mg) and Δ^9 -THC (10 mg).



felt an improvement of motor tics in frequency and intensity and of extreme vocal tics, particularly with respect to their frequency.

Rating of “premonitory experiences” prior to the occurrence of a tic showed that the patient felt that in parallel with the tic improvement, there was a concomitant reduction in the urge to tic especially during combined treatment with Δ^9 -THC and amisulpride (Table 1, Figure 1).

DISCUSSION

Anecdotal reports and two controlled clinical trials have suggested that Δ^9 -THC is effective in the treatment of tics in TS (Sandyk and Awerbuch 1988, Hemming and Yellowlees 1993, Müller-Vahl et al. 1998, Müller-Vahl et al. 1999, Müller-Vahl et al. 2001, Müller-Vahl et al. in press). Although various other drugs have been found to be useful in the treatment of tics, at present there is general agreement that classic and atypical NL are the most effective anti-tic agents (Kurlan 2001). In this single case study, we report for the first time a suc-

cessful treatment of tics with a combination of Δ^9 -THC and the atypical NL amisulpride.

The patient suffered from extreme vocal tics in severe intensity, complexity, and frequency and moderate motor tics. Combined treatment with Δ^9 -THC and amisulpride did not eliminate all the tics, but frequency of vocal tics decreased and motor tics improved significantly. A combination of Δ^9 -THC and amisulpride was superior compared to a combination of Δ^9 -THC and risperidone. Amisulpride was most effective at a high dose of 1200 mg/d, Δ^9 -THC at a low dose of 10 mg/d. The only side effect was minimal galactorrhea.

Single case reports are always of limited meaning. However, this patient was followed for more than 6 months. Tics improved after medication was started, deteriorated after withdrawal from Δ^9 -THC and improved again after continuation of combined treatment. A positive treatment effect could be observed using both global and complex measures, self and examiner rating scales. The patient herself noted not only a marked tic reduction but also an improvement of premonitory experiences prior to the occurrence of tics. One year before in this patient a comparable beneficial effect of Δ^9 -THC had been observed when participating in our double-blind placebo-controlled study. It is worthy of note that the patient desired that no deterioration would occur after withdrawal from Δ^9 -THC because a long-term treatment with Δ^9 -THC was not possible. Her health insurance refused to cover the costs. She herself could not meet them, and, furthermore, declined to use illegal cannabis.

From these preliminary results, therefore, it is suggested that Δ^9 -THC may augment the anti-tic effect of atypical NL such as risperidone and amisulpride. To the best of our knowledge, there is only one single report available suggesting a beneficial effect of amisulpride in TS (Trillet et al. 1990). To date, the neurobiology of TS is unknown. Most evidence, however, supports an active role of the dopaminergic system. It has been suggested that TS is due to dopaminergic hyperinnervation in the striatum or supersensitive postsynaptic dopamine receptors (Singer 1997). It has also been speculated that abnormalities within several neurotransmitter systems (including gamma-aminobutyric acid (GABA), acetylcholine, serotonin, opiates) contribute to TS pathology. Since it has been demonstrated that cannabinoids are effective in the treatment of tics, it can be speculated that the central cannabinoid receptor system might be involved in TS pathology as well (Müller-Vahl et al. in press).

In reserpine-treated rats, an animal model of PD, it has been demonstrated that Δ^9 -THC increases hypokinesia (Moss et al. 1981). Another study has shown that hypokinesia induced by the dopamine receptor antagonist haloperidol significantly increase after co-administration of Δ^9 -THC (Moss et al. 1984). It, therefore, has been suggested that cannabinoids in combination with NL might be of therapeutic value in hyperkinetic movement disorders such as TS (Moss et al. 1989).

Interpreting these data, different hypotheses can be advanced. The beneficial effect of a combination of NL and Δ^9 -THC may be due to an interaction between cannabinoid and the dopaminergic system. Dopamine D1 and D2 receptors both are co-localized with CB₁ receptors in various combinations on the cell bodies and terminal axons of striatal efferent neurons projecting to globus pallidus lateralis (GPI), globus pallidus medialis (GPM), and substantia nigra (SN) (Glass et al. 2000). Several animal studies have demonstrated a highly complex interaction between these two systems within the basal ganglia (Navarro et al. 1993, Giuffrida et al. 1999). Dopaminergic and cannabinoid receptors are both located in the outflow nuclei of the basal ganglia. Therefore, there may be an interrelation of these receptors in the regulation of motor activity (Giuffrida et al. 1999). Repeated stimulation of D1 (but not D2) dopamine receptors enhances catalepsy induced by a potent cannabinoid receptor agonist (Rodriguez de Fonseca et al. 1994). Cannabinoid receptor stimulation attenuates rotational behavior induced by a dopamine D1 (but not a D2) agonist with unilateral lesions of the dopaminergic nigrostriatal pathway (Anderson et al. 1995). Turning behavior induced by cannabinoid agonists can be blocked by D1 and D2 receptor antagonists (Souilhac et al. 1995). In the reserpine-treated rat model of PD it could be demonstrated that cannabinoid receptor agonists reduce D2 (but not D1) dopamine receptor-mediated alleviation of akinesia (Maneuf et al. 1997). Local administration of a D2-like (but not a D1-like) receptor agonist resulted in an eightfold increase of the endogenous cannabinoid release in the dorsal striatum (Giuffrida et al. 1999). Therefore, it has been suggested that the CB₁ receptor system acts as an inhibitory feedback mechanism countering dopamine-induced facilitation of motor activity (Giuffrida et al. 1999).

On the other hand it has been demonstrated that cannabinoids enhance GABAergic transmission in the GPI (Maneuf et al. 1996) and, therefore, enhance inhibitory motor effects resulting in reduced voluntary movements and Parkinson-like symptoms (Wickens and Pertwee 1995). Cannabinoid receptors are located at high concentrations on GABAergic terminals projecting from the striatum to the globus pallidus (GP) and substantia nigra pars reticulata (SNr) (Herkenham et al. 1990). GABA is the major (inhibitory) transmitter in these two motor striatopallidal pathways ("direct" and "indirect" pathway). This circuit is modulated by dopaminergic inputs from substantia nigra pars compacta (SNc), cholinergic striatal interneurons, and serotonergic projections. In PD it has been speculated that cannabinoid agonists such as nabilone reduce levodopa-induced dyskinesia due to an increased GABA transmission in the GPI (Sieradzan et al. 2001).

The distribution of neurotransmitters within the basal ganglia circuits makes different hypotheses possible to explain tic reduction after treatment with a combination of Δ^9 -THC and NL. It can be speculated that in TS, Δ^9 -THC enhances GABA transmission in the GPI resulting in a reduction of basal ganglia motor

output. On the other hand one might hypothesize that cannabinoids reduce tics by a functional interaction between the dopaminergic and the cannabinoid receptor system within the striatum. However, as long as TS pathology and the role of the central cannabinoid receptor system in this disease both are unknown, only speculation is possible.

In conclusion, from this single case it is suggested that the atypical NL amisulpride is effective in the treatment of tics in TS. Furthermore, there is evidence that this anti-tic effect can be augmented by additional treatment with Δ^9 -THC. Previous reports about successful treatment of TS with cannabinoids predominantly included males, because there is higher disease prevalence in male than in female subjects (3-4:1). This study, therefore, suggests that cannabinoids are effective not only in males but also in females suffering from TS.

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