Cannabinoids for Tourette's Syndrome (Review)

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[Intervention Review]

Cannabinoids for Tourette's Syndrome

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ABSTRACT

Background

Gilles de la Tourette Syndrome (GTS) is a developmental neuropsychiatric disorder characterised by the presence of chronic motor and phonic tics. Drugs currently used in the treatment of GTS either lack efficacy or are associated with intolerable side effects. There is some anecdotal and experimental evidence that cannabinoids may be effective in treating tics and compulsive behaviour in patients with GTS. There are currently no systematic Cochrane reviews of treatments used in GTS. There is one other Cochrane review being undertaken at present, on the use of fluoxetine for tics in GTS.

Objectives

To evaluate the efficacy and safety of cannabinoids as compared to placebo or other drugs in treating tics, premonitory urges and obsessive compulsive symptoms (OCS), in patients with GTS.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (in The Cochrane Library Issue 4 2008) , MEDLINE (January 1996 to date), EMBASE (January 1974 to date), PsycINFO (January 1887 to date), CINAHL (January 1982 to date), AMED (January 1985 to date), British Nursing Index (January 1994 to date) and DH DATA (January 1994 to date).

We also searched the reference lists of located trials and review articles for further information.

Selection criteria

We included randomised controlled trials (RCTs) comparing any cannabinoid preparation with placebo or other drugs used in the treatment of tics and OCS in patients with GTS.

Data collection and analysis

Two authors abstracted data independently and settled any differences by discussion.

Main results

Only two trials were found that met the inclusion criteria. Both compared a cannabinoid, delta-9-Tetrahydrocannabinol (Δ^9THC), either as monotherapy or as adjuvant therapy, with placebo. One was a double blind, single dose crossover trial and the other was a double blind, parallel group study. A total of 28 different patients were studied. Although both trials reported a positive effect from Δ^9THC, the improvements in tic frequency and severity were small and were only detected by some of the outcome measures.

Authors' conclusions

Not enough evidence to support the use of cannabinoids in treating tics and obsessive compulsive behaviour in people with Tourette's syndrome.

PLAIN LANGUAGE SUMMARY

Cannabinoids for Tourette syndrome

Cannabinoid medication might be useful in the treatment of the symptoms in patients with Tourette's syndrome. At the present time only two relevant studies have been conducted. Both studies used tetrahydrocannabinol (Δ^9THC). In both studies Δ^9THC was associated with tic reduction. However the sample size was small and a large number of multiple comparisons were made . There were only 28 participants in total, since eight participants took part in both studies. Possibly the patients who derived the greatest benefit and experienced the least adverse effects would be the most inclined to participate in further studies. There were a high number of drop outs/exclusions in the six week study and it is unclear whether intention to treat analysis (ITT) was performed. The results that are reported are analyses done on the patients who remained in the study on the study medication at the correct dose. In reality, patients do opt not to continue treatment if there is limited efficacy or unpalatable side effects. This introduces attrition bias. Whilst there were some significant results, the authors themselves accept that very few of these results are significant if a Bonferroni correction is performed. It is possible that cannabinoid medication has a beneficial effect which is too weak to be detected using ITT and such a small sample size. There is some weak evidence that cannabinoid medication may have an effect on obsessive compulsive behaviour but the measure used was an addition to the TSSL which has not been validated.There were no data on the effect of Δ^9THC on quality of life.There is not enough evidence to support the use of cannabinoids in treating tics and obsessive compulsive behaviour in people with Tourette's syndrome.

BACKGROUND

Gilles de la Tourette Syndrome (GTS) is a developmental neuropsychiatric disorder characterised by the presence of chronic motor and phonic tics. In Diagnostic and Statistical Manual IV (DSM 1V 1994) GTS is characterised by multiple motor and one or more vocal tics lasting more than a year, with an onset before the age of 18. Tics are recurrent, semivoluntary, brief movements that affect multiple muscle groups. Motor tics can be simple, rapidly executed movements or complex slower movements which appear more purposeful. Phonic tics can also be simple: consisting of meaningless sounds and noises such as grunts or sniffs, or complex: with linguistically meaningful utterances that can include coprolalia (an uncontrollable use of obscene language), echolalia (mechanical and meaningless repetition of the words of another person), or palilalia (words being rapidly and involuntarily repeated). Tics can be embarrassing or even painful to execute. Many patients with GTS experience a premonitory sensation preceding a tic, which is associated with an almost irresistible urge to perform the tic. There may be an overwhelming compulsion to do the same action a certain number of times, until it feels 'just right'. Tics vary in intensity over a period of weeks and months. In many cases they are associated with behavioural difficulties, which can include attention problems, motor hyperactivity, obsessive compulsive behaviours, lack of impulse control, anxiety, depression and self-injurious behaviour. The symptoms of GTS can be mild, moderate or severe according to their frequency, intensity and the degree to which they impair daily life.

It is important that treatment is individualised on the basis of the functional impairment caused by tics and the associated comorbid conditions. Medication should be reserved only for those problems that are functionally disabling and which are unable to be remedied by non-drug interventions. Some randomised controlled trials have shown that haloperidol and pimozide can be effective in reducing tics in many patients for much of the time (Ross 1978; Shapiro 1984; Shapiro 1989). However, only 20% to 30% of patients taking haloperidol or pimozide continue with the treatment owing to intolerable adverse effects (Chappell 1995). The newer atypical neuroleptics show fewer adverse effects and of these, risperidone has been the most extensively studied.Risperidone is a treatment with good supporting evidence for short-term safety and efficacy derived from at least 2 randomised placebo controlled tri-

als (RCT's) with positive results. Other atypical neuroleptics which have been studied include; olanzapine, sulpiride. tiapride and quetiapine, but the evidence for their efficacy and safety is less well established comprising only one positive RCT; open label studies; or accumulated clinical experience. Available trials indicate that risperidone can improve tics for between 30% and 62% of patients with GTS (Bruggeman 2001; Dion 2002; Gaffney 2002). IIn an international, multicentre study of more than 3000 patients it was found that clonidine, an alpha-2 adrenergic receptor agonist, is the most frequently prescribed medication. The evidence for its efficacy is, however, inconsistent with other studies on clonidine which found no improvement in tics or behaviour when using objective measures (Gancher 1990; Goetz 1987). The treatment of choice for attention deficit hyperactivity disorder (ADHD) is usually the stimulant medication methylphenidate. It was believed that such medication would exacerbate tics. However, a recent study by the Tourette's Syndrome Study Group (TSSG 2002) demonstrated that methylphenidate plus clonidine was effective in reducing ADHD in patients with comorbid tic disorders, without incurring tic exacerbation. ADHD is thought to occur in between 21 and 90per cent of patients with GTS. Obsessive compulsive behaviour is also common in GTS. For patiedemonstrated that methylphenidate plus clonidine was effective in reducing ADHD in patients with comorbid tic disorders, without incurring tic exacerbation. ADHD is thought to occur in between 21% and 90% of patients with GTS. Obsessive compulsive behaviour (OCB) is also common in GTS. For patients with OCB and comorbid tics, therapy using both a selective serotonin reuptake inhibitor and a neuroleptic may be required for effective symptom reduction (McDougle 1994). Drugs currently used in the treatment of GTS either lack efficacy or are associated with intolerable side effects. Conventional antipsychotic medication such as haloperidol can result in sedation, cognitive slowing, body weight gain, low mood and extrapyramidal symptoms. Extrapyramidal symptoms include: dystonia, which can take the form of fatigue, muscle rigidity, posturing and tongue protrusion; parkinsonian symptoms such as tremors, rigidity, lack of facial expression, drooling and difficulty in movement; akathisia; which is motor restlessness; or dyskinesia, which can take the form of torsion spasm, oculogyric crisis, a condition where the eyeballs rotate upwards and become fixed in that position, head dropping and stiff neck. The newer atypical antipsychotics, such as risperidone, cause drowsiness, dizziness, weight gain, anxiety, impaired glucose tolerance, headaches and the possibility of extrapyramidal symptoms. Clonidine, which can take up to six weeks to have an effect, causes sedation, dry mouth, itchy eyes, dizziness, headache and postural hypotension (a large decrease in blood pressure on standing, which may result in fainting). Methylphenidate, used to treat ADHD occurring comorbidly with GTS, can cause irritability, nervousness, insomnia, anorexia, abdominal pain and headaches. Fluoxetine, a selective serotonin reuptake inhibitor, can cause nausea, vomiting, anorexia and insomnia. No drug has a beneficial effect on the full range of symptoms found in GTS.

The cannabis plant contains many compounds. The most abundant and most psychoactive of the cannabinoids is delta-9-tetrahydrocannabinol (Δ^9THC). Cannabis contains over 60 cannabinoid compounds and some, such as cannabidiol, may modulate the response to THC. Two separate cannabinoid receptors, CB1 and CB2, were identified and cloned in 1990 and 1993, respectively (Matsuda 1990; Matsuda 1993; Munro 1993). The CB1 cannabinoid receptor subtype is found predominantly on neurones in the central nervous system. They are found throughout the brain but are most densely concentrated in the basal ganglia, hippocampus and cerebellum (Romero 2002). The endocannabinoid system regulates synaptic neurotransmission. There is experimental evidence that cannabinoids have an effect on the activity of most neurotransmitters Baker 2003. The endocannabinoid system regulates synaptic neurotransmission. There is experimental evidence that cannabinoids have an effect on the activity of most neurotransmitters (Baker 2003). Many neurological diseases occur because of disordered neurotransmission leading to excess excitation or a lack of inhibition. Smoking has been the route of administration for many cannabis users. This is not a viable option when using cannabis therapeutically, owing to the potential for long-term adverse effects from smoke inhalation. Oral preparations such as nabilone, a synthetic cannabinoid, and dronabinol have been used. However, oral administration is also problematic due to the uptake of cannabinoids into fatty tissue, from which they are released slowly, and the significant first-pass liver metabolism, which breaks down Δ^9THC and contributes further to the variability of plasma concentrations.

There are a variety of potential adverse effects associated with the therapeutic use of cannabinoids. Cannabis and Δ^9THC produce dose-related impairments in short-term memory, attention, hand-eye co-ordination, vigilance and the perception of time and distance. This profile of impairments may contribute to motor vehicle and other accidents. Cannabis can induce a schizophreniform psychosis in normal individuals, precipitate schizophrenia in predisposed individuals and exacerbate positive symptoms in schizophrenics (Johns 2001). Tolerance can develop to the recreationally desired high; this could encourage dose escalation or an increase in the frequency of use. There is evidence that some people have difficulty in stopping cannabis use. Withdrawal symptoms can include restlessness, irritability, anxiety, aggression, dysphoria (an emotional state characterized by anxiety, depression, or unease), tremor and insomnia. Neurocognitive deficits induced by cannabis are dose-related and may persist for some time after cessation. Thomas 1996 found that acute anxiety and panic attacks after cannabis use caused problems for 22% of a sample of 1000 cannabis users.

There is some anecdotal and experimental evidence that Cannabis sativa and Δ^9THC may be effective in treating tics and compulsive behaviour in patients with GTS. In 1988, Sandyk and Awerbuch (Sandyk 1988) reported three patients with GTS who experienced 'a significant amelioration of symptoms' when smoking marijuana. There is also a detailed single case report where marijuana was reported to provide effective treatment for the symptoms of GTS (Hemming 1993). Sixty-four patients with GTS were interviewed about their use of cannabis and, of the 17 who reported cannabis use, 14 experienced a reduction or remission of tics and also some beneficial effect on premonitory urges and obsessive compulsive symptoms (Muller-Vahl 1998).

There are currently no systematic Cochrane reviews of treatments used in GTS. Two other Cochrane reviews are presently being undertaken on the use of fluoxetine and pimozide for tics in GTS.

OBJECTIVES

To evaluate the efficacy and safety of cannabinoids compared with placebo or other drugs in treating tics and obsessive compulsive symptoms in patients with GTS.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomised controlled trials comparing any cannabinoid preparation with placebo or other drug(s) used in the treatment of tics and obsessive compulsive symptoms in patients with GTS. We also considered quasi-randomised trials. We excluded controlled clinical trials and observational studies.

Types of participants

Patients diagnosed clinically with GTS.

Types of interventions

1. Cannabinoid medication in any dosage and duration compared with placebo.
2. Cannabinoid medication in any dosage and duration compared with any other drug(s) for tic reduction and/or reduction of obsessive compulsive symptoms.

Types of outcome measures

Primary outcomes

Tic frequency and severity, including number, intensity, complexity and interference.
These can be measured by a clinician using standard rating scales such as the Yale Global Tic Severity Rating Scale, a video protocol, or a self-rating scale such as the Tourette Syndrome Symptom List.
Obsessive compulsive symptoms can be measured using the Yale-Brown Obsessive Compulsive Scale.

Secondary outcomes

Any measure of adverse effects that are either clinician or patient rated.

Search methods for identification of studies

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (in The Cochrane Library), MEDLINE (January 1996 to date), EMBASE (January 1974 to date), PsycINFO (January 1887 to date), CINAHL (January 1982 to date), AMED (January 1985 to date), British Nursing Index (January 1994 to date) and DH DATA (January 1994 to date).

We also searched the reference lists of located trials and review articles for further information.
We used the following search terms: Gilles de la Tourette Syndrome and all its derivations, such as Tourette Syndrome, cross referenced with cannabis, tetrahydrocannabinol, THC, marijuana, all cannabinoids including proprietary names, e.g. marinol, sativex, dronabinol, nabilone, dexabinol and levonanthradol, as MeSH headings and as text words.

The search was not restricted by language of publication.

Data collection and analysis

Two authors (HR and AC) assessed the identified studies and evaluated their methodological quality using the CONSORT checklist Moher 2001.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

See tables: 'Characteristics of included studies' and 'Characteristics of excluded studies'.

Two trials were found that met the inclusion criteria and compared a cannabinoid, delta-9-Tetrahydrocannabinol (Δ^9THC), either as monotherapy or as adjuvant therapy, with placebo. Two other studies were identified but were excluded as they were only representing the data from the same trials.

TRIAL DESIGN

Both trials were randomised double-blind studies. One was a single dose cross-over design; Muller-Vahl 2002, and the other was a parallel group study ; Muller-Vahl 2003/1.

Co medication was kept stable for the studies although one patient had to be excluded from the six week study because he started taking pimozide during the course of the study.

Participants

The mean ages of participants in the studies were 33 and 34 years. The overall age of the participants ranged from 18 to 68 years. All participants had a diagnosis of GTS according to DSM-III R. Eight participants took part in both studies. In the single dose study, seven of the 12 patients were unmedicated prior to the study. Five were taking additional medication for symptomatic treatment, two patients were medicated with pimozide, one with tiapride, one with diazepam and one with pimozide, clonazepam and fluoxetine. In the six week study, 15 of the 24 patients were unmedicated for at least six months prior to taking part in the study. Nine patients were taking medication for symptomatic relief, four were taking neuroleptics, two were taking selective serotonin reuptake inhibitors (SSRIs) and three were taking a combination of SSRIs and neuroleptics.

Interventions

The study medication was Δ^9THC administered in gelatin capsules of either 2.5 mg or 5.0 mg. The placebo capsules were identical in appearance and in taste. The dose of oral Interventions

The study medication was Δ^9THC administered in gelatin capsules of either 2.5 mg or 5.0 mg. The placebo capsules were identical in appearance and in taste. The dose of oral Δ9THC varied in the two studies. In the single dose study Muller-Vahl 2002, patients received different doses based on weight, gender, age and prior cannabis use. Females with age > 50 years, weight < 60 kg and no prior cannabis use were allocated 5 mg; all other female patients were allocated 7.5 mg. Males with age > 60 years, weight < 70 kg and no prior cannabis use were allocated 5 mg; males with age < 50 years, weight > 70 kg and prior cannabis use received 10 mg; all other males were given 7.5 mg. All patients were hospitalised for one night on the treatment day.

In the six-week study Muller-Vahl 2003/1 , patients were assigned randomly to Δ^9THC in gelatin capsules of 2.5 mg and 5.0 mg or to placebo. Patients assigned to the placebo group were given placebo throughout the study. The dose was titrated to a target dose of 10.0 mg. Starting at 2.5 mg/day the dose was increased by 2.5 mg every four days. The same dosing schedule was used to reduce the medication at the end of the study. If a patient was unable to tolerate the maximum dose, the medication was reduced by up to 5.0 mg until a tolerated dose was achieved.

Outcome measures

In the single dose trial Muller-Vahl 2002 tic severity was rated by patients before and three to four hours after treatment using the Tourette's Syndrome Symptom List (TSSL). Tic severity was also assessed before and after treatment using different examiner ratings: Shapiro Tourette's Syndrome Severity Scale (STSS), the Yale Global Tic Severity Scale (YGTSS) and the Tourette Syndrome Global Scale (TSGS). Patients were also asked to rate: severity of impulse control, obsessive compulsive behaviours (OCB), anxiety, depression, attention deficit hyperactivity disorder (ADHD) and premonitory experiences prior to tics, before and after the treatment. These were rated using: 0 = none; 1 = very mild; 2 = mild; 3 = moderate; 4 = severe; 5 = very severe. OCB was subdivided into obsessions and compulsions such as: checking, ordering, doing things right, counting, rituals, washing and doing things an exact number of times. Patients were also asked at the end of each treatment day to rate the global change (0, ± 10%, ± 20%, and so on up to ± 100%) and to document adverse reactions. At the end of the second treatment day they were also asked which day they assessed as more positive overall, taking into account global change and adverse effects; 10%, 20%, 30% etc.

In the six week study (Muller-Vahl 2003/1), tic severity was rated using several different examiner rating scales: the Tourette Syndrome Clinical Global Impressions Scale (TS-CGI); STSS; YGTSS; plus a video-based rating scale. Patients rated tics using TSSL and they also rated severity of premonitory urges.

Validity and reliability of outcome measures

The STSS and the YGTSS are valid and highly reliable outcome measures Advances in Neurology 2001. The TSGS is less reliable. The way the score is derived may exaggerate small differences in tic severity. This scale also combines information from different domains in a way that is not justified Advances in Neurology 2001. The TSSL is a self and parent report instrument. Self reports are easy to administer but the reviewer found no evidence that the TSSL had undergone rigorous psychometric validation. Goetz devised a video rating protocol which is reliable and valid. The Tourette Syndrome Clinical Global Impressions Scale (TS-CGI) has established validity and reliability Walkup 1992.

Risk of bias in included studies

Randomisation method and concealment of allocation

It was stated for both trials that randomisation was done by a psychiatrist not involved in the study and the codes were kept by him until the study was complete. There was no clear description of exactly how the patients were selected for randomisation and

selection bias is possible. No investigators or patients had access to the randomisation codes during the study.

Eligibility criteria
Both studies accepted patients with a clinical diagnosis of GTS using DSM III-R.

Patient numbers and baseline characteristics.
A total number of 28 different patients were studied. There were 12 patients in the single dose study Muller-Vahl 2002, eight of which also took part in the six week study Muller-Vahl 2003/1. The second study began with 24 patients comprising eight from the first study, plus 16 new participants. The small numbers of participants included in these two trials means that the results may not be applicable to all patients with Tourette's syndrome.

Drop outs
Seven patients dropped out of the six week study or had to be excluded. From the published data it appears that there were five drop outs/exclusions from the treatment group and two drop outs/exclusions from the placebo group. The difference in drop out between the two groups could cause attrition bias. It may be argued that those patients deriving least benefit from the treatment are the most likely to withdraw, leaving the better responders and thus producing an artificially inflated effect size. One patient withdrew because of adverse effects.

Blinding of patients and assessors
Both trials were conducted as double-blind trials. Due to the psychoactive nature of Δ^9THC, it might have been possible for participants and examiners to form an opinion about which treatment was being given. The participants may have been aware of physiological changes such as dizziness and the examiners may have noticed red eyes and behavioural indications typical of cannabinoid medication. This could have led to a Hawthorne effect in the patients and to possible ascertainment bias in the investigators.
Data analysis
In Muller-Vahl 2002 using the examiner ratings STSS, TSGS and YGTSS, global tic severity scores were lower after treatment with Δ^9THC than after treatment with placebo. However, the difference did not achieve statistical significance. No correction was made for analysing multiple tests although the chance of achieving a false significant result increases greatly as multiple analyses are carried out. When the subscores were analysed some improvements did achieve significance. Using the TSGS, complex motor tics (CMT) were found to be significantly reduced without using a correction for multiple testing. Some trends were reported in favour of Δ^9THC but trends are not statistically significant. Using the TSSL, the improvement in OCB was significant (although again not corrected for multiple testing). As all the scales ostensibly measure the same symptoms, if the results were large and truly significant then the difference between treatment and placebo groups should have been found using all measures rather than just in a few subscales of two of the measures.
In Muller-Vahl 2003/1 analyses were only carried out on patients who completed the treatment. Intention to treat analysis would have been preferable as the drop outs were likely to be patients who derived less benefit and excluding them from analysis could have given a false positive result.

Effects of interventions

We found only two studies which compared a cannabinoid therapy with placebo to treat the symptoms of Tourette's syndrome.
A number of outcome measures were used: the Tourette Syndrome Global Scale (TSGS); the Shapiro Tourette Syndrome Severity Scale (STSSS); the Yale Global Tic Severity Scale (YGTSS); the Tourette's Syndrome Symptom List (TSSL). A video rating protocol and the Tourette Syndrome Clinical Global Impressions scale (TS-CGI) were used in the six week study but not in the single dose study. Many of the measures were designed to assess the same outcome: tic reduction.
Muller-Vahl 2002
In this single dose crossover study, using the examiner ratings TSGS, STSSS and YGTSS, the following findings were reported:

TSGS
Tic severity scores demonstrated a greater reduction after Δ^9THC than after placebo but the difference was not statistically significant ($p = 0.132$). Further analysis of subscores found a significant improvement in scores for complex motor tics (CMT) ($p = 0.015$).

STSS
No significant difference was found between placebo and Δ^9THC.

YGTSS
No significant difference was found between placebo and Δ^9THC.

Using the patient rated scale TSSL, the following findings were reported:

TSSL
The authors reported a significant reduction in tics after treatment with Δ^9 THC compared with placebo ($p = 0.015$).
The authors added some additional ratings to the TSSL and using these non-validated additional ratings they reported a significant difference in OCB ($p = 0.041$).

Adverse events
No serious adverse effects were reported although one patient in the Δ^9 THC group stopped medication at day four due to anxiety

and restlessness. Five patients out of 12 reported mild transient adverse reactions lasting between one and six hours.

Muller-Vahl 2003/1

In this six-week parallel group study, using the following examiner ratings: TS-CGI, STSS, YGTSS and the video rating scale, the following results were reported:

TS-CGI

The authors reported significant differences between the Δ^9THC and placebo groups on the two visits when the patients were taking the maximum dose (p = 0.05 and p = 0.008, respectively). There was no overall significant difference using ANOVA. Authors reported a trend (p = 0.079).

STSS

The authors reported a significant difference on the visit when the patients were taking the maximum dose (p = 0.033). There was no overall significant difference using ANOVA.

YGTSS

No significant difference was found but a trend in favour of was reported (p = 0.06). Analysis of a subscore "motor global scale" found a significant difference at maximum Δ^9THC dose (p = 0.04). There was no overall significant difference using ANOVA. Authors reported a trend (p = 0.077).

Video rating

A significant difference was found between the scores for the treatment group and the placebo group on the visit when the patients were taking the maximum dose (p = 0.030).

There was no overall significant difference using ANOVA.

Using the patient rated scale TSSL, the authors reported as follows:

TSSL

On 10 different treatment days a significant difference was found between the treatment and placebo groups (p <0.05). Using ANOVA there was an overall significant difference between the two groups (p = 0.037).

Using the Bonferroni adjustment, the authors reported one significant group difference using the TS-CGI on the visit when the patients were taking maximum dose (p = 0.008).

Adverse events

No serious adverse events were reported. Five patients from the Δ^9THC group reported mild adverse effects such as tiredness, dry mouth, dizziness and muzziness. These adverse events did not cause anyone to reduce the study medication.

DISCUSSION

In the background section of this review we set out the reasons why cannabinoid medication might be useful in the symptomatic treatment of Tourette's syndrome. At the present time only two studies have been conducted. Both studies used tetrahydrocannabinol (Δ^9THC).

The positive finding was that in both studies Δ^9THC was associated with tic reduction. The major limitations of the two studies are the relatively small sample size and the large number of multiple comparisons made. There were only 28 different participants in total, since eight participants took part in both studies. Possibly the patients who derived the greatest benefit and experienced the least adverse effects would be the most inclined to participate in further studies, which could act as a form of selection bias. There were a high number of drop outs/exclusions in the six week study and the results from this study were not analysed using intention to treat analysis (ITT). The results that are reported are analyses done on the patients who remained in the study on the study medication at the correct dose. In reality, patients do opt not to continue treatment if there is limited efficacy or unpalatable side effects. This introduces attrition bias. Whilst there were some significant results, the authors themselves accept that very few of these results are significant if a Bonferroni correction is performed. It is possible that cannabinoid medication has a beneficial effect which is too weak to be detected using ITT and such a small sample size. There is some weak evidence that cannabinoid medication may have an effect on obsessive compulsive behaviour but the measure used was an addition to the TSSL which has not been validated.

There were no data on the effect of Δ^9THCon quality of life.

AUTHORS' CONCLUSIONS

Implications for practice

Although both trials reported a positive outcome for Δ^9THC, the limitations of the studies in terms of multiple comparisons and the small number of participants make it difficult to draw conclusions regarding the efficacy of Δ^9THC.

Implications for research

The reported trials were small and the duration of the longer trial was only six weeks, too short for a condition which can require treatment for many years. Longer trials with larger numbers of patients are necessary to establish the long term efficacy and safety of cannabinoids in treating the symptoms of GTS

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Muller-Vahl 2002

Methods	Single centre, double blind, placebo controlled, single dose, crossover trial , Duration 2 single treatment days separated by a 4 week washout phase
Participants	12 adult patients, 11 male 1 female.Mean age 34 years (Range 18-66 years)Exclusion criteriaUnder 18, history of psychosis and schizophrenia, significant concomitant illness, or pregnant
Interventions	THC 5.0 or 7.5 or 10.0 mg vs. placebo
Outcomes	1.Tic severity patient rated using Tourette's Syndrome Symptom list TSSL.2. Tic examiner rated using Shapiro Tourette's Syndrome Severity Scale STSS, Yale Global Tic Severity Scale YGTSS, and Tourette Syndrome Global Scale TSGS, 3. Patients also rated severity of impulse control; Obsessive Compulsive Behaviours OCB, subdivided into obsessions and compulsions such as checking ordering doing things "just right", counting, rituals, washing and doing things an exact number of times;anxiety;depression;Attention Deficit Hyperctivity Disorder ADHD; and Premonitory experiences PE, prior to tics before and after treatment;Patient rated global change and Adverse reactions
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Muller-Vahl 2003/1

Methods	Single centre, double blind, placebo controlled, parallel group 6 week study
Participants	24 adult patients 19 male 5 female. Mean age 33
Interventions	THC titrated to target dose10mg/day
Outcomes	Tic severity using Tourette syndrome Clinical Global Impressions scale; the Shapiro Tourette-syndrome Severity Scale; the Yale Global Tic Severity Scale; a video protocol for assessment of tic intensity and frequency; and a patient self rating scale the Tourette Syndrome Symptom List
Notes	

Risk of bias

Item	Authors' judgement	Description

Muller-Vahl 2003/1 (*Continued*)

Allocation concealment?	Yes	A - Adequate

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
M-V KR 2001	This is not a trial of the efficacy and safety of D9-THC. Instead it presents data to support the view that D9-THC does not have a negative impact on neuropsychological performance, when given as a single dose to 12 patients
M-V KR 2003	This study presents evidence that there were neither acute nor long term cognitive deficits in patients given 6 weeks treatment with D9-THC

DATA AND ANALYSES

This review has no analyses.

WHAT'S NEW

Last assessed as up-to-date: 28 October 2007.

Date	Event	Description
31 October 2008	New search has been performed	Review edited for submission
20 October 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 2, 2007

Review first published: Issue 4, 2009

Date	Event	Description
31 October 2008	Feedback has been incorporated	Substantive amendment

CONTRIBUTIONS OF AUTHORS

H.Rickards and C.E. Clarke instigated and supervised all stages of the review. A.Curtis carried out the literature searches, obtained the papers, and entered the data into RevMan.

DECLARATIONS OF INTEREST

There is no potential conflict of interest

SOURCES OF SUPPORT

Internal sources

- Birmingham and Solihull Mental Health Trust, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Cannabinoids [*therapeutic use]; Randomized Controlled Trials as Topic; Tetrahydrocannabinol [therapeutic use]; Tourette Syndrome [*drug therapy]

MeSH check words

Humans