Cannabis for dyskinesia in Parkinson disease : A randomized double-blind crossover study

C. B. Carroll, P. G. Bain, L. Teare, et al.

Neurology 2004;63;1245
DOI 10.1212/01.WNL.0000140288.48796.8E

CME

Cannabis for dyskinesia in Parkinson disease

A randomized double-blind crossover study

C.B. Carroll, PhD, MRCP; P.G. Bain, MD, FRCP; L. Teare, BM BCh, MRCP; X. Liu, MB, PhD; C. Joint, RGN; C. Wroath, BA, RGN; S.G. Parkin, BM BCh, MRCP; P. Fox, BM BCh, MRCP; D. Wright, PhD; J. Hobart, PhD, MRCP; and J.P. Zajicek, PhD, FRCP

Abstract—*Background:* The long-term treatment of Parkinson disease (PD) may be complicated by the development of levodopa-induced dyskinesia. Clinical and animal model data support the view that modulation of cannabinoid function may exert an antidyskinetic effect. The authors conducted a randomized, double-blind, placebo-controlled crossover trial to examine the hypothesis that cannabis may have a beneficial effect on dyskinesia in PD. *Methods:* A 4-week dose escalation study was performed to assess the safety and tolerability of cannabis in six PD patients with levodopa-induced dyskinesia. Then a randomized placebo-controlled crossover study (RCT) was performed, in which 19 PD patients were randomized to receive oral cannabis extract followed by placebo or vice versa. Each treatment phase lasted for 4 weeks with an intervening 2-week washout phase. The primary outcome measure was a change in Unified Parkinson's Disease Rating Scale (UPDRS) (items 32 to 34) dyskinesia score. Secondary outcome measures included the Rush scale, Bain scale, tablet arm drawing task, and total UPDRS score following a levodopa challenge, as well as patient-completed measures of a dyskinesia activities of daily living (ADL) scale, the PDQ-39, on-off diaries, and a range of category rating scales. *Results:* Seventeen patients completed the RCT. Cannabis was well tolerated, and had no pro- or antiparkinsonian action. There was no evidence for a treatment effect on levodopa-induced dyskinesia as assessed by the UPDRS, or any of the secondary outcome measures. *Conclusions:* Orally administered cannabis extract resulted in no objective or subjective improvement in dyskinesias or parkinsonism.

NEUROLOGY 2004;63:1245–1250

Treatment of Parkinson disease (PD) with levodopa may be compromised in the long term by the development of dyskinesia. One model of basal ganglia function suggests that cannabinoid agonists may exert an antidyskinetic function by inhibiting γ-aminobutyric acid (GABA) reuptake in the lateral part of the globus pallidus (GPl), thus augmenting GABAergic transmission in the indirect pathway.[1-4] This model is supported clinically by the finding that 14% of PD patients self-report improvement in their dyskinesia with cannabis use.[5] In the only previous randomized controlled trial (RCT) of a cannabinoid agonist, nabilone was associated with a 22% mean reduction of on-period levodopa-induced dyskinesia compared with placebo.[3] However, only seven patients completed this study and the nabilone was administered only twice (12 and 1 hour) prior to an acute levodopa challenge. Consequently, the issues of long-term tolerability of cannabinoid agonists for people with PD and whether the reported change in dyskinesias produces any meaningful change in patients' lives remain to be addressed. Furthermore, as cannabis contains over 60 cannabinoids, it is possible that the combination of cannabinoids found in cannabis may be more efficacious than any one cannabinoid alone.

Animal studies[6-8] and a previous open label study of cannabidiol for dystonia, which included two patients with parkinsonian features,[9] have indicated that cannabinoids may exert a pro-parkinsonian action, a view that requires corroboration.

We studied the use of cannabis as a potential treatment for PD dyskinesia by using a randomized, double-blind, placebo-controlled crossover design. We also evaluated the potential role of cannabis in treating other aspects of PD.

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the October 12 issue to find the title link for this article.

Patients and methods. *Participants.* Patients aged 18 to 78 with a clinical diagnosis of idiopathic PD were recruited from PD outpatient clinics in Devon and Cornwall.

Inclusion criteria were levodopa-induced dyskinesia rated at

From the Department of Neurology (Drs. Carroll, Parkin, and Hobart, and C. Wroath), Derriford Hospital, Plymouth; Peninsula Medical School (Drs. Zajicek, Teare, and Fox), University of Plymouth; Division of Neurosciences and Psychological Medicine (Drs. Bain and Liu), Charing Cross Campus, Imperial College London; Oxford Movement Disorders Group (C. Joint), Department of Neurology, Radcliffe Infirmary, Oxford; and School of Mathematics and Statistics (Dr. Wright), University of Plymouth, UK.

Received December 24, 2003. Accepted in final form June 1, 2004.

Address correspondence and reprint requests to Dr. Camille Carroll, Room N16 ITTC Building, Tamar Science Park, Plymouth, UK PL6 8BX; e-mail: cbc@doctors.org.uk

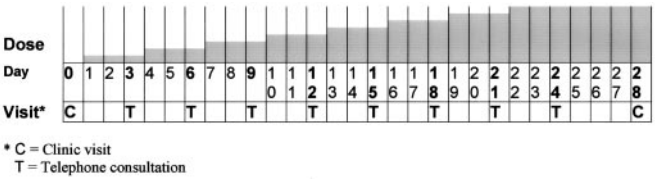

Figure 1. Dosing schedule.

≥2 (out of 12) on questions 32 to 34 of the Unified PD Rating Scale (UPDRS) and fixed antiparkinsonian medication for at least 1 month prior to study entry. Patients were excluded if they scored less than 26 on the Mini-Mental State Examination (MMSE), had a past or present history of ischemic heart disease or psychotic illness, had visual hallucinations while taking dopamine agonists, were unwilling to stop driving or operating dangerous machinery for the study period and 1 week afterwards, or if cannabinoids were taken currently or in the previous 30 days.

The study received ethical approval from the Plymouth Local Research Ethics Committee and was conducted under license from the Home Office between May and September 2003 at Tamar Science Park (Plymouth, UK). Written informed consent was obtained from all participants prior to enrollment. The study was performed under a Doctors and Dentists Exemption Certificate from the UK Medicines Control Agency.

Treatments. Active treatment consisted of capsules of Cannador, an ethanolic extract of *Cannabis sativa* standardized to 2.5 mg of Δ^9-THC and 1.25 mg of cannabidiol per capsule. Cannador was provided by the Institute for Clinical Research, IKF, Berlin. The placebo capsules contained synthetic oil vehicle and looked identical to the active drug. The dose of cannabis extract or placebo administered was based on body weight, with a maximum possible dose of 0.25 mg/kg of THC per day.[10] Medication was taken twice daily. All other medication was taken as usual and antiparkinsonian medication kept stable for the duration of the study.

Treatment schedule. The project consisted of two studies. First, an open label dose escalation safety study was conducted with cannabis extract in six patients. Then a second main study involved a RCT in which patients were randomly assigned to receive either active treatment followed by placebo or vice versa.

As cannabinoids are variably absorbed from the gastrointestinal system, both studies incorporated a dose titration phase in which the dose was escalated at 3-day intervals until the patient reached a maximum weight-adjusted dose or began to experience intolerable side effects, in which case the dose was dropped to the last tolerated dose. The treating physician (C.B.C.) contacted the patients every third day by telephone to advise about dose and document any adverse events. The dosing schedule for both the pilot and main studies is shown in figure 1.

Dose escalation study. The dose escalation safety study was an open label study of cannabis extract lasting 4 weeks.

Randomized controlled trial. The main study used a randomized controlled double-blind crossover design with two treatment phases, each of 4 weeks duration separated by a 2-week washout phase. Dose titration took place over the 4 weeks of the treatment phase, with the patient reaching a stable dose for a minimum of 4 days prior to each assessment. Compliance was checked by tablet count at the end of the study.

Objectives. The purpose of the dose escalation study was to assess the tolerability of cannabis extract in people with PD, in terms of dosing schedule, adverse events, and effect on PD severity.

The primary objective of the RCT was to examine the effect of cannabis extract on the severity and duration of dyskinesia in PD. Secondary objectives included assessing the effect of cannabis extract on the impact of dyskinesia on function, pathophysiologic indicators of dyskinesia, duration of dyskinesia, and quality of life, sleep and pain related to PD, as well as overall parkinsonism.

Assessment visits. For the dose escalation study, assessment visits occurred twice during the study—at baseline and at the end of the treatment phase.

For the RCT, assessment visits occurred three times during the study—at baseline and at the end of each treatment phase. In addition there were two pretrial visits for screening and distribution of patient-completed outcome measures.

Outcome measures. Baseline history, Mini-Mental State Examination (MMSE), and Hoehn and Yahr (H&Y) rating were obtained from each patient prior to entry into the study.

For the dose escalation study, the UPDRS and PDQ-39 were performed at baseline and at the end of the pilot study and the MMSE repeated at the end of the study.

For the RCT, the primary outcome measure was the UPDRS Part IV (items 32 to 34).[11] Secondary outcome measures were patient-based measures of functional ability—a validated dyskinesia activities of daily living (ADL) scale,[12] transition questions; physician-based measures of functional ability—UPDRS, Bain dyskinesia scale, Rush dyskinesia scale[13]; pathophysiologic indicators of dyskinesia—tablet arm drawing task; duration of dyskinesia—patient on-off diaries, designed according to the Working Group guidelines[14]; and Quality of life–PD Questionnaire (PDQ-39),[15] the McGill Pain Scale,[16] and a visual analogue sleep scale. The total UPDRS score was recorded while patients were in the off and then on state.

Intervention. At each assessment visit a levodopa challenge was performed according to the guidelines of the Working Group.[14] Patients arrived at the center in a practically defined off state (no antiparkinsonian medications from 9.00 PM the previous evening, fasting from midnight). A test dose of levodopa was administered in dispersible formulation (normal early morning dose + adjustment for normal dose of dopamine agonist + 25%). The trial medication was taken as normal on the mornings of assessments.

On assessment days, the UPDRS was performed in the practically defined off state. The levodopa challenge was then administered, following which the patient was video recorded and scored performing the tasks outlined in the Rush dyskinesia scale every 30 minutes for 4 hours. An independent blinded assessing physician (P.G.B.) subsequently rated the video recordings. The mean score was used in the analysis. The type of dyskinesia (chorea or dystonia) was also recorded. Dyskinesia was additionally rated by the Bain dyskinesia scale performed at 30-minute intervals for 4 hours. The score at each time point is the summation of dyskinesia severity scores (0 to 10) for head, voice, face, right arm, right leg, left arm, left leg, and trunk, giving a maximum score of 80.

At the time of objective worst dyskinesia patients were asked to copy a spiral and squared spiral on a digitized graphics tablet that allowed analysis of the amplitude and frequency of abnormal movements. Both arms were tested on each task and the data analyzed off-line. The UPDRS was repeated during a subjectively defined best on state.

In the RCT, as far as practicable, the same assessor carried out assessments at baseline and at the end of each treatment phase. Assessment data were stored and not made available at subsequent visits. Patients were shown how to complete the on-off diary and patient-based measures at the initial visit. The diary was used to calculate the percentage of the 24-hour day spent asleep and the percentage of the waking day spent on with dyskinesia, on with no dyskinesia, intermediate, or off. Patients were provided with a PDQ-39 questionnaire, ADL scale, on-off diary, McGill pain scale, and a visual analogue sleep scale to complete prior to the first and each subsequent assessment visit.

Blood analysis. Blood samples were taken at the final assessment visit of the RCT to allow measurement of THC levels following medication administration.

Blinding. All assessors (P.G.B., L.T., C.W., C.J., X.L., S.G.P.) and patients were blinded to treatment allocation for the duration of the study. A separate treating physician (C.B.C.) monitored the patients' progress. The degree of blinding was assessed at the end of each treatment phase by asking the patients which treatment they thought they had received.

Adverse events. Adverse events were classified according to ICH Good Clinical Practice (GCP) definitions. During both the pilot study and the main study patients were contacted every 3 days by telephone to monitor adverse events. Additionally, during the pilot study, an extensive checklist of adverse event questions was administered every 6 days.

Sample size. For the dose escalation study, six patients were recruited to the safety study.

For the RCT, based on previously published studies,[17,18] a sample size of 18 patients for the main study was calculated to be sufficient to enable detection of a reduction in the primary out-

come measure (UPDRS questions 32 to 34) by 1.5 points with 90% confidence to a significance level of 0.05.

Randomization. For the RCT, a random sequence was generated by the statistician (D.W.) using an Excel spreadsheet and used by pharmacy in conjunction with the patient's trial number to dispense either cannabis extract and then placebo or vice versa. Throughout the trial treatment allocation codes were kept in the trial pharmacy, located separately from the trial office.

Statistical analysis. In order to minimize data entry errors a double data entry system was used.

For the dose escalation study, a paired *t*-test was applied to compare the data at the two time points.

For the RCT, analysis was performed in accordance with an analysis plan devised prior to unblinding. For both primary and secondary outcomes the data were analyzed as a simple two-period crossover trial. A two-sample *t*-test was applied to period 1 − period 2 differences for the two groups of patients, those in the cannabis extract–placebo group vs those in the placebo–cannabis extract group. Categorical scale data were analyzed using the Mann-Whitney *U* test. The difference between the means of the two groups was taken as twice the size of the treatment effect.

Results. Fifty-nine patients were screened for participation in the study. Fourteen declined and 20 were found to be unsuitable for the study, mainly due to reluctance to stop driving. Six patients took part in the pilot study and 19 participated in the main study.

Dose escalation study. In the safety study, four participants were women and two were men with a mean age of 71 years (range 65 to 76) and a median H&Y of 3 (range 3 to 4). Mean duration of PD was 17 years (range 11 to 24), with mean duration of dyskinesia of 3.8 years (range 0.8 to 9 years). Two patients stopped taking medication on days 12 (due to worsening off periods) and 18 (due to panic attacks). Both patients attended for follow-up assessment and their data were included in the analysis.

RCT. In the main study, 7 participants were women and 12 were men, with a mean age of 67 years (range 51 to 78) and a median H&Y of 3 (range 2.5 to 4). Mean duration of PD was 14 years (range 4 to 32), with mean duration of dyskinesia of 4.5 years (range 0.7 to 11 years). The normal antiparkinsonian medications taken by the patients in the RCT are shown in table E-1 (available on the *Neurology* Web site at www.neurology.org). Two patients withdrew from the study after the initial baseline assessment: one developed diarrhea (on placebo), the other had a family bereavement. Data from the remaining 17 patients were analyzed. At the first assessment visit, two patients scored less than 2 on the dyskinesia scale derived from part 4 of the UPDRS. These patients completed the study and their data are included in the intention-to-treat analysis. The flow of patients through the trial is summarized in the CONSORT diagram in figure 2.

Medication. In the dose escalation study, four of the six patients failed to attain their target dose of cannabis extract, the mean dose achieved being 0.17 mg/kg/day of THC. In the RCT, patients reached a mean dose of 0.146 mg/kg/day (range 0.034 to 0.25 mg/kg/day) of THC on active treatment, and a dose equivalent of 0.182 mg/kg/day (range 0.032 to 0.25 mg/kg/day) on placebo. Eleven patients out of 17 failed to reach their target dose on active treatment, as did nine patients on placebo. Analysis of the blood results showed that in most patients a peak level of THC was reached within 2 hours of ingestion of cannabis extract, the peak level ranging from 0.25 ng/mL to 5.4 ng/mL, with no clear dose response. There was wide variability in blood level even between patients taking the same dose of cannabis extract.

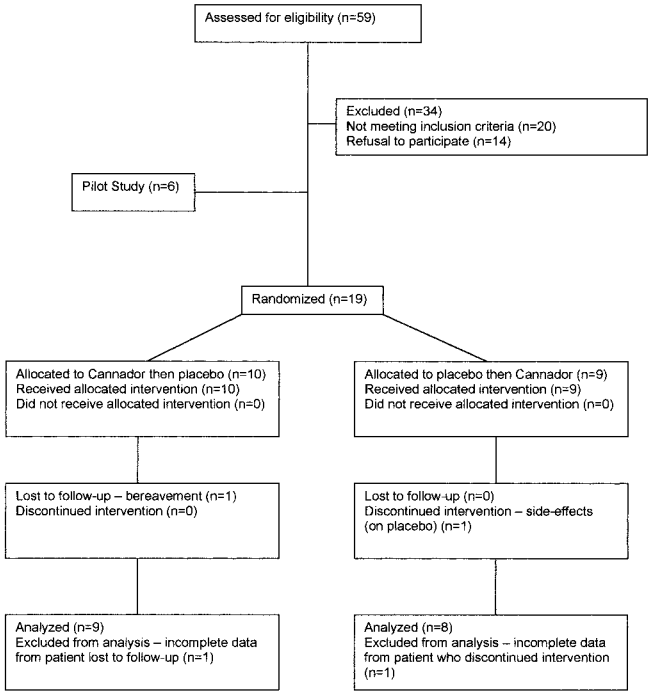

Figure 2. Consort flow diagram.

Dose escalation study. There was no effect of cannabis extract on total UPDRS scores (on or off) or PDQ-39, but an improvement in MMSE occurred following treatment (treatment effect: 1.5 ± 0.6, $p < 0.01$).

RCT. Primary outcome measure. For the historical items of the UPDRS, including the dyskinesia questions 32 to 34, the mean of the scores achieved in the on and off states was used in the analysis. The effect of treatment on dyskinesia score for each individual is shown in figure 3. The size of the overall treatment effect was +0.52 (i.e., a worsening), although this failed to reach significance ($p = 0.09$) (table 1).

Secondary outcome measures. All patients developed dyskinesia following the levodopa challenge. There was no significant effect of treatment on any of the secondary outcome measures (see table 1). Analysis of movement frequency during the graphic-tablet drawing task demonstrated that most patients had involuntary movements in the dyskinesia frequency range of 1 to 5 Hz; however, two patients also had coexisting action tremor of 6 to 8 Hz. The diaries were analyzed from the 12 patients who provided a minimum of 4 complete days of data. Patients did not feel better on cannabis extract (treatment effect −0.7, CI −1.5 to 0.2, $p = 0.14$) or find it helpful (treatment effect 0.3, CI −0.3 to 0.8, $p = 0.17$). In addition, there was no treatment effect on overall dyskinesia assessed using the Rush scale or the different types of dyskinesia (chorea: treatment effect 2.53 ± 5.21, $p = 0.32$; dystonia: treatment effect 0.14 ± 2.9, $p = 0.92$).

UPDRS and PDQ-39 subsection scores. Cannabis extract had no effect compared with placebo on the subsection scores of the UPDRS (Part I—mentation; Part II—ADL; Part III—motor; Part IV—complications of therapy; and a tremor score [questions 16, 20, and 21]) or PDQ-39

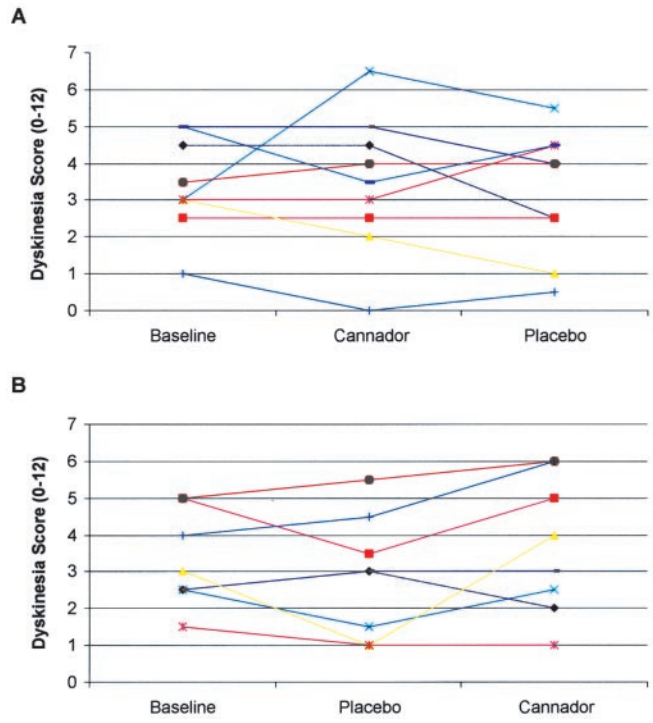

Figure 3. Dyskinesia score (derived from Unified Parkinson's Disease Rating Scale questions 32 to 34). (A) Patients who received cannabis extract followed by placebo. (B) Patients who received placebo followed by cannabis extract.

(mobility, ADL, emotion, stigma, social support, cognition, communication, and discomfort) (data not shown).

Category rating scales. Category rating scales were used at the end of each treatment phase to assess whether patients believed their symptoms had improved while on treatment relative to before the start of treatment, with the rating scale only being completed if patients were affected by that particular symptom. There was no subjective improvement in dyskinesia or pain on active treatment compared with placebo. However, there was a slight trend for patients to feel that their tremor and sleep quality improved while on active treatment (see table E-2 on the *Neurology* Web site at www.neurology.org).

Blinding. Overall 71% of patients correctly identified their treatment, whether cannabis extract or placebo (65% in phase 1 and 76% in phase 2).

Adverse events. There were no serious adverse events (e.g., requiring hospital admission). Mild adverse events were recorded during the dose escalation safety study, with an increasing incidence of adverse events with higher doses of cannabis extract. A similar spectrum of adverse events was recorded in both treatment and placebo groups during the RCT, although more common in the former (table 2). All adverse events were ameliorated by dose reduction.

Discussion. The results of our studies show that cannabis extract is relatively well tolerated by patients with PD. The pilot study showed no deterioration in MMSE score, PDQ, or UPDRS score following treatment. Indeed the MMSE score significantly improved, probably reflecting a practice effect. Although in our RCT adverse events were more

Table 1 *Outcome measure scores from RCT*

Measure	Baseline mean score ± SD	Size of treatment effect	95% CI of treatment effect	*p* Value
Dyskinesia score	3.3 ± 0.3	0.5	−0.1–1.1	0.09
Rush score	23.1 ± 3.0	−1.5	−5.5–2.5	0.44
Bain score	42.1 ± 6.6	−0.7	−11.9–10.6	0.90
Right arm amplitude (circle)	9.5 ± 1.0	−0.9	−3.8–2.0	0.53
Right arm amplitude (square)	11.0 ± 1.6	−0.1	−2.02–1.9	0.95
Left arm amplitude (circle)	11.7 ± 1.5	2.8	−2.1–7.7	0.24
Left arm amplitude (square)	9.9 ± 1.1	0.7	−2.2–3.5	0.62
Dyskinesia ADL	41.4 ± 4.6	−1.1	−9.3–7.1	0.78
PDQ-39	35.0 ± 3.3	−0.7	−6.1–4.8	0.8
Total UPDRS on	38.3 ± 3.7	2.4	−2.7–7.5	0.34
Total UPDRS off	64.3 ± 5.1	1.6	−3.7–6.8	0.53
McGill Pain score	20.4 ± 5.3	−1.8	−6.1–2.6	0.4
Sleep score	6.6 ± 0.5	0.4	−0.6–1.4	0.42
Diary dyskinesia	27 ± 14.8	4.19	−9.2–17.5	0.5
Diary on	34 ± 18.3	0.71	−9.3–10.72	0.88
Diary intermediate	23 ± 13.7	−6.01	−15.8–3.8	0.2
Diary off	16 ± 11.1	−3.76	−11.5–4.0	0.31
Diary sleep	31 ± 8.0	1.26	−1.83–4.4	0.38

RCT = randomized controlled trial; ADL = activities of daily living; UPDRS = Unified Parkinson's Disease Rating Scale.

Table 2 *Spontaneously reported adverse events during RCT*

	Number of patients reporting symptom	
	Cannador	Placebo
Physical		
UTI/cystitis	1	1
Dry mouth	4	1
Altered taste	1	0
Musculoskeletal pain	2	4
Diarrhea/loose stool	3	2
Constipation	3	0
Nausea	2	0
Dizzy/light-headed	2	1
Total physical	18	9
Psychological		
Drowsy/lethargic	9	6
Detached	4	0
Paranoia	1	0
Vivid dreams/nightmares	2	0
Confusion	1	0
Forgetful/poor concentration	3	0
Total psychological	20	6
Total adverse events	37	15

RCT = randomized controlled trial; UTI = urinary tract infection.

common on cannabis extract than placebo, these were dose dependent and did not result in withdrawal of the drug. A similar tolerability profile was described in a study of cannabis extract in multiple sclerosis (MS)[10] and in an open label study of cannabidiol for dystonia[9]; a titration phase was present in both of these studies. These results contrast with a further study[3] in which two out of nine patients were withdrawn because of vertigo and postural hypotension after nabilone treatment, perhaps reflecting the lack of a dose titration phase in that study. Our finding that cannabis extract is tolerable to people with PD may be important because cannabinoids have been postulated to have a neuroprotective action,[19,20] although their long-term tolerability in early disease remains to be demonstrated.

The main result of our RCT is that orally administered cannabis extract has no significant effect on dyskinesia as assessed by the UPDRS (items 32 to 34), Rush dyskinesia scale, Bain dyskinesia scale, magnitude of dyskinesia in spiral drawings, or subjective (diary, ADL, category rating) measures of dyskinesia. There was also no effect on global measures of quality of life (PDQ-39), pain (McGill), or sleep (visual analogue scale).

The lack of treatment effect obtained in this study may have been because it had inadequate power to detect a small change in dyskinesia. It is possible that the various assessment methods chosen in this study are insensitive to small changes in dyskinesia. In particular, UPDRS items 32 to 34 are based on historical information and are not validated as a dyskinesia assessment measure, although they are widely deployed[17,18,21] and data are readily available on which to base a power calculation. Indeed this study has highlighted some of the difficulties inherent in scoring historical items of the UPDRS, particularly the difference between the scores achieved in the on and off states.[22] The use of diary data are limited by incorrect labeling of dyskinesia by patients.[23] The difficulties associated with rating dyskinesia have been widely discussed and informed our choice of secondary outcome measures,[24] although it is hoped that the Movement Disorder Society Task Force may address this issue.

The lack of an antidyskinetic effect of cannabis extract found in this study could reflect failure to achieve sufficiently high systemic medication levels, as overall 11 patients (65%) did not attain the target dose. Analysis of serum levels of THC demonstrated wide variability in blood level achieved. The numbers were too small to allow correlation of blood level with clinical response. However, the mean doses achieved were similar to those in a study of cannabis extract in MS,[10] in which a treatment effect was demonstrated. Moreover, failure to achieve target dose was because of the development of cannabis-related adverse effects, suggesting that treatment with cannabis extract was optimal. Despite these difficulties, the absence of any beneficial effect on any measure of dyskinesia, including the category rating scale, makes it unlikely that a clinically relevant antidyskinesia effect has been missed in this study.

Our results contrast with the previously reported beneficial effect of nabilone (0.03 mg/kg) on the total dyskinesia score obtained using the Rush Dyskinesia Scale.[3] However, two of nine participants withdrew from the latter study and of the remaining seven patients, two had improvements of 62% and 42% in total dyskinesia compared to placebo, which skewed the data, as in the remaining five patients the improvements were modest, ranging from 3.8% to 17.4%. Furthermore, no difference was found in the effects of nabilone and placebo on the percentage of the on-period occupied by dyskinesia. The same group also found that nabilone was ineffective for primary dystonia.[25]

As the phenomenology of dyskinesia in PD is complex it is possible that cannabinoids differentially affect different types of dyskinesia.[26] However, our study found no difference in the effect of cannabis extract on dystonia or chorea, although it was not designed or powered to address this question.

Reassuringly, despite previous clinical experience[9] and predictions based on animal experiments,[8] there was no significant change in UPDRS off score, or diary records of off-time, although some patients reported a worsening of their underlying PD and increased off period severity. This is in accord with a previous study involving the cannabis agonist

nabilone.[3] In addition, cannabis extract had no demonstrable effect on the antiparkinsonian action of levodopa, as assessed by UPDRS on scores and on-time measured by the patient diary.

It is likely that current models of dyskinesia derived from our understanding of basal ganglia function are not sufficiently sophisticated to accurately predict the effects of modulating cannabinoid transmission, the complexity of which is illustrated by the contradictory results of behavioral experiments.[27-29] Similarly, there are theoretical arguments for cannabinoid agonists having both pro- and antiparkinsonian actions.[6-8,30] Future therapeutic strategies will require greater understanding of the complexities of basal ganglia connectivity and function. This study also highlights the difficulties encountered in extrapolating promising data from animal studies into the clinic. Nevertheless our data indicate that cannabis does not have a therapeutic role in the treatment of dyskinesia in patients with PD.

Acknowledgment

The authors thank the Neuroscience Research Group at the Tamar Science Park, in particular Jane Vickery and Susie Reilly.

References

1. Maneuf YP, Crossman AR, Brotchie JM. Modulation of GABAergic transmission in the globus pallidus by the synthetic cannabinoid WIN 55,212–2. Synapse 1996;22:382–385.
2. Maneuf YP, Nash JE, Crossman AR, Brotchie JM. Activation of the cannabinoid receptor by delta 9-tetrahydrocannabinol reduces gamma-aminobutyric acid uptake in the globus pallidus. Eur J Pharmacol 1996; 308:161–164.
3. Sieradzan KA, Fox SH, Hill M, Dick JPR, Crossman AR, Brotchie JM. Cannabinoids reduce levodopa-induced dyskinesia in Parkinson's disease: a pilot study. Neurology 2001;57:2108–2111.
4. Fox SH, Henry B, Hill M, Crossman A, Brotchie J. Stimulation of cannabinoid receptors reduces levodopa-induced dyskinesia in the MPTP-lesioned nonhuman primate model of Parkinson's disease. Mov Disord 2002;17:1180–1187.
5. Venderova K, Ruzicka E, Visnovsky P. Cannabis and Parkinson's disease: subjective improvement of symptoms and drug-induced dyskinesias. Mov Disord 2002;17(suppl 5):S77. Abstract.
6. Di Marzo V, Hill MP, Bisogno T, Crossman AR, Brotchie JM. Enhanced levels of endogenous cannabinoids in the globus pallidus are associated with a reduction in movement in an animal model of Parkinson's disease. FASEB J 2000;14:1432–1438.
7. Crawley JN, Corwin RL, Robinson JK, Felder CC, Devane WA, Axelrod J. Anandamide, an endogenous ligand of the cannabinoid receptor, induces hypomotility and hypothermia in vivo in rodents. Pharmacol Biochem Behav 1993;46:967–972.
8. Meschler JP, Howlett AC, Madras BK. Cannabinoid receptor agonist and antagonist effects on motor function in normal and 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP)-treated non-human primates. Psychopharmacology 2001;156:79–85.
9. Consroe P, Sandyk R, Snider SR. Open label evaluation of cannabidiol in dystonic movement disorders. Int J Neurosci 1986;30:277–282.
10. Zajicek J, Fox P, Sanders H, et al. Cannabinoids for the treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. Lancet 2003; 362:1517–1526.
11. Movement Disorder Society. Appendix: available dyskinesias clinical rating scales. Mov Disord 1999;14(suppl 1):75–80.
12. Katzenschlager R, Schrag A, Hobart J, Manson A, Evans A, Lees AJ. The impact of dyskinesias in Parkinson's disease: development of a patient-based outcome measure. J Neurol 2003;250(suppl 2):32.
13. Goetz CG, Stebbins GT, Shale HM, et al. Utility of an objective dyskinesia rating scale for Parkinson's disease: inter- and intrarater reliability assessment. Mov Disord 1994;9:390–394.
14. Melamed E, Olanow CW, Nutt JG, Lang AE. Dyskinesias assessment workshop: reports from the working groups. Mov Disord 1999;14(suppl 1):69–73.
15. Jenkinson C, Fitzpatrick R, Peto V. The Parkinson's Disease Questionnaire. Health Services Research Unit. Oxford: Joshua Horgan Print Partnership, 1998.
16. McDowell I, Newell C. The McGill pain questionnaire. In: Measuring health: a guide to rating scales and questionnaires. Oxford: Oxford University Press, 1987.
17. Paci C, Thomas A, Onofrj M. Amantadine for dyskinesia in patients affected by severe Parkinson's disease. Neurol Sci 2001;22:75–76.
18. Volkmann J, Allert N, Voges J, Weiss PH, Freund HJ, Sturm V. Safety and efficacy of pallidal or subthalamic nucleus stimulation in advanced PD. Neurology 2001;56:548–551.
19. Grundy RI, Rabuffetti M, Beltramo M. Cannabinoids and neuroprotection. Molec Neurobiol 2001;24:29–51.
20. Guzman M, Sanchez C, Galve-Roperh. Control of the cell survival/death decision by cannabinoids. J Mol Med 2001;78:613–625.
21. Metman LV, Del Dotto P, LePoole K, Konitsiotis S, Fang J, Chase TN. Amantadine for levodopa-induced dyskinesias. Arch Neurol 1999;56: 1383–1386.
22. Carroll CB, Bain PG. Do on-off variations cause discrepancies in the historical items of the UPDRS? Mov Disord 2004;19:605.
23. Vitale C, Pellecchia MT, Grossi D, et al. Unawareness of dyskinesias in Parkinson's and Huntington's diseases. Neurol Sci 2001;22:105–106.
24. Goetz CG. Rating scales for dyskinesias in Parkinson's disease. Mov Disord 1999;14:48–53.
25. Fox SH, Kellett M, Moore AP, Crossman AR, Brotchie JM. Randomised, double-blind placebo-controlled trial to assess the potential of cannabinoid receptor stimulation in the treatment of dystonia. Mov Disord 2002;17:145–149.
26. Vidailhet M, Bonnet AM, Marconi R, Durif F, Agid Y. The phenomenology of L-dopa-induced dyskinesias in Parkinson's disease. Mov Disord 1999;14(suppl 1):13–18.
27. Anderson LA, Anderson JL, Chase TN, Walters JR. The cannabinoid agonists WIN 55, 212–2 and CP 55,940 attenuate rotational behavior induced by a dopamine D_1 but not a D_2 agonist in rats with unilateral lesions of the nigrostriatal pathway. Brain Res 1995;691:106–114.
28. Maneuf YP, Crossman AR, Brotchie JM. The cannabinoid receptor agonist WIN 55,212–2 reduces D_2 but not D_1 receptor-mediated alleviation of akinesia in the reserpine-treated rat model of Parkinson's disease. Exp Neurol 1997;148:265–270.
29. Segovia G, Mora F, Crossman AR, Brotchie JM. Effects of CB1 cannabinoid receptor modulating compounds on the hyperkinesia induced by high-dose levodopa in the reserpine-treated rat model of Parkinson's disease. Mov Disord 2003;18:138–149.
30. Sanudo-Pena MC, Tsou K, Walker M. Motor actions of cannabinoids in the basal ganglia output nuclei. Life Sci 1999;65:703–713.