Bandolier Extra

Evidence-based health care October 2002

CANNABIS FOR SPASTICITY AND MULTIPLE SCLEROSIS

The single largest study to investigate the efficacy of cannabis in multiple sclerosis recruited its 667th and last patient on October 10 2002. The first 15 weeks of treatment will be completed in February 2003 and results of the trial are hope to be announced in the summer of 2003.

The trial

It will recruit 660 patients with multiple sclerosis from across the UK who have significant spasticity in some of their leg muscles. Each patient will be randomly allocated to one of three treatments: cannabis oil, tetrahydrocannabinol (a constituent of cannabis) or placebo capsules (containing only vegetable oil).

Patients and doctors will not know which treatment is being taken until after the study, and assessments of muscle stiffness and mobility will be made every few weeks. Side effects will be recorded and patients will be encouraged to reach a certain level of medication over an initial five week period, before an eight-week period of monitoring. Assessments will also be made of quality of life and disability by postal questionnaire.

While we wait for the results of the trial, people still want to know what evidence we have. This snippet examines the evidence to date.

Search

Bandolier therefore set out to examine what evidence does exist, and searched for papers on cannabis (plus its other names) using PubMed and the Cochrane Library, and reviews, and reference lists, and official reports. What we found is given in the Table on pages 3 and 4, together with the reference for each and a brief summary of what the paper was and found. Reviews and peripherally interesting papers are also included.

Results

Most of the results were anecdotal and impossible to interpret. Where test, abstinence and retest had been conducted, sometimes with blinded observations, results were reproducible. This was true also of two N of 1 designs, one of which was randomised, and double-blind, and with identically looking preparations of cannabinoid, codeine and placebo. There are several studies that were randomised and double-blind, but not always examining useful clinical outcomes. Because studies were often very small, and with self-selecting patients who were usually (though not always) previous cannabis users, the small benefits seen must be regarded as disappointing. They could easily be wrong just by the random play of chance.

Oral preparations of cannabinoids helped most, but not all patients, and some seemed only to respond to the smoked version. In the last few years some scientific basis has been adduced to support cannabinoid involvement in the control of spasticity, perhaps with endogenous cannabinoids being involved with maintaining spastic tone.

Clinical bottom line

There is only limited evidence mainly from anecdotal reports that cannabis (smoked or oral) benefits spasticity from multiple sclerosis or spinal cord injury. Some randomised N of 1 studies support this. The weight of evidence is not great, and more recent, though small, randomised trials show absolutely no effect, with some adverse effects.

Best randomised trial to date [1]

This was a randomised crossover trial of placebo, THC and plan extract given orally in sixteen patients with progressive multiple sclerosis and spasticity. Four weeks of treatment with placebo, 2.5-5 mg THC, or plant extract with equivalent THC (identical appearance) was followed by four weeks of washout before the next treatment. A lower dose was used for two weeks, and doubled, if well tolerated, for the second two weeks of treatment.

Muscle tone was measured on a categorical scale (0=normal, 1=slight increase, 2=more marked increase, 3=considerable increase, 4=limb rigidity in flexion or extension) for arms and legs. Patients had to have a score of at least 2 for inclusion. EDSS and several other tests of function and ambulation were used.

Reference	Summary
WB O'Shaughnessy. On the preparation of Indian hemp or gunjah. Transactions of the Medical and Physical Society of Bombay 1842 8: 421-461.	Paper available in full on line. A terrific historical narrative coupled with a series of cases where cannabis was used. Spasm of tetanus was particularly well controlled.
JR Reynolds. Therapeutic use and toxic effects of Cannabis indica. Lancet 1890 1: 637-638.	An interesting discourse on use of ethanolic extracts of cannabis. Regarded cannabis as useful in chronic painful conditions and spasm (but not epilepsy). Descriptive,but acutely observed by Fellow of the Royal Society and Physician to Queen Victoria.
M Dunn, R Davis. The perceived effects of cannabis on spinal cord injured males. Paraplegia 1974 12: 175.	Informal survey on 10 patients with spinal cord injury and spasm and pain who already took cannabis. Decreased spasticity in 5/8, decreased phantom pain in 4/9 with smoked cannabis.
Cunha et al. Chronic administration of cannabidiol to healthy volunteers and epileptic patients. Pharmacology 1980 21: 175-185.	Randomised, double blind study of 200-300 mg cannabidiol daily or placebo in 15 patients with epilepsy with frequent convulsions. Absence of convulsive crisis over 3-18 weeks in 4/8 on cannabidiol and 1/8 on placebo (sic).
Petro DJ. Marihuana as a therapeutic agent for muscle spasm or spasticity. Psychosomatics 1980 21: 81- 85.	This is a case report of two cases, one of whom had MS. Nocturnal leg spasms were relieved by smoking cannabis within five minutes. Abstention led to increased spasticity and pain, again relieved by use of cannabis.
Petro & Ellenberger. Treatment of human spasticity with delta 9-tetrahydrocannabinol. J Clin Pharmacol 1981 21: (8-9 Suppl): 413S-416S.	Nine patients with spasticity related to MS were examined by a blinded observer before and after 90 minutes intervals after oral capsules with 10 mg g, 5 mg or no synthetic THC. THC, but not placebo, was associated with a reduced spasticity score lasting for about 4 hours. Big improvements with 4/9 with THC and 1/9 with placebo. Subjective highs were experienced by one patient after THC and one after placebo.
Malec et al. Cannabis effect on spasticity in spinal cord injury. Arch Phys Med Rehabil 1982 63: 116-8.	Questionnaire to spinal cord injury patients. 9/24 users reported no spasticity while using cannabis, 11/24 reported some benefit.
Clifford DB. Tetrahydrocannabinol for the treatment of tremor in multiple sclerosis. Ann Neurol 1983 13: 669-671.	Eight patients with MS, disabling tremors and ataxia were given THC or single-blind placebo (?oral) and effect on tremor investigated. Two patients had some subjective and objective improvement with THC but not placebo.
RR Snider & P Consroe. Treatment of Meige syndrome with cannabidiol. Neurology 1984 34 (Suppl 1): 147.	Case report of use of cannabidiol in patient with severe cranial dystonia (Meige Syndrome) with severe untreatable spasms. 400 mg cannabidiol daily reduced spasm frequency by 50%, and withdrawal led to return of spasms to previous level.
Consroe et al. Open label evaluation of cannabinoid in dystonic movement disorders. Int J Neurosci 1986 30: 277-82.	Five patients with dystonia in open-label study with oral cannabidiol (100-600 mg/day). Improvement in dystonia scores in all five (20-50%). Some adverse events (lightheadedness, hypotension) and two patients had exacerbation of resting tremor.
Ungerleider et al. Delta-9-THC in the treatment of spasticity associated with multiple sclerosis. Adv Alcohol Subst Abuse 1987 7: 39-50.	13 patients with MS and spasticity unable to take other drugs. Random assignment to double-blind crossover between THC and placebo (five days) with two day washout. Decreased spasticity with increasing THC dose. Significant benefit by patient, but not physician, scoring of spasticity.
Meinck et al. Effect of cannabinoids on spasticity and ataxia in multiple sclerosis. J Neurol 1989 263: 120-2.	Chronic motor handicaps of one MS patient improved acutely while smoking cannabis cigarette.
Maurer et al. Delta-9-tetrahydrocannabinol shows antispastic and analgesic effects in a single case double-blind trial. Eur Arch Psychiatry Clin Neurosci 1990 240: 1-4.	N of 1 randomised comparison of oral THC 5mg, codeine 50 mg and placebo in patient with spasticity due to spinal cord injury. Three treatments used 18 times each. THC significantly better than placebo for sleep pain spasticity, micturition, concentration and mood. THC better than codeine for spasticity.

Reference	Summary
Martyn et al. Nabilone in the treatment of multiple sclerosis. Lancet 1995 345:579.	N of 1 trial of nabilone 1 mg every second day or placebo for four successive periods of four weeks in man with severe spasticity and MS. Nabilone reduced frequency of nocturia and severity of muscle spasm and improved wellbeing.
Voth & Schwartz. Medicinal applications of delta-9-tetrahydrocannabinol and marijuana. Ann Intern Med 1997 126: 791-8.	Systematic review of medicinal applications of cannabis, to 1996. No additional information on spasticity or MS.
Consroe et al. The perceived effects of smoked cannabis on patients with multiple sclerosis. Eur Neurol 1997 38: 44-8.	Questionnaire findings of 112 US and UK patients with MS and who used cannabis. Signs or symptoms reported to be much better in over 60% of patients were spasticity at sleep onset, pain in muscles, spasticity at night, pain in legs at night, tremor, depression, anxiety, spasticity on waking or walking.
Taylor HG. Analysis of the medical use of marijuana and its societal implications. J Am Pharm Assoc (Wash). 1998 Mar-Apr;38(2):220-7. Systematic Review.	Systematic review of medicinal applications of cannabis, to 1997. No additional information on spasticity or MS.
F Schon et al. Suppression of pendular nystagmus by smoking cannabis in a patient with multiple sclerosis. Neurology 1999 53:	Report of a patient with MS whose nystagmus improved with smoked, not oral cannabis, and was partly related to serum cannabinoids.
LF Dell'Osso. Suppression of pendular nystagmus by smoking cannabis in a patient with multiple sclerosis. Neurology 2000 54: 2190-1.	Letter. Another case report, but with no data.
F Schon et al. Suppression of pendular nystagmus by smoking cannabis in a patient with multiple sclerosis. Neurology 2000 54: 2190-1.	Response to letter. Reports original patient's nystagmus also responded to drinking red wine.
Williamson & Evans. Cannabinoids in clinical practice. Drugs 2000 60: 1303-14.	A review that does not add much. It incorrectly identifies a questionnaire study as a trial, appearing to add more weight of evidence than there is.
Baker et al. Cannabinoids control spasticity and tremor in a multiple sclerosis model. Nature 2000 404: 84-87.	Use of cannabinoid receptor agonism with THC and other agents ameliorated tremor and spasticity in mice with relapsing experimental allergic encephalomyelitis, an autoimmune model of MS.
Carter & Rosen. Marijuana in the management of amyotropic lateral sclerosis. Am J Hosp Palliat Care 2001 18: 264-70.	Useful pharmacological review, but no clinical data, so speculative.
Baker et al. Endocannabinoids control spasticity in a multiple sclerosis model. FASEB J. 200115:300-2.	Experimental work in mice suggesting that natural cannabinoids help control spastic tone.
P Robson. Therapeutic effects of cannabis and cannabinoids. British Journal of Psychiatry 2001 178: 107-115.	Review. No additional studies.
SH Fox et al. Randomised, double-blind, placebo-controlled trial to assess the potential of cannabinoid receptor stimulation in the treatment of dystonia. Movement Disorder 2002 17: 145-149.	Nabilone was ineffective in patients with generalised and segmental primary dystonia.
J Killestein et al. Safety, tolerability and efficacy of orally administered cannabinoids in MS. Neurology 2002 58: 1404-1407.	This was a randomised crossover trial of placebo, THC and plan extract given orally in sixteen patients with progressive MS and spasticity. Four weeks of treatment with placebo, 2.5-5 mg THC, or plant extract with equivalent THC (identical appearance) was followed by four weeks of washout before the next treatment. A lower dose was used for two weeks, and doubled, if well tolerated, for the second two weeks of treatment. Active treatments conferred no benefit. Plant extract, but not THC, had significantly more adverse events. Five patients on plant extract reported subjective increased spasticity and one had an episode of acute psychosis

Results

Six of the 16 patients had primary and 10 secondary progressive MS. The average age was 46 years, with MS for an average of 15 years, and the mean EDSS score was 6.2. All completed all scheduled visits for all three treatments.

Active treatments conferred no benefit. Plant extract, but not THC, had significantly more adverse events. Five patients on plant extract reported subjective increased spasticity and one had an episode of acute psychosis.

Comment

There really are no conclusions to be drawn from the best trial we have to date, or from the totality of evidence available. With case reports we are unlikely to know of them many people who may have tried cannabinoids and failed, so the bias we find from publication of positive results will be massive. Even the N of 1 trials are done in known responders. There may be patients who respond to cannabinoids and whose spasticity or other symptoms may be alleviated. They may be common, or rare as hen's teeth. We will have to wait for the results of the ongoing large randomised trial for the bigger picture.

What we do see is that newer studies, or those with better and designs less open to bias, are being more negative. The hope must be (and hope it has to be now) that something in the method of delivery of drug will confer unexpected benefits.

The large UK Cannabis in Multiple Sclerosis study organised from Derriford Hospital in Plymouth will look specifically at the question of whether cannabis, as either whole plant extract or one of its active components, can help the muscle stiffness and spasms that affect multiple sclerosis sufferers. Results are likely to be available in 2003.

You can visit the trial site at http://www.cannabis-trial.plymouth.ac.uk/.

Reference:

1. J Killestein et al. Safety, tolerability and efficacy of orally administered cannabinoids in MS. Neurology 2002 58: 1404-1407.