The single largest study to investigate the efficacy of can-
nabis in multiple sclerosis recruited its 667th and last pa-
tient 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 con-
stituent of cannabis) or placebo capsules (containing only
vegetable oil).

Patients and doctors will not know which treatment is be-
ing 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. Assess-
ments 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 re-
vews, 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 pa-
per was and found. Reviews and peripherally interesting
papers are also included.

Results

Most of the results were anecdotal and impossible to inter-
pret. Where test, abstinence and retest had been conducted,
sometimes with blinded observations, results were repro-
ducible. This was true also of two N of 1 designs, one of
which was randomised, and double-blind, and with identi-
cally looking preparations of cannabinoid, codeine and pla-
cebo. There are several studies that were randomised and
double-blind, but not always examining useful clinical out-
comes. 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 con-
trol of spasticity, perhaps with endogenous cannabinoids
being involved with maintaining spastic tone.

Best randomised trial to date [1]

This was a randomised crossover trial of placebo, THC and
plan extract given orally in sixteen patients with progres-
sive multiple sclerosis and spasticity. Four weeks of treat-
ment 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 toler-
ated, for the second two weeks of treatment.

Muscle tone was measured on a categorical scale (0=norm-
mal, 1=slight increase, 2=more marked increase, 3=consi-
erable 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.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Summary</th>
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<tr>
<td>WB O'Shaughnessy. On the preparation of Indian hemp or gunjah. Transactions of the Medical and Physical Society of Bombay 1842 8: 421-461.</td>
<td>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.</td>
</tr>
<tr>
<td>JR Reynolds. Therapeutic use and toxic effects of Cannabis indica. Lancet 1890 1: 637-638.</td>
<td>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.</td>
</tr>
<tr>
<td>Petro DJ. Marihuana as a therapeutical agent for muscle spasm or spasticity. Psychosomatics 1980 21: 81-85.</td>
<td>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.</td>
</tr>
<tr>
<td>Petro &amp; Ellenberger. Treatment of human spasticity with delta 9-tetrahydrocannabinol. J Clin Pharmacol 1981 21: (8-9 Suppl): 413S-416S.</td>
<td>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.</td>
</tr>
<tr>
<td>Clifford DB. Tetrahydrocannabinol for the treatment of tremor in multiple sclerosis. Ann Neurol 1983 13: 669-671.</td>
<td>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.</td>
</tr>
<tr>
<td>RR Snider &amp; P Consroe. Treatment of Meige syndrome with cannabidiol. Neurology 1984 34 (Suppl 1): 147.</td>
<td>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.</td>
</tr>
<tr>
<td>Consroe et al. Open label evaluation of cannabinoid in dystonic movement disorders. Int J Neurosci 1984 30: 277-82.</td>
<td>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.</td>
</tr>
<tr>
<td>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.</td>
<td>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.</td>
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<td>Consroe et al. The perceived effects of smoked cannabis on patients with multiple sclerosis. Eur Neurol 1997 38: 44-8.</td>
<td>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.</td>
</tr>
<tr>
<td>Williamson &amp; Evans. Cannabinoids in clinical practice. Drugs 2000 60: 1303-14.</td>
<td>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.</td>
</tr>
<tr>
<td>SH Fox et al. Randomized, double-blind, placebo-controlled trial to assess the potential of cannabinoid receptor stimulation in the treatment of dystonia. Movement Disorder 2002 17: 145-149.</td>
<td>Nabilone was ineffective in patients with generalised and segmental primary dystonia.</td>
</tr>
<tr>
<td>J Killestein et al. Safety, tolerability and efficacy of orally administered cannabinoids in MS. Neurology 2002 58: 1404-1407.</td>
<td>This was a randomised crossover trial of placebo, THC and plant 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.</td>
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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: