

# Cannabis and Cannabis Based Medicine Extracts: Additional Results

Ethan Russo

**SUMMARY.** This study reviews results in recent human clinical trials with cannabis based medicine extract (CBME), THC or cannabis.

In a study performed at Queen's Square, London, both High THC and THC:CBD fixed ratio sublingual CBME demonstrated significant benefits on mean maximum cystometric capacity, mean daytime frequency of urination, frequency of nocturia, and mean daily episodes of incontinence in 11 multiple sclerosis patients with intractable lower urinary tract symptoms.

A Phase II clinical study in Oxford, England with 24 MS and intractable pain patients was performed as a consecutive series of double-blind, randomized, placebo-controlled single patient cross-over trials with sublingual CBME. Pain scores on visual analogue scales were significantly improved over placebo with both High THC and High CBD CBME. Subjectively, spasm was significantly improved with High THC and THC:CBD fixed ratio extracts. Spasticity was also subjectively improved with the High THC CBME. All three extracts significantly improved objective measures of spasticity, while the High THC and

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[Haworth co-indexing entry note]: "Cannabis and Cannabis Based Medicine Extracts: Additional Results." Russo, Ethan. Co-published simultaneously in *Journal of Cannabis Therapeutics* (The Haworth Integrative Healing Press, an imprint of The Haworth Press, Inc.) Vol. 3, No. 4, 2003, pp. 153-161; and: *Cannabis: From Pariah to Prescription* (ed: Ethan Russo) The Haworth Integrative Healing Press, an imprint of The Haworth Press, Inc., 2003, pp. 153-161. Single or multiple copies of this article are available for a fee from The Haworth Document Delivery Service [1-800-HAWORTH, 9:00 a.m. - 5:00 p.m. (EST). E-mail address: [docdelivery@haworthpress.com](mailto:docdelivery@haworthpress.com)].

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10.1300/J175v03n04\_03

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THC:CBD fixed ratio CBME significantly improved objective measures of spasm.

In 34 intractable pain patients in Great Yarmouth, England, seven experienced substantial improvement over best available conventional treatment with CBME, 13 moderate, and eight some benefit. Many extended the range of their activities of daily living with acceptable levels of adverse effects.

Preliminary results of four Phase III clinical trials of CBME by GW Pharmaceuticals have revealed highly significant benefits in neuropathic pain in MS, pain and sleep disturbance in MS and other neurological diseases, multiple symptoms in MS, and neuropathic pain in brachial plexus injury, respectively. Most patients attained good symptomatic control with minimal side effects.

In Germany, a recent Phase II clinical trial has demonstrated significant benefit of oral THC in treatment of the tics of Tourette syndrome. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <docdelivery@haworthpress.com> Website: <<http://www.HaworthPress.com>> © 2003 by The Haworth Press, Inc. All rights reserved.]*

**KEYWORDS.** Medical marijuana, cannabis, alternative delivery systems, THC, cannabidiol, CBD, multiple sclerosis, chronic pain, Tourette syndrome, brachial plexus injury, pharmacotherapy

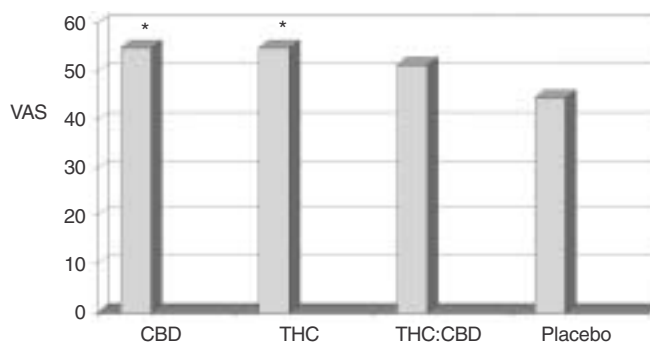
In 2001, interim results of a study of cannabis based medicine extracts (CBMEs) in bladder dysfunction were presented at the meeting of the International Association for Cannabis as Medicine (IACM) (Brady et al. 2001). A high-THC CBME and 1:1 THC:CBD CBME were compared to placebo in 17 multiple sclerosis patients with refractory lower urinary tract symptoms (LUTS). Eleven patients had evaluable data. Doses of up to 10 mg THC or 10 mg of THC and 10 mg of CBD were utilized. Mean maximum cystometric capacity (MCC) increased from 287 ml at baseline to 344 ml after eight weeks of CBME treatment (with 24 h of no drug). After 16 weeks, the bladder capacity measured 425 ml at maximum THC:CBD dosage. Mean daytime frequency of urination went from 9.3 to 7.5 with CBD:THC 1:1 and 6.9 with high-THC CBME. Similarly, nocturia episodes fell from 2.7 at baseline to 1.4 with the 1:1 mixture, and 1.5 with high-THC. Additionally, mean episodes of daily incontinence fell from a baseline of 2.1 to 1.0 with CBD:THC and 0.7 with high-THC CBME. These results will soon be published more formally.

In the past year, a small clinical trial of THC and a cannabis extract was performed with 16 subjects. Neither was observed to reduce spasticity, and adverse events were reported in the extract group (Killestein et al. 2002). Numerous criticisms were subsequently voiced in this regard (Russo 2003). Among these were that the plant extract was poorly categorized; in fact, it contained a fixed of THC to CBD with maximum doses of 5 mg of THC and 2 mg of CBD per day. The study additionally employed oral administration with no real dose titration. An additional study in Switzerland with more patients (57) and doses of up to 15 mg THC with 6 mg CBD divided tid has provided better results with reduction in spasms to the  $p < 0.05$  level and no significant side effects vs. placebo (Vaney et al. 2002). A study of an even larger cohort in the UK is pending publication.

The results of a Phase II study of CBME have recently been published (Wade et al. 2003). This clinical trial was performed in Oxford, England with 24 subjects with treatment-resistant MS, spinal or brachial plexus injury comparing THC, CBD, THC:CBD, and placebo sublingual extracts employing consecutive series of double-blind, randomized, placebo-controlled single patient cross-over trials. Subjective and objective measures of pain, spasticity, spasm et al. were monitored along with adverse effects. Results were monitored employing subjective and objective blinded ratings and visual analogue scales (VAS). Twenty of the subjects completed the trial. Results with statistical significance included:

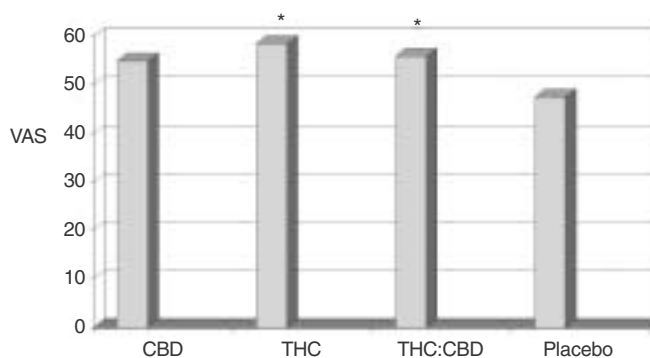
1. Pain scores were improved with both high-THC and high-CBD CBME vs. placebo ( $p < 0.05$ ) (Figure 1).
2. Spasm was improved with both the high-THC and fixed-ratio THC:CBD CBME ( $p < 0.05$ ) (Figure 2).
3. Similarly, spasticity was improved subjectively with the high-THC preparation ( $p < 0.05$ ) (Figure 3).
4. As might be surmised, the high-THC CBME improved subjective measure of appetite ( $p < 0.05$ ) (Figure 4).
5. The fixed-ratio THC:CBD CBME produced the best improvement in subjective sleep ( $p < 0.05$ ) (Figure 5).
6. Turning to blinded objective measures, all three extracts, high-THC, high-CBD and fixed-ratio THC:CBD CBME improved spasticity on a numerical symptom scale ( $p < 0.05$ ) (Figure 6).
7. Similarly, the high-THC and THC:CBD fixed-ratio CBME's yielded statistically significant objective improvement in spasm frequency ( $p < 0.05$ ) (Figure 7).

FIGURE 1. Pain Improvement, N = 20, Daily VAS

\* =  $p < 0.05$ 

Adapted from Wade DT, Robson P et al. 2003, Clin Rehab 17:18-26.

FIGURE 2. Spasm, N = 20, Daily VAS

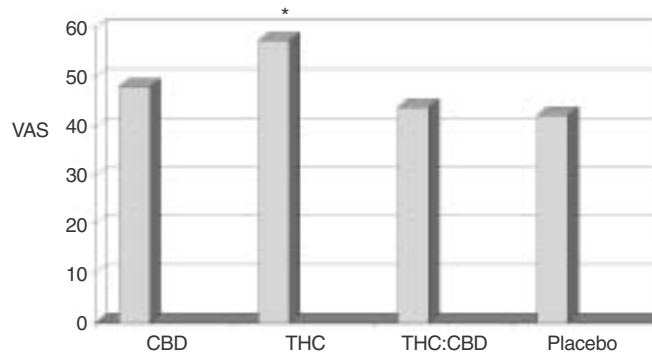
\* =  $p < 0.05$ 

Adapted from Wade DT, Robson P et al. 2003, Clin Rehab 17:18-26.

Adverse effects in the trial were predictable and well tolerated.

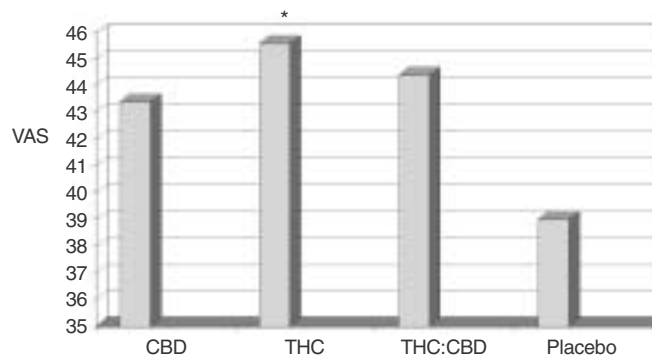
Additional Phase II work has been pursued in chronic pain patients intractable to conventional pharmacotherapy by the team of Notcutt et al. at James Paget Hospital in Great Yarmouth, UK. This work is pending more formal publication, but has been reported in 9 abstracts in the *Journal of Cannabis Therapeutics* from the 2001 meeting of the International Association for Cannabis as Medicine in Berlin (Notcutt 2002; Notcutt et al. 2002, 2002, 2002, 2002, 2002, 2002, 2002, 2002), as well

FIGURE 3. Spasticity, N = 20, Daily VAS



\* =  $p < 0.05$   
 Adapted from Wade DT, Robson P et al. 2003, Clin Rehab 17:18-26.

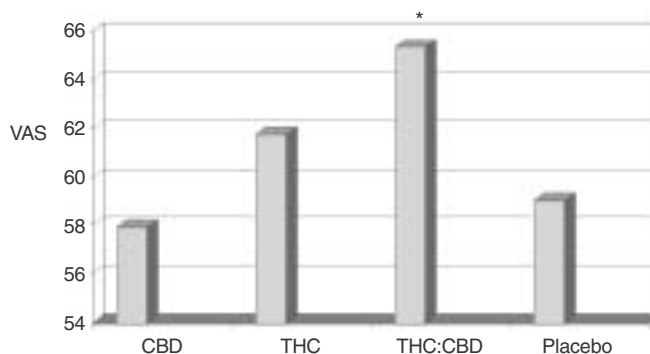
FIGURE 4. Appetite, N = 20, Daily VAS



\* =  $p < 0.05$   
 Adapted from Wade DT, Robson P et al. 2003, Clin Rehab 17:18-26.

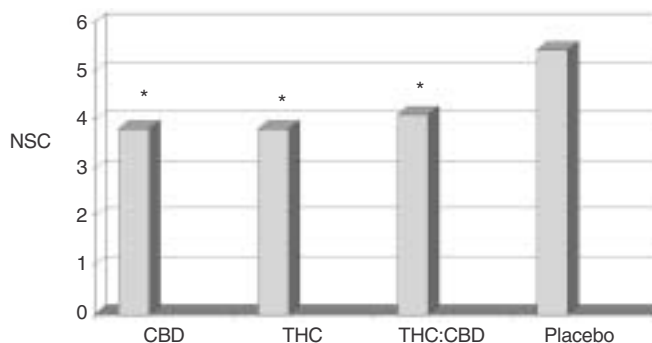
as the 2002 meeting of the International Cannabinoid Research Society in Asilomar, California (Notcutt 2003). Briefly stated, 34 N-of-1 studies were performed in a cohort of inadequately controlled pain patients, including those with MS (16), chronic back pain and sciatica (eight), other neuropathic pain (five), complex regional pain syndrome (CRPS, or “reflex sympathetic dystrophy”) (two), and polyarthralgia, stiff man syndrome and myopathy (one each). Subjects included both cannabis-experienced and cannabis-naïve individuals. After a two-week base-

FIGURE 5. Sleep, N = 20, Daily VAS

\* =  $p < 0.05$ 

Adapted from Wade DT, Robson P et al. 2003, Clin Rehab 17:18-26.

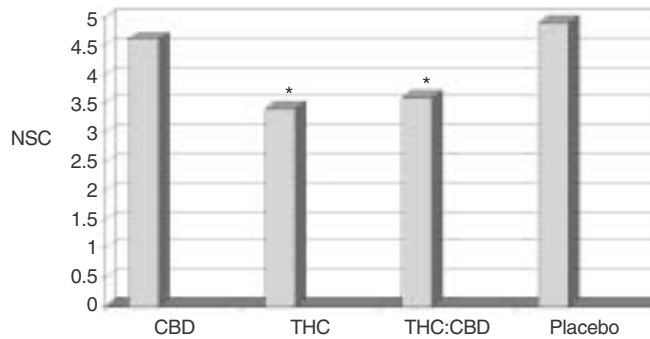
FIGURE 6. Spasticity Severity, Numerical Symptom Scale, N = 20, Observer Rated

\* =  $p < 0.05$ 

Adapted from Wade DT, Robson P et al. 2003, Clin Rehab 17:18-26.

line evaluation, a subsequent two-week open-label titration trial (one spray every 30 minutes to a limit of four with subsequent patient-directed upward titration) was pursued with fixed-ratio THC:CBD, followed by two separate four-week double-blind randomized trials of one week each of high-THC, high-CBD, fixed-ratio THC:CBD or placebo. General benefits were noted in CBME groups in pain, sleep, depression, activity and overall health compared to placebo. Interestingly, individ-

FIGURE 7. Spasm Frequency, Numerical Symptom Scale, N = 20, Observer Rated



\* =  $p < 0.05$

Adapted from Wade DT, Robson P et al. 2003, Clin Rehab 17:18-26.

ual dose requirements varied tremendously in the cohort, with symptomatic control requiring 5-80 mg per day of THC, CBD or the mixture. Seven patients experienced substantial improvement with CBME over best available conventional treatment, while 13 (32.8%) had moderate benefit, eight (23.5%) had “some” benefit, and six (17.6%) had none. Some dysphoria occurred at dose initiation, particularly in cannabis-naïve patients, but passed in 2-3 hours. Postural hypotension occurred in three patients with dose overload, while lesser adverse effects included mucosal stinging, staining of teeth, taste change and dry skin. Randomization was broken in four patients, one was removed due to distress, one continued single-blind after marital issues, one continued after an orthostatic hypotension event, and one continued single-blind after a gastroenteritis, deemed unrelated. Overall, the CBME was felt to be effective and acceptable to patients. Twenty-nine patients (85%) elected to continue into a long-term safety study. In the aftermath of this study, subjects were noted to be able to engage in many high level pursuits of which they were previously incapable.

In November 2002, preliminary results from four Phase III randomized, double-blind, placebo controlled Phase III clinical trials in the UK with 350 patients were released by GW Pharmaceuticals, and are available online: <[http://www.gwpharm.com/news\\_pres\\_05\\_nov\\_02.html](http://www.gwpharm.com/news_pres_05_nov_02.html)>. Results from these studies included highly statistically significant reductions in neuropathic pain, spasticity and sleep disturbance. The topics of the studies included the following:

1. Neuropathic pain in MS
2. Pain and sleep disturbance in MS and other neurological conditions
3. Multiple symptoms in MS
4. Neuropathic pain in brachial plexus injury

In the Phase III study of neuropathic pain in multiple sclerosis, 66 patients were studied in double-blind parallel groups with THC:CBD vs. placebo. Pain relief with THC:CBD CBME was greater than placebo ( $p < 0.01$ ), and sleep disturbance was relieved to the same level ( $p < 0.01$ ).

In the Phase III chronic refractory pain trial, 70 subjects with MS and other conditions were examined in double-blind parallel groups with THC:CBD CBME. Pain relief was observed with decreased usage of rescue medication as compared to placebo ( $p < .05$ ), and sleep disturbance was also diminished ( $p < .05$ ).

A larger cohort of 160 MS patients was studied in a third double-blind parallel group examining the fixed-ratio THC:CBD CBME. Spasticity was improved to a highly statistically significant degree ( $p < 0.01$ ), while trends of improvement were also noted for a variety of other associated symptoms.

Finally, a fourth study examined brachial plexus injury, an intractable pain syndrome most often encountered after motorcycle accidents in the UK. In the largest study and first ever controlled clinical trial in this disorder, 48 subjects were studied in a double-blind crossover protocol comparing THC, THC:CBD and placebo. THC and THC:CBD CBME both reduced pain greater than placebo to a highly statistically significant degree ( $p < 0.01$ ). THC and THC:CBD CBME both reduced sleep disturbance to a significant degree ( $p < 0.05$ ).

Certain other features of the trials deserve emphasis. Firstly, after 350 patient-years of experience with CBME, the improvements in clinical parameters involved were attained above and beyond those achievable with best-available "conventional" pharmaceuticals. Additionally, with self-titration, most patients were capable of alleviating their symptomatology without adverse effects on activities of daily living (ADL). The safety profile was judged, "excellent."

At the time of this writing (May 2003), five additional Phase III clinical trials including cancer pain and spinal cord injury are in process, and will be completed in 2003, at which time a cumulative 1000 patients shall have been studied.



Finally, a team in Germany has recently published a Phase II study of oral THC in Tourette syndrome (TS) (Muller-Vahl, Schneider et al. 2003), in which 24 patients were treated over 6 weeks with up to 10 mg a day in a randomized, double-blind, placebo-controlled study. Tics were assessed by a variety of measures both subjectively and objectively. Seven patients dropped out, but only one due to adverse effects. Significant benefits were noted ( $p < 0.05$ ) in a variety of measures with no serious adverse effects. The authors concluded that THC was safe and effective in treatment of tics associated with Tourette syndrome.

## REFERENCES

- Brady, C.M., R. DasGupta, O.J. Wiseman, K.J. Berkley, and C.J. Fowler. 2001. Acute and chronic effects of cannabis based medicinal extract on refractory lower urinary tract dysfunction in patients with advanced multiple sclerosis-Early results. Paper read at Congress of the International Association for Cannabis as Medicine, October 26, at Berlin, Germany.
- Muller-Vahl, K.R., U. Schneider, H. Prevedel, K. Theloe, H. Kolbe, T. Daldrup, and H.M. Emrich. 2003. Delta9-tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome: A 6-week randomized trial. *J Clin Psychiatry* 64 (4):459-465.
- Notcutt, W. 2002. Medicinal cannabis extracts in chronic pain. *J Cannabis Therapeutics* 2 (2):101-102.
- \_\_\_\_\_. 2003. Cannabis in the treatment of neuropathic pain. In *Medicinal uses of cannabis and cannabinoids.*, edited by B.A. Whittle, G.W. Guy and P. Robson. London: Pharmaceutical Press.
- Notcutt, W., M. Price, R. Miller, S. Newport, C. Sansom, and S. Simmonds. 2002. Medicinal cannabis extract in chronic pain: (1) Design of a comparative "N of 1" primary study (CBME-1). *J Cannabis Therapeutics* 2 (2):93-94.
- \_\_\_\_\_. 2002. Medicinal cannabis extract in chronic pain: (6) Design of long term safety study (CBME-SAFEX). *J Cannabis Therapeutics* 2 (2):98-99.
- \_\_\_\_\_. 2002. Medicinal cannabis extract in chronic pain: (7) Results from long term safety extension study (CBME-SAFEX). *J Cannabis Therapeutics* 2 (2):99-100.
- \_\_\_\_\_. 2002. Medicinal cannabis extract in chronic pain: (8) Evaluation of THC-CBD against THC in the management of chronic pain. *J Cannabis Therapeutics* 2 (2):100-101.
- \_\_\_\_\_. 2002. Medicinal cannabis extracts in chronic pain: (2) Comparison of two patients with back pain and sciatica. *J Cannabis Therapeutics* 2 (2):94-95.
- \_\_\_\_\_. 2002. Medicinal cannabis extracts in chronic pain: (3) Comparison of two patients with multiple sclerosis. *J Cannabis Therapeutics* 2 (2):95-96.
- \_\_\_\_\_. 2002. Medicinal cannabis extracts in chronic pain: (4) Cannabidiol modification of psycho-active effects of delta-9-THC. *J Cannabis Therapeutics* 2 (2):96-97.
- \_\_\_\_\_. 2002. Medicinal cannabis extracts in chronic pain: (5) Cognitive function and blood cannabinoid levels. *J Cannabis Therapeutics* 2 (2):97-98.
- Wade, D.T., P. Robson, H. House, P. Makela, and J. Aram. 2003. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. *Clin Rehab* 17:18-26.