

ABSTRACTS

**Cannabinoids and Pain Management Symposium:
American Academy of Pain Management
13th Annual Clinical Meeting,
September 28, 2002,
Reno Hilton, Reno, NV, USA**

Agenda:

08:00-09:00	John McPartland, DO: Progress in Neurobiology Related to Cannabinoids
09:05-10:05	Ethan Russo, MD: Cannabis: From Raw Plant to Pharmaceutical Products

10:05-10:20 Break

10:20-11:20	David Hadorn, MD, PhD: Trial Designs for Cannabinoids
11:25-12:25	William Notcutt, MD: Results from Cannabis-Based Medical Extract

12:25-1:55 Break

1:55-2:55	Mark Ware, MD: Canadian Cannabis: Grants, Trials and Outcomes
3:00-4:00	J. Hampton Atkinson, MD: University of California Center for Medicinal Cannabis Research (CMCR)
	David Hadorn, MD: Current and Planned Trials.

PROGRESS IN NEUROBIOLOGY RELATED TO CANNABINOIDS. J.M. McPartland, MS, DO, Faculty of Health & Environmental Science, UNITEC, Private Bag 92025, Mt. Albert, Auckland, New Zealand.

Abstract: Elucidating the active ingredients in cannabis proved difficult. It took a dozen scientists, working from 1838 until 1964, to isolate and fully characterize tetrahydrocannabinol (THC) and cannabidiol (CBD). Since then, progress in neurobiology related to cannabinoids has accelerated. Analogs of THC were soon synthesized, many with greater potency and efficacy than the parent molecule. In 1988 a specific receptor for THC was demonstrated in the CNS, called CB₁. CB₁ is expressed in cells related to nociception and pain, such as afferent C-fibers, dorsal horn cells, periaqueductal gray area, rostral ventrolateral medulla, thalamus, amygdala, and cerebral cortex. The receptor-mediated effects of THC are primarily inhibitory, dampening the transmission of nociceptive signals mediated by glutamate and substance P. A second cannabinoid receptor (CB₂) was discovered in peripheral tissues, primarily in cells of immune function. CB₂ dampens inflammatory pain mediated by prostaglandins, leukotrienes, 15-HETE, nerve growth factor, tumor necrosis factor-alpha, and interleukin-1 beta. THC is highly lipophilic, so it also causes nonspecific, non-receptor mediated effects on cell membranes (e.g., the blood-brain barrier) and some enzyme systems (such as CYP-450s, COX, and LO enzymes). Furthermore, cannabis contains more than merely THC; other cannabinoids, terpenoids, and flavonoids contribute to the pharmacodynamics and pharmacokinetics of cannabis. Different cannabinoids cause different conformational changes in CB₁ and CB₂; these activate different G-proteins, such as Gi, Go, and Gs. This complicated scenario explains why different varieties of cannabis induce different types of cannabinomimetic effects.

In 1992, researchers discovered anandamide, the first of several endogenous cannabinoids (endocannabinoids). Anandamide provides analgesia, and is produced upon demand, via a calcium-dependent, “depolarization-induced suppression of excitation.” After retrograde signaling of CB₁ receptors, anandamide undergoes re-uptake by a membrane transporter and degraded by the enzyme FAAH. Researchers are currently investigating anandamide reuptake inhibitors and FAAH inhibitors. Besides direct spinal effects, the cannabinoids also decrease pain by interacting with the descending antinociceptive (endorphin) path-

way. Lastly, cannabinoids inhibit the hypothalamus and amygdala, therefore extinguishing painful memory and fear conditioning, factors that turn chronic pain into human suffering.

CANNABIS: FROM RAW PLANT TO PHARMACEUTICAL PRODUCTS. Ethan Russo, MD, Montana Neurobehavioral Specialists, 900 North Orange St., Missoula, MT 59802, USA (E-mail: Erusso@blackfoot.net).

Abstract: Cannabis has a historical record as medicine for some 5000 years. This includes usage as a surgical anesthetic in Ancient China, among the Renaissance herbalists with hemp strains, and in more modern times with extracts of THC-predominant cannabis strains.

The biochemical bases for cannabis in pain management include its neuromodulatory roles on various neurotransmitter systems, its antioxidant and anti-inflammatory effects, and interactions with the endorphin system (Russo 2002).

The origin of cannabis' medicinal properties derives from glandular trichomes, where its therapeutic cannabinoids and terpenoids are produced. These, along with flavonoid components, combine in a synergistic fashion to promote analgesia and reduce adverse effects of THC (McPartland and Russo 2001).

Smoking of cannabis will likely never be an acceptable form of drug delivery to the FDA due to pulmonary sequelae and social ostracism, although some nations such as Canada and the Netherlands are allowing such prescription. Rather, the formulation of alternative delivery systems employing standardized preparations is most promising. Dose-metered inhalers of pure THC have produced pulmonary irritation in patients, but remain under development. Vaporization may represent a possible prescription alternative.

Oral administration, as with Marinol[®], is hampered by first pass hepatic metabolism of THC to the more psychoactive 11-OH-THC, poor and irregular gastrointestinal absorption, and loss of the ability to titrate dosages toward symptom reduction.

The latter is problematic with rectal suppository forms, which are poorly accepted by American consumers.

To date, transdermal skin patch preparations have yielded only about 10% of the necessary absorption, and harbor a risk of diversion of used material that would still contain active medication.

In contrast, the program of GW Pharmaceuticals in the UK has been pursued with Home Office approval employing Good Agricultural Practice (GAP). Cannabis is grown organically in compost employing female clones from plants with known THC and CBD content. Fertilization is prevented to maximize production of cannabinoids in a climate-controlled indoor setting with Integrated Pest Management (IPM). Cannabis flowers are picked at senescence.

The strains are subjected to a supercritical carbon dioxide extraction at room temperature, retaining cannabinoids and terpenoids with little pigment. Waxy ballast is removed by “winterization” with ethanol. Resulting Cannabis-Based Medicine Extracts (CBME) are then placed in aerosol devices for oro-mucosal delivery in clinical trials (Whittle et al. 2001).

These formulations allow active effects in 40 minutes with the ability to titrate doses and with good patient acceptance. Additionally, an Advanced Delivery System (ADS) has been developed, which allows for security and control of dosing, with the option for remote monitoring by researchers or treating physicians.

REFERENCES

- McPartland, J. M., and E.B. Russo. 2001. Cannabis and cannabis extracts: Greater than the sum of their parts? *Journal of Cannabis Therapeutics* 1 (3/4):103-132.
- Russo, E.B. 2002. Role of cannabis and cannabinoids in pain management. In *Pain management: A practical guide for clinicians*, edited by R. S. Weiner. Boca Raton, FL: CRC Press.
- Whittle, B.A., G.W. Guy, and P. Robson. 2001. Prospects for new cannabis-based prescription medicines. *Journal of Cannabis Therapeutics* 1 (3/4):183-205.

TRIAL DESIGNS FOR CANNABINOIDS. David Hadorn, GW Pharmaceuticals, Porton Down, Salisbury, England (E-mail: dhadorn@fastmail.fm).

Abstract: Research studies testing the effectiveness of cannabinoids face several methodological challenges. Inclusion and exclusion criteria must be based primarily on anecdotal information due to the scarcity of controlled trials. GW Pharmaceuticals, a UK company developing a range of whole-cannabis extracts for prescription use, selected chronic neuropathic pain and multiple sclerosis as their initial indications for re-

search and development. Uncertainty exists concerning whether patients should be included in trials when they have not previously experienced cannabis or its effects; most authorities currently feel that doing so is acceptable. Another consideration is whether dosages should be standardized (e.g., the “Fulton puff procedure”) as opposed to permitting patients to titrate dosage to a point of effect. Regulatory agencies generally expect standardized dosing, but the patient-controlled approach is more effective. Placebo controls are difficult to implement in cannabinoid research in view of the discernable “high” produced by THC. The extent to which placebo controls are needed outside of formal Phase III trials is controversial. Certain “active placebos,” such as CBD, can be used in comparative studies of differing strain effects, or standard treatments can be used as the comparator. Cross-over studies are well-suited for cannabinoid research and are much more powerful statistically than parallel group studies. However, regulatory agencies devalue such studies because of (largely overblown) concerns about carry-over effects from one period to the next. N-of-1 trials are also very useful in cannabinoid research, particularly for establishing dose and dosage patterns, exploring routes of administration, monitoring safety and tolerability, and identifying valid and reliable outcome measures. Again, however, these trials are generally not accepted by regulatory authorities. The need for randomization outside formal Phase III trials is questionable; what is important is control of confounding variables, and despite prevailing dogma this can be accomplished without randomization. Outcome measures should include both condition-specific and generic indicators of health and quality of life.

RESULTS FROM TRIALS OF CANNABIS BASED MEDICAL EXTRACTS. William Notcutt, James Paget Hospital, Lowestoft Road, Great Yarmouth, Norfolk, NR31 6LA, UK.

Abstract: Cannabis Based Medicinal Extracts (CBME) derived from cloned plants and delivered sublingually are now available for clinical study in the UK. This was the first clinical program and its goals were to identify the therapeutic windows, to study the effects of CBME of varying constituent composition on patients suffering with chronic, refractory pain, to study safety and tolerability and to determine the approaches to more extensive and detailed studies.

Single patient studies were undertaken (“N of 1”) as this was a new drug being used in heterogeneous group of patients with chronic, stable pain, poorly responsive to other treatment.

After a two-week assessment period the patients were started on a mixture of THC and CBD 1:1 for 2 weeks, open label. If they obtained benefits they went on to an eight-week randomized double-blind crossover placebo-controlled study. For 1 week periods they received either THC, CBD, THC:CBD or placebo. At the start of each week with a new extract, a supervised titration was undertaken.

A variety of assessments of pain, sleep, symptom control, depression, quality of life etc were undertaken. The results of these were used to determine whether patients had gained benefit. Those that did were able to go on to a long-term safety extension study.

Thirty-four patients were studied, 16 with MS, 8 with back pain post-spinal surgery and the remainder with a variety of mainly neuropathic problems, with a duration of pain between 1.5 and 36 years. Ages ranged from 26 to 66 years and 23 were women reflecting the patients with MS. Twelve had had some experience of cannabis for their symptoms and 7 had used it only on 1-2 occasions, often with adverse effects.

Two patients withdrew early due to inability cope with drug or the study. Seven patients who were frequent medicinal cannabis users received cannabinoid rescue medication to prevent them returning to their previous materials during placebo phases. Aggregated data from the remaining 25 patients demonstrates a fall in mean visual analogue scale (VAS) pain scores from 6 to 4 with both THC and THC:CBD mixture. CBD was of minimal benefit. There was a substantial improvement in sleep quality (15% → 55% of nights with good quality sleep) and the THC:CBD mixture was optimum. However, there was no significant increased duration of sleep. Depression scores fell and a Quality-of-Life assessment showed overall improvement.

The dose ranges showed a 25 and 30 fold (THC:CBD, THC) variation in daily consumption. The mean dose per day was 20 mg of THC alone or in the THC:CBD mixture.

Side effects were as anticipated. Drowsiness and dizziness were common during the initial uses of the extract but diminished as patients learned to titrate their drug more accurately. A similar outcome with euphoria (“high”)/dysphoria was found. Dry mouth was the most common problem and some had a burning stinging sensation due to the spray itself. Panic was infrequent and hallucinations rare but neither were caused major distress. One vasovagal episode and 2 episodes of acute

dysphoria occurred early on during the acute dosing period and reflected a titration that was too rapid.

Of all 34 patients, 2 withdrew early and 4 received no benefit. Twenty had moderate or substantial clinical benefit. Twenty-eight patients continued into a long term extension study, yielding 42 patient years of experience with the extracts.

This first study has shown that the extract is effective and easily titrateable by the sublingual route, but that dosing is highly individual. Substantial benefit, particularly to sleep, can be obtained from THC and THC:CBD in patients for whom there is little else available. Side effects were anticipated, tolerable and manageable.

The way is now open for a wide range of high quality clinical research in this area.

CANADIAN CANNABIS: GRANTS, TRIALS AND OUTCOMES.

Mark Ware, BA, MBBS, MRCP(UK), MSc, McGill University, Montreal (E-mail: Mware@total.net).

Abstract: There is a great deal of interest in the use of cannabis as a therapeutic agent, and good quality clinical research is needed to inform clinicians and policy makers in this heated debate. This talk presents results from preliminary studies of cannabis in pain management in Canada, including case reports, case series and prospective surveys, and summarizes existing research initiatives. The emphasis will be on raising awareness of practical issues and pitfalls in clinical cannabis research in Canada. An overview of the Health Canada Medical Marijuana Access Regulations will be included, which offers an opportunity for the long-term follow-up of medicinal cannabis users, particularly from a safety standpoint.

UNIVERSITY OF CALIFORNIA CENTER FOR MEDICINAL CANNABIS RESEARCH (CMCR). J. Hampton Atkinson, University of California San Diego (E-mail: jhatkinson@ucsd.edu).

Abstract: The Center for Medicinal Cannabis Research (CMCR) was established at the University of California in August 2000, with the overarching objective of conducting high quality scientific studies to ascertain the general medical safety and efficacy of cannabis products

and examine alternative forms of cannabis administration. Further the CMCR was intended to be a model resource for health policy planning by virtue of its close collaboration with federal, state, and academic entities. To date the CMCR has successfully released 3 calls for proposals to California investigators at private and state-funded academic and related institutions. Submitted proposals are evaluated for scientific merit by a national panel of experts; approved studies are forwarded for state and federal regulatory review. Seven clinical and pre-clinical studies have been approved overall, funded, and are in progress; 3 studies have received scientific and regulatory approval and are due to commence; 5 additional studies are undergoing state and federal review. Clinical studies in progress or forthcoming address efficacy of cannabis as analgesic for painful disorders due to HIV or cancer and as therapy for spasticity in multiple sclerosis and for nausea due to chemotherapy; related studies evaluate safety of cannabis; pre-clinical models intend to evaluate mechanisms of analgesia. A collegial working relationship with state and federal agencies, including the Drug Enforcement Agency, Food and Drug Administration, and National Institute on Drug Abuse, has developed.

CURRENT AND PLANNED TRIALS—GW PHARMACEUTICALS. David Hadorn, GW Pharmaceuticals, Porton Down, Salisbury, England (E-mail: dhadorn@fastmail.fm).

Abstract: GW Pharmaceuticals is a UK-based company developing a range of whole-cannabis extracts for prescription use. The company's initial indications for study, multiple sclerosis and neuropathic pain, were selected from a wealth of anecdotal information, animal studies, and limited data from controlled trials. Four Phase III trials on these indications are nearing completion, with several more specific trials in these areas underway, including bladder dysfunction in multiple sclerosis, neuropathic pain and sleep, and patients with spinal cord injury, allodynia, or brachial plexus avulsion. Cancer pain is being studied in a Phase III trial and a Phase II trial has begun in peri-operative pain. Initial work is also underway in rheumatoid arthritis and inflammatory bowel disease, glaucoma, cystic fibrosis, insomnia, and schizophrenia. Study preparations are whole-plant extracts, with principal cannabinoids being THC, CBD, or a 1:1 mixture of both THC and CBD. A pump ac-

tion oral spray delivers 2.5 mg of either or both cannabinoids per actuation. Initial dosing is performed in the clinic under medical supervision, followed by self-titration at home. Findings from Phase II studies showed that patients experienced relief of neuropathic pain, improvement in spasticity, bladder-related symptoms, and in sleep, mood and overall sense of well-being. An opiate-sparing effect was also observed in patients taking opiates for pain. Of the first 109 refractory patients enrolled in Phase II trials, 88 completed the acute phase, of which 86 elected to continue long term. Safety evaluation incorporating 250 patient-years of exposure revealed the extracts to be generally well tolerated, with a predictable pattern of generally mild adverse events. No evidence of tolerance was observed.