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FILE: ▪Cannabis (*Cannabis sativa*)
▪Sativex
▪Rheumatoid Arthritis Pain

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RE: Preliminary Study Finds Cannabis Medicine Effective for Rheumatoid Arthritis Pain

Blake D, Robson P, Ho M, Jubb R, McCabe C. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology*. 2005;1–3 doi:10.1093/rheumatology/kei183.

Cannabis (*Cannabis sativa*) is an alternative treatment for chronic, intractable pain not alleviated by conventional medications, for nausea and vomiting from chemotherapy, and for stimulating the appetite so patients who are losing weight can regain it. According to the authors of this clinical trial, the use of cannabis for rheumatic diseases, such as rheumatoid arthritis (RA), dates to 2800 BCE. However, the Chinese reference actually derives from the *Shen Nong Ben Cao Jing* which was not written until the 1st century. Cannabis contains 60 unique compounds, called canabinoids that interact with receptors in the called cannabinoid receptors. Very few (especially THC) actually bind at the cannabinoid receptors. The authors state that there are two types of cannabinoid receptors, appropriately name cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2). CB1 are found mostly in the central nervous system, and are thought to be important for modulating the perception of pain. CB2, primarily found on immune system cells, are being investigated as targets for immune modulating therapies. There is some evidence that there may be up to three more cannabinoid receptors.

This study was a multicenter, double-blind, randomized, placebo-controlled, parallel-group trial of Sativex® (GW Pharmaceuticals; United Kingdom), a blend of whole cannabis plant extracts, for the treatment of RA pain. (The centers are not disclosed.) Sativex is standardized to 2.7 mg tetrahydrocannabinol (THC) and 2.5 mg cannabidiol (CBD), which are "recognized as key therapeutic constituents that act synergistically together and with other plant constituents." Trace amounts of cannabinol, cannabichromene, cannabigerol, all shown to exhibit anti-inflammatory properties, were also present. Subjects received Sativex administered as an oromucosal spray, one spray in the evening, one half hour before bedtime. Subjects were instructed to increase the dose by 1 spray every 2 days until

therapeutic response was achieved, or a maximum of 6 sprays. The maximum dosage was then maintained for 3 weeks.

Inclusion criteria included a diagnosis of RA according the American College of Rheumatology (ACR) criteria. To be diagnosed with RA, subjects had to have at least 4 of the following symptoms: (1) morning stiffness in and around joints lasting at least 1 hour before maximal improvement; (2) soft tissue swelling (arthritis) of 3 or more joint areas observed by a physician; (3) swelling (arthritis) of the proximal interphalangeal, metacarpophalangeal, or wrist joint; (4) symmetric swelling; (5) rheumatoid nodules; (6) presence of rheumatoid factors, a protein in the blood detected by a standard blood test; (7) and radiographic erosions and/or periarticular osteopenia in hand and/or wrist joints. The first 4 criteria must have been present for at least 6 weeks.[1] To be eligible for the trial, the pain from RA had to not be adequately controlled by non-steroidal anti-inflammatory drugs (NSAID) and prednisolone (a corticosteroid drug). Excluded from the study was anyone with a history of psychiatric disorders or substance abuse, cardiovascular, kidney, or liver disorders, or epilepsy.

The primary outcome measures were morning pain with movement, as measured on a 0–10 numerical rating scale (NRS). A baseline NRS score was calculated as the average score during the last 4 days of a 14-day baseline period. The secondary outcome measures were NRS score for pain at rest, quality of sleep, morning stiffness, the Short-Form McGill Pain Questionnaire (SF-MPQ), and the 28-joint disease activity score (DAS28). The SF-MPQ contains 11 questions referring to the sensory dimension of the pain experience and four related to the affective dimension. Each descriptor is ranked on a 4 point intensity scale (0=none, 1=mild, 2=moderate, 3=severe). The pain rating index of the standard MPQ is also included as well as a visual analogue scale. The DAS28 counts how many of 28 different joints are symptomatic at different times and provides an estimate of RA improvement or progression.

Enrolled in the study were 58 RA-positive subjects (mean age 62.9 ± 9.8 years), who were randomized to the Sativex and placebo groups. The mean dose achieved by the end of the trial was 5.4 ± 0.84 sprays of Sativex and 5.3 ± 1.18 for placebo. Significant improvements were detected for pain on movement, pain at rest, quality of sleep, DAS28 and SF-MPQ compared to placebo. Morning pain on movement decreased significantly greater in the Sativex group versus placebo (2.2 vs. 1.4, respectively; $P = 0.044$). Morning pain at rest significantly decreased in the Sativex group versus placebo (2.2 vs. 1.2, respectively; $P = 0.018$). Quality of sleep significant improved in the Sativex group compared to control (2.3 vs. 1.2, respectively; $P = 0.027$). DAS28 score significantly decreased in the Sativex group compared to placebo (1.9 vs. 0.1, respectively; $P = 0.002$). SF-MPQ score for pain at rest also significantly improved in the Sativex group compared to control (–0.6 vs. 0.1, respectively; $P = 0.016$).

Non-significant differences in scores between the Sativex and placebo groups were detected for morning stiffness, SF-MPQ total intensity of pain, and SF-MPQ intensity of pain. Adverse events (AE) were mild to moderate, except for two (6%) in the Sativex group, which complained of constipation and malaise, and six (22%) in the placebo group. No

participants withdrew from the study due to AE. The authors conclude that Sativex, a cannabis-based medicine, was well-tolerated and was superior to placebo for improving pain scores, sleep quality, and DAS28.

One cannabis-based medicine, called Marinol® (dronabinol), is already available by prescription in the US. Marinol, which only contains THC, is approved by the FDA as an appetite stimulant, primarily for acquired immune deficiency syndrome (AIDS) and chemotherapy patientsis. Sativex was approved by Health Canada for prescription use in 2005 for multiple sclerosis patients for the treatment of neuropathic pain (pain due to damage to nerves) and spasticity.[2] If the results of this clinical trial can be verified by larger clinical trials, the use of cannabis-based medicine for RA pain might also be approved in Canada, perhaps, eventually in the US as well.

—John Neustadt, ND

References

[1]Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum.* Mar 1988;31(3):315-324.
[2]Sativex [web page]. December 2, 2005. Available at: http://en.wikipedia.org/wiki/Sativex. Accessed December 4, 2005.

More information can be found a the company's web site: www.gwpharm.com.

The American Botanical Council has chosen not to reprint the original article.