



P.O. Box 144345 Austin, TX 78714-4345 ■ 512.926.4900 ■ Fax: 512.926.2345 ■ www.herbalgram.org

HerbClip™

Mariann Garner-Wizard
Jennifer Minigh, PhD

Shari Henson
Heather S Oliff, PhD

Brenda Milot, ELS
Marissa Oppel, MS

Executive Editor – Mark Blumenthal

Managing Editor – Lori Glenn

Consulting Editors – Dennis Awang, PhD, Francis Brinker, Steven Foster, Roberta Lee, MD

Production – Cassandra Johnson, George Solis

AMERICAN
BOTANICAL
COUNCIL

Now in Our
20th Year

FILE: ■ **Cannabis** (*Cannabis sativa*)
■ **Marijuana**
■ **Chronic Pain**
■ **Sleep Disruption**

HC 090473-347

Date: February 29, 2008

RE: Review of Cannabis and Derivative Products Usage in Pain and Sleep

Russo EB, Guy GW, Robson PJ. Cannabis, pain, and sleep: Lessons from therapeutic clinical trials of Sativex®, a cannabis-based medicine. *Chem Biodivers*. 2007;4:1729-1743.

For patients with chronic pain, sleep disruption is a wearying symptom, negatively effecting quality of life. Recent studies have found that opioids and pain disrupt nocturnal sleep, prolong sleep latency, and limit sleep stages 3 and 4 and rapid eye movement sleep. Opioids disturb sleep, contribute to depression and enhance pain. "[N]ew approaches to chronic pain and... sleep disorders are necessary." Or, perhaps, old ones: cannabis (marijuana; *Cannabis sativa*) has been used since ancient times for pain and sleep disorders. Its "soporific qualities... were noted in... ancient Indian *ayurveda*... *Linnaeus* recognized [it] as *narcotica* and *anodyna*... *William B. O'Shaughnessy* reintroduced [it] to Western medicine... wherein it produced sleep and pain reduction [in] rheumatism and... other conditions." Today, animal and in vitro studies are clarifying the key role of endocannabinoids in regulating sleep-wake cycles. Anandamide (AEA) "seems to mediate sleep induction" interacting with oleamide. Among cannabis' compounds, tetrahydrocannabinol (THC), a CB₁ agonist, may work synergistically with cannabidiol (CBD) and cannabis terpenoids. Some cannabis terpenoids, particularly terpineol, are sedating. CBD modulates THC's effects in sleep quality and architecture, as has been seen in studies of cannabis medicines' effects on pain.

Sleep quality is often a secondary outcome in studies involving pain in multiple sclerosis, diabetic or HIV neuropathy, brachial plexus avulsion, rheumatoid arthritis, and other intractable or chronic conditions. Sleep quality and pain reduction results in 13 randomized, placebo-controlled clinical trials of cannabis-based medicines are discussed briefly and individually. Of them, nine used Sativex® (GW Pharmaceuticals, Salisbury, Wiltshire, UK) some with its high-THC and high-CBD variants (Tetranabinex® and Nabidiolex®, respectively); three used Cannador (European Institute for Oncological and Immunological Research, Berlin), including one comparing this plant-based medicine with synthetic THC as

Marinol® (Roxane Laboratories, Columbus, OH); one used smoked marijuana. In Phase I- III studies of Sativex in over 2000 subjects with 1000 combined patient years of use and a wide variety of pain conditions, 40-50% had improved subjective sleep measures. A Phase II double-blind crossover *N*-of-1 study of intractable pain is typical, with Sativex, while having little effect on the number of hours of sleep, producing "marked changes in... sleep quality [duration, depth, and relative disruption]." No tolerance or need for increased doses of Sativex has been seen in safety extension (SAFEX) studies of up to four years. A case report of Marinol reversing insomnia in three patients with intractable pruritis associated with cholestatic liver disease, and a limited study in which it reduced nocturnal motor activity in five dementia patients are mentioned; as well as early Brazilian assessments of CBD's effects on subjective sleep.

According to the authors, the first randomized, placebo-controlled trial of smoked cannabis in pain (HIV/AIDS-related neuropathy) found >30% reduction of pain vs. placebo but did not study sleep effects. The opinion is given that the Food and Drug Administration (FDA)'s guidelines for botanical medicines, "difficulties... in standardizing cannabis, and pulmonary issues associated with its inhalation, make it unlikely that regulatory approval [is] attainable in most nations of the world." Furthermore, while no head-to-head trials of Sativex and cannabis are planned, "comparison of [adverse events] from... SAFEX studies... on Sativex with those of smoked-cannabis... in... Canada and the Netherlands supports... that Sativex was much better tolerated, especially with respect to mental status and cognitive issues." The remark about pulmonary issues references a 2005 report by DP Tashkin. However, in May, 2007, Tashkin reported that, in a large, long-term study, smoking marijuana did not increase the risk of certain cancers. "Even the heaviest marijuana smokers... those who had smoked more than 22,000 marijuana cigarettes, did not have an increased risk of developing cancer." (Cavaliere C. Study finds no link between marijuana use and lung, head, or neck cancer. *Herbalgram* June 2007; # 73:22). Vaporizer technology can significantly reduce bronchial irritation from cannabis smoke.

Sativex and other cannabis medicines may have an enormous role to play in chronic pain, sleep disorders, and other areas, as none know better than Russo. Medical use of marijuana has in fact been approved in 12 US states so far, and is legal in many "nations of the world", regardless of FDA guidelines.

— *Mariann Garner-Wizard*

The original article cannot be reprinted as the publisher did not respond to ABC's reprint request.

The American Botanical Council provides this review as an educational service. By providing this service, ABC does not warrant that the data is accurate and correct, nor does distribution of the article constitute any endorsement of the information contained or of the views of the authors.

ABC does not authorize the copying or use of the original articles. Reproduction of the reviews is allowed on a limited basis for students, colleagues, employees and/or members. Other uses and distribution require prior approval from ABC.