REVIEW

Cannabis, Pain, and Sleep: Lessons from Therapeutic Clinical Trials of *Sativex®*, a Cannabis-Based Medicine

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Cannabis sativa L. has been utilized for treatment of pain and sleep disorders since ancient times. This review examines modern studies on effects of Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) on sleep. It goes on to report new information on the effects on sleep in the context of medical treatment of neuropathic pain and symptoms of multiple sclerosis, employing standardized oromucosal cannabis-based medicines containing primarily THC, CBD, or a 1:1 combination of the two (*Sativex®*). Sleep-laboratory results indicate a mild activating effect of CBD, and slight residual sedation with THC-predominant extracts. Experience to date with *Sativex* in numerous Phase I–III studies in 2000 subjects with 1000 patient years of exposure demonstrate marked improvement in subjective sleep parameters in patients with a wide variety of pain conditions including multiple sclerosis, peripheral neuropathic pain, intractable cancer pain, and rheumatoid arthritis, with an acceptable adverse event profile. No tolerance to the benefit of *Sativex* on pain or sleep, nor need for dosage increases have been noted in safety extension studies of up to four years, wherein 40–50% of subjects attained good or very good sleep quality, a key source of disability in chronic pain syndromes that may contribute to patients' quality of life.

Introduction. – Sleep disorders are important syndromes in modern medicine that include parasomnias, or sleep-disruptive events, as well common associated afflictions such as snoring and sleep apnea. The most common disorder is insomnia, or lack of sleep, said by the *National Institute of Neurological Disorders and Stroke* to afflict 60 million Americans [1]. Insomnia is a major risk factor for associated morbidity even in the absence of illness, and is associated with markedly increased prevalence of depression, anxiety, absenteeism [2], accidents [3], and utilization of health care resources [4]. Sleep disruption itself, as in shift work in nurses, may contribute notably to anxiety and functional bowel disorders [5]. When such sleep disturbances occur secondary to pain, they can be termed '*symptomatic insomnia*'. Pain at night at least three times a week was identified as a significant factor in excessive daytime sleepiness in older adults [6]. When sleep disturbance accompanies chronic pain or disease, attendant treatment becomes increasingly problematic. Despite the prevalence and pervasiveness of symptomatic insomnia, very few studies have addressed it, particularly with respect to possible effects of analgesics on sleep. For example, use of non-steroidal anti-inflammatory drugs may be associated with gastroesophageal reflux [7] that itself aggravates insomnia [8].

Fewer studies yet have employed modern methods of electroencephalography (EEG) or polysomnography to assess sleep disorders associated with chronic pain. Results of recent investigations are sobering, as formal sleep monitoring of patients with advanced cancers demonstrated that opioid treatment and pain disrupted nocturnal sleep, prolonged sleep latency, and limited attainment of sleep stages 3 and 4 as well as rapid eye movement sleep [9]. Further investigation indicated that such sleep disturbances were attributable to opioid treatment itself, which contributed to depression and even enhanced pain [10]. In light of such data, it is clear that new approaches to chronic pain and resultant sleep disorder are necessary.

Cannabis sativa L. and its derivatives have been known since ancient times for their analgesic, soporific, and hypnotic effects. While mentioned frequently as beneficial to sleep in a variety of pathological conditions in 19th-century sources on Indian hemp [11], modern studies on cannabinoids and their therapeutic effects on sleep have received little attention in modern medical literature until the last few years. As will be noted, these are indications for which standardized cannabis-based medicine promises palliation and symptomatic relief that may contribute greatly to patients' global impressions and subjective sense of relief of their condition.

The primary psychoactive ingredient of cannabis is Δ^9-tetrahydrocannabinol (THC), many of whose actions are mediated *via* the CB_1 G-protein coupled receptors that cluster in nociceptive areas of the brain [12], spinal cord [13][14], and peripheral nervous system [15] (see [16] for an excellent review). THC Activity mimics that of the natural endocannabinoids, anandamide (AEA, arachidonylethanolamide) and 2-arachidonylglycerol (2-AG), that are likewise partial agonists on the CB_1 receptor, that modulate pain responses in integrative centers such as the periaqueductal grey matter [17] and pain in relation to stress [18]. Another important phytocannabinoid, the non-psychoactive cannabidiol (CBD), is not only an analgesic, anti-inflammatory, and antioxidant in its own right [19–21], but it is also reported to allay various THC adverse effects including sedation, tachycardia, and anxiety [22]. Recent work has demonstrated that CBD antagonizes tissue necrosis factor alpha (TNF-α) in a rodent model of rheumatoid arthritis [23], and enhances adenosine receptor A2A signaling *via* inhibition of an adenosine transporter [24], suggesting an important therapeutic role in various inflammatory and chronic pain states.

Additional cannabis components including terpenoids and flavonoids also have analgesic properties that may be significant [25]. Historical and scientific aspects of cannabinoids and pain have been described for migraine [26], obstetrics and gynecology [27] , and gastroenterological conditions [28]. A clinical endocannabinoid deficiency has been hypothesized in relation to migraine, fibromyalgia, and idiopathic bowel syndrome [29].

In the current review, we will examine modern studies on effects of THC and CBD on sleep, and then report new information on the effects of cannabis-based medicines on sleep as a secondary outcome measure in the context of randomized clinical trials of medical treatment of chronic pain states, including neuropathic pain (NP), symptoms of multiple sclerosis (MS), and rheumatoid arthritis.

Clinical Studies of Cannabinoids and Sleep. – The soporific qualities of cannabis were noted in the ancient Indian *ayurveda* tradition [30]. Subsequently, the great

taxonomist *Linnaeus* recognized cannabis as *narcotica* and *anodyna* in his *Materia Medica* in the 18th century [31] (p. 214). *William B. O'Shaughnessy* reintroduced cannabis to Western medicine from India in the 19th century [32], wherein it produced sleep and pain reduction for victims of rheumatism and many other conditions. Benefits on sleep were noted in various pain states [11] throughout the 19th and early 20th century, when cannabis medicines subsequently fell from common medical usage due to lack of standardization and daunting problems with dosing and quality control.

Scientific study of cannabinoids entered the modern era in the early 1960s with the isolation of THC [33]. Early studies revealed that THC reduced sleep latency in normal and insomniac subjects, and caused some suppression of slow wave sleep (Stages 3 and 4) [34], often with a residual 'hangover' effect the next day [35]. No formal studies of cannabinoids to date have included electroencephalography or polysomnography in symptomatic conditions or chronic pain states.

In a recent case report [36], treatment with *Marinol*® (dronabinol, synthetic THC) effectively reversed serious insomnia in three patients afflicted with intractable pruritus associated with cholestatic liver disease. Similarly, in a limited trial of *Marinol*, 2.5 mg at night in five dementia patients, a reduction was observed in nocturnal motor activity ($p = 0.028$) [37].

A series of experiments with cannabidiol performed in Brazil were summarized in 1981 [38], with observations based on subjective sleep assessments. Of two subjects taking CBD 300 mg twice a day (BID) for 2 d, one reported having slept more heavily, but no performance abnormalities were evident. Ten more subjects took 200 mg CBD *vs.* placebo on four separate occasions with no significant differences in subjective functioning, or level of alertness. Two of four subjects taking CBD, 10 mg BID for 20 d, complained of isolated episodes of daytime somnolence on rare occasions. Another experiment compared placebo to CBD, 3 mg/kg/d divided BID in eight subjects. One reported somnolence for a week, another for the entire 30 d, and a third reported improvement in baseline insomnia.

Subsequently, this group assessed 15 subjects with 40, 80, and 160 mg oral doses of CBD as a hypnotic *vs.* nitrazepam, 5 mg, and placebo in a double-blind randomized trial. This low dose of benzodiazepine and lower dose of CBD produced little effect on sleep. The highest CBD dose, however, seemed to extend sleep and reduce episodic wakening in 10/15 subjects subjectively, while also reducing dream recall. No hangover symptoms were noted.

Cannabinoid Effects on Brain Chemistry in Sleep. – The key role of the endogenous cannabinoid system in regulation of sleep–wake cycles was suggested by the finding that the CB_1 antagonist/inverse agonist SR 141716A produces arousal in rats at the expense of slow-wave sleep [39]. This was further highlighted by the finding that the endocannabinoid anandamide (AEA) seems to mediate sleep induction and interacts with oleamide in this regard [40]. Subsequently, a Japanese group demonstrated the inhibition of serotonin and ketanserin (5-HT_{2A} antagonist) binding to the 5-T receptors by AEA [41]. A mild but similar response has recently been demonstrated for CBD [42], and cannabis terpenoids [43], suggesting a possible synergy with the CB_1 agonist, THC. Certain terpenoid components of cannabis are sedating in their own right (reviewed in [44], particularly terpineol [45]).

Recently, CBD was shown to inhibit uptake of AEA, and weakly inhibit its hydrolysis [46], making it, in effect, an inducer of AEA function, and suggesting a modulatory role for this agent in sleep. Additionally, a functional role for endocannabinoids in regulation of respiratory stability in sleep to prevent sleep apnea has been suggested [47]. Finally, it has recently been demonstrated that CBD administered intracerebroventricularly in rats increased wakefulness in the lights-on period, and increased enhancement of c-FOS expression in hypothalamus and dorsal raphe nucleus [48], supporting a clinical alerting effect for this agent [22], as discussed below.

New Data on Sleep Modulation with Cannabis-Based Medicine Extracts (CBMs). – *GW Pharmaceuticals* received a license from the *British Home Office* in 1998 to cultivate cannabis and extract it as a standardized botanical drug substance for formulation into finished pharmaceutical products. Early indications have focused on multiple sclerosis (MS) and chronic pain, especially neuropathic, or associated with cancer and rheumatoid arthritis. Chemovars of cannabis were selected *via Mendelian* genetics to express one predominant phytocannabinoid [49][50]. Cloned plants undergo liquid CO_2 extraction to produce botanical drug substances that contain predominantly THC (*Tetranabinex*®), CBD (*Nabidiolex*®), or a 1:1 combination of the two (*Sativex*®; *Fig. 1*) [51][52]. *Sativex* is administered oromucosally *via* a pump-action spray with each 100-μl pump-action actuation providing 2.7 mg of THC, 2.5 mg of CBD plus other phytocannabinoids, terpenoids, and phytosterols [25], in a base of 50% EtOH and 50% propylene glycol with 0.05% peppermint flavoring. Pharmacokinetic data on this material is available from recent publications [53]. The preparation has onset of activity in 15–40 min, which allows patients to titrate dosing requirements according to pain levels or other symptoms with an acceptable profile of adverse events.

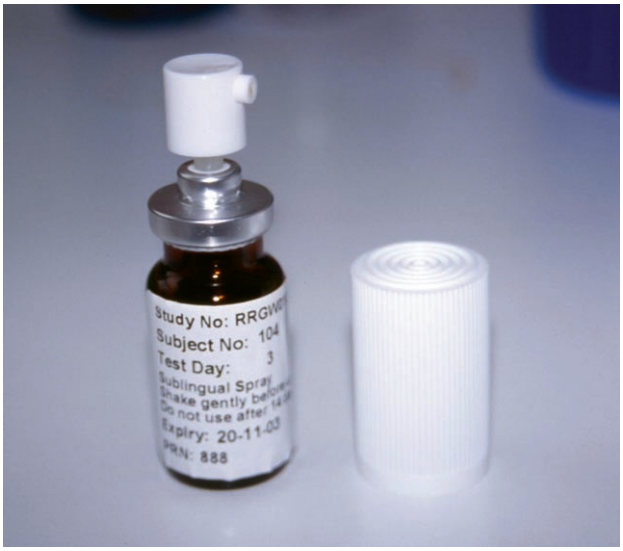

Fig. 1. Sativex *oromucosal cannabis based medicine* (photo: *Ethan Russo*, 2003)

A total of 1000 patient years of *Sativex* exposure in over 2000 experimental subjects has been amassed in Phase-II and -III clinical trials. A slight majority of subjects had no previous recreational or medicinal cannabis exposure, but comparative efficacy results have been identical in cannabis-experienced and cannabis-naïve cohorts with no evidence of inadequacy of subject blinding [54][55]. Patients are generally able to find a stable dose at which they obtain therapeutic relief without unwanted psychoactive effects. All randomized controlled trials (RCTs) were performed with *Sativex* added as an adjunct to existing drug regimens in patients with intractable symptoms, *i.e.*, patients considered treatment-resistant and remained on best available analgesic therapy and hypnotic medication, if prescribed. A concerted effort has been made in this review to include data from all available *Sativex* clinical trials; no negative data were excluded.

Sativex was approved in June 2005 for marketing as a prescription medicine in Canada under a *Notice of Compliance with Conditions* (NOC/c) for central neuropathic pain in multiple sclerosis (MS). An *Investigational New Drug* (IND) application to study *Sativex* in intractable cancer pain patients in the USA was approved by the FDA in January 2006. Two independent reviews of *Sativex* have recently been published [56][57].

The effects of oromucosal high-THC extract (*Tetranabinex*®), 15 mg, and THC-CBD extract doses of 5 and 15 mg of THC-equivalent were assessed by *Nicholson et al.* in eight subjects with respect to nocturnal sleep, early morning performance, memory, and residual sleepiness in a double-blind placebo-controlled four-way cross-over study with EEG monitoring [58]. While the THC extract, 15 mg, alone produced little effect on sleep architecture, sleep latency was reduced, memory was impaired, and residual sleepiness and mood changes were observed ($p < 0.05$). Both dose levels of combined THC-CBD extract decreased Stage 3 sleep ($p < 0.05$) over placebo, and the 15-mg doses increased wakefulness ($p < 0.05$) compared to 5-mg doses. The 5-mg doses of THC-CBD extract actually produced faster reaction times on the digit recall test ($p < 0.05$) over placebo. The authors noted that whereas impaired memory was observed the next day when 15-mg THC extract was given alone overnight, there were no such effects when THC was concomitantly accompanied by 15 mg of CBD, as in *Sativex*. Conclusions were that THC was sedative, while, in contrast, the presence of CBD was alerting, tended to counteract THC adverse effects on cognition, and impaired wakefulness.

In subsequent Phase-II and -III clinical trials, sleep quality was assessed with questionnaires completed by clinical trial subjects. Visual Analogue Scales (VASs) and Numerical Rating Scales (NRSs) are familiar instruments to many clinicians and have traditionally been used to quantify patient-rated subjective experiences. The two types of scale have similar sensitivity and reliability, but NRS is generally preferred by patients for ease of use. NRS and VAS are well-established and validated for the measurement of pain [59]. As is the case with pain, there is no objective gold standard by which to quantify the quality and quantity of sleep in patients participating in clinical trials. For this reason, most of the studies included in this review utilized NRSs or VASs to measure sleep and sleep disturbance. For example, *Wade et al.* [60] used VASs attached to the following questions: '*How was your quality of sleep last night*?'/'*How much sleep did you get last night*?'/'*How did you feel when you awoke this morning*?' The anchors at each extremity of the 10-cm line were '*best imaginable*' and '*worst*

imaginable' for the first two questions, and '*totally refreshed*' or '*totally unrefreshed*' for the third. As an example of NRS, *Rog et al.* [61] used an 11-box (0–10) scale attached to the following instruction: '*On a scale of 0–10 please indicate how your nerve pain disrupted your sleep last night. Please tick one box only*'. The anchors were '*did not disrupt sleep*' and '*completely disrupts (unable to sleep due to pain)*'. Such measures appear to have good face validity.

These and other studies of cannabis-based medicines on pain and sleep are summarized in the *Table.*

In a Phase-II study in 24 patients with intractable neurogenic symptoms including MS and chronic pain, *Tetranabinex*, *Nabidiolex*, and *Sativex* were tested in a double-blind-*N*-of-1 RCT *vs.* placebo by *Wade et al.* [66]. Significant improvement was seen with both *Tetranabinex* and *Sativex* on pain (especially neuropathic) ($p<0.05$), but *post-hoc* analysis showed symptom control was best with *Sativex* ($p<0.0001$), with slightly less intoxication than with THC-predominant extract. *Sativex* significantly improved sleep quality ($p=0.041$; Study GWN19902; *Fig. 2*) [66]. The authors noted that, compared to placebo, the CBD-predominant extract significantly improved pain, the THC-predominant extract yielded significant improvements in pain, muscle spasm, spasticity, and appetite, and combined THC:CBD extracts (*Sativex*) significantly improved muscle spasm and sleep. They also observed that the visual analogue scale for *Sativex* was significantly improved over baseline for 20 subjects in the sleep category ($p<0.05$). Of particular note in this trial was the confirmation of the CBD component as alerting, while high THC extract (*Tetranabinex*) improved sleep parameters (although not statistically significantly over placebo in this trial), while the combination of the two (*Sativex*) improved sleep synergistically.

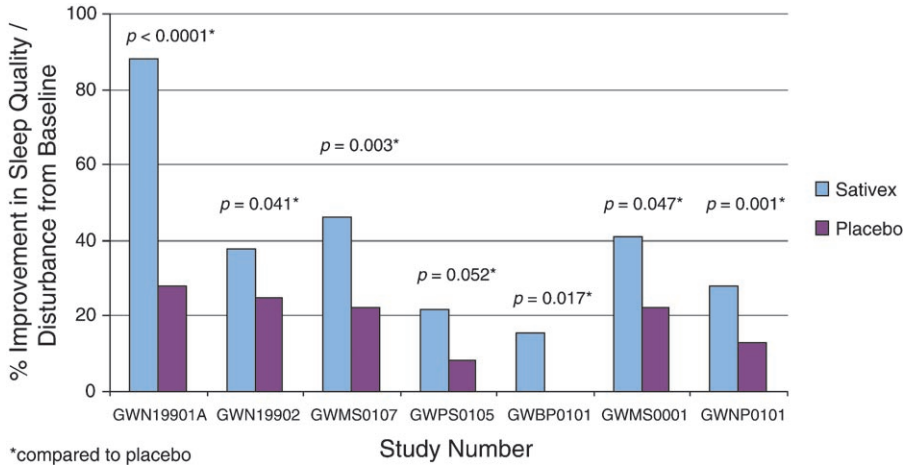

Fig. 2. *Compendium of results of* Sativex *on sleep in earlier Phase II–III RCTs in multiple sclerosis* (MS) *and intractable chronic pain*

In a Phase-II double-blind crossover *N*-of-1 study of intractable chronic pain in 34 subjects by *Notcutt et al.* [67], visual analogue scales for pain were significantly improved for *Tetranabinex* and *Sativex* extracts over placebo ($p<0.001$). *Sativex*

produced best results for pain in MS subjects ($p < 0.0042$). Marked improvement was observed on sleep duration ($p = 0.0001$) and quality ($p = 0.0001$; Study GWN19901A; *Fig. 2*). The authors commented that *Sativex*, while having little effect on the recorded sleep hours, rather produced marked changes in reported sleep quality from the 'poor' or 'fair' to 'good' categories. The sleep quality measure represented a global assessment by the subject of sleep duration, depth, and relative degree of sleep disruption. Finally, they posited that improvement of sleep by the drug might prove to be one of its major benefits in chronic pain and MS.

In a Phase-III randomized placebo-controlled clinical trial in central neuropathic pain due to MS over 5 weeks in 66 patients by *Rog et al.*, subjects showed mean NRS analgesia favoring *Sativex* over placebo ($p = 0.009$), and significant benefit of *Sativex* over placebo was observed in sleep disturbance ($p = 0.003$) [61] (Study GWMS0107; *Fig. 2*).

In another Phase-III RCT in intractable pain in 79 subjects with MS, diabetic neuropathy, or other conditions by *Notcutt et al.* [72], the *Sativex* cohort utilized escape analgesia a mean of 20.57% of days *vs.* 50.12% for placebo ($p = 0.002$). Sleep disturbance was also reduced by *Sativex vs.* placebo (Study GWPS0105; *Fig. 2*), with a treatment difference favoring the former ($p = 0.045$).

In a Phase-III double-blind placebo-controlled trial of peripheral neuropathic pain with allodynia in 125 subjects by *Nurmikko et al.* [73], *Sativex* produced highly statistically significant improvements in pain levels ($p = 0.004$) and dynamic allodynia ($p = 0.042$). Marked reductions in sleep disturbance were observed ($p = 0.001$; Study GWNP0101; *Fig. 2*) [73].

In the largest clinical study of brachial plexus avulsion and central neuropathic pain to date by *Berman et al.* [68] in 48 subjects in a double-blind cross-over design assessing oromucosal *Tetranabinex*, *Sativex*, and placebo, comparable benefits were noted in Box Scale-11 pain scores with *Tetranabinex* ($p = 0.002$) and *Sativex* extracts ($p = 0.005$). Sleep disturbance scores favored *Sativex* over placebo ($p = 0.017$) [68] (Study GWBP0101; *Fig. 2*), with sleep quality scores also favoring *Sativex* ($p = 0.019$).

In another Phase-III RCT focusing on mixed neurogenic symptoms in MS by *Wade et al.* [60], the greatest improvement following *Sativex* was noted in spasticity ($p = 0.001$). Subjects also demonstrated benefit on sleep disturbance ($p = 0.047$; Study GWMS0001; *Fig. 2*). From this cohort, 137 patients elected to continue on *Sativex* in safety-extension (SAFEX) studies [74]. Rapid reductions were noted in the first twelve weeks in pain VAS in 47 affected patients with sustained improvements for more than one year. During that time, there was no escalation of dose indicating an absence of tolerance to analgesic or other therapeutic benefits of the preparation. Similarly, no withdrawal syndrome (as defined by *Budney et al.* [75]) was noted in a subset of 25 patients who voluntarily stopped the medicine abruptly. Upon resumption, benefits resumed at the prior established dosages. Improvements in sleep were also maintained [74].

Additional data from patients with central and peripheral neuropathic pain who completed these RCTs have been collected in a second SAFEX study of some 507 subjects taking *Sativex* for at least one, and up to four years. These data confirm the continued efficacy of *Sativex* in maintaining improvements in subjective sleep parameters. As in the prior SAFEX in MS subjects with mixed symptoms [74], no

Table. *Clinical Studies of Cannabis Based Medicines on Pain and Sleep*

Drug	Clinical indication	Subject number (N)	Trial duration	Results/reference
Cannabis (smoked)	HIV neuropathy	50	5 days	>30% pain reduction *vs.* placebo ($p=0.04$), sleep NA [62]
Cannador	Spasticity in MS	419	15 weeks	Improvement over placebo in subjective pain associated with spasm ($p=0.003$), sleep ($p=0.025$) [63]
Cannador	Post-herpetic neuralgia	65	4 weeks	No benefit observed on pain, sleep NA [64]
Cannador	Post-operative pain	30	Single doses, 1 day each	Decreasing pain intensity with increasing dosage ($p=0.01$). Sleep NA formally. One complaint of sleep disturbance [65]
Sativex	Neurogenic pain	20	Series of 2-week *N*-of-1 crossover blocks	Improvement with *Tetranabinex* and *Sativex* on VAS pain *vs.* placebo ($p<0.05$), symptom control best with *Sativex* ($p<0.0001$). *Sativex* improved sleep quality ($p=0.041$) [66]
Sativex	Chronic intractable pain	24	12 weeks, series of *N*-of-1 crossover blocks	VAS pain improved over placebo ($p<0.001$) especially in MS ($p<0.0042$). Sleep duration and quality both improved ($p=0.0001$) [67]
Sativex	Brachial plexus avulsion	48	6 weeks in 3 two-week crossover blocks	Benefits noted in Box Scale-11 pain scores with *Tetranabinex* ($p=0.002$) and *Sativex* ($p=0.005$) over placebo. *Sativex* improved sleep disturbance ($p=0.017$) and sleep quality scores ($p=0.019$) [68]
Sativex	Central neuropathic pain in MS	66	5 weeks	Numerical Rating Scale (NRS) analgesia improved ($p=0.009$), sleep disturbance ($p=0.003$) *vs.* placebo [61]
Sativex	Peripheral neuropathic pain	125	5 weeks	Improvements in NRS pain levels ($p=0.004$), dynamic allodynia ($p=0.042$), sleep disturbance ($p=0.001$) *vs.* placebo [69]
Sativex	Rheumatoid arthritis	56	5 week	Improvements over placebo morning pain on movement ($p=0.044$), morning pain at rest ($p=0.018$), DAS-28 ($p=0.002$), and SF-MPQ pain at present ($p=0.016$), sleep quality ($p=0.027$) [70]

Table (cont.)

Drug	Clinical indication	Subject number (*N*)	Trial duration	Results/reference
Sativex	Pain after spinal injury	117	10 days	NSD in sleep disturbance and NRS pain scores, but improved Brief Pain Inventory ($p=0.032$) and Patients Global Impression of Change ($p=0.001$, odds ratio 3.4).
Sativex	Intractable cancer pain	177	2 weeks	Improvements in NRS analgesia *vs.* placebo ($p=0.0142$), *Tetranabinex* NSD. Sleep quality NSD [71]
Sativex	Intractable lower urinary tract symptoms in MS	135	8 weeks	Improvement in bladder severity symptoms ($p=0.001$) and nocturia episodes ($p=0.01$) over placebo.

dose escalation over time was necessary to maintain efficacy, supporting a lack of tolerance to this clinical benefit. Specifically, in an initial combined cohort of 287 subjects with central or peripheral neuropathic pain (*Fig. 3*), *ca.* 40% of subjects attained good-to-very-good sleep quality with maintenance of up to two years. Fewer than 20% of subjects had less than satisfactory results in their assessments of sleep quality.

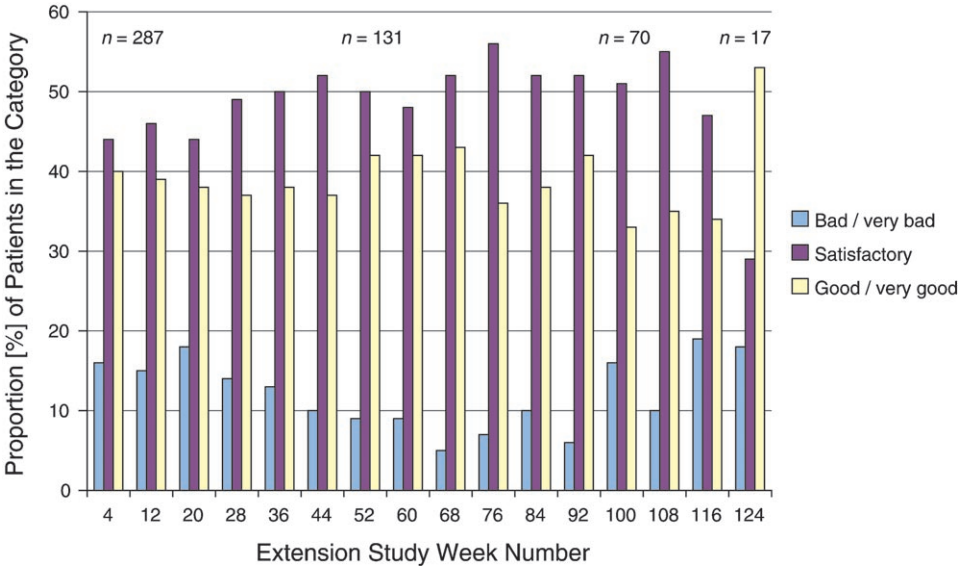

Fig. 3. *Cumulative data on sleep disturbances* (sleep quality scores) *in a long-term safety-extension* (SAFEX) *study of central and peripheral neuropathic pain patients treated with* Sativex (Study GWEXT0102)

An examination of adverse event profiles from the two SAFEX studies (137 and 537 subjects, resp.) reveals that complaints attributed to poor sleep or residual fatigue are infrequent after regular use of *Sativex* (*Fig. 4*).

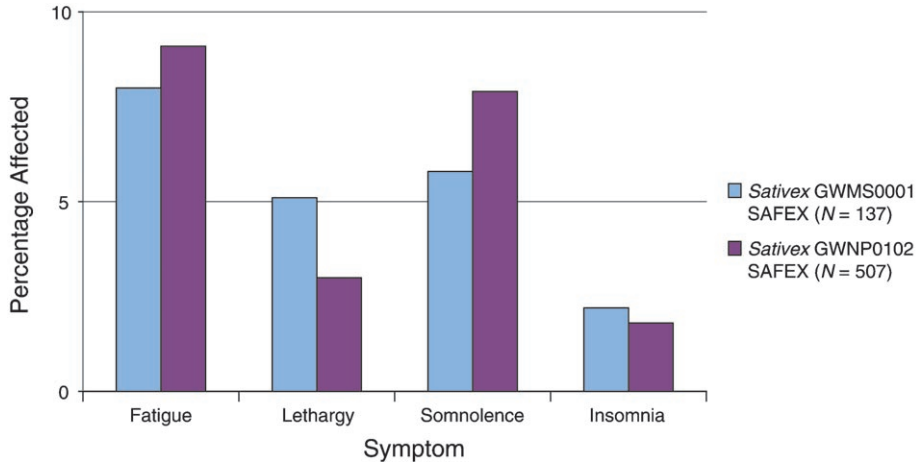

Fig. 4. *Graph of fatigue and other adverse events attributable to sedation or sleep disturbance in safety-extension studies of mixed symptoms of multiple selerosis* (MS) (SAFEX GWMS0001, $N=137$), *and peripheral and central neuropathic pain* (SAFEX GWNP0102, N = 507) *taking* Sativex *for greater than one and up to four years.* Rates of associated complaints are all less than 10%.

In a Phase-II double-blind, randomized placebo-controlled five-week study of 56 rheumatoid arthritis patients with *Sativex* by *Blake et al.* [70], employing nocturnal treatment only, subjects received a maximum of 6 sprays each evening (16.2 mg THC + 15 mg CBD). In the final treatment week, many study measures favored *Sativex* over placebo: morning pain on movement ($p=0.044$), morning pain at rest ($p=0.018$), 28-joint disease activity score (DAS-28; $p=0.002$), and Short Form *McGill* Pain Questionnaire (SF-MPQ) pain at present ($p=0.016$). Sleep quality favored *Sativex* over placebo ($p=0.027$) (*Fig. 5*, *a*).

Results of a Phase-III study ($N=177$) comparing *Sativex*, *Tetranabinex*, and placebo in intractable pain due to cancer unresponsive to opiates by *Johnson* and *Potts* [71] demonstrated that *Sativex* produced highly statistically significant improvements in analgesia ($p=0.0142$), while *Tetranabinex* was not significantly different from placebo, suggesting that the presence of CBD in the *Sativex* preparation contributed to pain control. Sleep quality in this study was not significantly improved over placebo, perhaps due to its short duration of only three weeks.

Similarly, in a Phase-II study of neuropathic pain after spinal injury, whereas no significant difference was noted in the primary outcome measure of average daily pain due to a large placebo response, the Brief Pain Inventory (BPI) did improve ($p=0.032$), as did the Patients Global Impression (PGI) of change ($p=0.001$, odds ratio 3.4). No changes in sleep over placebo were noted in this brief ten-day trial (unpublished findings).

In a Phase-III RCT of MS patients with intractable lower urinary tract symptoms and frequent accompanying pain in 135 subjects, *Sativex* produced a significant

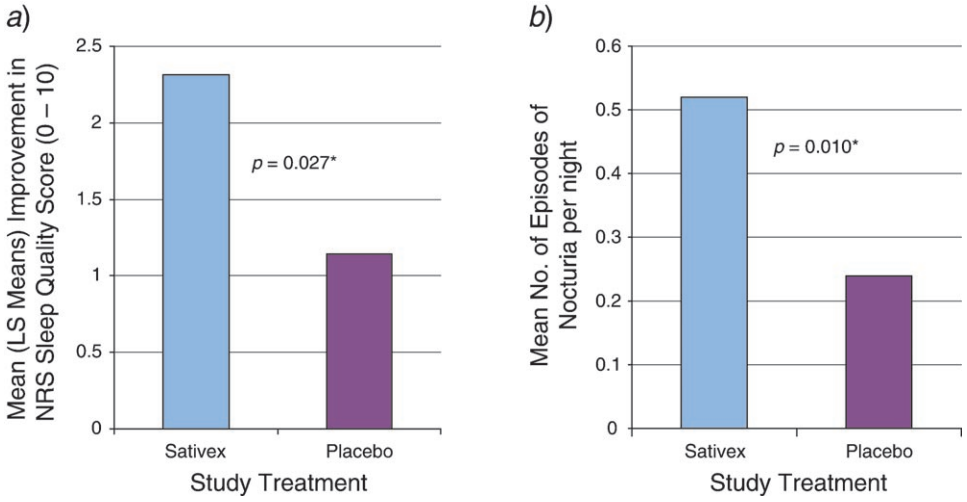

Fig. 5. a) *Effect of* Sativex vs. *placebo on rheumatoid arthritis sleep quality GWCRI016* ($N=58$; 0–10 NRS, 0 = 'very good' and 10 = 'very bad'). b) *Effect of* Sativex vs. *placebo on nocturia in intractable lower urinary tract symptom patients with multiple sclerosis* ($N=135$).

improvement over placebo in bladder symptom severity ($p=0.001$) and in nocturia episodes ($p=0.010$) affecting sleep (*Fig. 5, b*) (*Fowler et al.*, *GW Pharmaceuticals* data on file, manuscript in preparation).

Common Adverse Events (AE) of *Sativex* acutely in RCTs have included complaints of bad taste, oral stinging, dry mouth, dizziness, headache, nausea, or fatigue, but do not generally necessitate discontinuation, and proved less common over time. Cumulative subject withdrawals from the RCTs secondary to AEs attributable to *Sativex* have occurred in 10.7% of all subjects, and in 10.8% of MS subjects (data on file, *GW Pharmaceuticals*, May 24, 2006). Figures ranged from 12.5% in the first Phase-II trial [60], while 0% of *Sativex* subjects withdrew due to attributable AEs in studies of lower urinary tract symptoms in MS [76] and brachial plexus avulsion [68].

Placebo-controlled trials have also been conducted with an oral plant-derived cannabis-based medicine, *Cannador*, which contains variable THC:CBD ratios [22]. This was examined in a large trial alongside *Marinol* (synthetic THC) and placebo in MS patients (*Table*). In neither the acute trial (CAMS) reported by *Zajicek et al.* [63], nor its 12-month long-term follow-up [77], were significant improvements noted in sleep with *Cannador* or *Marinol*. These data would support the proposition that benefits of cannabis-based medicines on sleep in the context of symptomatic treatment may be specific to a preparation's formulation and/or delivery system, and the improvement with one preparation cannot necessarily be extrapolated to another. Another study of *Cannador* in post-operative pain (*Table*) showed decreased pain with increasing dosage, but sleep was not assessed formally (NA) [65]. One subject noted sleep disturbance. Finally, *Cannador* was utilized in a four-week study of post-herpetic neuralgia (*Table*), but no benefit was observed on pain, and sleep was NA formally [64].

Results are recently available from the first RCT of smoked cannabis on pain, in sensory neuropathy due to HIV/AIDS or its treatment (*Table*) [62]. A greater than 30% reduction in pain *vs.* placebo was noted in this five-day trial, but sleep effects were not reported. An additional study is planned in California to assess effects of cannabis on sleep disturbance in similarly affected patients (http://www.cmcr.ucsd.edu/geninfo/drummond_abs.htm). The FDA has recently published guidelines for botanical medicines that mandate parameters required for *New Drug Approval* [78]. The difficulties inherent in standardizing herbal cannabis, and pulmonary issues associated with its inhalation [79], make it unlikely that regulatory approval would be attainable in most nations of the world [54].

No head-to-head trials of *Sativex vs.* smoked cannabis have been performed, but a comparison of AE profiles from self-selected SAFEX study subjects on *Sativex* with those of smoked-cannabis patients utilizing standardized cannabis in government programs in Canada [80] and the Netherlands [81][82] supports the concept that *Sativex* was much better tolerated, especially with respect to mental status and cognitive issues [54].

Discussion. – Chronic pain, neurological illness, and sleep disorders are clearly co-morbid conditions. Upwards of 80% of MS patients suffer from debilitating fatigue symptoms and complain of significant sleep disturbance. Additionally, chronic pain accompanies MS in up to 60% in some surveys, with a citation of 48% in a recent study [83], further compromising the ability of patients to attain rest. *Tachibana et al.* [84] noted that such problems in MS arise from legion sources: pain, spasticity, muscle spasm, restless legs syndrome, myoclonus, and lower urinary tract symptoms, resulting in sleep disturbance in 80% of 28 subjects. It was felt by these authors that these problems were rarely addressed therapeutically. MS may also be associated with sleep apnea, a condition that has recently been demonstrated to respond favorably to treatment with THC in an animal model [47].

A recent study of sleep and fatigue in 60 MS subjects is quite germane [85], with over half noting difficulty with sleep disturbance at least two nights per week. Fatigue and excessive daytime sleepiness affected 64 and 32% of subjects, respectively. Those problems correlated best to difficulties with middle-of-the-night insomnia that subjects attributed most often to pain/discomfort (21.7%) or nocturia symptoms (72.5%). These symptoms were improved by *Sativex* treatment in the above discussed RCTs. Comparison of rates of fatigue, lethargy, somnolence, and insomnia in *Sativex* SAFEX subjects (*Fig. 4*) supports very remarkable amelioration compared to MS patients in the *Stanton* study [85], many of whom were already taking pharmacotherapy for such symptoms. The authors of the latter study specifically recommended symptomatic treatment of pain and nocturia as strategies to minimize sleep disturbance and its diurnal sequelae.

Similar sleep complaints affect patients with other etiologies of neuropathic pain. A current review article strongly suggested treatment of chronic pain with agents that concomitantly improve sleep [86]. A survey of 173 adults with neuropathic pain reported significantly higher rates of sleep disturbance and daytime somnolence *vs.* controls [87], with improvement after institution of specific treatment. Unfortunately, sleep disturbance continued in 43% of 140 subjects suffering from diabetic neuropathy despite treatment [88].

In a recent review [89], the authors state, '*The alterations of THC on sleep EEG and its rebound effect, its side effects before sleep induction, and its residual effects after awakening have contraindicated its clinical use as a sedative hypnotic*'. Data from the clinical research on *Sativex* reviewed in this article are not consistent with this conclusion. Rather, the available evidence to date would suggest that *Sativex* improvement in subjective sleep parameters, and satisfaction in patients with MS and neuropathic pain, with symptomatic relief of pain, spasms, nocturia, and related complaints. From limited sleep-laboratory information, it seems unlikely that its use will result in significant change in sleep architecture. *Sativex* does not benefit all patients, but in those who do respond, the beneficial effects are maintained consistently over time without evidence of tolerance, and are not accompanied by unusual cognitive sequelae [54]. Of course, additional in-depth studies are needed to confirm these contentions and might include formal neuropsychological testing and polysomnography.

Sativex patients and their caregivers have remarked to their physicians how the medicine had transformed their lives through its ability to allow them more restful sleep, increase their daytime level of function, and markedly improve their quality of life. Its addition to the pharmacopoeia may be welcomed by patients, families, and physicians.

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