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The Solution to the Medicinal Cannabis Problem

by Ethan Russo, MD

I. Overview

Chronic pain affects a significant proportion of the American population. Given the tremendous public health challenges attendant to pain treatment in this country, it is clear that new and better approaches are necessary to supplement the current armamentarium of pharmaceutical and complementary approaches. A recent nationwide poll indicates that 19% of adult Americans, or 38 million people, suffer chronic pain, and 6% (12 million) have treated pain with cannabis (http://abcnews.go.com/images/Politics/979a1TheFightAgainstPain.pdf)[1]. It appears that the cannabis plant may hold important therapeutic promise for the treatment of chronic pain, but its medical use has to this point been fraught with strident controversy that has persisted for almost a decade, with no resolution in sight. The voters of ten states, some 70-80% of the public, and many doctors and scientists feel that seriously ill patients should not be prosecuted for using herbal cannabis (the scientific name for marijuana), while the federal government denies that there is scientific evidence to support such use of a crude plant substance. The Supreme Court has ruled in the 2005 case of *Gonzales v. Raich* that the federal government does have the power to regulate the intrastate noncommercial cultivation and possession of cannabis for personal medical use.

Is there a solution to the medicinal cannabis question? This author believes so, but such a solution must respect the same time-honored process that any prescription medicine must undergo to reach the US market: proof of safety and efficacy through randomized clinical trials (RCT) leading to Food and Drug Administration (FDA) approval. While the Supreme Court acknowledged the scientific basis for the belief that cannabis has medical value, Justice Breyer was specific in his direction that it should be subjected to standard procedures of regulatory scrutiny. This author's personal contact with hundreds of chronic pain patients in the USA and Europe leads him to believe that there are many "unheard voices" in this reservoir of despair that would readily accede to use of a safe and effective non-smoked cannabis-based pharmaceutical who would never consider current black market options, even if legalized.

What might be the characteristics of such a cannabis-derived prescription medicine? Firstly, it must be standardized, rendered uniform in consistency and quality, as for any pharmaceutical product. Next, it must have a suitable and practical delivery system that provides predictable dose increments and onset of effects, but that minimizes risks to patients, such as intoxication, dependency or lung damage. Additionally, it must be controlled and regulated through the conventional pharmaceutical supply chain to ensure that it is used by people who are genuinely ill, not those seeking to abuse or divert the product.

All seriously ill patients seek to alleviate their suffering, but few wish to resort to obtaining their medications through unregulated and unlawful channels that are fraught with myriad dangers. Rather, patients prefer a safe and effective evidence-based pharmaceutical solution that their doctors can knowledgeably and confidently prescribe,

that their pharmacists will supply, and that their health insurance or third party payers will cover.

It is very unlikely that crude herbal cannabis could ever fulfill these criteria or gain FDA-approval, for it is too variable strain-to-strain, may harbor disease-causing molds, bacteria, pesticides, or heavy metals, and is generally smoked, a delivery system that poses risks common to tobacco: cough, phlegm, bronchitis, and inhalation of potentially carcinogenic pyrolytic by-products.

Early efforts to produce cannabinoid-based pharmaceutical products have been disappointing. Since 1985, synthetic THC (tetrahydrocannabinol, the main psychoactive component of cannabis) has been available in the USA as an oral agent for nausea in cancer chemotherapy, and later, for treatment of AIDS-wasting. However, its oral absorption is slow and variable, and many patients complain of feeling intoxicated or dysphoric during its usage. Some patients prefer crude herbal cannabis and claim that its added natural ingredients produce herbal synergy and are more effective than THC alone. Inhalation of cannabis, as in smoking or newer vaporizers, produces a rapid peak of activity that maximizes risk of intoxication and reinforcement that could promote possible dependency. Transdermal patches and rectal suppositories avoid pulmonary risks, but have yet to prove practical or reach late stage clinical trials.

An ideal delivery system for cannabis would have reliable intermediate onset, obviate smoking, allow dose titration, provide relief of symptoms, but yet be chemically definable and safe for physicians to prescribe. Recently, a promising approach meeting these criteria has advanced through clinical trials and been accepted for prescription in Canada. The product, called Sativex®, employs an oromucosal spray composed of complex cannabis extracts, whose effects begin in 15-40 minutes, maintaining a therapeutic window of symptom control without creating a "high" that many interviewed patients regard as an undesirable side effect. This product combines climate-controlled, greenhouse-grown unique cannabis chemovars with high expression of THC and cannabidiol (CBD), respectively. CBD is a non-psychoactive cannabis component that reduces pain and inflammation in its own right, attenuates anxiety and intoxication from THC, while boosting THC's other beneficial effects. CBD, however, is virtually absent from North American black market cannabis strains. Efficacy for this cannabis profile in human clinical trials has been demonstrated in chronic neuropathic pain, spasms, spasticity, sleep disturbance and bladder problems of multiple sclerosis, intractable pain in cancer, and symptoms of rheumatoid arthritis in some 2000 patients with 1000 patient-years of exposure[2-11], more fully discussed subsequently. Interestingly, this has occurred with no tolerance developing to benefits, no dose escalation, and no evidence of drug dependency or withdrawal in patients taking the medicine for one to four years. Most importantly, after initial titration, patients have achieved effective symptom control without notable intoxication, thus increasing and enhancing activities of daily living, and sometimes allowing a previously-debilitated patient to return to work or school. No reports of abuse or diversion of this cannabis-derived spray has occurred in clinical trials, long term extension studies, or general prescription use. Thus, while it has been effective for patients, there is little to suggest that people "like it too much," or would seek it as an agent of drug abuse.

Thus, the solution to the medicinal cannabis problem rests with a pharmaceutical approach. The Institute of Medicine recognized the analgesic potential of cannabis in its

1999 report[12], but called for alternative delivery systems beyond smoking. This is the only manner in which regulatory standards for a cannabis-based medicine are attained, patient needs are met, the risks of abuse or diversion are significantly reduced, and crude plant material is not smoked. A properly investigated cannabis-based pharmaceutical can be approved by regulatory authorities without contravening the United Nations Single Convention or other related international treaties[13]. The development of such a medicinal cannabis prescription will additionally promote open and mutual therapeutic relationship with physicians, and maintain honest and honorable standing with the laws of our nation.

II. Aspects of Food and Drug Administration New Drug Application

Most drugs of old were derived from plants, and the *National Formulary* and *US Pharmacopoeia* formerly contained numerous botanical agents. However, pharmaceutical development has changed over the past 50 years as research has focused more on receptor function and computer modeling of potential therapeutic agents[14]. Contemporaneously in the past two decades, the American public has become increasingly interested in natural health approaches, especially herbal treatments. This led in 1994 to the passage of the Dietary Supplement and Health Education Act (DSHEA), wherein such agents are treated more as foods for which "structure and function" claims are allowable. The FDA has no jurisdiction to regulate a dietary supplement until or unless a compelling danger to the public health by such a product is demonstrated. In order for a manufacturer to claim that an agent is useful in the treatment of a disease or condition, however, it must take that agent through the standard drug approval process, at which point the FDA does have jurisdiction and oversight. A potential prescription drug must apply first for Investigational New Drug (IND) status, and once it has fulfilled all criteria of safety, efficacy and consistency (standardization), it may qualify for New Drug Approval (NDA).

Heretofore, many experts did not believe that a complex botanical (plant-based) product could ever become FDA approvable, partly because of inherent prejudices in favor of single molecule, synthetic medicines, and additionally because no clear mechanism existed for entering complex botanicals into the FDA process. The latter situation has clearly changed with the finalization in June 2004 of the FDA *Guidance for Industry Botanical Drug Products* monograph[15] (http://www.fda.gov/cder/guidance/4592fnl.pdf). To briefly summarize, this document provides a blueprint by which botanical agents, defined as finished products containing vegetable matter, may be approved as prescription drugs, "intended for use in diagnosing, mitigating, treating or curing disease---"(p. 3). The Botanical Guidance permits some flexibility in the early stages of research. At the point of NDA submission, however, all conventional requirements must be fulfilled. As botanicals represent combinations of components, particular attention is necessary to product composition, which may be defined through quality control methods including spectroscopic and chromatographic techniques, chemical assays of particular markers (e.g., THC or other phytocannabinoids), biological assays of activity, raw material and process controls in manufacture, and process validation with batch analysis. To qualify for NDA status, a botanical not previously designated "Generally Recognized As Safe" (GRAS) must demonstrate its safety and efficacy in randomized, double-blind and placebo-controlled or dose-response trials. A requirement for any significant home preparation or processing

of the product by patients is considered undesirable. In treatment of chronic conditions with such an agent, clinical exposure to it for 6-12 months in long-term safety-extension (SAFEX) studies is considered sufficient[15]. A botanical agent administered by a non-oral route requires addition pharmacology and toxicology documentation before initiation of RCTs.

The *Botanical Guidance*[15] additionally indicates that a botanical raw material (BRM) (or crude herb) becomes a botanical drug substance (BDS) upon its processing through extraction, blending, addition of excipients, formulation and packaging in a defined, exacting and precisely defined manner. This material should be studied for its pharmacokinetic (PK) and pharmacodynamic (PD) effects. Non-binding recommendations were also published that include rigorous bioassays, and monitoring of heavy metal, pesticide, microbial and fungal contamination. Additional long-term animal toxicity studies in two species will likely be required, as well as reproductive toxicity, genotoxicity, and carcinogenicity documentation prior to NDA. Studies of effects in subjects with renal or hepatic insufficiency are additionally recommended.

III. Politics Aside: The Case for Medicinal Cannabis in Treatment of Pain

A. Historical Data

A body of literature dating back several thousand years supports the premise that cannabis preparations are effective in treatment of various kinds of pain. Much of this information is summarized in previous publications[16-21], and includes attestations addressing neuropathic, musculoskeletal, dermatological, gastrointestinal, visceral, obstetric and gynecological pain conditions in innumerable cultures around the world. Many authors have eloquently supported the prospect of using such leads to "mine the past" for evidence for new drug discovery[22], but in the modern regulatory arena, such information counts for very little, indeed.

B. Modern Anecdotal Information

An increasing recognition of the analgesic and palliative potential of cannabis preparations has developed over the past generation. Entire books[23, 24] have been devoted to support this premise. Such reports, however, are considered *anecdotal.* They, are of no force or effect for regulatory purposes, and do not constitute proof of safety and efficacy sufficient to allow FDA-approval of cannabis or any particular cannabis preparation. Such proof can only be supplied in the form of appropriate RCTs with accompanying safety and standardization documentation.

A call has come from numerous quarters to re-assign cannabis to Schedule II of the federal Controlled Substances Act[25-27]. However, such a reclassification alone would not solve the current problem. If herbal cannabis were so rescheduled, what form should it take? How would it be standardized? Who would account for quality control, let alone liability attached to any attendant medical misadventures? In order for a Schedule II substance to be made available by prescription, it must be contained in one or more specific dosage forms, as is the case for opium. Each and every one of such dosage forms must pass FDA muster.

Outside the US, national governmental efforts to provide standardized herbal cannabis to patients have not met with success. In The Netherlands, a government program supporting herbal cannabis has been poorly supported by its physicians, and in a

survey reported in September 2005[28], only 40 persons in that country were found to be using the government sponsored cannabis. Similarly, in Canada, where access to medicinal cannabis was court-mandated for qualifying individuals with serious or life-threatening diseases, as of September 2005, only 850 patients qualified with documentation supplied by their physicians[29], and only 250 of those had purchased seeds or herbal cannabis from the government. This could be attributed in part to suggestions to physicians not to take part in the program by the Canadian Medical Association[30], and a refusal of Canada's sole malpractice insurance carrier to underwrite liability issues attendant to the recommendation of herbal cannabis. Similar patterns would likely eventuate in the USA were herbal cannabis available medically. The Dutch and Canadian programs have concluded it important to subject their herbal cannabis to gamma irradiation to reduce risks of microbiological deterioration, creating attendant controversy, as this processing technique has never been tested for safety with any smoked product.

C. Cannabis and the Scientific Method

The analgesic and palliative effects of cannabis and cannabinoid preparations have been amply reported over the past generation, and have similarly been reviewed at length in previous citations. In essence, these effects result from a combination of receptor and non-receptor mediated mechanisms. THC and other cannabinoids exert many actions through cannabinoid receptors, G-protein coupled membrane receptors that are extremely densely represented in central[31], spinal[32, 33], and peripheral[34] nociceptive pathways. Endogenous cannabinoids (endocannabinoids) even regulate integrative pain structures such as the periaqueductal grey matter[35]. The endocannabinoid system also interacts in numerous ways with the endogenous opioid[36] and vanilloid[37] systems that also modulate analgesia, and with a myriad of other neurotransmitter systems such as the serotonergic, dopaminergic, glutamatergic, etc. (reviewed[18]) pertinent to pain. Research has shown that the addition of cannabinoid agonists to opiates enhances analgesic efficacy markedly in experimental animals[38], helps diminish the likelihood of the development of opiate tolerance[39], and prevents opiate withdrawal[40]. The current author has suggested that a clinical endocannabinoid deficiency may underlie the pathogenesis of migraine, fibromyalgia, idiopathic bowel syndrome and numerous other painful conditions that defy modern pathophysiological explanation or adequate treatment[41].

Thus, the theoretical basis for utilizing cannabis-derived medications in treatment of pain is on a very firm foundation. Until very recently, however, very few cannabinoid RCTs in the area of pain management had been performed. These will be reviewed in the following section.

IV. Pros and Cons of Medicinal Cannabis Delivery Systems

A. Synthetics

1. THC ("dronabinol")

After initial investigations of analgesic effects by Noyes et al. in the 1970s[42-44], tetrahydrocannabinol, as Marinol®, was approved for treatment of chemotherapy-associated nausea in 1985, and AIDS wasting in 1992. Results from pain studies have been mixed. Marinol was employed in two studies of central and peripheral neuropathic pain with oral doses up to 25 mg without clear benefit on pain or allodynia, and with

prominent side effects[45, 46]. In a similar study of two-five year duration showed early benefits on pain that were not maintained[47]. In a Swedish study[48] of Marinol doses to up to 10 mg/d in 24 multiple sclerosis patients with central neuropathic pain, median numerical pain scale in final week was reduced in the Marinol group (p=0.02), and median pain relief was improved over placebo (p=0.035). Moreover, pure oral THC in isolation may induce intoxicating and sedative complaints[49], as well as dysphoria, perhaps attributable to metabolism of THC to 11-hydroxy-THC. When queried in surveys comparing Marinol to whole cannabis products, most medical patients who have utilized both prefer herbal cannabis[18].

Other THC delivery forms are in early research stages. THC hemisuccinate suppositories are twice as bioavailable as oral THC[50-53], but have not been assayed in RCTs of pain, and may not prove to be acceptable as a delivery method by consumers in the USA. THC skin patches are currently under investigation, but available pharmacokinetic data[54, 55] indicate that serum delivery attained to date if only a fraction of that required to produce therapeutic effects. The gradient required to obtain THC delivery transcutaneously ensures that a large residual fraction would be left in the patch, and represent a diversion risk upon disposal.

The development of an inhaled prescription form of THC poses significant challenges. Pure THC aerosols have been investigated since the mid-1970s, hampered by the physical properties of the molecule and its irritating and cough-inducing effect when employed in isolation[56]. Some authorities posit that concomitant terpenoid and flavonoid components are necessary for local anesthetic and anti-inflammatory benefits[57]. In a recent Phase I clinical trial designed to develop aerosol THC for acute migraine[58], coughing and intoxication were quite prominent in most subjects, even at lowest dose levels. Certain conditions with breakthrough or paroxysmal pain (e.g., acute muscle spasm, trigeminal neuralgia or cluster headache) might merit this approach, but such rapid dose delivery is unnecessary for treatment of many chronic pain conditions, and poses its own drawbacks (*vide infra)*.

2. Nabilone

Nabilone, or Cesamet®, is a synthetic cannabinoid similar to THC, but ten-fold more potent, and assessed as having a lower "abuse potential"[59]. It is available in the UK, Canada, Australia and some European countries[60] as an anti-emetic in chemotherapy. Analgesic effects of this drug were noted in patients with neuropathic pain[61], but with prominent drowsiness and dysphoria.

3. Ajulemic acid

Ajulemic acid (CT-3) is synthetic cannabinoid derivative with analgesic and anti-inflammatory properties in animal models[62, 63] that has advanced to Phase II clinical trials. Ajulemic acid binds to the peroxisome proliferator-activated receptor gamma, involved in inflammatory mechanisms[64], and also suppresses monocyte interleukin-1beta production *in vitro*[65]. Ajulemic acid seems to have promising anti-inflammatory and analgesic properties, but recent reports suggest that this agent does bind to CB_1, and could produce psychoactive effects[66]. Clinical research is currently confined to treatment of interstitial cystitis.

B. Herbal Cannabis

1. Smoking

Despite the frequent anecdotal citations of cannabis as analgesic in patient surveys and in the lay press, few RCTs with smoked cannabis have been completed[67]. Perhaps the first study to demonstrate analgesic efficacy was an examination of 50 subjects with HIV-related neuropathic pain, in whom 13 of 25 who utilized cannabis noted a greater than 30% pain reduction vs. placebo ($p=0.04$)[68].

Efficacy alone, however, is not sufficient to attain NDA status. Smoked cannabis would face virtually insurmountable hurdles from a regulatory standpoint, but the obvious sequelae of the delivery system (smoking) would alone seem to limit prospects for FDA regulatory approval. Foremost among these are pulmonary sequelae, which have recently been recently extensively reviewed[69]. It is inarguable that chronic smoking of cannabis produces increased cough, phlegm, bronchitic complaints, and even bronchoscopic and histological changes similar to those in tobacco smokers. Although the largest epidemiological study to date has failed to support an etiological link between cannabis smoking and development of cancer[70], this does not clear the path for FDA approval in the USA. As the Botanical Guidance makes clear[15] (p. 43), "All parenteral, topical, *inhalation,* or other non-orally administered botanical products are considered to be drugs, not dietary supplements, and must be studied under an IND for any use." The presence of tars, polyaromatic hydrocarbons (PAH) and similar toxic components in cannabis smoke would seemingly preclude the possibility of FDA-approval irrespective of the above epidemiological findings. Specifically, it is doubtful that any botanical whose delivery system creates known or potential carcinogens would receive a green light for prescription usage.

Apart from pulmonary risks, the smoked route of cannabis administration has also raised alarms with respect to vascular sequelae[71], specifically the claim of an increase in risk of myocardial infarction in the hour after smoking[72], likely secondary to tachycardia. Additionally, a case of "cannabis arteritis" associated with smoking was recently reported[73].

Infectious disease risks associated with contamination of herbal cannabis (Figure 1) by bacteria or fungal pathogens have also been reviewed[69], but have been further highlighted by a recent outbreak of meningococcal meningitis spread by sharing of joints in Vancouver, British Columbia[74]. These other public health threats contribute to a body of evidence that would likely preclude FDA acceptance of smoked cannabis.

Cannabis smoking is relatively inefficient, with up to 70% of THC destroyed in the process of burning[75], and additional losses in sidestream smoke, with systemic THC bioavailability ranging from 10-27%[76, 77].

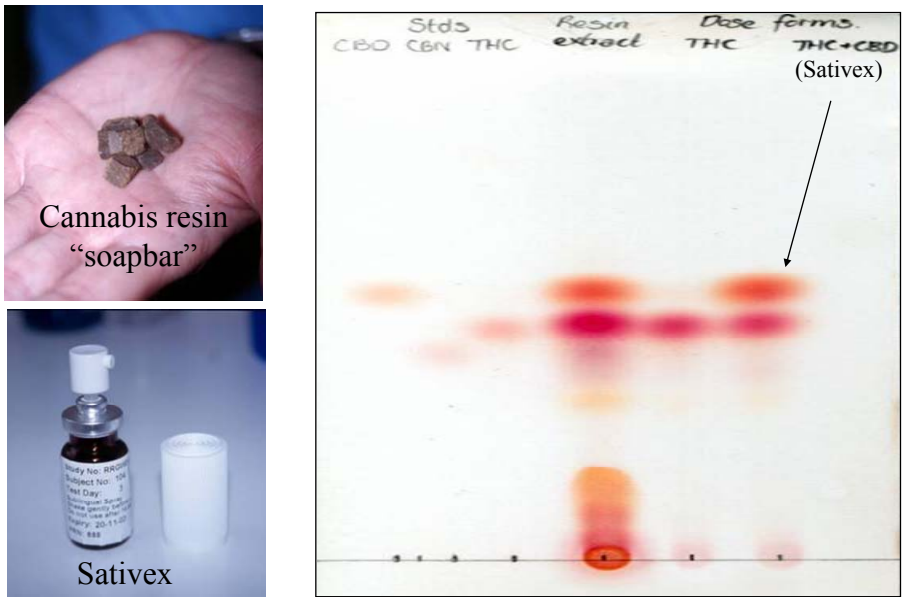

Figure 1: Thin-layer chromatography (TLC) of a sample of hashish (cannabis resin, or "soapbar") as obtained on the black market in the UK, compared to Sativex® oromucosal spray. Although the hashish, probably of Moroccan origin, contains both THC and CBD, adulterants including hair, dung, and petroleum distillates are common (TLC courtesy of Ian Flockhart, Applied Analysis, UK; other photos by Ethan Russo).

2. Vaporization

A variety of devices have appeared on the black market in the last decade with the aim of mitigating smoking-associated sequelae of cannabis usage, through vaporization of the herbal material to volatilize cannabis components without burning. Earlier devices failed to demonstrate compelling reductions in combustion products[78, 79]. More recently, studies with the Volcano® vaporizer[80] have begun. In a pilot study comparing use of the vaporizer to smoked NIDA cannabis[81], the device markedly reduced carbon monoxide levels, and a majority of 18 subjects preferred it to smoking. However, results of laboratory analyses indicate that THCA, the herbal precursor of THC prior to heating, is incompletely decarboxylated to the active form even at the highest vaporizer temperature setting, and that the efficiency of delivery of pure THC is also incomplete at that level[82]. Of greater concern, at the highest machine setting (corresponding to an air temperature of 230°C), 5% of yield of the vapor consisted of potentially carcinogenic polyaromatic hydrocarbons[83]. While this technology has proven quite popular with cannabis consumers, the failure to eliminate potentially carcinogenic pyrolytic end-products make it a virtual impossibility that it can pass regulatory scrutiny by the FDA in the current form. Furthermore, as a medical device, it lacks portability and convenience.

3. Oral ingestion

Following oral administration of cannabis or cannabinoids, bioavailability is a primary issue, since absorption is erratic and far from complete unless a lipid carrier is employed[76] and often requires one to two hours or more. Such lengthy onset of action precludes ready dosage titration. Additionally, patients suffering from nausea or vomiting may be unable to employ this route of delivery. Some data have suggested that a "first pass effect" of hepatic metabolism occurs after oral usage, producing 11-hydroxy-THC, which may be more psychoactive than THC itself. It is clear that some patients are plagued by undesirable psychoactive effects even on dosages of 2.5 mg of THC equivalent. Advantages of oral usage include a lack of pulmonary risk, and prolonged half-life compared to inhalation techniques.

C. Cannador

Cannador is an encapsulated oral cannabis extract that has been employed in several European studies. It is said to be standardized, but its THC:CBD ratios vary in published reports[84]. In a large Phase III study of patients with spasticity in MS (CAMS)[85], there was failure to achieve statistically significant benefit on the Ashworth Scale. Nevertheless, an improvement was seen in the treatment group over placebo with respect to subjective pain associated with spasm ($p=0.003$). In a subsequent long-term follow-up, a statistically significant improvement in pain of cannabinoids vs. placebo was also noted[86], but differences between Cannador and Marinol were not clear.

Cannador was also employed in two other recently reported pain RCTs. In a double-blind crossover study of postherpetic neuralgia vs. placebo employing a maximal tolerable dose of Cannador in 26 subjects, no effect was noted on pain[87]. In a study of 65 patients with post-operative pain (CANPOP)[88] without concomitant analgesics or opiates, 11/11 (100%) of subjects receiving 5 mg THC-equivalent required rescue medicine, while 15/30 (50%) receiving 10 mg THC-equivalent and 6/24 (25%) receiving 15 mg THC-equivalent did so. Most patients considered the psychoactive sequelae unpleasant or strange, but only 3/65 (4.6%) characterized feelings as "high" or "stoned." These results may indicate inadequate dosing via oral absorption, inadequate provision of CBD or the advisability of concomitant opiates in the post-operative pain trial.

D. Sativex®

An oromucosal spray (Figure 1) known by the brand name of Sativex® is currently approved for prescription in Canada under a Notice of Compliance with conditions (NOCC) for treatment of central neuropathic pain in multiple sclerosis. It is a highly standardized medicinal product derived from the active components of two selected chemovars of *Cannabis sativa* plants grown under conditions of Good Agricultural Practice (GAP). One chemovar yields a high and reproducible proportion of Δ^9-tetrahydrocannabinol (THC) (approximately 96% of total cannabinoids[89]), a psychoactive and analgesic component. The other chemovar yields primarily cannabidiol (CBD) (approximately 90`% of total cannabinoids[89]), a non-psychoactive, analgesic, and anti-inflammatory drug that also counteracts many adverse events associated with THC[84]. Sativex is combination of the THC-predominant extract (Tetranabinex®) and the CBD-predominant extract (Nabidiolex®)[90]. Dried inflorescences of unfertilized female cannabis plants are extracted and processed under current Good Manufacturing Practice

(GMP) conditions to yield a botanical drug substance (BDS) of defined composition. The contents of the principle actives in the BDS are well controlled and reproducible from batch to batch, and represent some 70% (w/w) of the total[89]. Minor cannabinoids are present (5 – 6%)[57]. The remainder of the BDS consists of terpenes (6 – 7%, most GRAS), sterols (6%), triglycerides, alkanes, squalene, tocopherol, carotenoids and other minor components (also GRAS) derived from the plant material[57], such that over 95% of components are characterized. The medicine is formulated into a spray for sub-lingual and oro-mucosal administration. Each 100 µL pump-action spray increment contains 2.7mg of THC and 2.5mg of CBD, the minor components, plus ethanol and propylene glycol excipients and peppermint flavoring. Detailed pharmacokinetic data on this material is available[91] (Figure 2, purple trace). The preparation has onset of activity in 15-40 minutes, which allows patients to titrate dosing requirements according to their symptoms, with a very acceptable profile of adverse events. Experience in well over 1000 patient years of Sativex exposure in over 2000 experimental subjects has been amassed in Phase II-III randomized, double-blind, placebo-controlled clinical trials herein discussed. A slight majority of subjects have had no previous recreational or medicinal cannabis exposure. All studies were performed in self-titration protocols with Sativex added adjunctively to existing drug regimens in patients with intractable or uncontrolled symptoms. Sativex has met all regulatory requirements for safety and quality (manufacturing consistency) of Health Canada, and the Medicines and Health Products Regulatory Agency (MHRA) in the UK.

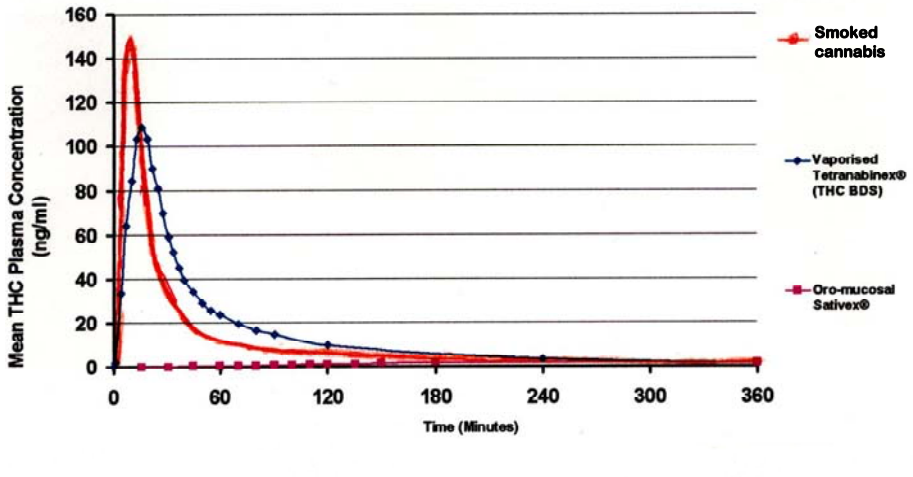

Figure 2: Comparison of pharmacokinetic peaks of Sativex® oromucosal spray containing 10.8 mg THC and 10 mg CBD (purple trace), vaporized Tetranabinex® with 6.65 mg THC (GWPK0114, data on file, GW Pharmaceuticals, blue trace), and smoked cannabis from a cigarette containing an estimated 34 mg THC[76, 77] (red trace). Note that the mean THC plasma concentration with Sativex never exceeds 2 ng/ml.

In a Phase II clinical trial in 20 patients with intractable neurogenic symptoms[11], patients were treated with THC-predominant, CBD-predominant, and 1:1 preparation (Sativex) in a double-blind crossover trial against placebo. Significant improvement was seen with both THC- and CBD-predominant extracts on pain (especially neuropathic) ($p<0.05$). However, post-hoc analysis revealed that overall symptom control was best with Sativex ($p<0.0001$), with less intoxication than with THC-predominant extract.

In another Phase II double-blind crossover study of intractable chronic pain[6], in 24 subjects who did not employ rescue medication, visual analogue scales (VAS) were 5.9 for placebo, 5.45 for CBD-predominant, 4.63 for THC-predominant and 4.4 for Sativex extracts ($p<0.001$). Sleep was also most improved on the latter ($p<0.001$). Of 28 subjects, 11 preferred Sativex overall, while 14 found Tetranabinex and Sativex equally satisfactory. For pain in the MS patients, Sativex produced best results ($p<0.0042$).

In a Phase III study of intractable pain associated with brachial plexus injury[2], roughly equivalent benefits were noted in Box Scale-11 pain scores with Tetranabinex ($p=0.002$) and Sativex extracts ($p=0.005$).

On the basis of these results with oromucosal cannabis based medicines, Professor Carlini of Brazil, a member of the International Narcotics Control Board, has stated[92](p.463), "However, any possible doubts that might exist on whether or not Δ^9-THC is an useful medicine for MS symptoms, were removed by the results obtained in four very recent randomized, double-blind, placebo-controlled trials."

In a controlled double-blind clinical trial of intractable central neuropathic pain[8], 66 MS subjects showed mean Numerical Rating Scale (NRS) analgesia favoring Sativex over placebo ($p=0.009$), with sleep disturbances scores also improved ($p=0.003$).

In a Phase III double-blind placebo-controlled trial of peripheral neuropathic pain with allodynia[93], Sativex produced highly statistically significant improvements in pain levels ($p=0.004$) with additional benefit on dynamic allodynia ($p=0.042$) and sleep disturbance ($p=0.001$) measures.

In a SAFEX study of Phase III double-blind placebo-controlled trial in 160 subjects with various symptoms of MS[9], 137 patients elected to continue on Sativex[10]. On VAS of symptoms, rapid declines were noted over the first twelve weeks in pain (n=47) with slower sustained improvements for more than one year (Figure 3).

A dedicated Phase II double-blind, randomized placebo-controlled parallel group study of 56 rheumatoid arthritis patients with Sativex was recently undertaken in the UK over a period of 5 weeks[3]. Nocturnal treatment was initiated with a single spray each evening (2.7 mg THC + 2.5 mg CBD) and titrated upward every other night according to need to a maximum of 6 sprays per evening (16.2 mg THC + 15 mg CBD), after which stable dosing was pursued for a minimum of three weeks. In the final treatment week, many study measures favored Sativex over placebo: morning pain on movement ($p=0.044$), morning pain at rest ($p=0.018$), quality of sleep ($p=0.027$), DAS 28 measure of disease activity ($p=0.002$), and SF-MPQ pain at present ($p=0.016$).

Finally, the recently announced results of a Phase III study comparing Sativex, THC-predominant extract and placebo in intractable pain due to cancer unresponsive to opiates[5] with strong neuropathic pain components, demonstrated that Sativex produced highly statistically significant improvements in analgesia ($p=0.0142$), while the Tetranabinex failed to do so in this trial, confirming the key importance of the inclusion of CBD in the Sativex preparation.

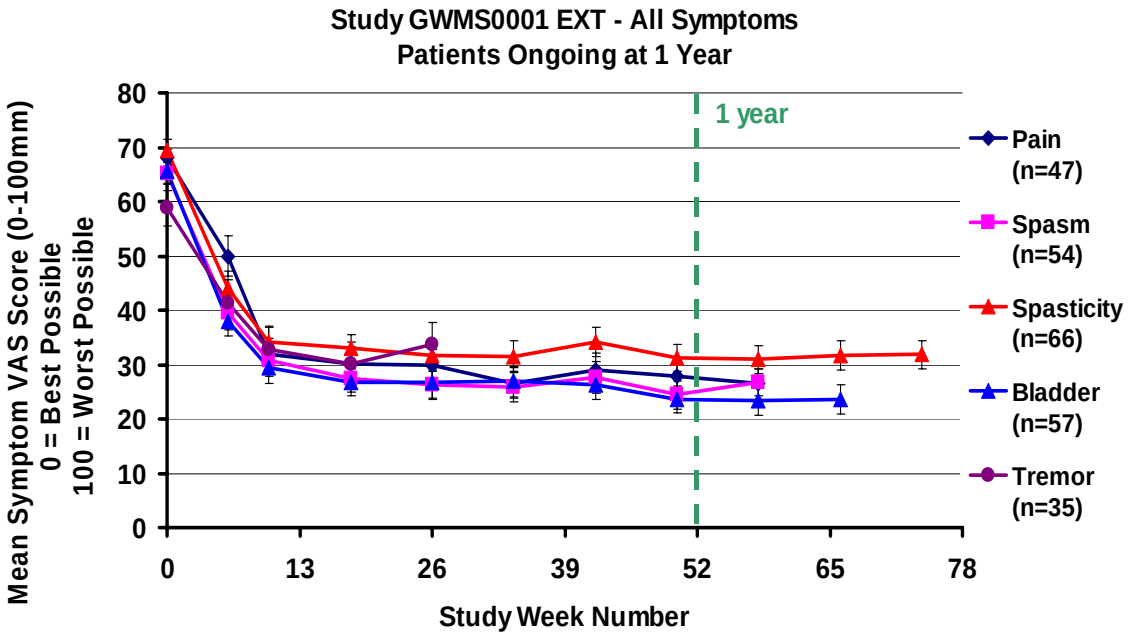

Figure 3: Graphic representation of visual analogue scales of various symptoms of multiple sclerosis in Sativex patients[9] that continued in SAFEX studies for over one year. Note the continued decline in symptoms with extended usage.

Analysis of sleep parameters in seven Phase II and III trials of MS and neuropathic pain and two corresponding SAFEX studies to date demonstrate significant to highly statistically significant and durable benefits of Sativex on this important clinical symptom[94].

Common adverse events (AE) of Sativex acutely in RCTs have included complaints of bad taste, stinging, dry mouth, dizziness, nausea or fatigue, but these rarely necessitate discontinuation, and are less common in regular usage (*vide infra).*

Sativex contains no known potentially carcinogenic components. Sativex, Nabidiolex and Tetranabinex have failed to produce genotoxicity or mutagenicity in rodent tests[95]. CBD (and THC) have proven cytotoxic for glioma cells, while cytoprotective for normal brain cells[96].

While no "head-to-head" comparisons of Sativex to Marinol or smoked THC have been performed in RCTs, examination of respective AE profiles is possible. The issue of central neuropathic pain in MS has been studied with Marinol (N=24)[48], and Sativex (N=33)[8] with positive benefits in each ($p=0.02$ and $p=0.009$, respectively). However, it is interesting to compare the AEs in the two trials (Figure 4A, 4B) and note that these generally favor Sativex, despite the fact that ≤10 mg of THC was employed in the Marinol trial[48], while a mean of 25.9 mg of THC-equivalent was utilized by Sativex patients[8].

Adverse Event	Marinol (THC ≤10 mg/d)	Sativex (mean THC 25.9 mg/d)
Dizziness	58%	52%*
Somnolence	46**	9
Fatigue	4	6
Feeling drunk	8	3
Dry mouth	13	12
Nausea	13	9
Headache	25**	3

* Incidence is higher than in other clinical trials ** Difference appears significant

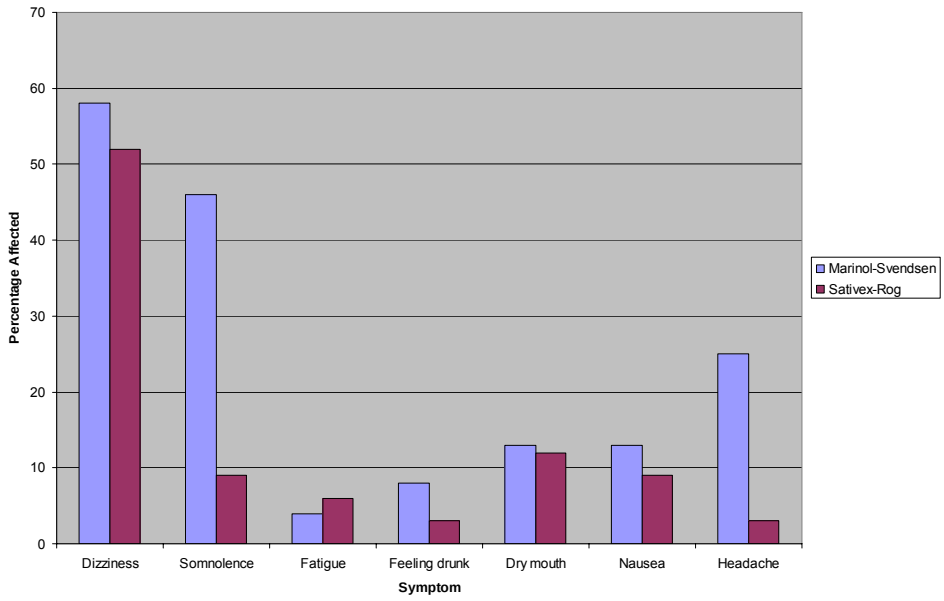

Figure 4A, B: Table and graphic representation of adverse effects of Marinol[48] (N=24) vs. Sativex[8] (N=33) in respective RCTs in treatment of neuropathic pain in multiple sclerosis.

A series of studies have been done in the Netherlands and Canada examining survey reports of AEs in patients who have employed herbal cannabis in legal programs in those countries. Although these smoked cannabis studies were not placebo controlled RCTs, again a comparison of attributable AEs to self-selected patients in Sativex SAFEX studies is possible, including those with multiple symptoms of MS (N=137)(GWMS0001

SAFEX) continuing on from a previous study[9], and a composite of various studies above reviewed with central or peripheral neuropathic pain (N=507)(GWNP0101 SAFEX), all of whom took Sativex for more than a year, and up to four years in some subjects.

In Canada, the effects of government supplied herbal cannabis in the Marihuana Medical Access Regulations program was studied in 30 chronic pain subjects[97], half of whom had previously used black market supplies. Some may have continued to do so. MMAR cannabis had a THC content of 9.63-13.89%, with CBD undetectable. Average daily dose employed was 2.75 g, and 28/30 (93.3%) of subjects smoked as their delivery technique. A comparison of AE profiles (Figure 5A, 5B) reveals dizziness as the sole parameter favoring MMAR material, while results otherwise clearly favored Sativex, especially parameters pertaining to sedation and appetite. It should be emphasized that certain Sativex patients crossed over from placebo to Sativex in the SAFEX studies, and thus, certain early AE were noted prior to the development of tolerance.

Programme	MMAR-PPS	GWMS0001	GWNP0102
N =	30	137	507
Adverse Event	% affected	% affected	% affected
Fatigue	20	8	9.1
Lethargy	10	5.1	3
Appetite ↑	60	0.7	1
Dizziness	3.3	15.3	27
Anxiety	6.7	0.7	2
Palpitations	3.3	0	1.4
Tachycardia	13.3	0	0.6
Confusion	6.7	0	0
Weight gain	23.3	stable	stable

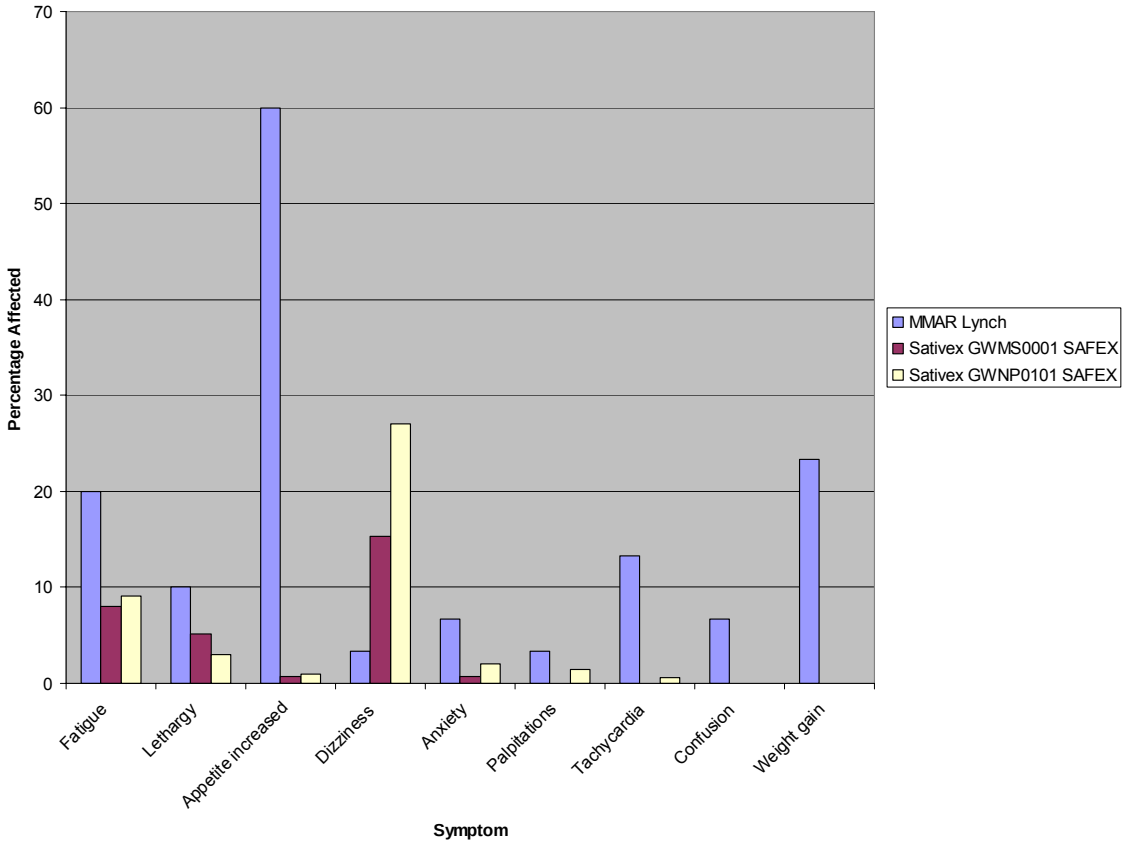

Figure 5A, B: Table and graphic representation of AE reported with smoked cannabis in chronic pain patients in the Canadian MMAR program[97](N=30) vs. Sativex SAFEX studies of MS (N=137) and central and peripheral neuropathic pain (N=507).

The Dutch Office of Medicinal Cannabis has previously allowed prescription by physicians and distribution through pharmacies of two proprietary herbal cannabis strains provided as herbal material: SIMM 18 with THC 13.7% and CBD 0.7%, and Bedrocan with THC 18% and CBD 0.8%. Results in 200 subjects (60.9% of whom previously employed black market supplies), the majority of whom employed cannabis for pain, were analyzed by the PHARMO Institute[98]: 73.5% used cannabis in tea(!), 20.5% smoked with tobacco, 6.5% vaporised, 5.5% smoked with a waterpipe, and 7% used other means (oral). Examination of comparative AE profiles (Figure 6A, B) reveal that nausea was marginally reported more frequently in Sativex patients (perhaps as a function of ethanol in the preparation), while most other side effects were notably more common with crude cannabis.

Adverse Event	% Reporting	Mild	Moderate	Severe
Languor/Dullness	42.5	52.1	41.7	6.3
Dry Mouth	38.1	55.8	23.3	20.9
Giddiness	33.6	73.7	15.8	10.5
Muscle weakness	31.9	38.9	44.4	16.7
Hunger	25.2	26.7	40.0	33.3
Feeling hot or cold in hands or feet	23.5	42.9	32.1	25.0
Red eyes	16.0	63.2	21.1	15.8
Disorientation to time or place	15.1	44.4	50.0	5.6
Airway irritation	14.3	64.7	29.3	5.9
Better hearing	11.8	64.3	21.4	14.3
Improved color vision	10.9	46.2	30.8	23.1
Confusion	10.9	69.2	23.1	7.7
Tachycardia	10.9	46.2	30.8	23.1
Nausea	9.2	63.6	27.3	9.1
Headache	8.4	100.0	0	0
Anxiety/Panic	5.0	67.0	33.0	0
Insomnia	5.0	66.7	16.7	16.7
Agitation	4.2	60.0	40.0	0
Delusion	3.4	50.0	25.0	25.0
Excitability	3.4	50.0	50.0	0

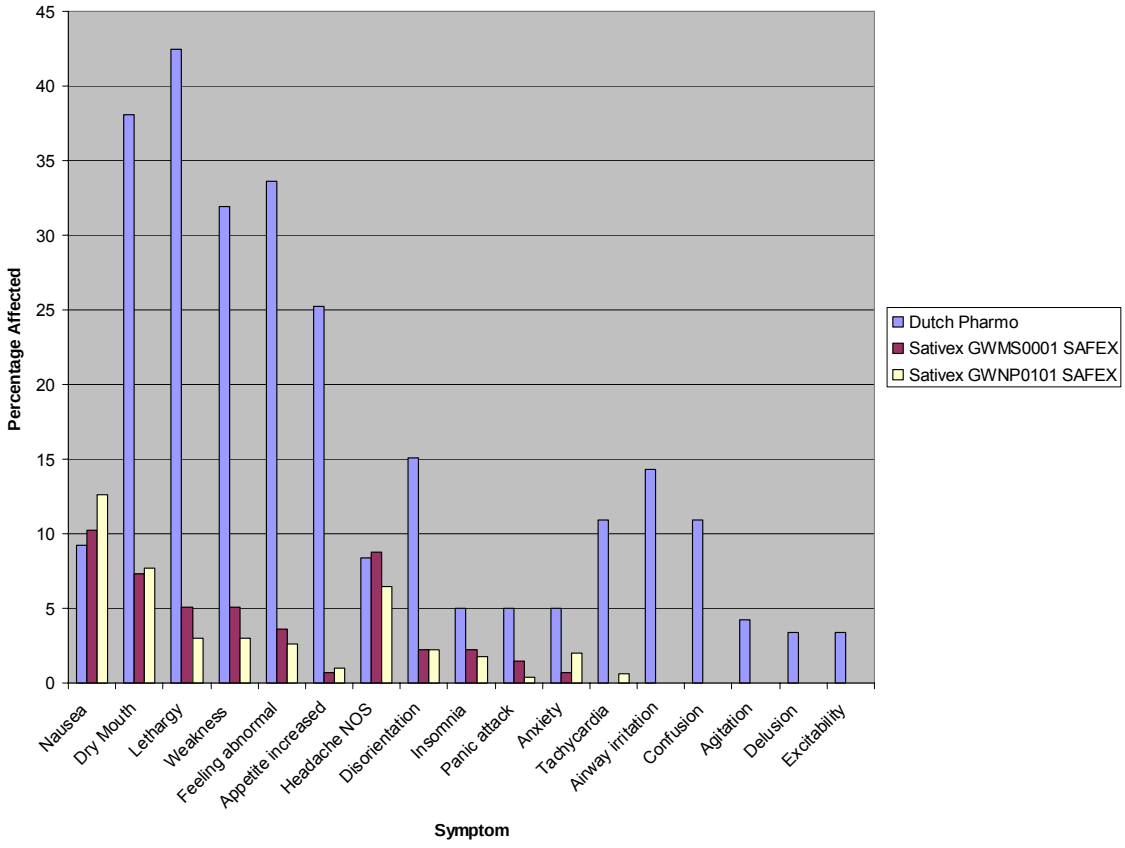

Figure 6A, B: Table of AE reported in the PHARMO study[98] of cannabis from Dutch pharmacies (N=200), with graphic comparison to AE in Sativex SAFEX studies of MS (N=137) and central and peripheral neuropathic pain (N=507).

Another company, Maripharm, previously supplied herbal cannabis to Dutch pharmacies, and this material had a content of 10.2% THC with CBD <1%. Some 107 subjects with predominantly chronic pain and neurological conditions employed this material, primarily via smoking[99]. Comparison of AEs reported in the article (Figure 7A, B) clearly favors Sativex with respect to dry mouth and cognitive sequelae.

Programme	Maripharm-Gorter	Sativex GWMS0001	Sativex GWNP0101
N =	107	137	507
Symptom	% Affected	% Affected	% Affected
Dry mouth	27.4	7.3	7.7
Lethargy	13.9	5.1	3
Feeling abnl	10.6	3.6	2.6
Dist. in attn.	11.7	5.1	3.2
Euphoric mood	13.3	0.7	4.3

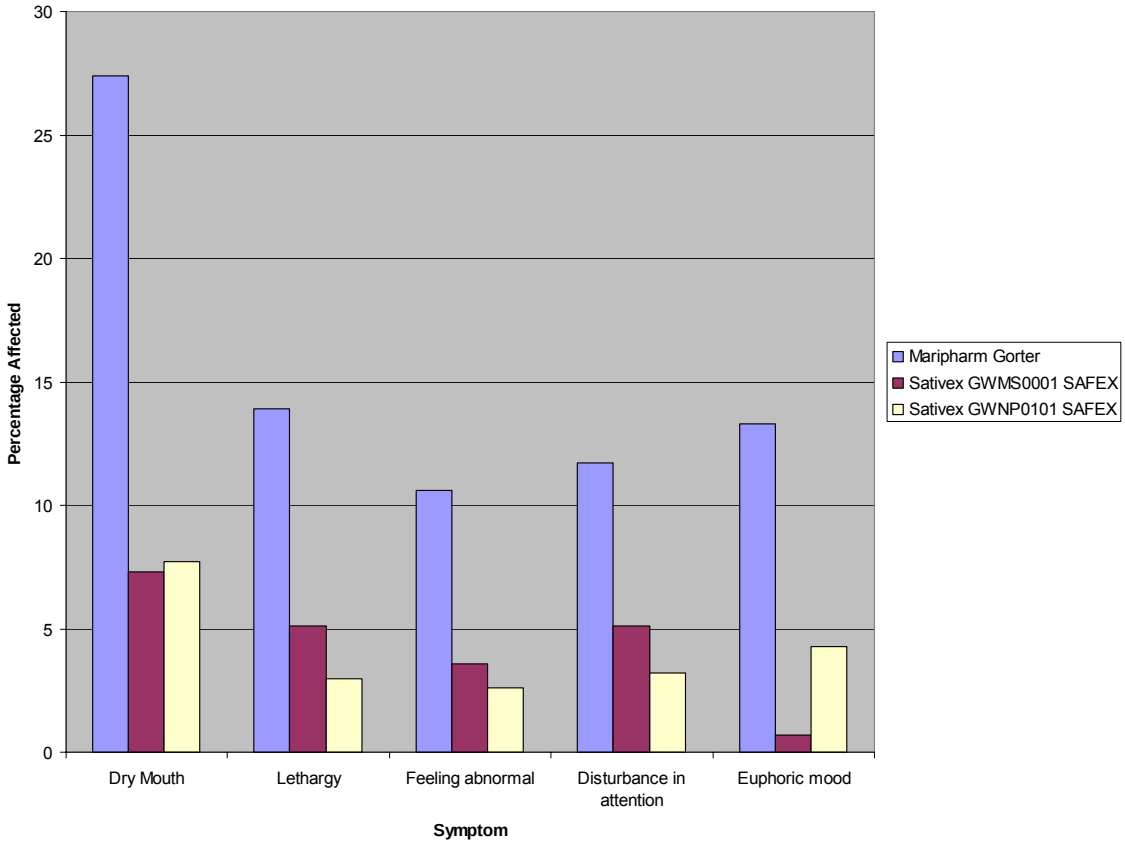

Figure 7A, B: Table and graphic representation of AE reported in the study of Maripharm cannabis from Dutch pharmacies (N=107)[99], in comparison to AE in Sativex SAFEX studies of MS (n=137) and central and peripheral neuropathic pain (N=507).

Additional AEs were also analyzed in online material (http://www.neurology.org/cgi/content/full/64/5/917/DC1), and can be compared to Sativex (Figure 8A, B). In every instance, the AE profile markedly favors Sativex.

Programme	Maripharm	GWMS0001	GWNP01001
N =	107	137	507
Symptom	% affected	% affected	% affected
Eye irritation	11.8	0	0.2
Feeling high	38.8	3.6	4.9
STM loss	27.2	4.4	1.4
Sleepiness/Som	38.7	5.8	7.9
Hunger	32.4	0.7	1
↓ Concntrn/ Attn	30.1	5.1	3.2
↓Motvtn/ Interest	19.6	0.7	0
Anxiety	14.4	0.7	2
Euphoria	24.7	0.7	4.3
Depression	18.1	0.7	1.6
Dry mouth	59.9	7.3	7.7
↓ Coordination	26	0.7	0.4

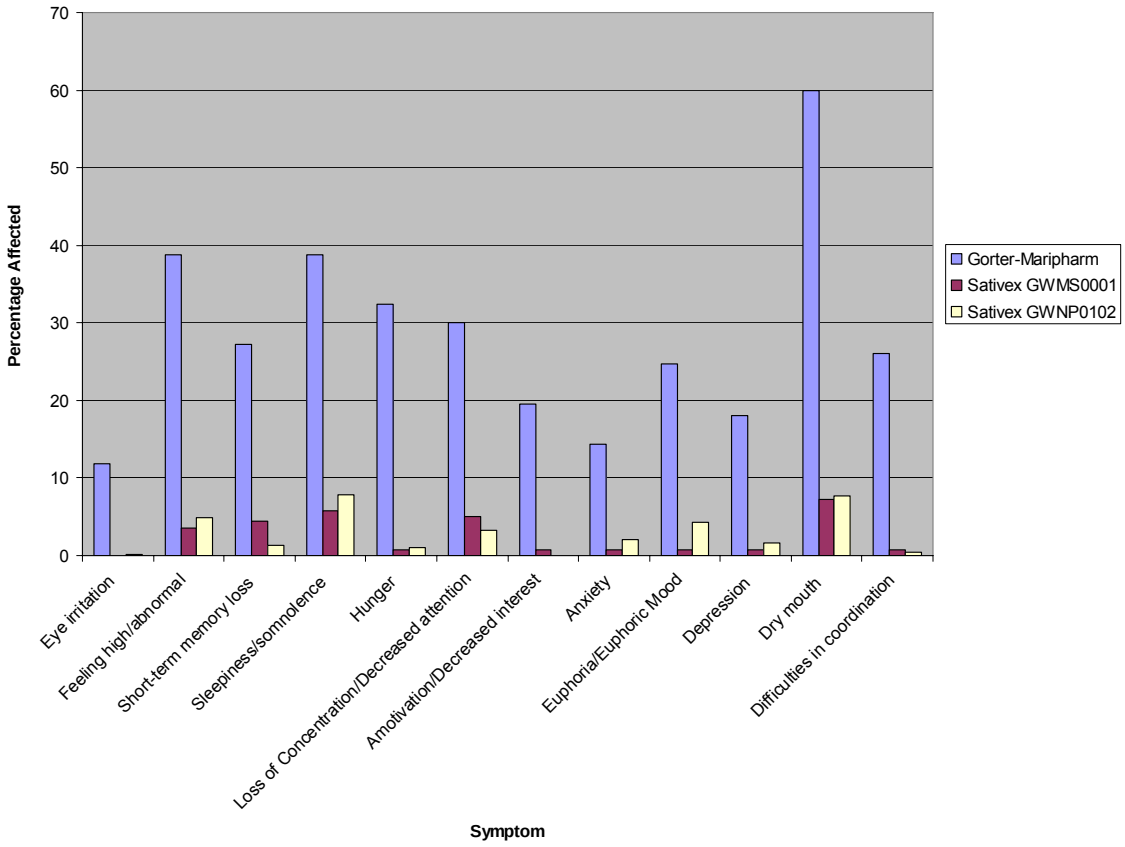

Figure 8A, B: Table and graphic representation of supplemental AE reported in the study of Maripharm cannabis from Dutch pharmacies (N=107)[99], in comparison to AE in Sativex SAFEX studies of MS (n=137) and central and peripheral neuropathic pain (N=507).

Two conclusions are possible in consideration of these results:

1) Sativex allows attainment of higher daily THC doses than oral THC, probably due to oromucosal delivery and the actions of CBD.
2) *The AEs attributable to Sativex are significantly less frequent than those reported with other delivery systems of standardized herbal cannabis.*

V. Sativex and Medicinal Cannabis Controversies

A. Herbal Synergy: Does It Exist?

The contributions of cannabis components beyond THC to its medicinal effects has been widely debated[100, 101] with some authors supporting the concept of herbal synergy[57, 102, 103], the likes of which has been convincingly demonstrated for endocannabinoids via "the entourage effect" of active and seemingly inactive metabolites[104, 105]. Such synergy would be apparent under conditions in which the activity of a minor component complemented the major, diminished the adverse event profile, or otherwise contributed to a preparation's stability or efficacy. The case in support of CBD as a synergist to THC has recently been examined in detail[84]. To enumerate just a few examples, CBD displays anti-anxiety effects[106], is anti-psychotic in high doses[107, 108], inhibits metabolism of THC to the possibly more psychoactive 11-hydroxy-THC[109], inhibits glutamate excitotoxicity, displays anti-oxidant effects[110], and has anti-inflammatory and immunomodulatory activity in its own right[111]. CBD and perhaps other cannabis components[57] are synergistic to THC[112] by virtue of potentiation of benefits, attenuation of side effects, summation, and the provision of pharmacokinetic and metabolic advantages. To do so, however, sufficient quantities of CBD must be present, and this was a prime motivator behind the composition of Sativex as the combination of two chemovars, as cannabis plants do not naturally contain high percentages of both cannabinoids simultaneously[113]. In contrast, North American strains of cannabis are virtually devoid of CBD[114, 115].

B. Pharmacokinetics and Cannabinoid Dose Titration

It has previously been mentioned that phytocannabinoids are lipid soluble and oral absorption is slow and erratic. Cannabis users occasionally allege in press interviews that the smoking of cannabis allows easy dose titration due to its rapid onset (Figure 2), but this method also produces extremely high serum (and presumably brain) levels. Such high serum levels are, of course, the goal of recreational usage, but inappropriate and unnecessary for therapeutic applications (Figure 2), as intoxication is an undesirable side effect for most patients who are merely seeking pain relief. In fact, outside of early dosage titration, most Sativex patients experience no "high" and report subjective

intoxication levels on visual analogue scales that are in the single digits out of 100 (Figure 9), indistinguishable from placebo[10]. *The Sativex research program to date has debunked the notion that noticeable psychoactive effects are necessary for symptomatic benefits to be realized from a cannabis-derived medicine.*

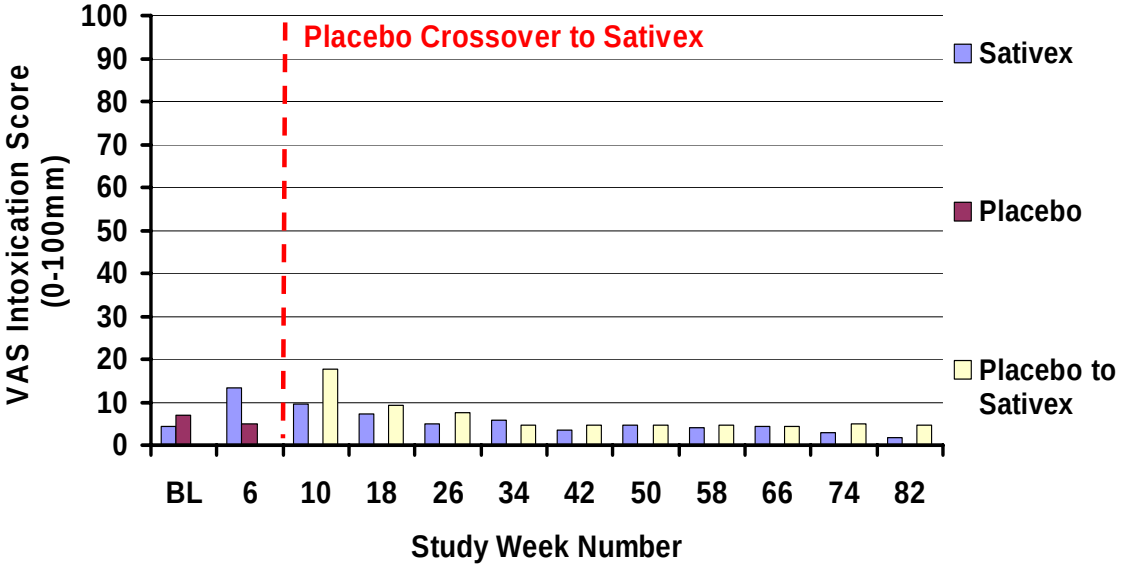

Figure 9: Visual analogue scores of intoxication of Sativex (blue bars) vs. placebo (purple bars) in MS patients[9] with various symptoms. SAFEX subjects were followed subsequently, and placebo subjects then titrated onto Sativex (cream bars). Note that after early titration, their intoxication scores are similarly indistinguishable from placebo.

C. Anti-inflammatory Drugs and Cyclo-oxygenase (COX) Inhibition

Current concern has been prominent in relation to morbidity and mortality associated with non-steroidal anti-inflammatory drugs (NSAID), wherein older COX-1 agents may predispose to gastric ulceration and hemorrhages, while newer COX-2 agents have been associated with increased risk of myocardial infarction and cerebrovascular accidents[116, 117]. Recent study has demonstrated, however, that the anti-inflammatory and analgesic effects of Tetranabinex (high THC) and Nabidiolex (high CBD) extracts must occur via independent mechanisms, as they produce no COX inhibition of either isozyme at relevant pharmaceutical concentrations[118].

D. Blinding in Cannabis Randomized Clinical Trials

The issue of adequacy of blinding in RCTs of psychoactive drugs has frequently been called into question. However, all information to date supports the preservation of blinding in Sativex studies. Sativex and its placebo are identical in appearance, color, taste and inclusion of peppermint flavoring. Approximately 40-50% of RCT participants

have had prior experience of cannabis whether recreationally or therapeutically, but *post hoc* analysis of patients in two studies[7, 8] reveals no differences in efficacy or AE profile in cannabis-experienced vs. cannabis-naïve subjects. Furthermore, this analysis also showed that Sativex had differential efficacy in various MS symptoms[119]. If those patients achieving efficacy in one symptom had thereby become unblinded, one would anticipate that their other symptoms would also have improved. It was also noted that there was no difference in efficacy among previously cannabis-naïve or experienced patients who experienced dizziness as an AE. Intoxication issues in the RCTs have been previously addressed[10].

E. Cannabis, Drug Abuse Liability and DEA Scheduling

Recreational cannabis abuse and dependence remain hot-button issues, with recent description of the elements of a cannabis withdrawal syndrome[120], while other authorities questioned its validity[121]. The addictive potential of a drug is determined by its degree of intoxication, reinforcement, tolerance, withdrawal and dependency. Drug abuse liability (DAL) is further determined by historical rates of an agent's abuse and diversion.

When enacting the Controlled Substances Act, Congress placed herbal cannabis in Schedule I of the Act, which is reserved for drugs that are considered to be addictive or dangerous, have severe abuse potential, and lack any recognized medical use. Upon its FDA approval in 1985, Marinol was transferred to Schedule II, the category for drugs with high abuse potential and liability to produce dependency, but certain recognized medical uses. After subsequent study showed little abuse or diversion of the product[49], Marinol was reassigned in 1999 to Schedule III, a category denoting a lesser potential for abuse or lower dependency risk.

Intoxication is the primary purpose of recreational cannabis smoking, and remains a likely sequela of therapeutic usage of smoked herbal materials. It has similarly been a pitfall of Marinol therapy[49]. As previously noted, in contrast, intoxication has been occasionally encountered in Sativex RCTs early in dose titration, but is rarely problematic in long-term usage (Figure 9).

The reinforcement properties of a drug are mediated in part by the rapidity of its delivery[122]. Sativex onset of effects is 15-40 minutes, with peak activity in a few hours. This is considerably slower than most drugs of highest abuse potential. Cannabidiol attenuates THC intoxication effects[84], and certainly may lower DAL potential. Information from Sativex RCTs and SAFEX studies does not indicate any particular reinforcement or euphoria[10].

A marked degree of tolerance is seen in a wide variety of measures of initial cannabinoid intoxication: tachycardia, hypothermia, orthostatic hypotension, dry mouth, ocular injection, intraocular pressure decreases, etc.[123]. In well over 1000 patient-years of experience, no dose tolerance to Sativex has been observed, however, and therapeutic efficacy is maintained for all symptoms studied to date (Figure 3). In SAFEX studies in MS and peripheral neuropathic pain, Sativex doses have been stable or even decreased after months to years of administration[10] (Figure 10).

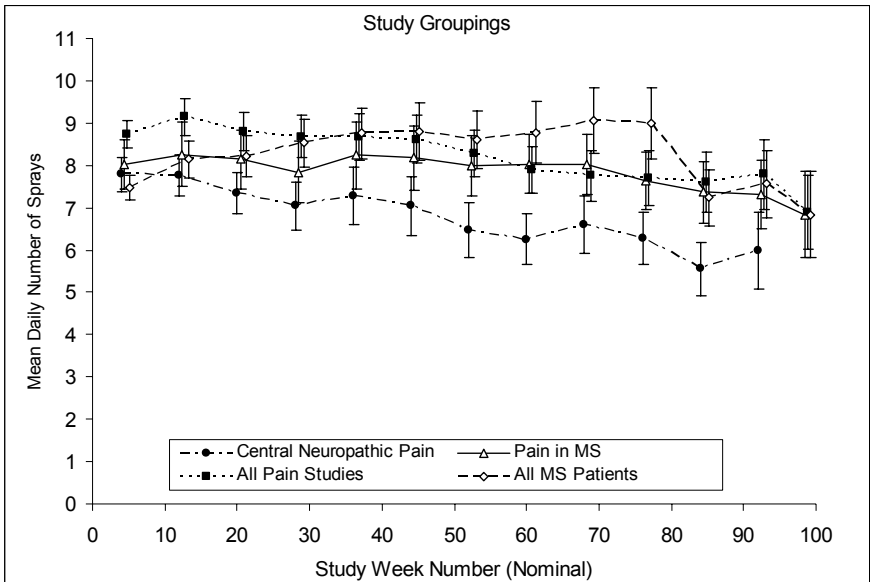

Figure 10: Mean daily sprays of Sativex employed in GWNP0101 SAFEX studies of central and peripheral neuropathic pain (N=507). Note that daily dosing required to produce pain control is stable or even declines slightly over the course of two years.

Simultaneously, symptomatic pain control is maintained[10] (Figure 11) with slow continued improvement.

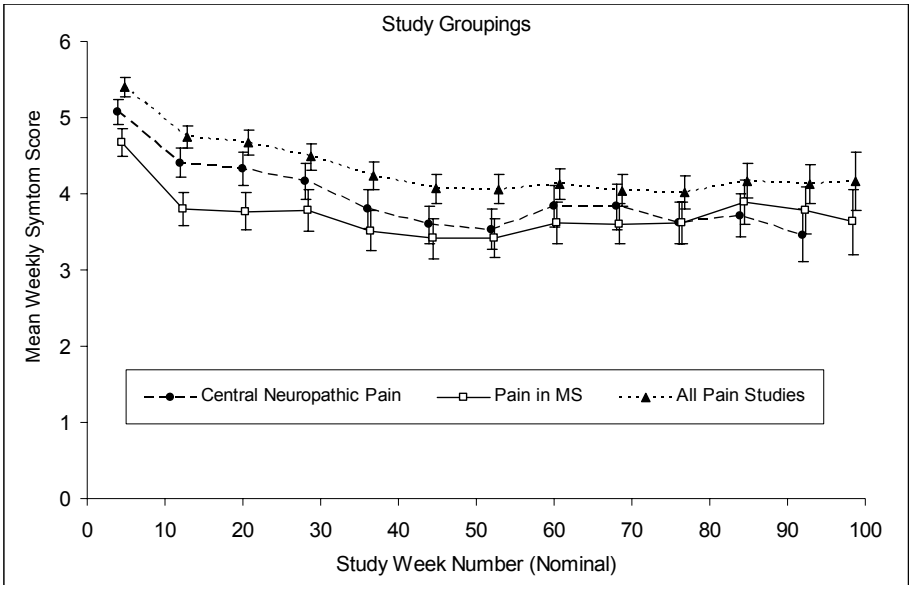

Figure 11: Box scale-11 numerical rating scales of central and peripheral neuropathic pain patients in GWNP0101 SAFEX subjects taking Sativex for two years (N-507). Note that no tolerance develops, and a slow, steady decline in pain levels results.

In contrast to withdrawal effects reported in some long-term recreational cannabis users[124], in a cohort of 24 volunteers with MS who abruptly stopped Sativex after more than a year of continuous administration, no significant evidence for a formal withdrawal syndrome was observed. Rather, patients suffered recrudescence of symptoms after 7-10 days, but easily re-titrated to prior dosages with renewed efficacy[10].

The above appears to show that Sativex has a lower dependency risk than herbal cannabis, due to slower onset, low therapeutic dosages, virtual absence of intoxication in regular therapeutic application, and lack of observed withdrawal even after prolonged usage. Finally, no known abuse or diversion incidents after Sativex usage have occurred to date (as of November 2005). Formal post-marketing surveillance in Canada and DAL studies are planned as part of the US regulatory approval process. Sativex is expected to be placed in Schedule IV of the Misuse of Drugs Act in the UK upon its marketing approval in that country.

F. Cognitive Issues

A detailed analysis of cognitive factors surrounding cannabis-derived medicines is beyond the scope of this chapter. The cognitive impact of cannabis use has been

previously reviewed[125, 126]. The issue has been less studied in therapeutic contexts with cannabis based medicines. It has been reported that the effects on memory of heavy chronic recreational cannabis seem to diminish with a few weeks' abstinence without residua[127].

Components of the Halstead-Reitan battery have been performed in two Sativex studies. In neuropathic pain with allodynia[7], no changes were seen vs. placebo. In central neuropathic pain in MS[8], four of five measures showed no significant differences. The Selective Reminding Test did not change significantly on Sativex over the course of the trial, but placebo patients did register an unexpected improvement ($p=0.009$).

Depression and anxiety have been posited as sequelae of recreational cannabis usage (reviewed[126]), but slight improvements were noted with Sativex in MS patients with central neuropathic pain[8] on Hospital Anxiety and Depression Scales, although these did not attain statistical significance. Examinations of long-term AE profiles in the figures also indicate little liability for mood disorders for this preparation.

The debate about an etiological role for cannabis in psychosis continues (reviewed[126]). If such an association exists (which is not supported by epidemiological data[128]), it would logically have some relation to dose, with a greater liability with chronic high dose exposure. The lower serum levels of Sativex in therapeutic usage, coupled with the anti-psychotic properties of CBD[129], would hopefully minimize such risks. Sativex RCTs to date have excluded children and adolescents and anyone with a history of serious mental disorder. Once more, the long-term AE profile of Sativex would seem to indicate few symptoms of paranoia, thought disorder or similar changes.

G. Immune Function

Deleterious effects of cannabinoids on immune function have frequently been claimed in the literature, but generally these effects are noted in experimental animals exposed to 50-100 times the psychoactive dose[130]. No changes in white blood cell, CD4 or CD8 cell counts were noted in small group of patients who had used herbal cannabis therapeutically for over 20 years[125]. A recent study of MS patients in the CAMS trial with Cannador showed no effects on major immune parameters[131], nor were any seen with smoked cannabis in a short-term RCT in HIV patients[132]. Hematological parameters have been normal in all Sativex RCTs to date, with no indication of anergy or hyper-immune sequelae.

H. Cannabinoid-Drug Interactions

Certainly, a risk of additive sedative effects may be possible with cannabinoids and other such drugs (reviewed in more detail[16]). In Sativex, these sedative influences are actually counteracted by CBD[133].While there have been concerns about cannabinoid interference in metabolism of other drugs, particularly the effect of CBD on hepatic cytochrome P450 complex, no such changes were observed in a study of Sativex, Tetranabinex and Nabidiolex at relevant concentrations in an experimental protocol[134]. Thus, Sativex should be safe to use in conjunction with fentanyl and other such drugs. In practice, Sativex has been employed as an adjunctive medicine in complex intractable pain patients on regimens including the full range of opiates, tricyclic antidepressants, anticonvulsants, etc., without evidence of untoward drug-drug interactions.

I. Driving Safety

The issue of driving safety and drug use is an important topic in modern public health. While it is well established that significant alcohol intake impairs the ability to properly operate a motor vehicle, and that blood ethanol levels may accurately assess inherent risks, such relationships with cannabis usage, particularly in a recreational context, are much more problematic. While some retrospective studies of motor vehicle accidents or road crashes have claimed an etiological relationship to cannabis usage, others[135] have not supported a valid link, unless cannabis was concomitantly employed with alcohol. In a recent comprehensive review[136], the weight of evidence was interpreted to support a very low risk for cannabis in such accidents, and one less than that associated with many common therapeutic medications including benzodiazepines and older antihistamine formulations[137]. A recent conference report also supports these findings[138].

The matter is further complicated when consideration turns to driving and medicinal cannabinoid usage. In the situation of Marinol, the information provided by the manufacturer to physicians indicates (http://www.solvaypharmaceuticals-us.com/static/wma/pdf/1/3/1/9/Marinol5000124ERev52003.pdf)(p. 5), "Patients receiving MARINOL® capsules should be specifically warned not to drive, operate machinery, or engage in any hazardous activity until it is established that they are able to tolerate the drug and to perform such tasks safely."

The Sativex Product Monograph in Canada states http://www.bayerhealth.ca/display.cfm?Object_ID=272&Article_ID=121&expandMenu_ID=53&prevSubItem=5_52 (p. 8):

> SATIVEX® may impair the mental and/or physical abilities required for certain potentially hazardous activities such as driving a car or operating machinery. Patients should be warned not to drive or engage in activities requiring unimpaired judgment and coordination. Patient should also be cautioned about the additive/synergistic effects of SATIVEX® with other CNS depressants, including opioids, GABA inhibitors, sedative/hypnotics, and alcohol.

Specific testing of the effects of Sativex upon driving skills has not yet been undertaken, but other factors may have bearing on the issue. While THC forms a key component of Sativex, the presence of almost equal amounts of the non-psychoactive CBD may serve to counteract intoxication and other side effects[84, 139, 140], as was specifically observed in a Phase I trial of Sativex in normal subjects, in which CBD exerted alerting effects on sleep and eliminated counter-balanced residual THC effects the morning following nocturnal administration[133]. Neuropsychological testing in peripheral neuropathic pain patients[7] and in multiple sclerosis patients with central pain[8] (*vide supra)* support the concept that few perceptual or cognitive changes of note are observed with Sativex (reviewed[141]). Finally, *post hoc* analysis of safety-extension patients with MS taking Sativex for over one year indicate that in the 73% of 119 subjects completing a questionnaire, 59% noted an improvement in total disability, 63% improved in at least one activity, 20% reported a decreased need for equipment or assistance, 95% noted positive changes in General Life Benefits, and 12-32% of caretakers noted easier administration to demands of activities of daily living.

A new report by an expert panel[142] provides a comprehensive analysis of the issue of cannabinoids and driving. Among other recommendations, it suggests utilization of scientific standards to assess driving ability, such as roadside sobriety tests, as opposed to *per se* standards that may include measurement of inactive cannabinoid metabolites that serve as markers of past usage without providing accurate commentary upon a driver's actual driving ability status. In an effort to provide some framework for measuring putative impairment by cannabis that would be accessible to law enforcement, the panel did endorse the validity of measures of THC itself[142] (p. 7):

> Based on the results of culpability studies and from meta-analyses of experimental studies, per se laws for DUIC {driving under the influence of cannabis} should specify a legal limit for THC in blood serum of 7-10 ng/mL as a reasonable choice for determining relative impairment by cannabis. This corresponds to THC concentration in whole blood- the parameter commonly used in U.S. jurisdictions- or 3.5-5 ng/mL.

Of note, no studies demonstrated relevant impact of cannabis on driving skills at plasma levels below 5 ng/ml of THC.

It is thus interesting to compare pharmacokinetic values of THC obtained by smoking and those from Sativex (equivalent to four rapid oromucosal sprays) (Figure 2), in which THC levels remained below this threshold. GW Pharmaceuticals hopes to collaborate with Bayer HealthCare in Canada in the performance of actual driving tests on patients with neuropathic pain before and after stabilization on Sativex to better ascertain its effects, and appropriate advice that physicians should provide regarding this important issue.

VI. Conclusions

The need for useful additional medicines in treatment of chronic pain conditions is clear, and the data supporting a role for certain cannabis based drugs in such treatment is compelling. An evident path for approval of such drugs by the FDA has been provided in the form of the *Botanical Guidance*[15]. With its approval in Canada, Sativex is the only cannabis based medicine to date that has provided the necessary evidence-based data on safety, clinical efficacy, and product quality and consistency to pass regulatory muster. The same cannot necessarily be said for other preparations that lack equivalent efficacy and especially, safety data. Upon successful completion of additional clinical trials and other regulatory safety mandates, Sativex or other agents that provide an equivalent level of scientific support may soon be added to the available armamentarium of treatment options to treat chronic pain in the USA, to the likely mutual benefit of patients and their care-givers.

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