Letter to the editor

Letter: Cannabinoid medicines and the need for the scientific method

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To gain the widespread trust of physicians and medical consumers, cannabinoid medicines must be standardized, efficacious and safe preparations as demonstrated in statistically significant randomized clinical trials (RCTs) acceptable to regulatory bodies in various countries and adhering to the modern scientific method.

Dr. Grinspoon has stated that a dual status for cannabinoid medicines (approved vs. illegal) is developing [1]. However, US Food and Drug Administration (FDA)-approved medicines and crude herbal materials cannot be considered equivalent when it comes to their status as modern medicines. Herbal cannabis as currently available for patient use is a highly variable product with respect to composition. Procedures for standardized prescription botanical products have been formalized in the USA [2], providing a blueprint for regulatory approval of phytopharmaceuticals (botanical medicines). Although there is no proven etiological association of cannabis smoking to the development of lung cancer [3], it is inarguable that it produces lung irritation, chronic cough and pulmonary cytological alterations [4]. Communal sharing of cannabis cigarettes may pose infectious disease risks, such as transmission of meningococcal meningitis [5]. These facts alone render smoked cannabis ineligible for regulatory acceptance as a prescription product in most nations. Existing state laws allowing medicinal use of cannabis still require physician recommendation and supervision; most practitioners would prefer to prescribe an FDA-approved pharmaceutical form.

Although vaporization of cannabis below its combustion point reduced respiratory complaints [6] and serum carbon monoxide levels [7], it failed to eliminate all potentially carcinogenic polyaromatic hydrocarbons [8], and remains as inefficient and unpredictable as smoking in THC delivery [7, 9]. Assertion that smoked cannabis may be “the gold standard” for cannabinoids is unsubstantiated, as a notable dearth of published RCT data exists [10, 11] and represent only first steps in a long journey toward FDA approval. Anecdotal claims of efficacy for smoked cannabis mean little in the regulatory realm [12]. Studies of smoked cannabis, its inhaled vapor [7] or pure THC [13] reveal steep pharmacokinetic THC curves and evidence of marked intoxicating effects at reported therapeutic dosages. A delivery system that allows relief without undesirable adverse events is necessary. Material must also be free of pathogenic micro-organisms. Problems in cultivation in Dutch and Canadian government-approved herbal cannabis programs have led authorities to gamma-irradiate their products.

Progress is apparent in developing other cannabis based prescription medicines. Large scale clinical trials have been undertaken, notably in Europe, as with investigation of Cannador cannabis extract in treatment of spasticity associated with multiple sclerosis (MS) [14] and other disorders. The most advanced program is that for Sativex®, an oromucosal spray derived from two standardized whole cannabis extracts, Tetrabinox® (rich in tetrahydrocannabinol, THC) and Nabidiolex® (rich in cannabidiol, CBD) [15], providing 2.7 mg of THC, 2.5 mg of CBD and other components with each actuation. Extracts derive from clonal strains grown in organic media under climate-control in accordance with Good Agricultural and Manufacturing Practices. Phytocannabinoids, terpenoids and others are monitored to ensure consistency [16, 17].

Sativex was approved for prescription in Canada for central neuropathic pain in multiple sclerosis in June 2005. It is available on a named-patient basis in the United Kingdom and the Catalunya Autonomous Region (Spain). The FDA has granted an Investigational New Drug Application for Sativex to proceed to advanced stage clinical trials for intractable cancer pain in the USA.

Numerous Phase II-III clinical trials of Sativex have been completed in central and peripheral neuropathic pain, spasticity, and urinary symptoms in MS, rheumatoid arthritis and cancer pain [18-26], with significant benefits in intractable symptoms failing to respond to conventional treatment. Visual analogue scales of intoxication after initial dose titration most frequently remained in single digits on a 100-point scale, proving this preparation need not produce psychoactive change.
to achieve therapeutic benefit. Most patients desire symptom control from medicine, not euphoria or any alteration in mental status or capabilities. No dose tolerance or significant withdrawal symptoms have been observed with Sativex in up to five years of Safety-Extension studies, even upon abrupt discontinuation [19].

The onset of therapeutic effects of Sativex after oromucosal administration is in 15-40 minutes [27] with steady pharmacokinetic contour [28]. This is much less than the 1-2 hour interval noted with THC in sesame oil [29], and sufficiently fast to allow titration to symptom relief without reinforcement. Most clinical trial subjects have stabilized on an effective tolerable dose of Sativex within 7-10 days via self-titration. In over 2000 patient-years of clinical trial and SAFEX monitoring and two year’s market experience in Canada, no abuse or diversion has resulted. Three studies have examined adverse event profiles of patients employing smoked cannabis in government-approved programs in Canada [30], and the Netherlands [31, 32]. A comparison to Sativex SAFEX patients confirms that adverse events with smoked cannabis are far more frequent and prominent [12], especially for cognitive function and alertness. In contrast, cough and pulmonary complaints are not reported with Sativex.

Sativex has proven itself distinct from mere THC due to its unique composition and delivery. CBD contributes notably as an analgesic and anti-inflammatory antioxidant [33-35], but also attenuates intoxication, tachycardia and other THC effects [15, 36]. CBD provides beneficial immunomodulatory effects in autoimmune disorders (rheumatoid arthritis, inflammatory bowel disease) via inhibition of tissue necrosis factor-alpha [37] and adenosine uptake via its A2A receptor [38]. However, North American and most European cannabis drug strains are virtually devoid of CBD [39-41].

Marinol did demonstrated analgesic benefit in central neuropathic pain in MS [42]. Similar benefits were noted with Sativex [25] but with a lower adverse event profile, despite that total doses of THC were 2 ½ times higher in the Sativex group, demonstrating the contribution of CBD to improvement in THC’s therapeutic index [12].

In an RCT in intractable cancer pain, Sativex produced statistically significant analgesic efficacy, while Tetranabinex (without CBD) did not [26], highlighting the necessity of providing the most efficacious preparation possible in this challenging clinical context. Finally, will patients give up cannabis smoking for a prescription alternative? Yes, apparently. Some 50% of Sativex clinical trial subjects have had therapeutic or symptomatic oromucosal administration is in 15-40 minutes [27] with steady pharmacokinetic contour [28]. This is much less than the 1-2 hour interval noted with THC in sesame oil [29], and sufficiently fast to allow titration to symptom relief without reinforcement. Most clinical trial subjects have stabilized on an effective tolerable dose of Sativex within 7-10 days via self-titration. In over 2000 patient-years of clinical trial and SAFEX monitoring and two year’s market experience in Canada, no abuse or diversion has resulted. Three studies have examined adverse event profiles of patients employing smoked cannabis in government-approved programs in Canada [30], and the Netherlands [31, 32]. A comparison to Sativex SAFEX patients confirms that adverse events with smoked cannabis are far more frequent and prominent [12], especially for cognitive function and alertness. In contrast, cough and pulmonary complaints are not reported with Sativex.

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Patients worldwide are seeking symptom relief with an approved pharmaceutical that their physicians can prescribe with confidence that is standardized, safe, effective and reimbursed by governmental agencies and third-party payers. Thus, there may be a clear division between those who are ill, and those seeking a thrill. Sativex is the new gold standard for cannabinoid medicines and with its advent, one solution to the cannabinoid prescription problem is close at hand.

Acknowledgements

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References


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