Cannabinoids 2007;2(2):16-19

Letter to the editor

Letter: Cannabinoid medicines and the need for the scientific method

Ethan B. Russo

GW Pharmaceuticals, Vashon, Washington, USA

Author's address: Ethan B. Russo, erusso@gwpharm.com

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, Tetranabinex® (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 immunodulatory 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 recreational exposure to cannabis. Some 70% of subjects experienced sufficient benefit to request its continuation in SAFEX studies [12]. No differences in efficacy in cannabis-experienced vs. cannabis-naïve Sativex patients have ever been evident.

The evidence supports the feasibility of developing a cannabis-based medicine that adheres to regulatory norms without exceptions. Advantages of such an approach are numerous and include necessary safety, quality controls and accountability exclusive of the black market gamble.

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 cannabis prescription problem is close at hand.

Acknowledgements

The author is Senior Medical Advisor of GW Pharmaceuticals.

References

1. Grinspoon L. On the future of cannabis as medicine. Cannabinoids. 2007 (in press).
2. Food and Drug Administration. Guidance for industry: Botanical drug products. In: Services UDoHaH, editor: US Government; 2004. p. 48.
3. Hashibe M, Morgenstern H, Cui Y, Tashkin DP, Zhang ZF, Cozen W, et al. Marijuana use and the risk of lung and upper aerodigestive tract cancers: results of a population-based case-control study. Cancer Epidemiol Biomarkers Prev.. 2006 ;15(10):1829-34.
4. Tashkin DP. Smoked marijuana as a cause of lung injury. Monaldi Arch Chest Dis.. 2005;63(2):93-100.
5. Zanocco V. Meningococcal cases linked by sharing joints. [cited 2005 April 8]; Available from: http://www.vch.ca/news/docs/2005_04_07_mening_joints.pdf
6. Earleywine M, Smucker Barnwell S. Decreased respiratory symptoms in cannabis users who vaporize. Harm Reduct J. 2007;4(1):11.
7. Abrams DI, Vizoso HP, Shade SB, Jay C, Kelly ME, Benowitz NL. Vaporization as a smokeless cannabis delivery system: a pilot study. Clin Pharmacol Ther. 2007 (in press).
8. Gieringer D, St. Laurent J, Goodrich S. Cannabis vaporizer combines efficient delivery of THC with effective suppression of pyrolytic compounds. J Cannabis Ther. 2004;4(1):7-27.
9. Hazekamp A, Ruhaak R, Zuurman L, van Gerven J, Verpoorte R. Evaluation of a vaporizing device (Volcano) for the pulmonary administration of tetrahydrocannabinol. J Pharm Sci. 2006;95(6):1308-17.
10. Abrams DI, Hilton JF, Leiser RJ, Shade SB, Elbeik TA, Aweeka FT, Benowitz NL, Bredt BM, Kosel B, Aberg JA, Deeks SG, Mitchell TF, Mulligan K, Bacchetti P, McCune JM, Schambelan M. Short-term effects of cannabinoids in pati-

ents with HIV-1 infection. A randomized, placebo-controlled clinical trial. Ann Intern Med. 2003;139:258-66.
11. Abrams DI, Jay CA, Shade SB, Vizoso H, Reda H, Press S, Kelly ME, Rowbotham MC, Petersen KL. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology. 2007;68(7):515-21.
12. Russo EB. The solution to the medicinal cannabis problem. In: Schatman ME, editor. Ethical issues in chronic pain management. Boca Raton, FL: Taylor & Francis 2006. p. 165-94.
13. Miller J, Meuwsen I, ZumBrunnen T, de Vries M. A Phase I evaluation of pulmonary dronabinol administered via a pressurized metered dose inhaler in helathy volunteers. American Academy of Neurology; 2005; Miami Beach, FL; 2005.
14. Zajicek J, Fox P, Sanders H, Wright D, Vickery J, Nunn A, Thompson A; UK MS Research Group. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. Lancet. 2003;362(9395):1517-26.
15. Russo EB, Guy GW. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. Med Hypotheses. 2006;66(2):234-46.
16. Potter D. Growth and morphology of medicinal cannabis. In: Guy GW, Whittle BA, Robson P, editors. Medicinal uses of cannabis and cannabinoids. London: Pharmaceutical Press 2004. p. 17-54.
17. de Meijer E. The breeding of cannabis cultivars for pharmaceutical end uses. In: Guy GW, Whittle BA, Robson P, editors. Medicinal uses of cannabis and cannabinoids. London: Pharmaceutical Press 2004. p. 55-70.
18. Wade DT, Makela P, Robson P, House H, Bateman C. Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. Mult Scler. 2004;10(4):434-41.
19. Wade DT, Makela PM, House H, Bateman C, Robson PJ. Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in multiple sclerosis. Mult Scler. 2006;12:639-45.
20. Wade DT, Robson P, House H, Makela P, Aram J. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. Clin Rehabil. 2003;17:18-26.
21. Notcutt W, Price M, Miller R, Newport S, Phillips C, Simmonds S, Sansom C. Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 "N of 1" studies. Anaesthesia. 2004;59:440-52.
22. Berman JS, Symonds C, Birch R. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. Pain. 2004;112(3):299-306.
23. Brady CM, DasGupta R, Dalton C, Wiseman OJ, Berkley KJ, Fowler CJ. An open-label pilot study of cannabis based extracts for bladder dysfunction in advanced multiple sclerosis. Mult Scler. 2004;10:425-33.
24. Blake DR, Robson P, Ho M, Jubb RW, McCabe CS. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. Rheumatology (Oxford). 2006;45(1):50-2.
25. Rog DJ, Nurmiko T, Friede T, Young C. Randomized controlled trial of cannabis based medicine in central neuropathic pain due to multiple sclerosis. Neurology. 2005;65(6):812-9.
26. Johnson JR, Potts R. Cannabis-based medicines in the treatment of cancer pain: a randomised, double-blind, parallel group, placebo controlled, comparative study of the efficacy, safety and tolerability of Sativex and Tetranabinex in patients with cancer-related pain. British Pain Society; 2005 March 8-11; Edinburgh, Scotland; 2005.
27. Robson P, Guy GW. Clinical studies of cannabis-based medicine. In: Guy GW, Whittle BA, Robson P, editorss. Medicinal uses of cannabis and cannabinoids. London: Pharmaceutical Press 2004. p. 229-70.
28. Guy GW, Flint ME. A single centre, placebo-controlled, four period, crossover, tolerability study assessing pharmacokinetic effects, pharmacokinetic characteristics and cognitive profiles of as single dose of three formulations of cannabis based medicine extracts (CBMEs)(GWPD9901), plus a two period tolerability study comparing pharmacodynamic effects and pharmacokinetic characteristics of a single dose of a cannabis based medicine extract given via two administration routes (GWPD9901 EXT). J Cannabis Ther. 2003;3(3):35-77.
29. Calhoun SR, Galloway GP, Smith DE. Abuse potential of dronabinol (Marinol). J Psychoactive Drugs. 1998;30(2):187-96.
30. Lynch ME, Young J. Report on a case series of patients using medicinal marijuana marijuana for management of chronic pain under the Canadian Medical Marijuana Access Regulations. Symposium on the Cannabinoids; 2005; Clearwater, FL: International Cannabinoid Research Society; 2005. p. 42.
31. Janse AFC, Breekveldt-Postma NS, Erkens JA, Herings RMC. Medicinal gebruik van cannabis.: PHARMO Instituut [Institute for Drug Outcomes Research]; 2004 April 2004.

32. Gorter RW, Butorac M, Cobian EP, van der Sluis W. Medical use of cannabis in the Netherlands. Neurology. 2005;64(5):917-9.
33. McPartland JM, Russo EB. Cannabis and cannabis extracts: Greater than the sum of their parts? J Cannabis Ther. 2001;1(3-4):103-32.
34. Pertwee RG. Cannabidiol as a potential medicine. In: Mechoulam R, editor. Cannabinoids as therapeutics. Basel, Switzerland: Birkhäuser Verlag 2005. p. 47-65.
35. Hampson AJ, Grimaldi M, Axelrod J, Wink D. Cannabidiol and (-)Delta9-tetrahydrocannabinol are neuroprotective antioxidants. Proc Natl Acad Sci U S A. 1998;95(14):8268-73.
36. Nicholson AN, Turner C, Stone BM, Robson PJ. Effect of delta-9-tetrahydrocannabinol and cannabidiol on nocturnal sleep and early-morning behavior in young adults. Journal of clinical psychopharmacology. 2004;24(3):305-13.
37. Malfait AM, Gallily R, Sumariwalla PF, Malik AS, Andreakos E, Mechoulam R, et al. The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis. Proc Natl Acad Sci U S A. 2000;97(17):9561-6.
38. Carrier EJ, Auchampach JA, Hillard CJ. Inhibition of an equilibrative nucleoside transporter by cannabidiol: a mechanism of cannabinoid immunosuppression. Proc Natl Acad Sci U S A. 2006;103(20):7895-900.
39. ElSohly MA, Ross SA, Mehmedic Z, Arafat R, Yi B, Banahan BF, 3rd. Potency trends of delta9-THC and other cannabinoids in confiscated marijuana from 1980-1997. J Forensic Sci. 2000;45(1):24-30.
40. Mehmedic Z, Martin J, Foster S, ElSohly MA. Delta-9-THC and other cannabinoids content of confiscated marijuana: potency trends, 1993-2003. International Association of Cannabis as Medicine; 2005 September 9-10; Leiden, Netherlands: International Association of Cannabis as Medicine; 2005.
41. King LA, Carpentier C, Griffiths P. Cannabis potency in Europe. Addiction. 2005;100(7):884-6.
42. Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. BMJ. 2004;329(7460):253.