

Cannabis in acute migraine treatment project: Response to National Institutes of Health Critique

Ethan Russo, M.D.

I recently received
the "formal" critique
of our team's proposal
by the NIH
Review Committee.

Although I would
admit to discouragement,
and my doubts
as to how to rectify
deficiencies that may not
in fact exist,
my research partners
and I intend to
re-submit this proposal
to NIH for the
Spring cycle.

AS A NEUROLOGIST with research interests in migraine and ethnobotany, it was natural that I would be interested in the controversy concerning medical marijuana. Over the years, I have had numerous patients relate to me the efficacy of smoked Cannabis in allaying their migraine symptoms.

In 1997, with benefit of some financial support from MAPS, I submitted an application to the National Institutes of Health (NIH) for a grant to study the use of smoked marijuana in the treatment of migraine. This application process has been mandated by the Federal government as necessary for the approval of any therapeutic clinical Cannabis studies. To date, the Short-term Effects of Cannabinoids in HIV Patients study of Dr. Donald Abrams and his team remains the only other application of this type to NIH. That study was recently approved, while the Cannabis in Acute Migraine Treatment Project was rejected.

I recently received the "formal" critique of our team's proposal by the NIH Review Committee. After examining it, I feel that virtually all points of that criticism can be adequately addressed. My team plans, with additional support from MAPS, to submit a revised grant application to NIH for its June 1, 1998 grant cycle. The following is a review of the points of the critique along with my initial inclinations as to how they might be addressed.

Study design

It is always a daunting task to defend one's work, particularly when the effort involved was as intense as for this one, and with so much at stake. The entire protocol was written so as to incorporate systematically the approaches and procedures that were outlined by Dr. Robert Temple (Associate Director for Medical Policy, FDA Center for Drug Evaluation and Research) at the NIH *Workshop on the Medical Utility of Marijuana* in February 1997.

The study is designed to examine migraine sufferers who have either failed to respond to or tolerate subcutaneous sumatriptan injection, the current *ne plus ultra* in acute headache manage-

ment. Patients selected for the study would then be initially treated with one of the following: smoked Cannabis with 4% THC content (the highest potency provided by NIDA), oral dronabinol 10 mg. (synthetic THC), placebo capsules, or an injected meperidine/hydroxyzine mixture (a common emergency room fallback approach).

Criticisms

The criticisms leveled at the protocol by the NIH are multiple, and occasionally contradictory. One reviewer felt the protocol too ambitious, another not sufficiently rigorous. Finding middle ground acceptable to all was not the intent of this study. Rather, the guidelines from Dr. Temple did not call for either a preliminary "open label" study of therapeutic marijuana use or definitive "Phase 3" studies. They did call for comparison of smoked marijuana to oral dronabinol, as well as a control. We arrived at the figure of 30 study subjects through a sophisticated statistical analysis that indicated that this number would be sufficient to demonstrate clinically relevant differences between the four study drugs.

Precedent of anecdotal accounts

Another criticism revolved around the inclusion in the protocol of multiple "anecdotal" accounts as evidence of the efficacy of Cannabis in headache treatment. It bears repeating that this agent has been used therapeutically and continuously for 4000 years or more, and was pre-eminent, or nearly so in migraine treatment for eight decades among American and European physicians (Grinspoon and Bakalar, 1997; Mikuriya, 1973; Russo, 1998). We might still be using it were it not for the government's prohibition of Cannabis on false pretenses in 1937. During that previous era, there were no controlled studies, nor were any needed for this agent. Doctors as prominent as Queen Victoria's personal physician, J. Russell Reynolds (Russell, 1890), Sir William Gowers (Gowers, 1888), and Sir William Osler, the father of modern medicine (Osler and McRae, 1915), preferred Cannabis for migraine patients because it worked effectively and safely. In more modern times, there have been no controlled studies of therapeutic use of Cannabis solely because they have been politically prohibited. This is precisely why studies such as ours should be allowed to proceed.

Ethan Russo, M.D.

Department of Neurosciences Western Montana Clinic
515 West Front Street, Missoula, MT 59807-7609
E-mail: ptm5739@montana.com

The proposal contained many scientific citations as to proposed mechanisms for Cannabis' analgesic effects and modulation of serotonergic mechanisms, but apparently these were not sufficiently compelling to the reviewers.

One critique suggested that marijuana might work on headaches due to its soporific effect, promotion of relaxation, or because of its anti-nausea properties. I find this unsupported by the facts. Most people who use Cannabis therapeutically do not fall asleep; rather, many use only enough to reduce symptoms so that they may return to their prior activities. Several of my patients use it in this manner. It is well known that relaxation techniques may modestly reduce migraine pain, but transiently, and incompletely. As to nausea, the 5-HT₃ antagonists ondansetron and granisetron are powerful agents in its control, but have no effect on migraine pain (Peroutka, 1990). These criticisms betray a basic lack of familiarity with migraine pathogenesis.

Elements overlooked by reviewers

The critique contained many instances calling for elements that the protocol in fact already contained: use of visual analogue scales for symptom quantification, clear exclusions for pregnancy, drug abuse, etc. Perhaps the protocol was not carefully read, or the appendices that contained some of this material were not circulated. In any event, it is difficult to be criticized for omissions that did not, in fact, occur. A valid request would be tighter controls for women in childbearing years to ensure that pregnancy risks are minimized (i.e., contraception, spousal vasectomy, etc.).

One reviewer suggested that anyone who ever smoked marijuana be excluded from participation in the study. I have never seen this as a criterion for previous studies, and it seems totally unnecessary. We planned a mixture of experienced and Cannabis-naïve subjects to more closely test "real-world" clinical issues.

Objections to confidentiality procedure

Objections were raised as to confidentiality procedures. We outlined every reasonable precaution for locked records, limited access, etc. I personally felt these were adequate. It is true to say they are not foolproof, but short of draconian police-state tactics, they would be the best that could be provided. The study would receive the usual intense monitoring by NIH personnel, and additionally the local Investigational Review Board, which happens to be located one floor below that where the study would be performed.

A stinging personal criticism was leveled at me, questioning my ability to carry out the study due to a perceived lack of experience in "human trials." This seems to be a variation of the old chestnut that one has to have a job to get a job. In fact, I have been carrying out "human trials" for twenty years: it is called the practice of medicine, where every prescription is an experiment with its failures, side effects and pitfalls. To say that this study contains elements beyond my expertise is unfounded, unsubstantiated, and inaccurate. As a faculty member of two universities at an undergraduate, graduate, and professional level, and with personal recommendations from two distinguished chairmen of university departments of pharmacy for this study, I had hoped not to be

The critique
contained many instances
calling for elements that
the protocol in fact
already contained.

disparaged in this manner.

One critic upbraided me for inclusion of an anecdote that suggested Cannabis was no better than standard pharmaceutical for one patient. Is that surprising? Nothing works for everyone. That is called clinical variation, and inclusion of such information is required in a critical review of the subject in order for it to retain the kind of scientific objectivity that I am not applying in this document written for readers of the *MAPS Bulletin*.

Inclusion criteria questioned

One reviewer questioned selection criteria for patients. How would we know that they really had migraine, and not some more dire brain disease? It was even suggested that patients might require MRI scans before entry (each scan costs \$1,200). Actually, established criteria exist, provided by the IHS (International Headache Society) and were incorporated in our questionnaires (*Headache*, 1988). Each subject can be clinically examined prior to entry, and this has been sufficient for virtually all previous clinical headache protocols. Imaging studies for migraine patients are not always necessary.

Another questioned whether 30 study subjects could be recruited. I believe that I could find them solely from my patient clientele! Many headache patients are seeking better treatments and are very open to "new ideas," for better or worse, even ones that are currently illegal. Let us crunch a few numbers. Migraine afflicts 14% of females and 8% of males (Linet et al., 1989), for a composite of 11%. One fourth of those are severe or 2.75% (Stewart et al., 1992). About 70% of people respond to subcutaneous administration of sumatriptan (Mathew, 1997). About 30% fail, or an even greater number have sufficient side effects that they prefer not to use it. Multiplying that by an estimated adult local population of 60,000, that would be: $60,000 \times 0.0275 \times 0.30 = 495$ potential subjects. I feel that this is, in fact, a very conservative figure. Obviously, not all would wish to be part of a study in which they would smoke marijuana, but this is a university town, and many would not object; some may be doing so now. I am confident we can recruit sufficient subjects if only allowed to do so.

Question of placebo

Another issue concerned use of placebo. One reviewer mistakenly thought that certain subjects would be stuck with placebo or other treatment for their entire course of ten treatments. I believe they failed to understand the randomization scheme as it was presented. Here I was caught in a bind. I would prefer not to use placebo: it is inhumane. It was my intention to eschew "dummy dope" that would require subjects to smoke an inert material with the attendant risks, but no benefits. It has previously been shown that even marijuana-naïve subjects can detect when they are receiving placebo as compared to active Cannabis. The placebo was included in the protocol because it was considered essential by the NIH Committee on the Medical Utility of Marijuana. Moreover, no subject in our study would receive placebo more than once.

Another questioned our use of intramuscular meperidine. Once more, I included it because, for better or worse, it seems to be

the drug of choice in treating migraine in emergency rooms across the United States. I personally never use it, and do not recommend it. However, it does provide a recognized point of comparison to a potential alternative treatment such as smoked Cannabis. Alternatives such as morphine increase nausea, while butorphanol (Stadol) has been associated with myriad dangers (Fisher and Glass, 1997).

One reviewer felt a two hour period of observation was insufficient, and suggested patients be kept overnight. This requirement alone would serve to more than triple the cost of the study (not that we the taxpayers should be concerned). Since migraine is primarily an outpatient disease, this stipulation represents extreme overkill, and would impair subject recruitment, perhaps prohibitively. One of the main aims of this study is to ascertain whether people can function better after migraine treatment with Cannabis. They can not do that wasting time and money in the hospital. What about that confidentiality anyway? In this small town, your nurse might be a friend of your cousin, and tell him you were in the hospital.

We plan to treat patients up to ten times in a six month period. Another fear expressed was that patients might not have 10 headaches during business hours in the 6-month period of time that each patient will be enrolled in the study. I feel this is unlikely. Most headaches are generated in AM hours, and our selected study subjects will have sufficient frequency of attacks to ensure that many will reach this goal. Our statistical analysis did not require that all study subjects meet the ten-treatment goal.

Rigor of clinical measures

A difficult issue revolved around whether our clinical measures would be adequate to answer the questions asked. In fact they are more rigorous than those employed in the studies that established the efficacy of sumatriptan in migraine treatment (Cady et al., 1991). Again, I am confident that useful results will be obtained if the study is ultimately allowed to proceed.

One reviewer wondered how non-responders to sumatriptan might be characterized, and why they might be better treated with Cannabis. The initial issue has been studied (Visser et al., 1996). The answer is that sumatriptan non-responders may be obese, or take the medicine too early. Beyond that, the study found no features distinguishing responders from non-responders. I would add one other observation from my clinical experience: people with chronic daily headache (a difficult subset of migraine) respond poorly to subcutaneously sumatriptan. Because this proposal focuses on migraineurs with episodic attacks, CDH patients would not be accepted for inclusion.

Inadequacy of review process

Finally, I would level criticism of my own at The National Institutes of Health. Not unexpectedly, none of the reviewers of my protocol were on the panel of the *Workshop on the Medical Utility of Marijuana* that proposed criteria for clinical Cannabis studies. What is surprising, and unacceptable is that this group was apparently not informed of NIH's own expressed suggestions for such studies

...of 29 members

of the review team...

only eight were neurologists,

and none appear to be

headache specialists.

into the medical use of marijuana. Unfortunately, government agencies have a longstanding tradition of ignoring their own commissions' recommendations. Additionally, of 29 members of the review team for the Division of Neurological Diseases and Stroke, only eight were neurologists, and none appear to be headache specialists. I do know this much: none are members of the American Association for the Study of Headache, the premier research organization devoted to the study of migraine. I am, and would have hoped for examination by a jury of my peers.

As if that were not enough, this proposal was initially assigned to the AIDS Division of the National Institute on Drug Abuse, although it pertained to neither HIV nor "abuse," and was not re-assigned until I pointed out the inherent contradiction. This indicates that the NIH bureaucracy has been operating as a "split-brain preparation." That is, the right hemisphere has no idea what the left hemisphere is doing.

In summary, I am extremely disappointed with the repudiation of this proposal. It has considerably greater merit and validity than the criticisms would allow. Although I would admit to discouragement, and my doubts as to how to rectify deficiencies that may not in fact exist, my research partners and I intend to re-submit this proposal to NIH for the spring cycle.

Contributions of interested parties to MAPS, earmarked for this purpose, will be most appreciated. •

References

- Cady, R.K., Wendt, J.K., Krichner, J.R., et al., "Treatment of Acute Migraine with Subcutaneous Sumatriptan," *JAMA* 265:2831-2835, 1991.
- Fisher, M.A., and Glass, S., "Butorphanol (Stadol): A Study in Problems of Current Drug Information and Control," *Neurology* 48:1156-1160, 1997.
- Gowers, W.R., *A Manual of Diseases of the Nervous System*, Blakiston, Philadelphia, 1888.
- Grinspoon, L. and Bakalar, J.B., *Marijuana: The Forbidden Medicine*, Yale Univ., New Haven, 1993.
- Headache Classification Committee of the International Headache Society, "Classification and Diagnostic Criteria for Headache Disorders, Cranial Neuralgias, and Facial Pain," *Cephalalgia* 8 (suppl. 7):1-96, 1988.
- Linnet, M.S., Stewart, W.F., Celentano, D.D., "An Epidemiological Study of Headache Among Adolescents and Young Adults," *JAMA* 261:2211-2216, 1989.
- Mathew, N.T., "Serotonin 1D (5-HT 1D) Agonists and Other Agents in Acute Migraine," *Neurol. Clinics* 15:61-83, 1997.
- Mikuriya, T.H. (ed.), *Marijuana: Medical Papers 1839-1972*, Medi-Comp Press, Oakland, CA, 1973.
- Osler, W. and McCrae, T., *The Principles and Practice of Medicine*, Appleton and Co., New York and London, 1915.
- Peroutka, S.J., "Developments in 5-Hydroxytryptamine Receptor Pharmacology in Migraine," *Neurol. Clinics* 8:829-839, 1990.
- Russell, J.R., "Therapeutic Uses and Toxic Effects of Cannabis Indica," *Lancet* 1:637-638, 1890.
- Russo, E.B., "Cannabis for Migraine Treatment: The Once and Future Prescription: An Historical and Scientific Review," accepted for publication in *Pain*, 1998.
- Stewart, W.F., Lipton, R.B., Celantano, D.D., "Prevalence of Migraine Headache in the United States," *JAMA* 267:64-69, 1992.
- Visser, W.H., de Vreind, R.H.M., Jaspers, N.H.W.M., and Ferrari, M.D., "Sumatriptan-Nonresponders: A Survey in 366 Migraine Patients," *Headache* 36:471-475, 1996.