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LETTER TO THE EDITORS

**Mahmoud A. ElSohly · Stephen R. Wachtel · Harriet Wit**

# Cannabis versus THC: response to Russo and McPartland

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This communication is in response to the Letter to the Editor authored by E. Russo and J. McPartland, in which they criticized the work previously reported by our group (Wachtel et al. 2002). Their letter contains several statements with unwarranted criticisms. For the sake of brevity, this response will comment on the major issues raised by Russo and McPartland relative to our original publication.

The first issue has to do with the potency of the marijuana cigarettes used in the study. Russo and McPartland refer to the NIDA marijuana cigarettes as being "...a crude-low-grade product (2–4% THC) containing leaves, stems and seeds, often three or more years old after processing, with a stale odor lacking in terpenoids", and state that "customary clinical cannabis employed by patients is composed solely of unseeded flowering tops with a potency of up to 20% THC". First of all, NIDA has made available for research different grades of marijuana samples including placebo (extracted cannabis with no THC), low potency (1–1.8% THC), medium potency (up to 2.5% THC), and relatively high potency (approximately 4% THC). More recently, NIDA has made available hand-rolled cigarettes of approximately 8% THC. To carry out a clinical trial with subjects who had little or no exposure to marijuana, 4% THC cigarettes would be of much higher potency than most subjects could tolerate. Even if samples containing 20% THC were available, it would be irresponsible to administer these to subjects in a research study such as the one we conducted. Second, NIDA cigarettes have only occasional seeds, which result from the large-scale manufacturing process. The number of seeds and small stem particles that pass through the process into the final product is small, but such particles are occasionally found in the cigarettes. This does nothing to lessen the usefulness of the cigarettes. Current procedures at the University of Mississippi involve reprocessing of the starting material to further minimize any seeds or stem particles in the final product. Unprocessed loose material that contains seeds and stems is occasionally used by investigators who prefer to process the material themselves, but it is certainly not the norm in research with marijuana. Moreover, regardless of the potency of the cigarettes used in our study, these cigarettes were compared with placebo cigarettes spiked with an equivalent amount of THC. Thus, the comparison was based on THC content, and the actual potency of the marijuana cigarettes is immaterial. We used a potency that could be tolerated by the subjects.

Second, the authors contend that the concentration of CBD in the plant material used was not enough. In fact, most street or "therapeutic" cannabis contains mainly THC with small amounts of CBD and other cannabinoids. Analysis of confiscated samples seized in the United States between 1980 and 1997 shows an average THC content of regular marijuana ranging from 1.24% in 1980 to 4.15% in 1997, with CBD averaging from 0.01% to 0.61% for the same years, and other cannabinoids ranging from 0.13% to 0.38% (ElSohly et al. 2000). As for sensimilla samples over the same time frame, the THC content averaged from 5.77% in 1993 to 11.53% in 1997 with CBD ranging from 0.25% in 1990 to 1.2% in 1994 (ElSohly et al. 2000). Furthermore, examination of the specimens seized in the State of California in the year 2001 (459 samples) showed a mean THC content of 6.05% with a corresponding mean of CBD of 0.53% [NIDA potency monitoring data, on file at the University of Mississippi (unpublished)]. Therefore, the evidence suggests that the concentration of CBD in street or "therapeutic" cannabis is usually less than 10% that of THC. The suggestion by the authors that "clinical grade

M. A. ElSohly
University of Mississippi, University,
Mississippi, USA

S. R. Wachtel
Northwestern University,
Evanston, Illinois, USA

H. Wit (✉)
Department of Psychiatry,
University of Chicago,
5841 S. Maryland Ave., MC3077, Chicago, IL 60637, USA
e-mail: hdew@uchicago.edu

cannabis" should have about equal amounts of CBD and THC does not reflect current (unofficial) "clinical" practice. There is currently no agreed-upon formula for "clinical grade" cannabis, and there is little empirical basis for the suggestion that CBD or other constituents ameliorate the adverse effects of THC. Moreover, one could question the need for a product with high THC content if it must be countered by other components such as CBD.

Third, the authors point out the existence of other components of the cannabis plant including terpenes and flavonoids. We are well aware of the fact that cannabis and the crude drug marijuana contain over 400 chemicals belonging to 18 different classes (Turner et al. 1980; Ross and ElSohly 1995; ElSohly 2000). Indeed, this was the point of conducting the published study, to determine whether other components (other than THC) in the cannabis plant contribute significantly to the subjective effects of the drug.

Fourth, the comment relative to Marinol and its effects compared to those of smoked cannabis are not relevant to our report. We agree with the authors that the smoked herbal cannabis (marijuana) is not just a vehicle for THC delivery. We also recognize that various cannabis preparations have medicinal properties and support the development of useful medications derived from cannabis. However, there is a consensus among the scientific community, echoed in the Institute of Medicine Report on medical marijuana (Joy et al. 1999), that smoked cannabis is not a viable dosage form for future long-term therapeutic use. In seeking to utilize the beneficial components of cannabis, scientists must strive for harmless delivery systems.

Finally, with regard to the information obtained informally from interviews with patients who claim that marijuana is more effective than pharmaceutical THC, we wish to draw attention to the powerful effect of expectancies in influencing responses to drugs (Peck and Coleman 1991; Kirk et al. 1998; Quitkin 1999). Many years of experience in medicine have shown that patients' beliefs and expectancies about a drug exert a strong influence on their responses to the drug in a number of organ systems. The only way to discover the purely pharmacological effects of drugs or herbal products is by conducting rigorous placebo-controlled, double-blind studies such as the one we conducted.

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