Marijuana to Prevent Nausea and Vomiting in Cancer Patients: A Survey of Clinical Oncologists

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ABSTRACT: Marijuana, if rescheduled by the Drug Enforcement Agency, would be the only Food and Drug Administration (FDA)-approved drug to be administered by smoking. American physicians need timely, factual information about probable usage patterns and potential adverse effects of medical marijuana, and a factual complete review of the literature on the subject. We mailed a survey to 1,500 American clinical oncologists. Of particular interest was whether and how often in the past 24 months these physicians recommended smoked marijuana, synthetic tetrahydrocannabinol, or 5-HT$_3$ (serotonin) antagonists (ondansetron [Zofran], granisetron [Kytril]) for their patients. We also inquired whether and how often the oncologists would prescribe marijuana in the form of cigarettes, were it to be FDA-approved. Completed surveys were received from 1,122 (75%) of the oncologists. The percentages of oncologists who prescribed or recommended selected antiemetics more than five times between 1992 and 1994 were 98% for 5-HT$_3$ antagonists, 6% for dronabinol (Marinol), and 1% for smoked marijuana. We also found that 332 (30%) of the oncologist-respondents to this nationwide survey supported rescheduling of marijuana for medical purposes; however, two thirds (67%) of the 332 respondents who were in favor of rescheduling estimated that they would write less than one prescription per month for marijuana cigarettes. A comprehensive literature review failed to provide persuasive evidence to recommend marijuana as a needed antiemetic medicine.

IN THE UNITED STATES, only a single study of smoked marijuana as an antiemetic has been published in a medical journal, and in that study, 20% of subjects withdrew from the study because of adverse effects.' In most national cancer centers, marijuana has never been rated highly as a drug of choice in managing nausea and vomiting associated with cytotoxic chemotherapy. The National Cancer Institute does not recommend rnarijuana, nor does the American Cancer Society. Purified synthetic delta-9-tetrahydrocannabinol (THC) known as dronabinol (Marinol) , a widely available medicine available to physicians on prescription, has the same antiemetic effects as smoked marijuana but does not have marijuana's irritant and toxic effects on the respiratory epirhelium. Nevertheless, there is increasing in tense political pressure and public pressure to force the Drug Enforcement Agency (DEA) to reschedule marijuana as a medicinal drug. In 1995, a bill approving marijuana as medicine (AB 1529) was approved by both houses of the California Stare Legislature. Legislation for federal approval of marijuana as medicine has also been submitted to the US House of Representatives by US Congressman Barney Frank.

When marijuana cigarettes are used as antiemetic medicine, the hot irritating smoke is sucked directly and deeply into the respiratory tract. Marijuana can be ingested orally (eg, in the form of brownies), but it requires a larger dose and there is a longer latent period before it becomes effective. To date, there are 14 published studies in English, with 600 subjects, comparing cannabinoids with either placebo or other antiemetic drugs.'-" Marijuana compared favorably with several weaker antiemetics against mild to moderate emetogenic anticancer drugs. Several in depth analyses of these studies have been published.[15,16] In one of the few recent studies on the subject, Vinciguerra et al' found that smoked mari-

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TABLE. Antiemetic Agents Prescribed by Clinical Oncologists (N =1,122) Between 1992 and 1994

No. of Times Prescribed	*No. of Respondents (%)*
5-HT$_3$ Serotonin Receptor Antagonists	
Ondansetron (Zofran) or	
Granisetron (Kytril)	
Never	16 (1.6)
1-10	48 (5)
11-25	117 (11)
26-50	144 (14)
51-100	166 (16)
101-250	213 (21)
25 1-300	156 (15)
501-1,000	95 (9)
>1,000	66 (7)
Dronabinol (Marinol)	
Never	558 (51)
1-2	241 (22)
3-10	228 (21)
11-25	40 (4)
26-50	11 (1)
>50	11 (1)
Marijuana	
Never	945 (89)
1-2	72 (7)
3-10	36 (3)
>10	11 (1)

juana did perform better than dronabinol to reduce nausea and vomiting due to cancer chemotherapy; however, smokers were required to inhale deeply and to hold the inhaled smoke for a full 10 seconds before exhalation. For beneficial effect, at least four marijuana cigarettes had to be smoked to the butt end for each day of chemotherapy. More than 20% of subjects dropped out of the smoking group before the end of the study, and another 22% of the marijuana group reported no beneficial effects from smoking.'

Doblin and Kleiman[17,18] surveyed 2,430 oncologists in 1990, Completed surveys were returned by 37% of those surveyed. Those who responded but did not answer critical questions were sometimes simply ignored in the results. "Of those who expressed an opinion on the matter, 54% of oncologists who responded, favored rescheduling marijuana as medicine."" The authors reported that substantial numbers of patients are not getting the medical care that their oncologists would prefer to provide to them. According to Doblin and Kleiman, only federal restrictions on the medical use of marijuana prohibits marijuana's widespread use by clinical oncologists. Several journalists and commentators subsequently criticized the Food and Drug Administration (FDA) as a heartless prohibitionist federal bureaucracy that for purely political reasons was denying physicians and their suffering cancer patients compassionate use of legal, smoked marijuana. Few of those journalists and commentators noted that the Doblin-Kleiman study was sponsored by the Alliance for Cannabis Therapeutics (ACT), a pro-marijuana advocacy group. Moreover, few reporters were told that Mr. Doblin, the senior author, is the president and founder of the Multidisciplinary Association for Psychedelic Studies (MAPS), whose main purpose according to their newsletter is to help researchers secure federal approval and funding of studies of psychedelic drugs.

Schwartz and Beveridge[19] surveyed 180 members of the American Society of Clinical Oncology (ASCO). Although they surveyed a much smaller sample than Doblin and Kleiman, their response rate of completed surveys was 80% vs 3'7% for the Doblin-Kleiman study. Schwartz and Beveridge[19] found that natural or synthetic cannabinoids, ie, marijuana leaf or dronabinol, ranked ninth as an antiemetic medicine of choice for mild to moderately emetogenic cancer chemotherapy. Cannabinoids, including marijuana, represented only 2% of the antiemetic drugs recommended or prescribed by oncologists. The Schwartz and Beveridge study was criticized"" because of the small sample size and the fact that it was supported, in part, by a grant of $1,000 from Glaxo Inc, manufacturer of Zofran (ondansetron) .

To answer those criticisms and to obtain current data on antiemetic preferences, we conducted a second, much larger survey of American clinical oncologists without external funding. The results are described in this paper.

MATERIALS AND METHODS

In mid-1994, we mailed to 1,500 oncologists in clinical practice a survey concerning the use of 5-HT$_3$ antagonists, dronabinol, and smoked marijuana as antiemetic drugs. Survey recipients' names were chosen from the 1993 ASCO directory, with a focus on individuals having a background in internal medicine and subspecializing in adult oncology. We excluded radiation oncologists and surgical oncologists. Then, surveys were mailed to every third consecutive ASCO member who met the criteria. The short survey asked the oncologists for their age, the number of years spent in clinical oncology practice, the number of prescriptions per average month for dronabinol (Marinol) , marijuana cigarettes, and ondansetron (Zofran) or granisetron

(Kytril). The oncologists were also asked whether they believed the DEA should reschedule marijuana to allow it to be prescribed as medicinal cigarettes and if so, to estimate the number of such prescriptions that they would write during an average year. Finally, we asked whether the respondents favored legalization of marijuana as a recreational drug. A project assistant assigned a unique number to each questionnaire and to the ASCO directory listing so that subsequent mailings could be sent out to increase the response rate. Only the project assistant was privy to this code. Two dollar bills were included in the second mailing as a small recompense for the respondent's time. Separate analyses of those who received payment and those who did not were almost identical, question by question, and results are therefore combined. A self-addressed, stamped envelope was included in each mailing. The survey instrument was reviewed by several experts in clinical oncology and a biostatistician. It was then pilot tested for clarity, brevity, and bias, by six clinical oncologists in northern Virginia. The survey was personally funded by one of us (R.H.S.), without external grants or payments. The statistical package used for analysis of this survey was Statistical Analysis Systems (SAS, 6.10) for Windows.

RESULTS

Of the 1,500 surveys mailed, 1,122 completed surveys were returned for a response rate of 75%. The mean age of respondents was 47 years and the mean number of years in clinical oncology practice was 15. The Table summarizes respondents' prescribing preferences and the frequency of prescribing.

Frequency of Use of 5-HT$_3$ Serotonin Receptor Antagonists

Between mid-1992 and 1994, 98% of respondents had prescribed Zofran or Kytril to some cancer patients. The median number of annual prescriptions was 84. One of every five oncologists prescribed these medicines to more than 250 patients per year. Only 5% of those who prescribed these 5-HT$_3$ serotonin receptor antagonists did so 10 times or less.

Frequency of Use of Dronabinol

Between 1992 and 1994, 614 (51%) of the respondents had prescribed dronabinol (Marinol). Of these, 22% used it only once or twice and 469 (23%) prescribed dronabinol 3 to 10 times.

Frequency of Use of Marijuana

Only 177 (12%) of respondents had ever recommended marijuana cigarettes. Of this number, 72 had recommended it once or twice. Only 11 respondents (1%) recommended marijuana more frequently than five times per year.

Support Toward Rescheduling Marijuana for Medical Use

Three hundred five respondents (28%) favored rescheduling of marijuana as prescription medicine, 536 (48%) were opposed to rescheduling, and 272 (24%) were uncertain. Should the DEA reschedule marijuana to class II, 340 (30%) of the 1,122 respondents noted that they might prescribe marijuana for one or more of their oncology patients. Only 54 (9%) said they would prescribe marijuana cigarettes more than 10 tirnes annually. Regarding the alleged superiority of marijuana cigarettes over dronabinol, 141 (13%) respondents believed that marijuana cigarettes had better antiemetic efficacy than the purified synthetic drug taken by mouth in the form of a capsule. Oncologists often commented that they would use marijuana cigarettes infrequently and only for compassionate reasons on patient request. Several oncologists added a comment that they would restrict its use to young adults because they had fewer adverse effects from the drug and because they were likely to have used the drug previously and had favorable impressions of it.

Support for Legalization of Marijuana for Recreational Uses

Of the 1,122 respondents, 761 (70%) opposed legalization of marijuana, 176 (15%) were undecided, and another 176 (15%) favored legalization. Of the 340 oncologists who favored marijuana rescheduling for medical reasons, 176 (50%) were also in favor of legalizing it for recreational purposes.

DISCUSSION

Several commentaries and editorials in prestigious British and American medical journals have taken the position that marijuana cigarettes can help alleviate suffering from postchemotherapy nausea and pernicious vomiting.[21-25] In contradistinction, all 10 state-of-the-art reviews of antiemetic drugs for cancer patients published in the past 5 years either fail to include marijuana at all or assign a minor role for it.[26-35] Not a single recent review on the subject by an expert in anti-

emetic drugs for oncology patients has given marijuana high marks. In the past 6 years, marijuana has not been studied as a palliative agent against the highly emetogenic anticancer drugs. Marijuana has not been vigorously compared for efficacy against state-of-the-art antiemetic agents such as 5-HT_3 antagonists (ondansetron or granisetron), high-dose dexamethasone, or combination drugs. Rarely in medicine has there been such a dichotomy between what experts write in review articles, based on scientific studies, and what some journal editors allow to be published as commentary or opinion. Widespread publicity given to a few isolated studies[1,17,18] and commentaries and editorials in highly respected medical journals"" have misled many physicians about the true effectiveness of marijuana as medicine. Anecdotal vignettes, no matter how poignant, are not scientific data, although they appear to carry more weight with a large segment of the public and with some journalists. The issue of medical marijuana has already been decided in the negative by experts on the basis of a careful review of scientific data.[36] Because of a 1994 US Appellate Court decision, explicit stringent guidelines are available that govern decisions concerning rescheduling. Lawsuits originally filed in 1972 by the National Organization for Reform of Marijuana Laws (NORML), in concert with several other organizations, had not been successful under the Appellate Court decision.[36] The court ruled that marijuana, in its natural form as smoked cured dried cannabis leaf particles, had not been proven to meet these standards. A comprehensive expert review of marijuana as medicine was undertaken at the request of the US Assistant Secretary of Health, Philip Lee, MD.[37] Opinions were solicited from recognized experts at the National Institute on Allergy and Infectious Diseases, the National Cancer Institute, the National Eye Institute, and the National Institute for Neurological Disorders and Stroke. These experts concluded:

> There is no evidence to suggest that smoked marijuana might be superior to currently available therapies for glaucoma, weight loss associated with AIDS, nausea and vomiting associated with cancer chemotherapy, muscle spasticity associated with multiple sclerosis, or intractable pain.

CONCLUSION

Only 1% of the 1,122 clinical oncologists who responded to our survey currently recommend marijuana to more than five patients per year. Seventy percent of these oncologists do not favor DEA rescheduling of marijuana. If marijuana were to be rescheduled, most clinical oncologists would prescribe it infrequently. Two thirds (67%) of the 332 respondents who were in favor of rescheduling estimate that they would write less than one prescription per month for marijuana cigarettes. In an exhaustive computer-generated literature search on the subject of marijuana as an entiemetic, including cross-checking all references and reviews on the subject, only one comparative study of marijuana as an antiemetic for oncology patients could be found in a peer reviewed journal,* In several other studies of THC compared with older antiemetics, patients who did not experience a "high" often had a poor response to THC in any form.[2,3,6,8,38] Seipp and nursing colleagues[38] clearly described the vexing problems encountered in conducting marijuana studies and preventing its euphoric properties from conducting a fair evaluation of its antiemetic efficacy.

Adverse effects from marijuana administration are common, perhaps more so than from many other antiemetic agents, In multiple studies involving 329 patients, THC-related toxicities included somnolence (31%) , ataxia (8%), dizziness (6%), and orthostatic hypotension (3.6%) .[16] The *Medical Letter*[39] cautions: "Some patients complain of dizziness, inability to concentrate, or disorientation. It (THC) causes decrements in cognitive performance and short-term memory and a significant decrease in coordination, especially for complex tasks." There is no scientific evidence that smoked marijuana has fewer adverse effects than orally administered dronabinol, although marijuana advocates claim that it is easier for individuals to find their optimal dose by smoking the crude drug as a cigarette.

Multiple state-of-the-art antiemetics with proven effectiveness against highly emetogenic cytotoxic chemotherapy agents are widely available to physicians. Few oncology centers regularly prescribe marijuana in any form for this purpose. There are no studies from the United States or even from counties such as the Netherlands, where smoked cannabis is freely available without legal consequences or DEA restrictions, which prove the effectiveness of medical marijuana against highly emetogenic cancer drugs such as cisplatin. A careful review of every study published in a reputable medical journal[1-16] and

reviews of antiemetic drugs for cancer patients[26-35] should lead most physicians to conclude that, pending publication of persuasive well-conducted clinical studies, marijuana leaf should not be permitted to become the first US Food and Drug Administration-approved medicine in the form of a cigarette.

ADDENDUM

In 1996, by popular referendum, laws permitting the use of marijuana cigarettes as medicine passed in the states of California and Arizona. As we understand the new law in California, individuals, without age limitation, need only to assert that a doctor has prescribed marijuana for a medical condition for which there is some evidence (not necessarily published studies in medical journals) that marijuana is of benefit. Vague wording permits a wide latitude regarding what complaints might be benefitted by smoking marijuana. The law appears to have a high potential for a slippery slope, leading to widespread misuse. There is as yet no method for the state to monitor misuse. There is no requirement under the California law for a medical examination, no documentation of medical necessity, and not even the need for a bona fide prescription. There is no requirement for follow-up visits to a physician, no need to determine and document the continued need for long-term use, and no regulation to monitor adverse effects from the drug. There is also no requirement to warn individuals that the drug may cause drowsiness, unsteadiness, or incoordination. It is unclear if the state, doctor, or pharmacist must still accept legal responsibility in case of harm.

If our southern states should pass medical marijuana laws, we strongly suggest that such requirements be included. Because of the understandable desire to help those with serious cancer, glaucoma, or AIDS, California voters may unwittingly have given all Americans a gift of a modern Trojan horse.

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