



Steven M. Dubinett, M.D.
Division Chief

Joseph P. Lynch, III, M.D.
Associate Chief

Tisha S. Wang, M.D.
Associate Chief

Stephanie Hope
Division Administrator

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Rick Doblin, PhD
Founder and President
Multidisciplinary Association for Psychedelic Studies
3141 Stevens Creek Blvd. #40563
San Jose, CA 9511

Re: FDA Response Letter

Dear Dr. Doblin:

I am in receipt of the letter from the FDA addressed to you in response to your application concerning the proposed study to assess the safety and efficacy of inhaled botanical cannabis in veterans for treatment of PTSD. I am hereby responding to your request for my assessment of the aforesaid FDA response letter in consideration of the fact that my work is cited in that letter.

The FDA letter correctly points out that the smoke contents of marijuana include the same toxic and pro-carcinogenic components that are found in tobacco smoke. This raises a possible concern that the pre-rolled cigarettes you propose to use as a cannabis delivery method in your study might harm the lung by analogy with the well-proven harmful effects of tobacco cigarettes on lung health, particularly with regard to the increased risks related to chronic bronchitis, COPD and lung cancer. While it is true that symptoms of chronic bronchitis, including cough, increased sputum production and wheezing, have been shown to be associated with smoking marijuana, these symptoms are proxy measures and clinical data support that they are not always indicative of the clinical endpoints of COPD and lung cancer.

The weight of evidence from well-conducted observational cohort studies have failed to show an association of cannabis smoking with COPD as defined by the pulmonary physiologic abnormality that characterizes COPD, namely a ratio of the forced expired volume in 1 second to the forced vital capacity (FEV₁/FVC) (1,2). Regarding the few studies in which the FEV₁/FVC was found to be significantly reduced, the latter reduction has been attributed to the finding that marijuana smoking is



Division of Pulmonary and Critical Care Medicine, Clinical Immunology & Allergy

David Geffen School of Medicine at University of California, Los Angeles

10833 Le Conte Avenue, Room 37-131 CHS, Box 951690, Los Angeles, California 90095-1690

Phone: (310) 825-5316, Fax: (310) 206-8622

also associated with an increase in FVC (possibly related to the unique manner in which marijuana is smoked, including larger inhalations and longer breath-holding times compared with the usual technique of smoking tobacco, analogous to the breathing profile of competitive swimmers, among whom larger lung volumes have been found), thereby lowering the FEV₁/FVC ratio at the same time that the FEV₁ is well-preserved.

Regarding an association of marijuana with emphysema, CT scans provide the most accurate evidence of the presence of emphysema. Only four studies have reported thoracic CT findings in marijuana smokers. The first of these was a large population-based study in which thoracic CT scans were performed in 75 marijuana-only smokers (MS), 92 tobacco-only smokers (TS), 91 smokers of both marijuana and tobacco (MTS) and 81 nonsmokers failed to find evidence of emphysema in the MS and NS, while emphysema was found in 18.5% of the TS and 16.5% of the MTS, implying that when emphysema does occur in dual smokers of marijuana and tobacco, it is attributable to smoked tobacco and not to marijuana (3). Two additional studies of CT findings in marijuana smokers have been published, both of which were derived from the Subpopulations and intermediate outcome measures in COPD study (SPIROMICS) cohort. These two studies, examined CT findings only in MTS and TS with COPD, with the interesting findings that current and former marijuana smokers within this sample had a significantly *lower* percent emphysema compared with TS (4,5) but no difference in airway wall thickness (5). The most recently published paper erroneously reported a significant increase in the presence of emphysema in CT scans of marijuana smokers in comparison with nonsmoking controls (6). However, the authors of this study failed to take into consideration that 50 of the 56 marijuana smokers included in their study also smoked tobacco, so that only 6 of the 56 marijuana smokers smoked marijuana alone, indicating that, in keeping with prior research, their findings were most likely attributable to tobacco rather than marijuana.

Since the smoke of marijuana contains pro-carcinogenic constituents, especially benz(o)pyrene, in concentrations similar or nominally greater than found in tobacco smoke, there is understandable concern that smoking marijuana might increase the risk of developing lung cancer. I was an investigator in the population-based case-control study (UCLA/USC Case-Control Study) of the association of marijuana smoking with lung and upper aerodigestive tract (UAT) cancers in which we examined 611 lung cancer cases, 601 UAT cancers and 1040 controls in Los Angeles County (7). While tobacco smoking was clearly shown to be associated with the development of lung and UAT cancers in a dose-dependent manner, marijuana smoking was not shown to have a positive association with these cancers. Further, marijuana smoking showed reduced odds for developing these cancers, even among the heaviest quintile of marijuana smokers, although these odds ratios did not meet the level of statistical significance. Our study was the largest of six case-control studies included in a pooled analysis of cannabis smoking and lung cancer risk by the International Lung Cancer Consortium (8). The pooled odds ratio for these six case-control studies was 0.95 (95% CI: 0.66-1.38; p=0.807), indicating a null association of cannabis with lung cancer. The single case-control study among the six included in the pooled analysis that reported a significantly positive association with lung cancer (OR 2.17; CI 1.4-4.52; p=0.039) was the New Zealand study of Aldington et al., which included only 78 cases of lung cancer and 324 controls (9). Moreover, the findings reported by the latter authors were based on those from the heaviest (3rd tertile) of marijuana smokers that included only 4 controls and 14 cases, numbers that precluded valid statistical analysis. However, a systematic review and meta-analysis of the association of marijuana use with the risk of cancer concluded that currently available evidence is insufficient to incriminate marijuana as being associated with the development of lung or head and neck cancer (10).

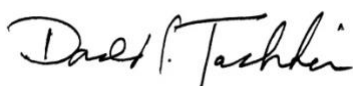
Given the absence of sound evidence to implicate marijuana smoking as a significant risk factor for the development of COPD or lung cancer (the major pulmonary consequences of smoking tobacco), along with the need to study novel potential remedies, such as medical marijuana, to alleviate the suffering of veterans from the debilitating effects of post-traumatic stress disorder (PTSD), I believe

that the potential benefit of the proposed study of pre-rolled marijuana cigarettes in veterans afflicted with this disorder outweighs concerns regarding any potential harm to lung health.

References:

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Sincerely,



Donald P. Tashkin, MD, FCCP, ATSF
Distinguished Emeritus Professor of Medicine
Department of Medicine
Division of Pulmonary and Critical Care Medicine
David Geffen School of Medicine at UCLA Health Sciences
10833 Le Conte Ave.
Los Angeles, CA 90095
310-825-3163 – office
310-206-5088 - FAX
dtashkin@mednet.ucla.edu – e-mail

