RESPONSE TO REVIEWERS

July 07, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 11412-Review.doc).

Title: A case of cannabinoid hyperemesis syndrome with long-term follow-up

Author: Jae Myung Cha, Richard A. Kozarek and Otto S. Lin

Name of Journal: *World Journal of Clinical Cases*

ESPS Manuscript NO: 11412

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) This is an interesting case study of cannabinoid hyperemesis syndrome, which is characterized by chronic, heavy use of cannabis, recurrent episodes of severe nausea and intractable vomiting, and abdominal pain. Overall, the paper is well written. I have only a minor comment: Cannabis is known for its antiemetic properties. Why such a substance should cause such a syndrome? Please give some possible explanations in the discussion.

Answer: Thank you for your comment. As described in our Discussion, the exact mechanism of CHS is still unknown. In the last few years, there has been increasing recognition that even though cannabis may have short-term anti-emetic properties, in some patients there seems to be a paradoxical chronic vomiting syndrome with unusual clinical characteristics as described in our paper. Similar to the purported mechanism for cyclic vomiting syndrome, disturbances of the hypothalamic- pituitary-adrenal axis and the presence of autonomic instability have been postulated as a possible mechanism of CHS. We added additional details to our analysis of the possible mechanism of CHS in the Discussion section.

(2) This very well written clinical case of cannabinoid hyperemesis syndrome (CHS) by Cha et al. presents evidence that CHS is easily diagnosed with characteristic clinical features and excellent prognosis can be achieved with cannabinoid abstinence. These findings are significant given the recent increase in recreational and medical use of marijuana in the USA. I only have one comment. It is stated that the 44-year old man presented with a "long history of addiction to marijuana". More detail needs to presented to define what is meant in this case of addiction to marijuana. In other words, how many times a day, times per week or times per month did this patient use marijuana and for how long? In addition, how long did the patient use marijuana before developing CHS?

Answer: Thank you for your comment. We completely agree with your opinion that history of addiction to

marijuana is important in this case report. As described, marijuana was used for the past 20 years. This patient was a heavy user and smoked at least 4-8 marijuana doses ("joints") per day prior to his abstinence.

(3) The manuscript on this clinical case of cannabinoid hyperemesis syndrome (CHS) is a general description of such case that largely overlaps with previous reports on CHS. For this reviewer it is surprising the absolute absence of data or figures to support the description of the CHS case. Whereas no doubt it is important to raise the awareness of clinicians of potential CHS cases, the structure of the manuscript would be more on the kind of "Comment" or "Point of view" or similar opinion articles. Specifically some points that recall my attention are the following. CHS apparently is largely defined by the fact that chronic cannabinoid users that develop abdominal pain and hot water showering behavior and both are relieved by cannabis cessation. It is important to better understand the CHS to correlate changes of cannabinoid metabolites (blood/urine) when diagnosed and their evolution according to cessation and symptom disappearance. It is not clear the importance of long-term cannabis cessation (stated 9 years) if CHS symptoms stop early after cessation. Minor comment. Introduction. Cannabis is the most illegal recreational drug used. Other legal recreational drugs have higher rates of consumption e.g. tobacco and alcohol.

Answer: Thank you for your comments. As CHS cases can be diagnosed with clinical criteria without any laboratory or radiological findings, most cases in the past have been reported without data or figures to support the diagnosis of CHS. This patient had undergone an extensive work-up to rule out other conditions prior to the diagnosis of CHS. Standard laboratory and radiological tests, including complete blood counts, comprehensive metabolic panels, lipase levels, endoscopic examinations and abdominal and pelvic CT scans, have all been normal. Blood or urine cannabinoid metabolites were not measured in our patient since it was clear that he was a habitual marijuana user from his history; however, a urine toxicology screen (to rule out other recreational drugs) had been performed at an outside hospital and was negative. These details are now described in the revised manuscript. With regard to your minor comments, other legal recreational drugs such as tobacco and alcohol, which boast higher rates of consumption, are now mentioned in the revised manuscript.

(4) Interesting case report article. Major concern is the total absence of the cannabinoid neuropharmacology related to the case report on the introduction and the almost total absence of cannabinoid mechanisms of action related to the case report on the discussion. Saying "Most cannabinoids act through two receptors, CB1 and CB2, which act by reducing anterior pituitary hormone and increasing corticotrophin release.[15]" is an over simplification of cannabinoid mechanisms of action related to the case report (for both hyperemesis and thermoregulation) and need to be properly addressed. Not sure I understood the text on discussion "… in patients who are not determined to get better." Can authors clarify what they mean with that? Minor: Needs updated references on first paragraph of the introduction and review the text as is lacking spaces between words.

Answer: Thank you for your comments. Unfortunately, cannabinoid neuropharmacology is still not well understood, particular with regard to the mechanism of CHS. It is suspected that CHS is caused by disturbances in the hypothalamic-pituitary-adrenal axis and the presence of autonomic instability, but there is no direct proof of this pathophysiology at this time. Concerning the phrase "… in patients who are not determined to get better,"

this refers to the fact that some patients are psychologically addicted to marijuana and exhibit considerable denial when confronted with the possibility that marijuana, which has purported anti-nausea properties, may be the cause of their chronic nausea and abdominal pain symptoms. We have come across this difficulty several times in our clinical practice, and thus believe that patients who are not determined to get better may have difficulty maintaining abstinence from marijuana for long periods of time. These comments are now included in the Discussion. Thank you also for your minor comment. The references and typesetting have been corrected

Thank you again for reviewing our manuscript in the *World Journal of Clinical Cases*.

Sincerely yours,

Jae-Myung Cha, M.D., PhD
Otto S. Lin, MD, MSc
Digestive Disease Institute, Virginia Mason Medical Center,
C3-Gas, 1100 Ninth Avenue, Seattle, USA
Tel: 425-625-7373
E-mail: otto.lin@vmmc.org