

November, 18th, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 14196Review.doc).

**Title:** Self-medication of achalasia with cannabis, complicated by a cannabis use disorder

**Authors:** Luquiens Amandine, Lourenco Nelson, Benyamina Amine, Aubin Henri-Jean

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 14196

We thank the reviewer for his interest in our work and his relevant comments to our manuscript (reviewers comments are written in italic). The manuscript has been improved according to the suggestions of reviewers. Please find below our responses to his comments.

*1. Though the authors provide recent references to support statements throughout the manuscript, a number of statements are made in the Background and Discussion sections that would benefit from additional citations, such as the sentences beginning with "The effectiveness of medical treatment is inconsistent..." and "The mechanism of action could involve smooth muscle relaxation..."*

Thank you for this comment. We added five additional references: "Wen, Z.H., E. Gardener, and Y.P. Wang, Nitrates for achalasia. Cochrane Database Syst Rev, 2004(1): p. CD002299." , "Baker, D., et al., The biology that underpins the therapeutic potential of cannabis-based medicines for the control of spasticity in multiple sclerosis. Multiple Sclerosis and Related Disorders, 2012. 1(2): p. 64-75. ", "Office On Drugs And Crime, WORLD DRUG REPORT. Vol. 1. 2006: United Nations Publication. ", "Leung, L., Cannabis and its derivatives: review of medical use. J Am Board Fam Med, 2011. 24(4): p. 452-62." And "Su, J.Y. and A.C. Vo, 2-Arachidonylglycerol ether and abnormal cannabidiol-induced vascular smooth muscle relaxation in rabbit pulmonary arteries via receptor-pertussis toxin sensitive G proteins-ERK1/2 signaling. Eur J Pharmacol, 2007. 559(2-3): p. 189-95."

*2. The authors should state whether the study conformed to the Declaration of Helsinki.*

Our research was conducted in accordance with the Helsinki Declaration, and the patient gave written informed consent for publication. We precised this in the manuscript adding a sentence.

*3. The Discussion section, particularly in terms of the potential addiction risk of cannabis, should be elaborated upon.*

For more clarity on the addictive potential issue, we added two paragraphs: one in the background section: "Medical cannabis extract (Nabiximols) is approved in several countries for the treatment of refractory spasticity in multiple sclerosis [5]. Commercialized nabiximols is standardized to contain dronabinol and Cannabidiol (CBD) in a ratio of 1:1 and is sprayed under the tongue using a dose pump. Cannabidiol is the most important non-psychoactive cannabinoid found in the cannabis plant. It is not a cannabinoid (CB) receptor agonist. Dronabinol is the international non-proprietary name for (-)-trans-delta-9-tetrahydrocannabinol (THC). THC is used to refer to the naturally occurring (-)-trans-isomer of delta-9-tetrahydrocannabinol from the cannabis plant (*Cannabis sativa* L.). THC is a CB receptor agonist. THC is responsible for most of the pharmacological actions of cannabis, including the psychoactive effects. Medical cannabis showed positive results for spasticity in patients

with multiple sclerosis [6] or paraplegia [4] and in the treatment of anorexia, nausea, and neuropathic pain. “

And one in the discussion section:

“Cannabis abuse potential is well documented [12]. Although smoked cannabis contains over 400 other chemicals (~60 are cannabinoids), its reinforcing effects are known to be due to Delta-9-THC [13]. A ratio 1:1 of CBD and THC seems to be protective from addiction-onset risk [14]. Medical cannabis seems to have a much less addictive potential than those of smoked cannabis [15]. However, particular attention should be given to cannabis addiction risk to vulnerable patients.”

*4. The manuscript would benefit from editing for grammar by a native English speaker. Indeed, there are a number of instances where grammar should be revised (e.g., “...1.5 year before...,” “...on the contrary of food intakes...,” “...let him still with impaired...,” and “...more weight lose and...”).*

The manuscript has already benefitted from an editing by “Nature Publishing Group Language Editing”.

However we changed the notified sentences as suggested and we thank the reviewer for having highlighted these errors:

“...1.5 year before...,” was changed for “one year and a half”

“...on the contrary of food intakes...,” was changed for “whether the food intakes were pre-medicated by cannabis use at this time period.”

“...let him still with impaired...,” was changed for “did not allow to facilitate food intakes”

“...more weight lose and...” was changed for “loss”

We also added as required a “Core-tip section” and a “Comments section”.

Please find the Conflict of interest statement, and the Informed Patient Consent Statement.

We kindly ask for an exemption from providing the Institutional review board (IRB) statement, which cannot be available. The case report «Self-medication of achalasia with cannabis, complicated by a cannabis use disorder - Cannabis in achalasia and manometry» was written retrospectively, with the written patient’s consent. No review board is required or available in our Institution for this kind of case report, as it has no impact on the care providing process.

We hope the submission process could go forward despite the missing statement.

Sincerely yours,

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