

Dear Editor

I would like to thank the reviewers for their constructive and apt comments related to this article and their support for the publication of the work.

In reply to the reviewers' comments the manuscript has been revised as follows:

Citations have been added to the two sentences: Analgesia subsection, next to last sentence of the third paragraph (ending, " . . . uninjured fibers.") Anticonvulsant subsection, second paragraph, 4th sentence (ending " . . . brain underdevelopment.")

Page 5, lines 3-5: the author states that flupirtine has been shown to be an effective analgesic drug in a range of pain conditions. A very similar drug, retigabine, has been approved by the regulatory agencies as adjunctive treatment of drug-resistant partial onset seizures in patients aged 18 years or older. Could the author comment about the experimental and clinical pharmacological effects of retigabine in pain conditions?

The focus of the article is towards the pharmacological profile of flupirtine. Inclusion of reference to retigabine as an analgesic when the drug has not been discussed elsewhere would imbalance the article.

Page 10, lines 15-24: I would suggest not giving so much importance to the neuroprotective effects shown by high-concentration (millimolar) flupirtine during the analgesic use in cancer patients, since the plasma concentrations reached by flupirtine following the administration of analgesic doses are in the low micromolar range. However, I would comment more about the adjunctive possible pharmacological targets of high-concentration flupirtine.

Section related to neuroprotective effects of high-concentration flupirtine has been deleted.

Page 12, lines 12-18: please, discuss with more depth the endothelium-dependent vasorelaxant effects of flupirtine observed in swine coronary arteries in the context of other published data on the effects of Kv7 channel openers observed in the coronary arteries.

Text has been added relating to other Kv7 channel openers and the endothelium

Page 13, paragraph on myometrial effects: please, add any known data on embryo-fetal toxicity and teratogenicity of flupirtine.

Comment added to text.

Page 16, lines 4-8: I would suggest including the references to the two important documents of the European Medicines Agency by which the agency first restricted the use of flupirtine in 2013 and then recommended to withdraw the marketing authorisation for flupirtine this year: https://www.ema.europa.eu/documents/referral/flupirtine-containing-medicines-article-107i-procedure-restrictions-use-flupirtine-containing_en-0.pdf

https://www.ema.europa.eu/documents/referral/flupirtine-article-31-referral-withdrawal-pain-medicine-flupirtine-endorsed_en.pdf

References with citations have been added to article.

Page 5, line 25: should “motor neurons” be deleted?

‘Motor neurons’ has been deleted.

Page 6, lines 17-19: I would suggest adding as important information that δ -subunit containing GABAA receptors mainly contain $\alpha 4$ and $\alpha 6$ subunits and do not bind benzodiazepines.

Sentence has been added to the paragraph relating to benzodiazepine insensitivity.

Page 8, line 19: please correct “flupitine” to “flupirtine ”

Text has been corrected.

Page 9, line 9: please correct “caplain” to “calpain”

Text has been corrected.

Please find the revised manuscript as per the recommendations of the reviewers.

Yours

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