

PEER-REVIEW REPORT

Name of journal: World Journal of Pharmacology

Manuscript NO: 42393

Title: Pharmacology and clinical applications of flupirtine: current and future options.

Reviewer's code: 00503494

Reviewer's country: United States

Science editor: Li-Jun Cui

Date sent for review: 2018-09-23

Date reviewed: 2018-10-14

Review time: 21 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input checked="" type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

This manuscript is a solid review of a variety of conditions that could potentially be treated by flupirtine. My only suggestions for improvement are that the following two sentences need citations: Analgesia subsection, next to last sentence of the third paragraph (ending, " . . . uninjured fibers.") Anticonvulsant subsection, second



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paragraph, 4th sentence (ending " . . . brain underdevelopment.")

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ No

BPG Search:

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ No

PEER-REVIEW REPORT

Name of journal: World Journal of Pharmacology

Manuscript NO: 42393

Title: Pharmacology and clinical applications of flupirtine: current and future options.

Reviewer's code: 04430827

Reviewer's country: Italy

Science editor: Li-Jun Cui

Date sent for review: 2018-10-10

Date reviewed: 2018-10-17

Review time: 7 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input checked="" type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

This is a well-written and exhaustive review on flupirtine, an opener of voltage-dependent type 7.2-7.5 K⁺ (KV7.2-7.5) channels approved for acute pain treatment in some countries and being to be withdrawn from the European market due to the occurrence of several cases of serious hepatic toxicity. Main comments 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? 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. 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. Page 13, paragraph on myometrial effects: please, add any known data on embryo-fetal toxicity and teratogenicity of flupirtine. 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

Minor comments Page 5, line 25: should “motor neurons” be 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. Page 8, line 19: please correct “flupitine” to



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

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