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Manuscript Type: Therapeutic Advances

Dear WJCC Editorial Office,

I thank you for the opportunity to address the appreciated Reviewers comments and I provide below a summary of our responses and submit a revised manuscript with our changes in Track Changes. I hope you could now consider manuscript suitable for publication in WJCC.

Yours sincerely

Fabio Guerriero

REVIEWER 1 EVALUATION

1. The whole manuscript has been checked by English mother-tongue Colleague Matthew Francis (my coauthor in other Pubmed-indexed manuscripts). and all spelling errors and grammar have been corrected.

REVIEWER 2 EVALUATION

1. The core-tip has been changed into "informative" rather than "indicative", as suggested.
2. Thanks for this comment, it is important. Now psychiatric condition - in particular risk of overdose, abuse, misuse or drug diversion - are more elaborated in the manuscript, with attention to specific alerts a clinician should assess in each patient under opioid trial.
3. Caution with transition from oral to transdermal route has been added, as suggested.
4. A sentence about risk of sudden opioids withdrawal has been added.

REVIEWER 3 EVALUATION

1. The whole manuscript has been checked by English mother-tongue Colleague Matthew Francis (my coauthor in other Pubmed-indexed manuscripts). and all spelling errors and grammar have been corrected. All suggested semantic changes have been done.
2. Thanks for the suggestion. As suggested, introduction and other sections of the manuscript has been updated with requested information. In particular – and this is such important – it has been highlighted that opioid trial shall be part of multimodal treatment (ie. physical activity, behavioral therapy, etc).