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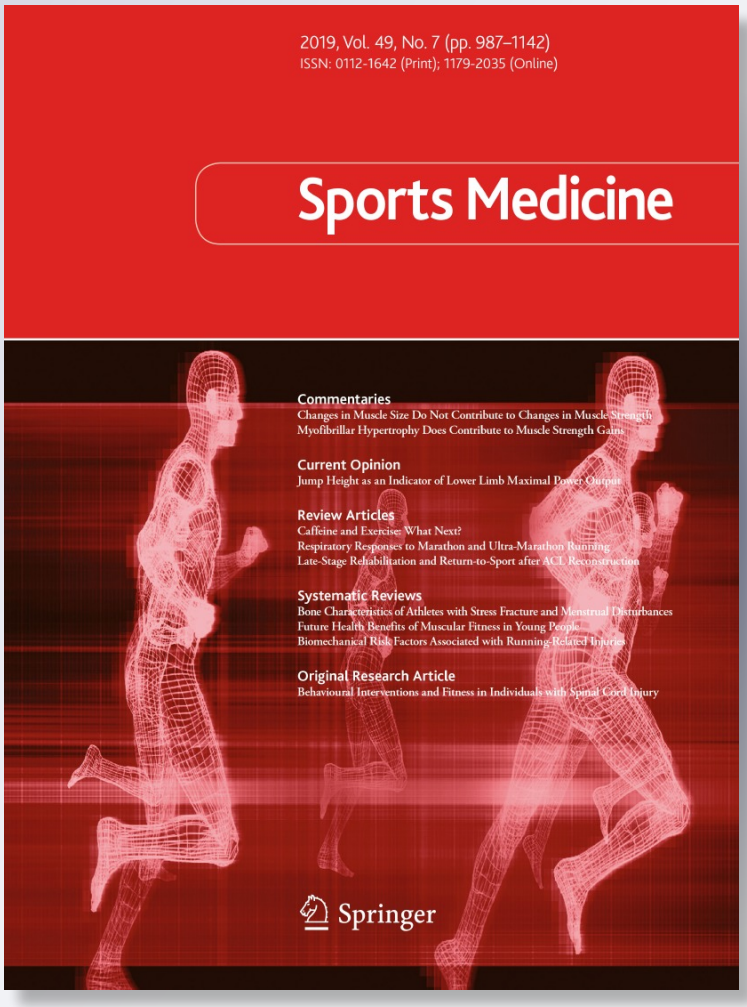

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LETTER TO THE EDITOR

Comment on "Review of WADA Prohibited Substances: Limited Evidence for Performance-Enhancing Effects"

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Dear Editor,

We read with great interest the review by Heuberger and Cohen entitled *"Review of WADA Prohibited Substances: Limited Evidence for Performance-Enhancing Effects"* [1]. In general terms, the authors summarise well the current lack of sufficient empirical evidence regarding the substances and methods included in the World Anti-Doping Agency (WADA) Prohibited List. However, although the review is well focused in 2018, we believe further information about the status of tramadol in 2019 is required. We write this letter to provide additional insights into the status of tramadol in cycling.

On 21 June, 2018, L'Union Cicliste International announced that tramadol will be banned in competition from the 1 March, 2019 [2]. According to the most recent report available from WADA, 4.3% of urine and blood sample analyses from cyclists contained tramadol [3]. Despite the L'Union Cicliste International banning tramadol in competition, WADA intends to keep tramadol on the monitoring programme until at least 2020 [4]. Notably, tramadol has been included in the monitoring programme since 2012 to detect potential patterns of abuse and to study its possible effects on performance and athletes' health. According to Heuberger and Cohen [1], there is scant evidence on the effect of tramadol on physical performance.

However, they omitted in their review a recent clinical trial from our laboratory in which we tested, for the first time, the effects of this substance in a group of cyclists at physical, cognitive and brain levels [5]. The purpose of the study (funded by WADA; reference 15C01DS) was to test the hypothesis that acute oral administration of tramadol would improve exercise performance during a 20-min cycling time trial in a group of cyclists (experiment 1). Furthermore, given the common side effects reported following the consumption of tramadol (e.g. drowsiness, somnolence and nausea [6]), we tested if sustained attention would be impaired during the 20-min time-trial while the participants performed an oddball sustained attention (cognitive) task (experiment 2). Tramadol might enhance cycling performance via its effect on effort and pain perception, but at the expense of reducing the ability to stay focused, i.e. to sustain attention, given that drowsiness and somnolence are commonly reported after tramadol ingestion. As tramadol will be prohibited in cycling from 2019, we believe these results are highly relevant for this topic of research.

In this double-blind, randomised, controlled within-subject experiment, participants ingested tramadol or placebo 120 min before the 20-min cycling time trial. The results of experiment 1, with a sample of 28 cyclists (19 male individuals, maximal power output: 4.72 W/kg and nine female individuals, maximal power output: 4.1 W/kg), revealed that tramadol improved performance by ~5% during a 20-min cycling time trial. Tramadol appeared to allow participants to achieve a higher power output without modifying the rate of perceived exertion. The methodology of experiment 2 was almost equivalent to that of experiment 1, except that participants (28 different male cyclists, maximal power output: 4.76 W/kg) completed a sustained attention (cognitive) task during the 20-min cycling time trial. The cognitive task consisted of a random presentation of a sequence of visual stimuli of a frequent blue circle (non-target), a small rare blue circle (target 1) and a rare square (target 2) on a computer screen. Participants were required to respond to both target 1 and target 2 and not to respond to the non-target. Interestingly, and contrary to the results observed in experiment 1,

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tramadol did not improve performance or impair sustained attention at the behavioural level compared to the placebo condition (i.e. neither response accuracy nor reaction time significantly differed between experimental conditions). Nonetheless, electrical brain activity measured during exercise following tramadol ingestion revealed an interesting pattern of results. We found a lower brain activity in the alpha frequency band linked to (task-relevant) stimulus processing in the tramadol recipients compared with placebo. Higher alpha activity has been deemed as an indicator of increased alertness [7]. In a study using a similar task, the reduction in the alpha frequency, observed when rare targets are presented, was interpreted to be a higher mental effort to detect infrequent targets [8].

Therefore, our results could point to the need for a greater cognitive resource allocation to detect infrequent targets in individuals receiving tramadol vs. placebo. The contradictory findings between experiment 1 and 2 might be explained by: (1) the simultaneous performance of a cognitive task in experiment 2 did not allow cyclists to allocate the same amount of resource to the physical test; and (2) the duration of the protocol. Fatigue could be an important factor that could mediate the impact of tramadol (i.e. the greater the fatigue, the larger the painkiller effect). Hence, at present, it is premature to state that tramadol enhances cycling performance or that it might have a negative effect on the ability to stay focused. Our laboratory is currently conducting a further trial to address some of the questions arising from the previous study.

In conclusion, whether tramadol will be finally included in the list of prohibited substances remains a question that WADA should address in the not-so-distant future supported by further empirical studies.

Compliance with Ethical Standards

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Conflict of interest Darías Holgado, Thomas Zandonai and Daniel Sanabria have no conflicts of interest that are directly relevant to the content of this letter. The authors alone are responsible for the views expressed in this publication and they do not represent the decisions, policy or views of the World Anti-Doping Agency.

References

1. Heuberger JAAC, Cohen AF. Review of WADA prohibited substances: limited evidence for performance-enhancing effects. Sports Med. 2018;1:1. https://doi.org/10.1007/s40279-018-1014-1.
2. UCI. Inside UCI. http://www.uci.org/inside-uci/press-releases/the-management-committee-approves-agenda-2022-commits-to-greater-gender-equality-and-strengthens-its-ethics-regulations. Accessed 11 Nov 2018.
3. World Anti-Doping Agency. WADA publishes 2017 monitoring program figures (13 June 2018); 2018. https://www.wada-ama.org/en/media/news/2018-06/wada-publishes-2017-monitoring-program-figures. Accessed 11 Nov 2018.
4. World Anti-Doping Agency. The 2019 monitoring program; 2018. https://www.wada-ama.org/sites/default/files/wada_2019_french_monitoring_program.pdf. Accessed 23 Jan 2019.
5. Holgado D, Zandonai T, Zabala M, Hopker J, Perakakis P, Luque-Casado A, et al. Tramadol effects on physical performance and sustained attention during a 20-min indoor cycling time-trial: a randomised controlled trial. J Sci Med Sport. 2018;21:654–60.
6. Beakley BD, Kaye AM, Kaye AD. Tramadol, pharmacology, side effects, and serotonin syndrome: a review. Pain Physician. 2015;18:395–400.
7. Nielsen B, Nybo L. Cerebral changes during exercise in the heat. Sports Med. 2003;33:1–11.
8. Peng W, Hu Y, Mao Y, Babiloni C. Widespread cortical alpha-ERD accompanying visual oddball target stimuli is frequency but non-modality specific. Behav Res Med. 2015;295:71–7.