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BRIEF REPORT

Tramadol and Cycling: Is It the End of a "Painful" Relationship? An Insight From 60,802 Doping-Control Samples From 2012 to 2020

Thomas Zandonai,[1,2,3] Ana M. Peiró,[1,2,4,5] Caterina Covelli,[6] Xavier de la Torre,[6] and Francesco Botré[6,7]

[1]Department of Pharmacology, Pediatrics and Organic Chemistry, Miguel Hernández University of Elche, Elche, Spain; [2]Neuropharmacology on Pain and Functional Diversity (NED), Institute of Health and Biomedical Research of Alicante (ISABIAL Foundation), Alicante, Spain; [3]Department of Social and Developmental Psychology, Sapienza University of Rome, Rome, Italy; [4]Pain Unit, Department of Health of Alicante, General Hospital, Alicante, Spain; [5]Clinical Pharmacology Unit, Department of Health of Alicante, General Hospital, Alicante, Spain; [6]Laboratorio Antidoping, Federazione Medico Sportiva Italiana, Rome, Italy; [7]REDs—Research and Expertise on Anti-Doping Sciences, Institute of Sport Science (ISSUL), University of Lausanne, Lausanne, Switzerland

Purpose: To assess the prevalence of tramadol use among athletes from 2012 to 2020. ***Methods:*** All urine samples were collected from national and international in-competition doping-control tests that took place in Italy between 2012 and 2020. The analysis of the samples was performed by gas chromatography coupled with mass spectrometry with electronic ionization and acquisition in selected ion monitoring. The cutoff tramadol concentration was >50 ng/mL. ***Results:*** Of the 60,802 in-competition urine samples we analyzed, 1.2% (n = 759) showed tramadol intake, with 84.2% (n = 637) of these coming from cyclists and 15.8% (n = 122) from other sports. In cycling, a strong and significant negative correlation was found ($r = -.738$; $P = .003$), showing a decrease of tramadol use compared with the other sports. ***Conclusions:*** The decrease in tramadol prevalence in cycling in the last years may be due to (1) the deterrent action of antidoping regulations and (2) the fact that tramadol may not have any actual ergogenic effect on performance.

Keywords: analgesics, opioids, athletes, WADA, sport

Opioid addiction is becoming an increasingly alarming problem in the United States and worldwide, with the misuse and abuse of these narcotics being surprisingly widespread.[1] Vulnerability to opioid addiction is difficult to pinpoint and to predict, and many literature studies highlight that this substantial increase of opioid abuse is generating a full-fledged health crisis that is growing at an alarming rate.[2] In particular, the recent spread of tramadol abuse, especially among youth, workers, and students, has become a serious issue in many countries across the world.[3]

Would athletes have the same risks for abuse? Although most opioids are prohibited and sanctioned in sports (eg, oxycodone, morphine), the painkiller tramadol (an m-opioid receptor agonist, and a serotonin and norepinephrine reuptake inhibitor)[4] is currently only on the monitoring program for the World Anti-Doping Agency (WADA), and is banned only in cycling.

A previous study indicated a prevalence of 1.4% of tramadol use in sports competitions as measured on 9851 urine samples between 2013 and 2017 (Doping Control Laboratory).[5] Recently, an opinion paper summarizing the prevalence of tramadol in sports showed a higher prevalence in cycling compared with other sports, confirming data from other WADA-accredited laboratories.[6] This consumption may be due to various factors. First, there is a common misconception that tramadol may be endowed with performance-enhancing properties. Second, the fact that, since tramadol is a painkiller, it is generally relatively easy to obtain a prescription for it. Additionally, the prescription dispensation of tramadol was significantly associated with greater risks of mortality, cardiovascular events, and fractures than that of codeine.[7] Finally, but equally relevant, tramadol as an opioid has an important potential for addiction and abuse.[6]

This brief report presents the analysis of 60,802 urine samples from the WADA-accredited antidoping laboratory in Rome, Italy, in order to assess the prevalence of tramadol use.

Methods

Samples

All urine samples were collected from national and international in-competition doping-control tests that took place in Italy between 2012 and 2020. Samples were anonymously analyzed as part of the WADA Monitoring Program at the WADA-accredited antidoping laboratory in Rome, Italy. The sample size consisted of national and international athletes that were tested during sports competitions held in Italy. According to the WADA Code, we analyzed urine samples collected from participants that were regularly enrolled in the national and international sports federations of each discipline (elite amateur levels and Paralympics sports).

Laboratory Analysis

Concerning the techniques employed in the analysis of the samples, we used gas chromatography (GC) coupled with mass spectrometry (GC/MS) with electronic ionization and acquisition in selected ion monitoring. The GC/MS system was a GC 7890 Agilent technologies interfaced with an Agilent 5975 MS, with an HP5 column (17 m × 0.2 mm × 0.33 µm). The parameters for GC were the following: oven program—85°C (1 min), 15 to 270 °C, 50 °C/min to 310 °C (3.5 min); injection—1 µL, pulsed splitless; injector

Peiró https://orcid.org/0000-0002-2385-3749
de la Torre https://orcid.org/0000-0001-8037-6750
Botré https://orcid.org/0000-0001-5296-8126
Zandonai (tzandonai@umh.es) is corresponding author, https://orcid.org/0000-0002-7606-9675

Table 1 Tramadol Findings in Cycling and Other Sports Collected in Competition and Analyzed at the Rome Laboratory From 2012 to 2020

Year	2012	2013	2014	2015	2016	2017	2018	2019	2020
Cycling	14.0% (948)	9.4% (1067)	9.8% (1135)	5.3% (896)	6.8% (1048)	9.3% (1050)	6.5% (783)	2.6% (862)	0.6% (524)
Other sports	0.7% (4220)	1.7% (3546)	0.9% (3762)	2.4% (477)	1.1% (3143)	1.2% (3516)	1.2% (3176)	1.5% (2066)	0.0% (0)
Archery		2.0% (49)					2.2% (46)	1.6% (62)	
Athletics	0.2% (476)		0.6% (676)		0.3% (301)	2.5% (204)		1.1% (380)	
Basketball					0.3% (405)				
Bodybuilding									
Boxing				0.7% (133)	1.1% (90)				
Canoe kayak				1.9% (52)					
Football	0.0% (3003)	0.4% (3078)	0.0% (2551)		0.1% (1894)	0.1% (2879)	0.4% (2309)	0.2% (1589)	
Gymnastics						1.2% (81)			
Handball					0.8% (131)				
Marathon								1.8% (55)	
Open water						1.4% (71)			
Powerboating									
Rowing		1.5% (67)		1.6% (63)	1.3% (78)	0.9% (107)			
Rowing (Paralympic)									
Rugby	0.5% (184)	0.9% (109)		4.0% (101)	1.2% (160)	1.2% (174)	1.0% (2001)		
Shooting									
Swimming	2.0% (149)	0.7% (143)	2.4% (211)	4.0% (128)					
Short track		5.0% (40)							
Triathlon		1.%7 (60)	1.2% (83)		3.6% (84)			0.6% (163)	
Volleyball	0.9% (217)		0.4% (241)				1.2% (240)	3.1% (197)	
Water polo	0.5% (191)								

Note: Data describe the prevalence of tramadol (>50 ng/mL) in percentage values (when the size of the analyzed samples/year is >40).

temperature—270 °C. We followed the protocol that is normally used for narcotics and stimulants.[8] The urine samples were alkalinized with NaOH and NaCl was added for a salting out effect. The samples were extracted with tert-butyl methyl ether. The organic extracts were then taken to dryness under a reduced nitrogen flow at room temperature and reconstituted with an extraction solvent before GC/MS analysis. Diphenylamine was added as an internal standard.

The estimated tramadol concentration was >200 ng/mL according to the WADA monitoring program in force until 2019. For the samples collected in 2020, the reporting limit of tramadol was >50 ng/mL.

Statistical Analysis

Qualitative variables were presented as percentages, and a simple linear regression analysis was performed. Statistical significance was set at P value ≤ .05. All data management and analyses were performed using GraphPad Prism (GraphPad Software Inc).

Results

A total of 1.2% (n = 759; males = 705; females = 54) of the samples showed tramadol intake. Outstandingly, 84.2% (n = 637; males = 606; females = 31) were found in cycling, while the residual 15.8% (n = 122; males = 99; females = 23) were from athletes competing in other sports (see Table 1). A strong and significant negative correlation (r = –.738; P = .003) was evidenced in cycling, showing a 9-year decrease in tramadol use in contrast to the other sports (r = .077, P = .470), in which tramadol intake levels were about the same (see Figure 1A). The percentage of males and females in cycling and other sports of each year are represented in Figure 1B and 1C, respectively.

Discussion

This short report confirms the general trend reported by the WADA, attesting a decrease in the use of tramadol in cycling in the last decade, with the current prevalence at around 1.1% (2019 data).[9] Our data describe, for the first time, a strong reduction of tramadol use among cyclists. Various factors could be the cause of this negative trend.

First, previous results reported in literature contradict the belief that tramadol has performance-enhancing effects. Cyclists seem to take this weak opioid in an attempt to relieve the pain and fatigue that are typical of endurance sports. Indeed, only one experiment in which tramadol was taken showed an increase in performance with a higher average power output (+5%) during a 20-minute cycling time trial.[10] However, when the authors added a sustained attention task before or during the exercise, tramadol did not affect the performance.[10–12] There have been concerns on whether tramadol may decrease vigilance and sustained attention during exercise, potentially putting cyclists' safety at risk. Recent empirical studies do not support this hypothesis, although more studies are needed to confirm this finding.[10–12]

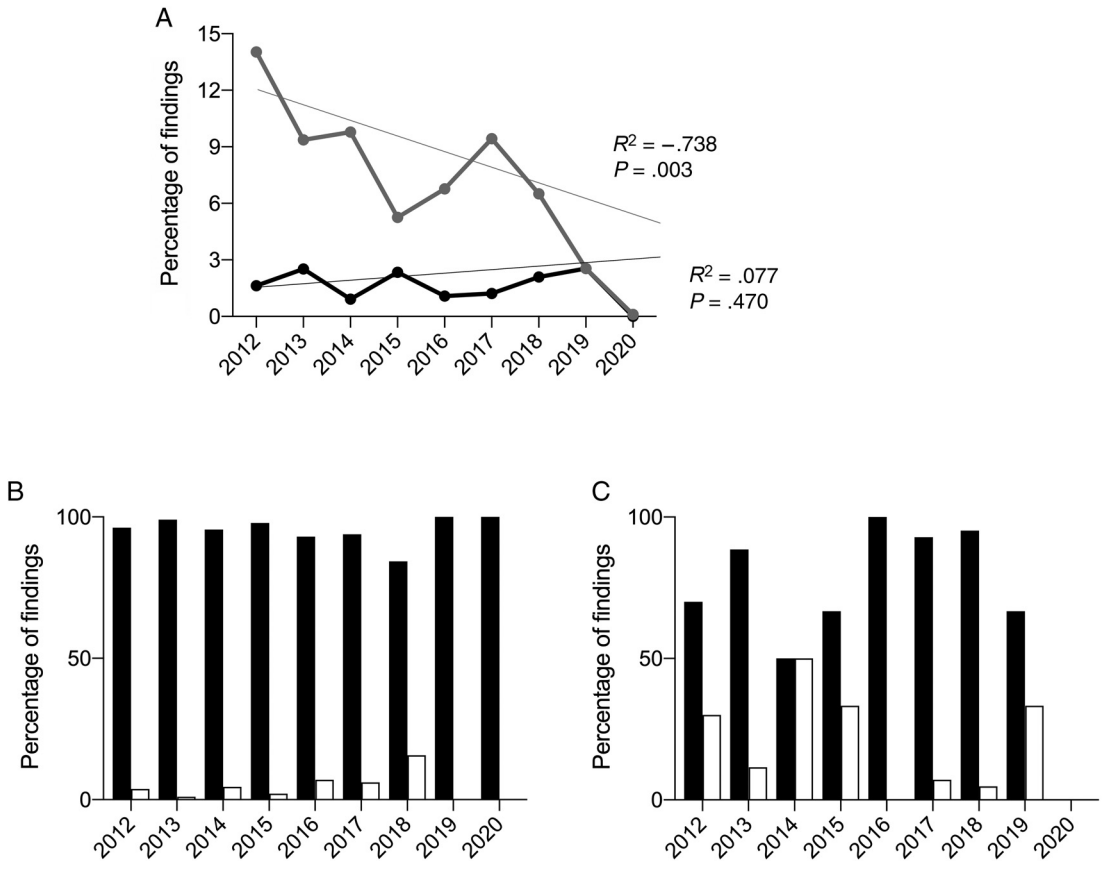

Figure 1 — (A) Prevalence trend of tramadol in cycling (dark gray line) and in other sports (black line). (B, C) The percentage of males (black bars) and females (white bars) in cycling and other sports for each year, respectively.

Moreover, given the absence of clear evidence concerning the improvement of performance due to the administration of this substance, individual differences in drug tolerance should also be taken into account. For this reason, it could be interesting to add protocols of pharmacokinetic measurements during exercise in future studies, as suggested recently by Zandonai et al.[6]

A second reason for the decrease in tramadol use we found in cyclists could be the deterrent action implemented by anti-doping authorities, driven by a long debate and discussion within the sporting environment in the last years. From March 1, 2019, the *Union Cycliste Internationale* has banned this drug. Interestingly, a recent study carried out on 711 samples collected from 361 different cyclists between March and November 2019, did not show any positive cases.[9]

Like the general population, athletes are vulnerable to misusing tramadol for nonmedical purposes, and are at high risk of incurring uncontrolled side effects. Notwithstanding tramadol being generally considered a "safe" opioid pain reliever with a low addictive potential, very few data are available on its long-term safety and effectiveness, including its increasing potential for abuse.[6] It is therefore of crucial importance to not underestimate tramadol use, especially concerning prevention, in the protection of athletes' well-being.

The current findings provide novel insights into tramadol prevalence in sports. Nonetheless, they should be interpreted in light of potential study limitations. Our data refer to only one WADA-accredited antidoping lab. It would be informative to replicate the current findings in other countries. Another limitation lies in the fact that our sample comprised a large number of males and only a few females. While there is much evidence to suggest that gender is an important factor in the modulation of pain, this has not yet been applied to sports due to the scarce number of female athletes involved in the studies.[6] Therefore, future studies should also seek to explore the effects of tramadol on exercise performance in females.

Practical Implications

Finally, considering the results achieved so far with an acute dose of tramadol, it would perhaps be sensible, and functional, to shift the focus to other opioid drugs used by athletes which: (1) are still relatively poorly studied (eg, codeine); (2) can have more pronounced effects due to stronger pharmacological properties on pain or cognitive processes; and (3) can be used in combination with other biologically active substances, causing potential, atypical drug–drug interactions that can induce a higher risk of drug-related side effects.

Conclusions

In recent years, the debate about the use of tramadol in cycling has pervaded the sport's environment. This brief report, through an extraordinary number of samples collected from different sports disciplines, evidenced a clear decreasing use of tramadol in cycling in the last decade.

References

1. Wilson N, Kariisa M, Seth P, Smith H, Davis NL. Drug and opioid-involved overdose deaths—United States, 2017–2018. *MMWR Morb Mortal Wkly Rep*. 2020;69(11):290–297. doi:10.15585/mmwr.mm6911a4
2. Mattson CL, Tanz LJ, Quinn K, Kariisa M, Patel P, Davis NL. Trends and geographic patterns in drug and synthetic opioid overdose deaths-United States, 2013–2019. *MMWR Morb Mortal Wkly Rep*. 2021;70(6):202–207. doi:10.15585/mmwr.mm7006a4
3. Peprah P, Agyemang-Duah W, Appiah-Brempong E, Akwasi AG, Morgan AK. "With tramadol, I ride like a Jaguar": a qualitative study of motivations for non-medical purpose tramadol use among commercial vehicle operators in Kumasi, Ghana. *Subst Abus Treat Prev Policy*. 2020;15(1):49. doi:10.1186/s13011-020-00292-4
4. Miotto K, Cho AK, Khalil MA, Blanco K, Sasaki JD, Rawson R. Trends in tramadol: pharmacology, metabolism, and misuse. *Anesth Analg*. 2017;124(1):44–51. doi:10.1213/ANE.0000000000001683
5. Baltazar-Martins JG, del Mar Plata M, Muñoz-Guerra J, Muñoz G, Carreras D, Del Coso J. Prevalence of tramadol findings in urine samples obtained in competition. *Drug Test Anal*. 2019;11(4):631–634. doi:10.1002/dta.2575
6. Zandonai T, Escorial M, Peiró AM. Codeine and tramadol use in athletes: a potential for abuse. *Front Pharmacol*. 2021;12:661781. doi:10.3389/fphar.2021.661781
7. Xie J, Strauss VY, Martinez-Laguna D, et al. Association of tramadol vs codeine prescription dispensation with mortality and other adverse clinical outcomes. *J Am Med Assoc*. 2021;326(15):1504–1515. doi:10.1001/jama.2021.15255
8. Strano Rossi S, de la Torre X, Botrè F. A fast gas chromatography/mass spectrometry method for the determination of stimulants and narcotics in urine. *Rapid Commun Mass Spectrom*. 2010;24(10):1457–1466. doi:10.1002/rcm.4542
9. Salamin O, Garcia A, Gonzalez-Ruiz V, et al. Is pain temporary and glory forever? Detection of tramadol using dried blood spot in cycling competitions. *Drug Test Anal*. 2020;12(11–12):1649–1657. doi:10.1002/dta.2923
10. Holgado D, Zandonai T, Zabala M, 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(7):654–660. doi:10.1016/j.jsams.2017.10.032
11. Bejder J, Andersen AB, Bonne TC, et al. Tramadol does not improve performance or impair motor function in trained cyclists. *Med Sci Sport Exerc*. 2019;52(5):1169–1175. doi:10.1249/MSS.0000000000002217
12. Zandonai T, Holgado D, Ciria L, et al. Novel evidence on the effect of tramadol on self-paced high-intensity cycling. *J Sports Sci*. 2021;39(13):1452–1460. doi:10.1080/02640414.2021.1877440