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# Examining the Effects of Tramadol, on the WADA Prohibited List, on Sports Performance

## WADA Yasaklılar Listesine Giren Tramadolün Spor Performansı Üzerine Etkilerinin İncelenmesi

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**ABSTRACT**

Tramadol, an opioid analgesic, was added to the World Anti-Doping Agency (WADA) Prohibited List in 2024. Tramadol has been widely used by athletes to manage sports-related pain. Its intensive use, particularly in certain sports, has raised suspicions that it is being used as a doping agent. The potential to impair sports performance, cognitive side effects, and abuse have been investigated in several studies. This study reviewed the literature on tramadol and its effects on sports performance and explained the WADA process. In reviewing the literature, although studies have shown that tramadol does not affect performance, the World Health Organization has banned its use in competition in light of studies showing its effect on performance.

**Keywords:** Doping, sports pharmacy, opioid analgesic, WADA monitoring program, pain, performance enhancer

**ÖZ**

2024 yılı itibariyle opioid bir analjezik olan tramadol, Dünya Dopingle Mücadele Ajansı (WADA) Yasaklılar Listesine girmiştir. Tramadol, spora bağlı ağrıyı tolere etmek için sporcular tarafından son yıllarda sıklıkla kullanılmaktadır. Özellikle belirli branşlardaki yoğun kullanımı doping olarak kullanıldığı şüphelerini doğurmuştur. Spor performansını etkileme potansiyeli, bilişsel düzeydeki yan etki profili ve kötüye kullanım ihtimali çeşitli çalışmalarla araştırılmıştır. Çalışmamızda; tramadol ve tramadolün spor performansı üzerine etkileri ile ilgili literatür incelenmiş ve WADA tarafından yasaklanma süreci açıklanmıştır. Literatür değerlendirildiğinde, tramadolün performansı etkilemediğine dair çalışmalar bulunmasına rağmen, WADA tarafından performans üzerine olan etkilerini içeren çalışmalar göz önünde bulundurularak müsabaka içi kullanımı yasaklanmıştır.

**Anahtar Sözcükler:** Doping, spor eczacılığı, opioid analjezik, WADA izleme programı, ağrı, performans artırıcı

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## INTRODUCTION

Tramadol, which has been in the WADA Monitoring Program for 12 years, has entered the WADA Prohibited List as of 2024, and its in-competition use by athletes is prohibited. Tramadol, included under the heading "Narcotics" on the 2024 WADA Prohibited List, is a weak opioid agonist and has an analgesic effect. It is used clinically to treat moderate to severe pain. It is preferred by athletes to relieve pain caused by the effort required by exercise or pain resulting from sports injuries (1). However, tramadol may provide an advantage in training and competitions because it can allow the athlete to tolerate pain by preventing or delaying the occurrence of pain. Therefore, it can be described as a performance-enhancing substance (2). Although it appears to have an indirect effect on performance compared with other banned substances (e.g., anabolic steroids), it has the potential to affect competition results for competitions won by minimal margins. In addition, it may impair cognitive performance with side effects, such as dizziness, drowsiness, and fatigue, and there is a possibility of causing accidents during competitions and harming athletes. Additionally, it has the potential for abuse, which is believed to affect sporting spirit (3). This study aimed to examine tramadol in detail, on the WADA Prohibited List as of 2024, and the reasons why it is preferred in sports, its effects on sports performance, and the banning process through WADA reports and literature data available in different databases (PubMed, Scopus, ScienceDirect and Web of Science). We believe that the current study may contribute to a better understanding of the current tramadol ban practice and increase the knowledge level of athletes and health personnel.

### *Doping*

#### *WADA: Prohibited List and Monitoring Program*

The World Anti-Doping Agency (WADA) is an independent international organization established to combat doping in sports and to protect athletes and the spirit of sports internationally. For this purpose, WADA publishes the World Anti-Doping Code, the primary document that harmonizes the anti-doping policies, rules, and regulations of public authorities worldwide for sports organizations and monitors compliance with the World Anti-Doping Code (4). The World Anti-Doping Code, published on January 1, 2021 and still in force, prohibits "the presence of a prohibited substance or its metabolites or markers in an athlete's sample" and "the use or attempted use, possession, trafficking or attempted trafficking by athletes of a prohibited substance or prohibited method, or the administration or attempted administration of such substance or method to any athlete in competition" (4,5). Substances mentioned in anti-doping rule violations and prohibited for use by athletes are listed on the WADA Prohibited List. The Prohibited List identifies prohibited substances and methods with potential to enhance or mask performance. A substance or method is included in the Prohibited List if it meets any of the following three criteria.

1-Medical or other scientific evidence, pharmacological effects, or experience that the substance or method, alone or in combination with other substances or methods, has the potential to enhance or improve sports performance;

2-Medical or other scientific evidence, pharmacological effect or experience that the use of the substance or method represents an actual or potential health risk to the athlete;

3-WADA's determination that the use of the substance or method violates the spirit of sport. The Prohibited List, reviewed and updated annually by the WADA in consultation with experts, is published three months before it comes into force each year and enters into force on January 1. However, in exceptional cases, a substance or method may be added to the Prohibited List at any time of the year. Athletes and other persons are responsible for knowing the substances and methods included in the Prohibited List and what constitutes an anti-doping rule violation (4). WADA designed the WADA Monitoring Program to monitor and identify patterns of abuse of substances that are not on the Prohibited List but are potentially harmful in sports and to decide whether to include them on the Prohibited List (3,4). Within this program, WADA publishes the substances and methods to be monitored annually in the WADA Monitoring Program each year. Laboratories accredited or approved by the WADA will notify the WADA if the use of these substances is reported or their presence is detected. WADA annually provides sport-specific information on monitored substances to the International Federations and National Anti-Doping Organizations. The reported use or detection of a monitored substance is not considered an anti-doping rule violation (4). When the 2024 WADA Prohibited List and Monitoring Program was examined, tramadol was found to have left the WADA Monitoring Program, moved to the WADA Prohibited List, and was under the category of narcotics. Narcotics were recognized as doping substances and were included as "Narcotics and Analgesics" in the first prohibited products list published by the International Olympic Committee in 1968. It was included on the WADA Prohibited List as "Narcotics", first published in 2004. Substances in this category include potent analgesics that belong to the opioid class. These compounds substantially affect pain treatment and are prohibited for in-competition use.

### *Pain in Sports and Analgesic Use*

Pain is an inevitable part of athletes' lives (6). This is because exercise causes pain and discomfort when performed at a certain intensity or for a long time (2). Peripheral muscle fatigue develops to a unique threshold for each individual, and when it reaches this critical threshold, exercise is either stopped voluntarily or the intensity of the exercise is significantly reduced (7). The feeling of pain caused by exercise has a negative impact on training and performance (2). Pain in athletes may be caused by exercise-related muscle pain or due to an injury. Injuries and associated pain can affect an athlete's occupational health and well-being. For example, injuries can lead to a painful rehabilitation process, may affect the results of the competition and the ranking, may lead to early or unwanted termination of a sporting career, may cause permanent disability, and can damage mental health throughout a sporting career. Since the sporting career depends on the functionality of the body, frequent or serious injuries pose a threat to athletes' careers (6). However, the view that "no pain, no gain" prevails in various sports branches (2). The effort required to achieve success in sports, the pain of competition, and health risks have been accepted by athletes, coaches, and sports medicine specialists. For this reason, athletes who are away from training and competition due to injury or disability may be under pressure to return to sports immediately. Similarly, medical staff may be subject to pressure and may be forced to negotiate between the recovery of athletes and the decision to return to competition quickly. This situation may sometimes result in

failure to pay attention to the health of the injured athlete, failure to return to sports activities too early, and use of analgesics to achieve this (6). The limited time allocated for the athlete's recovery causes a more frequent use of analgesic drugs and increases the risk of potential abuse and associated harm (1).

### *Analgesics and Sports Performance*

Analgesics are commonly used by athletes. It has been established that athletes use analgesics four times more frequently than the general population of the same age (2). Athletes can use analgesics to relieve fatigue, inflammation, and pain caused by injuries or overtraining (3,8). In addition to their normal therapeutic uses, they can be used to accelerate recovery after exercise, increase performance or prevent performance decline due to pain or minor injuries, cope with stressors caused by injuries, or act as prophylactics (6). In a study conducted with Danish elite athletes (69.5%) and national team athletes (30.5%), almost all athletes (93%) used painkillers due to sports-related pain. In the study, athletes who had experience with pain relievers (93%, n=631) were asked about their reasons for using these products in sports. Although it was determined that the most common causes were to relieve headaches (82%) and to compete in a significant competition despite an injury or disability (64%), it was also found that the use to increase the level of performance in the competition/match (22%) was at a considerable rate (6).

The desire to achieve enhanced performance may lead athletes to use illegal substances. For example, in a study on drug use and doping knowledge in Italian male elite cyclists under 23 years of age (n=40), 75.0% (n=30) of the athletes used at least one drug in the last three months and a total of 84 drugs were used, including tramadol (3.3%). As a result of the study, it was determined that in addition to excessive use of prescription drugs, athletes have limited knowledge about doping (9). The tendency to use analgesics more frequently in and outside of competition than in the general population, to take more than one drug simultaneously, and to administer these drugs at higher therapeutic doses suggests that athletes use these analgesics to increase performance (2).

### *Analgesic Drugs*

Analgesic drugs prevent or reduce pain perception through their effects on the central nervous system. Analgesics are an essential part of pain management in sports, and they are administered by athletes or healthcare professionals. The effects of analgesics depend on the type, dosage, and type of drug (6). Analgesics include non-opioid, adjuvant, and opioid analgesics (10).

### *Non-opioid Analgesics*

Non-steroidal anti-inflammatory drugs (NSAIDs) paracetamol, and metamizole are non-opioid analgesics. NSAIDs, which comprise the majority of this class, have antipyretic, anti-inflammatory, and analgesic effects. Paracetamol and metamizole are antipyretic and analgesic drugs, but they do not have anti-inflammatory effects. The anti-inflammatory effects of drugs in this group are weaker than those of steroidal glucocorticoids. The analgesic effects of opioid analgesics are generally weaker than those of opioid analgesics, which have potent analgesic effects but do not have anti-inflammatory effects (10).

### *Adjuvant Analgesics*

Adjuvant analgesics are a broad group of drugs that belong to different classes. Although these drugs are typically administered for indications other than pain management, they are used to treat a variety of painful conditions. This group includes tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, anticonvulsants, topical anesthetics, corticosteroids, bisphosphonates, and cannabinoids (11).

### *Opioid Analgesics*

Opioid analgesics are alkaloid compounds obtained from Papaver somniferum L, and they relieve pain by acting on the central nervous system (12). Opioids are the most potent drugs used to treat severe pain, and they have been used for thousands of years.

Opioid analgesics exert their effects by imitating peptide hormones known as endogenous opioid peptides or endorphins. Endogenous opioid peptides are natural opioid receptor ligands (13). Opioid analgesics, like endogenous opioid peptides, exert their effects by binding to opioid receptors to reduce pain sensation (12). Opioid receptors include four classes: mu (μ/MOR), kappa (κ/KOR), delta (δ/DOR) opioid receptors, and nociceptin opioid peptide (NOP) receptors. All opioid receptors are broadly distributed in the central and peripheral nervous systems (13). μ-opioid receptors are responsible for analgesia, respiratory depression, euphoria, constipation, addiction, respiratory depression, nausea, and vomiting; κ-opioid receptors are responsible for analgesia, diuresis, sedation, and dysphoria; δ-opioid receptors are responsible for analgesia, convulsions, and anxiolysis (13,14). Although opioid drugs, also called narcotics, differ chemically, they exert their effects through μ-opioid receptors, which are their primary targets and to which they bind with high affinity (12). Opioid drugs consist of natural alkaloids such as morphine and codeine, as well as synthetic derivatives such as heroin, fentanyl, hydromorphone, methadone, buprenorphine, meperidine, oxycodone, and tramadol.

### *Tramadol*

### *Discovery and Chemical Structures*

Tramadol, an atypical opioid with strong analgesic activity, was first synthesized in Germany by Grünenthal GmbH in 1962 (12). Tramadol was approved in Germany in 1977 and was approved by the Food and Drug Administration (FDA) in 1995 (15,16).

The chemical formula of tramadol is 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol (Figure 1). Tramadol, which can be obtained via chemical synthesis, is a mixture of both dextro (+) and levo (-) enantiomers (16).

### *Physiological and Clinical Effects*

Since its discovery in 1962, *in vitro* and *in vivo* studies have demonstrated the potent analgesic activity of tramadol. Extensive clinical trials have demonstrated the efficacy and safety of tramadol for the treatment of moderate to severe pain, including inflammatory, postoperative, and cancer-related pain. Moreover, tramadol has been shown to be efficacious in relieving neuropathic pain, a type of pain for which the use of conventional opioids is constrained by the side effects associated with long-term treatment (15).

Tramadol has a moderate affinity for μ-opioid receptors (Ki=2.1 μM) and a weak affinity for δ- and κ-opioid receptors (Ki=57.6 μM and 42.7 μM, respectively). Its affinity for the μ-opioid receptor is approximately 6000 times less than that of morphine, 100 times less than that of dextropropoxyphene, 10 times less than that of codeine, and is equivalent to that of dextromethorphan (15,17,18). Tramadol differs from typical opioid drugs in that it modulates the reuptake of noradrenaline (NA) and serotonin (5-HT) monoamines in presynaptic terminals and is described as an atypical opioid (16,19). In addition to its effect on μ-opioid receptors, it blocks monoamine reuptake, leading to increased NA and 5-HT levels in central synapses. The mechanism of action of tramadol against pain is shown in Figure 2. Tramadol is a racemic mixture of dextro (+) and levo (-) enantiomers, and both enantiomers contribute to its analgesic effect through different mechanisms. The (+) enantiomer of tramadol has a stronger affinity for the μ-opioid receptor than the (-) enantiomer and inhibits serotonin reuptake by approximately four times more potently than the (-) enantiomer. The (-) enantiomer inhibits noradrenaline reuptake more potently (12,15,18,20). O-desmethyltramadol, the first hepatic metabolite of tramadol described in the literature, has a 200-fold greater affinity for μ-opioid receptors than the dextro form of tramadol and is responsible for the majority of opioid-induced analgesic effects associated with tramadol use (12,15,21,22).

### *Pharmacokinetic Properties*

Tramadol is frequently prescribed today due to its effectiveness in treating moderate to severe pain. Tramadol is available in several pharmaceutical formulations, including capsules, tablets, syrup, cream, ointment, gel, and parenteral. After oral administration, tramadol is rapidly absorbed, reaching a peak serum concentration within 2 hours for capsules and 5 hours for sustained-release tablets. Oral bioavailability after a single dose was 70% due to hepatic first-pass metabolism. Tramadol is rapidly distributed in the body, with approximately 20% bound to plasma proteins. After a single oral dose of 100 mg, the half-life of tramadol is 5.1 hours, whereas that of the O-desmethyltramadol metabolite is 9 hours. The excretion of tramadol occurs almost exclusively (90%) via the kidney. Additionally, approximately 10-30% of tramadol is excreted as an unmetabolized drug, and 60% is excreted as metabolites (12,15,18). It has been reported that the most appropriate dose for moderate to severe acute pain is 3 mg/kg intravenously, and this dose application causes minimal respiratory depression (18). Clinically, tramadol is administered as 50-100 mg orally or parenterally every 6 hours in the treatment of pain. The analgesic effect of tramadol is about one-tenth that of morphine when administered parenterally and about one-third that of morphine when administered orally (23). The maximum tramadol dose is 400 mg/day (12).

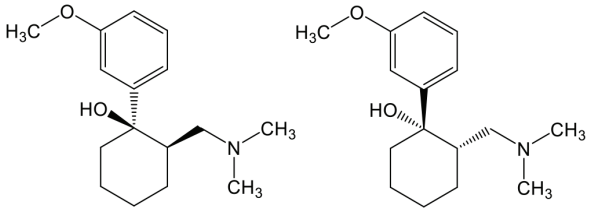


**Figure 1.** Tramadol [(1RS,2RS)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol]

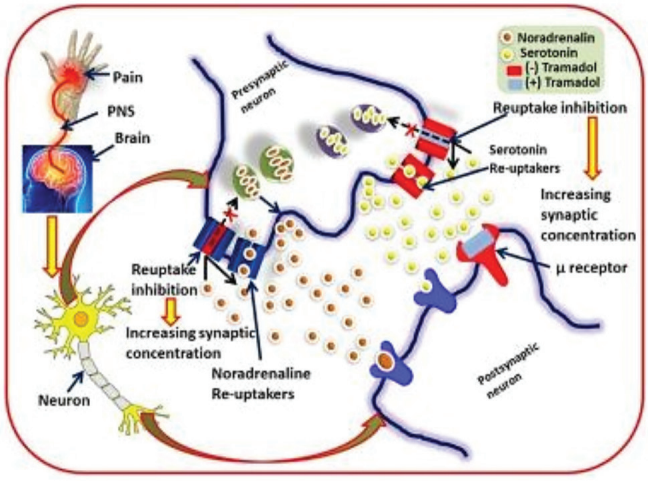


**Figure 2.** Mechanism of action of tramadol on pain

### *Side Effect Profile*

The complementary and synergistic mode of action of the two enantiomers of tramadol, both opioid and monoaminergic, resulted in a significant reduction in the typical side effect profile of opioids. The safety profile and increased tolerability are other factors associated with racemic mixture preference. The order of side effects is (-) enantiomer > (+) enantiomer > racemate (18). In all areas of administration, the side effect profile of tramadol is dose-dependent, a mixture of opioid (indigestion, nausea, vomiting, fatigue, and drowsiness) and monoaminergic (headache, dizziness, dry mouth, and sweating) effects (18). The most common side effects are nausea, vomiting, dizziness, fatigue, drowsiness, sweating, and dry mouth. Less common side effects include diarrhea and cardiovascular complications (tachycardia and postural hypotension), whereas rare side effects include respiratory depression, seizure, tremor, bradycardia, anxiety, and psychosis. Coadministration of tramadol with other drugs or alcohol causes tramadol intoxication. In particular, symptoms of tramadol intoxication begin at doses above 500 mg and after 4 hours of administration. Tramadol overdose is associated with insomnia, drowsiness, nausea, irritability, hypertension, increased heart rate, seizures, coma, and serotonin syndrome (16). The side effects of tramadol in the treatment of acute and chronic pain are less frequent and intense than those of other opioids. Tramadol causes much less constipation, urinary retention, sedation, and respiratory depression than equivalent analgesic doses of other weak opioids. This increases its preference for long-term use (15,18,24).

### *Abuse and Addiction Profile*

The pharmacodynamic and pharmacokinetic properties of tramadol are unlikely to cause addiction. Slight potential for abuse may arise because of its relatively low affinity for μ-opioid receptors and its effect on serotonin and noradrenaline, neurotransmitters that play critical roles in mood. Epidemiological data, controlled clinical trials, and post-marketing surveillance studies have shown that the development of tolerance and addiction is quite low, especially when compared to morphine. In addition, fewer withdrawal symptoms

were observed with tramadol use than with equivalent doses of other opioids (15,16,18).

Epstein et al. (23) compared the results of intravenous placebo, morphine (10 and 20 mg; iv), or tramadol (100 and 200 mg; iv) administration for 5 minutes to 10 experienced opioid addicts. No tramadol dose showed morphine-like effects, and there was little evidence of physical dependence. When the use of parenterally administered tramadol was evaluated, the abuse potential of tramadol was reported to be low. However, a different pattern of action was observed when tramadol was administered orally. In this study, placebo, oxycodone (20 and 40 mg; po), or tramadol (175, 350, and 700 mg; po) were administered orally to 12 experienced opioid addicts. Tramadol and oxycodone have been reported to decrease pupil diameter, increase ratings on the 'feel drug' and 'liking' scales, and be available for abuse. However, maximal responses to tramadol occurred much later than maximal responses to oxycodone (23). This delay, in effect, is thought to be related to the conversion of tramadol to the opioid agonist O-desmethyltramadol. Furthermore, since the formation of O-desmethyltramadol is mainly dependent on hepatic metabolism, the opioid agonist effect observed with oral administration cannot be observed with parenteral administration because O-desmethyltramadol concentrations are much higher after oral administration than after parenteral administration (25). Abuse reports obtained through a post-marketing surveillance program indicate that the abuse rate of tramadol is low, and the majority (97%) of abuse cases occur in individuals with a history of substance abuse (26,27). Tramadol abuse was investigated by Skipper et al. (28) among physicians who were concerned about substance abuse, and different results than expected were found. It was reported in the study that a total of 872 narcotic agents were mentioned by physicians and that opioids ranked second after alcohol in terms of abuse. Tramadol was the third most commonly reported substance among opioids, constituting 10% of all opioids mentioned in terms of abuse, leaving behind fentanyl, codeine, propoxyphene, oxycodone, morphine, and butorphanol (28). Addiction and abuse are not limited to patients with a previous history of opioid addiction, as shown in several cases in previous studies (29). For example, in a study conducted to investigate the drug addiction and abuse potential of tramadol in individuals without a history of substance abuse, it was observed that individuals without a history of substance abuse could become addicted to tramadol. In the study, high doses (750 mg-2000 mg) of tramadol were used, and it is stated that high doses abused for a long time probably increased the addictive potential of tramadol (30). Additionally, tramadol addiction may vary between individuals. CYP2D6 is a member of the cytochrome P450 (CYP450) enzyme family and is the main enzyme responsible for the formation of O-desmethyltramadol, the active metabolite of tramadol. The CYP2D6 gene is highly polymorphic and has genetic variants that can lead to poor, normal, or accelerated (ultra-rapid) tramadol metabolism. Therefore, patients who over-metabolize drugs with the CYP2D6 gene are at higher risk of tramadol opioid addiction. For this reason, it would be more accurate to evaluate addiction individually (13,31).

### *Tramadol Use in Sports*

The analgesic approach pharmacologically constitutes the cornerstone of pain management in acute traumatic musculoskeletal injuries (32). Tramadol is a potent analgesic that can be used for pain management in severe sports-related injuries. In addition, it can be used by athletes because of its ergogenic effect, which can provide faster recovery between training sessions and reduce pain perception during training (3). Tramadol may enable athletes to perform beyond standard pain thresholds through analgesia resulting from its μ-opioid receptor agonist effect (2). In addition, although several studies (15,18) have shown that tramadol is unlikely to cause euphoria, its use by athletes may be linked to its mood-enhancing effects via its impact on serotonin and norepinephrine. Suppression of pain sensation, increased pain tolerance, and improved mood may encourage an athlete to push harder, leading to small performance gains (2,8). Tramadol is used by athletes to a considerable extent. In the study conducted by Baltazar-Martins et al. (3), the analysis of 9851 urine samples collected during competitions at national and international events was evaluated to assess the detection of tramadol levels at the Madrid Doping Control Laboratory between 2013 and 2017. The 135 urine samples analyzed were identified as "tramadol findings" because they contained urine tramadol concentrations above the WADA recommended limit of detection (LOD) (>50 ng/mL). Urinary tramadol concentrations ranged from 53.5 to 45 311 ng/mL, and the concentration of 113 samples (83.7% of the tramadol findings) was >1000 ng/mL. Although it is difficult to determine the dose of tramadol from tramadol concentrations in urine, it is known that ingestion of 100 mg of tramadol results in peak urine concentrations of ~100-150 ng/mL approximately 10-12 hours after ingestion. Accordingly, most of the tramadol findings in the present study corresponded to the use of tramadol doses above the therapeutic dose or the intake of tramadol over several consecutive days. It was also found that tramadol findings differed between sports branches in the study; 65.2% of tramadol samples were obtained from cycling athletes, 8.1% from triathlon, and 5.9% from rowing athletes. Tramadol was detected in 9.7% of the urine samples analyzed during cycling. In sports such as athletics, basketball, football, and aquatics, the prevalence of samples containing tramadol was <1% although some samples had urinary tramadol concentrations above 10.000 ng/mL. This may be a sign of tramadol abuse by some athletes involved in these sports. The urinary tramadol concentration found in some analyzed samples indicates that tramadol was taken at doses high enough to endanger athletes, especially in cycling races where the risk of accidents is frequent (3). According to the WADA 2017 Monitoring Program Figures Report, 122.706 urine samples were analyzed in WADA-approved laboratories, and 900 samples were determined to contain a concentration of tramadol above the LOD (>50 ng/mL). The overall prevalence of tramadol symptoms across all sports was 0.7%. Although the number of sports in which tramadol findings were detected was quite high, 60.9% of all tramadol findings were obtained in cycling, 9.8% in football, and 4.4% in athletics. Considering the number of samples analyzed on a branch basis, it is seen that the sports branches with the highest tramadol findings are cycling, rugby, and rowing (33).

According to the WADA 2018 Monitoring Program Figures Report, 130.701 urine samples were analyzed in WADA-approved laboratories, and 1160 samples were determined to contain a concentration of tramadol above the LOD (>50 ng/mL). The overall prevalence of tramadol symptoms across all sports was

0.9%. Although the number of sports in which tramadol findings were detected was still quite high, 49.5% of all tramadol findings were obtained in cycling, 14.1% in football, and 5.1% in athletics. Considering the number of samples analyzed on a branch basis, it is seen that the sports branches with the highest tramadol findings are cycling, rugby, and archery (34). As can be seen in the findings of the WADA Monitoring Program (33,34), tramadol has been frequently used by athletes in various sports, especially cycling. Sometimes, athletes may use tramadol to mask the pain caused by the injury and quickly return to sports activities before fully recovering. This situation has the risk of making the injury worse prolonging healing time, or causing permanent damage. Tramadol is a strong painkiller; if the athlete needs tramadol to relieve pain after an injury, the athlete's decision on whether or not to participate in the competition may need to be re-evaluated. Although tramadol can provide analgesic and ergogenic gains in sports, it can also cause conditions that may affect the safety of athletes during performance, such as dizziness, loss of alertness, drowsiness, and difficulty in concentrating (3,8). Decreases in cognitive function and lack of attention during some sports, such as cycling, can result in serious injuries (2). Chronic use of tramadol to manage exercise-induced pain may also result in addiction (3). Considering that athletes who use tramadol to increase performance use high doses, the risk of developing an addiction to the drug increases in such athletes. In addition, the type of tramadol used, age, gender, body weight, genetic polymorphisms, and mental disorders can significantly affect the rate of drug abuse (13,31). The International Cycling Union has stated that the commonly reported adverse side effects of tramadol, such as dizziness, drowsiness, and loss of attention, in addition to the risk of addiction, are incompatible with cycling races and endanger other competitors. Accordingly, to protect the health of each rider and ensure the safety of the competitions, the use of tramadol has been banned as of March 1, 2019 (35). When the literature is reviewed, it is seen that there are clinical trials (36-39) investigating the effects of tramadol on exercise performance; these trials are shown in Table 1. In one of these trials, Holgado et al. (36) tested the potential ergogenic effect of tramadol during cycling and whether it reduces the ability to focus on a specific task. The study was designed to be randomized, double-blind, placebo-controlled. The 19 men and 9 women, were given 100 mg tramadol or placebo orally. The study examined whether

**Table 1.** Clinical trials investigating tramadol and its effects on sports performance

| Study | Study design | Participants | Dose | Results |
|---|---|---|---|---|
| Holgado et al. (36) 2018 first experiment | Randomized, double-blind, crossover-design, placebo-controlled | 19 men, 9 healthy women volunteers | 100 mg of tramadol or placebo | The average power output was higher with tramadol than with placebo (tramadol: 220 W and placebo: 209 W) |
| Holgado et al. (36) 2018 second experiment (36) | Randomized, double-blind, crossover-design, placebo-controlled | 28 healthy volunteers | 100 mg of tramadol or placebo | No significant difference was observed between tramadol and placebo regarding average power output (tramadol: 234 W and placebo: 230 W). No behavioral differences were found between the attention task conditions |
| Bejder et al. (37) (2020) | Randomized, double-blind, crossover-design, placebo-controlled | 16 healthy male volunteers | 100 mg of tramadol or placebo | No significant difference was observed between tramadol and placebo regarding average power output (tramadol: 298 W and placebo: 294 W) and performance time (tramadol: 1474 s and placebo: 1483 s). Tramadol did not impair the ability to complete a certain cognitive and fine motor task performance during submaximal exercise |
| Zandonai et al. (38) (2021) | Randomized, double-blind, crossover-design, placebo-controlled | 29 healthy volunteers | 100 mg tramadol/day 1.5 g of paracetamol or placebo | No significant difference was found between tramadol (227 W) and placebo (221 W) [only a significant difference was found between tramadol and paracetamol (213 W), but no difference was found between paracetamol and placebo]. It did not cognitively impair the ability to focus during high-intensity effort |
| Mauger et al. (39) (2023) | Randomized, double-blind, crossover design, placebo-controlled | 27 healthy volunteers | 100 mg of tramadol or placebo | Higher average power output (tramadol: 270 W and placebo: 261 W) and shorter performance time (tramadol: 3758 s and placebo: 3808 s) were found with tramadol compared with placebo |

acute oral administration of tramadol improves performance by reducing perceived exertion and fatigue during a cycling time trial (first experiment). In another experimental design, in addition to the first experimental procedure, participants performed a visual task during the time trial to investigate whether information processing and behavioral responses in a sustained attention task would be affected by tramadol (second experiment). In the first experiment, the average power output with tramadol intake during the cycling time trial was found to be higher than that with placebo and was observed to improve trial performance by ~5%. It has been observed that the average heart rate obtained with tramadol intake is higher than that with placebo. However, in the second experiment, no difference in average power output was found between tramadol and placebo. Time-frequency analysis of electroencephalography data showed that tramadol has effects on brain functions related to stimulus processing. On the other hand, tramadol was found to have no effect on behavioral performance in the sustained attention task and did not impair cognitive performance in the ability to maintain attention during exercise. It has been stated that the reason for these different results between the first and second experiments is unclear (36). In another study, Bejder et al. (37) investigated the potential for a therapeutic dose of tramadol to affect average power output and motor-cognitive task performance during a cycling time trial. For this purpose, a randomized, double-blind, placebo-controlled trial was conducted with 16 highly trained cyclists. Participants were given 100 mg of tramadol or placebo, and the experiment consisted of an hour of submaximal effort followed by 15 km of cycling. It has been stated that taking 100 mg of tramadol did not increase the average power of highly trained cyclists. Additionally, 100 mg of tramadol did not impair cognitive and fine motor performance during submaximal exercise. However, during the study, three subjects taking tramadol reported nausea and vomiting upon completion of the experiment. The analysis after excluding these subjects showed that tramadol intake resulted in a higher mean power than placebo. This suggests that highly trained cyclists taking 100 mg of tramadol can improve their time trial performance without the occurrence of side effects. Additionally, the urinary detectability of 100 mg of tramadol ingestion in highly trained men was investigated, and it was found to be detectable for 24 hours. The analgesic effect of tramadol is expected to be negligible 24 h after ingestion; therefore, the detection window is sufficient for doping detection.

Zandonai et al. (38) aimed to test tramadol's potential ergogenic and cognitive effects of tramadol with those of placebo and paracetamol in a randomized, double-blind, and placebo-controlled study. Participants were orally administered 100 mg of tramadol, 1.5 g of paracetamol, or placebo and completed the cycling time trial. This study showed that 100 mg of tramadol did not cause changes in physical performance during a cycling time trial that included an attention task. It has been reported that tramadol provides a higher average power output than paracetamol, but there is no significant difference between tramadol and placebo (or paracetamol and placebo). Additionally, the results showed that tramadol increased behavioral and neural efficiency at rest but did not cognitively impair the ability to focus during high-intensity effort. Another finding was that although tramadol did not affect physical performance, it did affect the physiological responses recorded during exercise. Similar to the study by Bejder et al. (37) and the first experiment by Holgado et al. (36), tramadol caused a higher heart rate than placebo and paracetamol (38). The result obtained in the study by Zandonai et al. (38) that tramadol did not cause changes in physical performance is consistent with the results obtained from the second experiment by Holgado et al. (36) and the results obtained by Bejder et al. (37). However, this contradicts the findings of the first experiment of Holgado et al. (36). It is stated that this difference in results may be due to the error in the first experiment of Holgado et al. (36) or the inclusion of a cognitive task that would reduce the effect of tramadol in both the second experiment of Holgado et al. (36) and the study by Zandonai et al. (38). However, Bejder et al. (37) found that tramadol had no effect on physical and cognitive performance, although the study design did not include cognitive tasks. Regarding the different results obtained in the studies, it has been stated that tramadol may affect performance, but because this effect is relatively small, the trials conducted on this subject to date may have been insufficient to detect this effect (38). Mauger et al. (39) investigated the ergogenic effect of acute intake of tramadol on cycling performance, pain perception, and effort during constant-intensity cycling in a placebo-controlled study of highly trained cyclists. This study found that highly trained cyclists maintained a significantly higher power output and completed a competitive time trial significantly faster after the acute ingestion of 100 mg of tramadol. Tramadol reduced the perception of effort for a given power output but had no noticeable effect on pain intensity during cycling. When the previous studies in the literature are examined, in the first experiment by Holgado et al. (36), an average power output of 11 W (5%) higher with tramadol use was observed, while an average power output of 7 W was observed for participants who were not affected by the side effects of tramadol by Bejder et al. (37). Consistent with previous studies, Mauger et al. (39) found that participants taking tramadol achieved an average power increase of 9 W and an average improvement in the time to complete a cycling time trial of 1.3%. This difference would have a significant ergogenic effect on a group of highly trained cyclists and could change their ranking at the end of the competition (39).

### *Process of Entry of Tramadol Into the Prohibited List*

Tramadol entered the WADA Monitoring Program for the first time in 2012 under the title of narcotics and was included in the Monitoring Program every year between 2012 and 2023 (40). In 2024, tramadol was removed from the WADA Monitoring Program and placed on the WADA Prohibited List (41).

In September 2022, with the recommendation of the Expert Advisory Group, an in-competition ban on tramadol was approved, and it was decided that this ban would be valid as of January 1, 2024. The purpose of the delay in implementation was stated to be to provide an additional year for communication and training of athletes, their communities, and medical staff to better understand the implementation of the tramadol ban in competitions. In addition, time has been given to the scientific community to determine the details of the relevant procedures, laboratories to update their procedures, sports authorities to develop educational tools for athletes and medical and support staff to consider the safe use of tramadol for clinical purposes in the anti-doping context (42,43). Monitoring data from the WADA Monitoring Program have shown the significant use of tramadol in sports such as cycling, rugby, and

football. WADA-funded research studies by Holgado et al. (36) and Mauger et al. (39) have been reported to confirm the potential of tramadol to improve physical performance in sports. Accordingly, the washout period for tramadol, i.e., the time between the last therapeutically administered dose of tramadol and the start of the in-competition period, was determined as 24 hours. Furthermore, as stated under the title of narcotics in the Prohibited List, all optical isomers of narcotics are prohibited; accordingly, both isomers of tramadol (dextro/levo) are prohibited for in-competition use (44,45).

## DISCUSSION

It is believed that tramadol can improve exercise performance through its effects on effort, pain perception, and mood. Accordingly, clinical trials (36-39) investigating whether or not tramadol is doping have been conducted with a dose of 100 mg. However, evidence has shown that athletes who used tramadol in competitions took much higher doses (3). Doses above the therapeutic dose may have a more significant effect on performance improvement. Additionally, studies have addressed the acute use of tramadol; its effects with long-term effects have not been tested. Performance improvement may be beneficial for long periods of intense physical workloads. Furthermore, most studies have been conducted on male subjects. For this reason, there is a need for further studies examining the effects of tramadol at different doses and long-term use in sports, with the participation of more female participants. In addition, highly trained athletes may have higher pain tolerance due to regular training. Therefore, it is possible to obtain different results in highly trained athletes than in the general population. While examining the effects of tramadol on sports performance, studies on highly trained athletes are needed to provide more accurate results.

## CONCLUSION

Athletes tend to treat exercise-induced pain and sports-related injuries with the use of analgesic drugs during training and competition. One of the preferred analgesics is tramadol, a weak opioid agonist used to treat moderate to severe pain. The efficacy of tramadol in a wide range of acute and chronic pain conditions, the availability of various formulations, and its low side effects compared with other opioids make tramadol a preferable option for athletes. Although tramadol is used to treat pain, it is believed that tramadol may improve sports performance through its effects on pain perception or mood. In this regard, various studies have investigated the effects of tramadol on performance, which has been included in the WADA Monitoring Program for 12 years. Some studies have shown that it affects performance, can be abused by athletes, and has the potential for cognitive effects. As a result, tramadol has been banned for in-competition use by WADA as of 2024 due to its effects on performance and potential for side effects. The use of doping by athletes to increase performance and achieve success in competitions can result in penalties, bans, and health damage. Athletes should be aware of the health effects of tramadol when used individually. Both athletes and their medical support staff should be aware of the tramadol prohibition. To avoid doping sanctions, athletes competing in competitions must stop using tramadol before the competition.

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### *Authorship Contributions*

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