

# Does tramadol have a place in the dental armamentarium? An atypical opioid in dental practice from the pharmacological perspective – Part I. General tramadol administration

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## ABSTRACT

Pain is common in dental practice. It is not only a reason for patients seeking dental treatment, but it can also accompany performed procedures and often occurs after them. The management of acute pain consists of causative treatment and pharmacotherapy, with non-steroidal anti-inflammatory drugs (NSAIDs) being the drugs of choice in routine dental practice. These agents, however, may not be potent enough in cases with pain of greater intensity. This paper focuses on tramadol, an atypical opioid, which is the most popular analgesic of this type in the world and can be considered a valuable option for the management of

moderate to severe pain in dentistry and oral surgery. The characteristics of the agent were described, as well as its singular mechanism of action and biotransformation. Adverse effects that can occur during tramadol pharmacotherapy were discussed together with interactions significant in clinical practice. The available tramadol formulations were presented, with particular attention to the drug combinations examined in pain management in a dental setting.

**Keywords:** tramadol; pain management; dental pain; dentistry; oral surgery.

## INTRODUCTION

Pain is common in dental practice. It is not only a reason for patients seeking dental treatment, but it can also accompany performed procedures and often occurs after them, especially in oral surgery: in most cases, it is acute [1, 2, 3]. Generally, causative treatment plays the main role in the management of acute pain (e.g. root canal treatment or dental extraction in case of irreversible pulp inflammation), and pharmacotherapy is a valuable help for dentists [4]. While intraoperative pain is controlled with the means of proper local anaesthesia, postprocedural ailments can be treated with analgesics [3, 5]. The timely administration of analgesics can also alleviate the ailments before causative treatment [6]. Due to the inflammatory nature of the pain encountered, non-steroidal anti-inflammatory drugs (NSAIDs) are usually the first choice in routine dental practice, both before and after procedures [6, 7]. The insufficient anti-inflammatory properties of paracetamol (acetaminophen) restrict the use of its formulations in dentistry to the treatment of pain with mechanical components, such as postoperative pain in dentoalveolar surgery, especially after tooth extraction [3]. The agent enhances the action of NSAIDs, which justifies its use in compound formulations with analgesics from that group [4]. However, NSAIDs and paracetamol are not always potent enough to alleviate patient symptoms. An increase in pain intensity requires the use of other drugs in therapy. Moderate and severe pain, with numerical pain scale scores equal to 5 or more, is an indication of the use of opioid analgesics [8]. In such cases, tramadol is an option worth considering.

## TRAMADOL – AN ATYPICAL OPIOID

Tramadol, ( $\pm$ )-trans-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexan-1-ol, is an unusual opioid agent with additional properties that make it a valuable tool in pain management. Being the most commonly used opioid analgesic in the world, tramadol is currently listed on the second step of the WHO analgesic scale although, surprisingly, it is not included on the WHO list of essential drugs [9, 10, 11, 12]. Indications for tramadol administration in medicine are wide and, among others, include the treatment of postoperative pain, pain associated with labour and acute myocardial infarction, as well as trauma pain in prehospital and emergency department settings [8]. Tramadol is very popular in dental practice, which results from the wide indication of its prescription [10, 13]. The drug is used to treat moderate and severe pain in dentistry and dentoalveolar surgery [10, 14].

Tramadol was first synthesized in 1962 and launched under the name Tramal in 1977 by the West German pharmaceutical company Grünenthal. In 1995 it was approved by the US Food and Drug Administration and by other countries in the years that followed [14, 15]. The drug is a centrally acting analgesic. Regardless of structural similarity to morphine and codeine, the pharmacodynamic characteristics are distinct from those of the more classic opioids, which makes tramadol the first member of the “atypical opioids” group [11, 16, 17].

## MECHANISM OF ACTION

Despite the decades that have passed since its discovery, the exact mechanism of action of tramadol remains still a matter of intense research [11]. The drug is a weak, pure agonist of  $\mu$  ( $\mu$ ),  $\kappa$  ( $\kappa$ ), and  $\delta$  ( $\delta$ ) opioid receptors, with the highest affinity for the first type [18]. Surprisingly, the action of tramadol is largely independent of  $\mu$  opioid receptor stimulation, its analgesic effect is only partially reversed by naloxone, the opioid antagonist [11, 19]. The action of the drug was estimated to depend on the agonism of opioid receptors in 40%, and on the inhibition of monoamine reuptake in 60%, with the crucial effect of increased serotonergic and noradrenergic transmission [6, 19]. A growing body of evidence suggests that, except for the main dual (monoamine and opioid) mechanism of its analgesic action, tramadol affects other mediators involved in pain signalling. These include voltage-gated sodium ion channels, potassium ion channels, transient receptor potential V1 (TRPV1) channels, glutamate receptors,  $\alpha$ 2-adrenoceptors, and adenosine receptors. Tramadol also influences the mechanisms involving substance P, calcitonin gene-related peptide, prostaglandin E2, and proinflammatory cytokines [11, 16]. Inhibition of TRPV1 channels together with lowering pro-inflammatory cytokine levels can implicate the usefulness of the drug even in pulpal pain management, which still poses a therapeutic challenge [20]. Tramadol also modifies the crosstalk between neuronal and non-neuronal cells in peripheral and central sites modulating peripheral and central neuronal hyperexcitability. Given the wide spectrum of molecular targets, tramadol, as an analgesic, relieves a wide range of types of pain and its anxiolytic and antidepressant properties could help improve pain management outcomes [16]. Other interesting characteristics of this atypical opioid include some weak immunostimulatory properties, in contrast to the immunosuppressive action of classic opioid agents such as morphine, fentanyl, meperidine (pethidine), and methadone [21, 22].

Tramadol is commercially available as a racemic mixture of hydrochloride salts of (+)tramadol and (–)tramadol. Both enantiomers exhibit a weak  $\mu$  opioid receptors agonism, in the case of (+)tramadol slightly more pronounced than (–)tramadol and equal to about 1/6000 of morphine agonism. The enantiomers differ in their impact on monoamine transmission: the effect of (+)tramadol is based on enhanced serotonin signalling by inhibition of reuptake and stimulation of presynaptic release, while (–)tramadol acts mainly as a norepinephrine reuptake inhibitor [9, 15]. The racemic mixture poses superior analgesic properties than either enantiomer alone [23].

## METABOLISM

Tramadol is mainly metabolized in the liver by N- or O-demethylation followed by glucuronic or sulphuric acid conjugation [9]. The process of O-demethylation is especially important. Cytochrome P450 2D6 (CYP2D6) is responsible for the O-demethylation of tramadol to the first main hepatic metabolite O-desmethyltramadol also known as M1, which both

enantiomers are biologically active and play an important role in tramadol analgesic action. (+)O-desmethyltramadol (+M1) compared to the parent compound, exhibits about 300 times greater affinity to  $\mu$  opioid receptors [18, 24]. The agonism of tramadol is weak compared to morphine, and it is the derivative that is mainly responsible for the opioid effects of tramadol administration and the increase of the analgesic effect with time [9, 11]. The negative enantiomer of M1, (–)O-desmethyltramadol, exerts analgesic action in a mechanism of norepinephrine uptake inhibition. Recent trials with the use of a racemic mixture of M1 enantiomers in pain management bring promising results [25]. Both tramadol and M1 are mainly eliminated through the kidneys [26]. The elimination half-time reported for tramadol and its active derivative, following a single oral dose of 100 mg, is approx. 5 h and 9 h, respectively [15]. The longer elimination half-time of O-desmethyltramadol may promote bioaccumulation with regular dosing [27]. The second metabolite of tramadol, N-desmethyltramadol (M2), is a product of N-demethylation. It is deprived of analgesic properties and lowers the seizure threshold [9, 13]. Although M1 is the main metabolite formed at low concentrations of tramadol substrates, the formation of M2 predominates at high supratherapeutic substrate concentrations [28].

Cytochrome P450 2D6 (CYP2D6) genetic polymorphism contributes to the wide variation of tramadol metabolism and its effects among patients [26]. Based on the metabolizer status, CYP2D6 phenotypes can be classified into the following groups: ultra-rapid metabolizers (UMs) carrying at least 3 active copies of CYP2D6, extensive metabolizers (EMs) with 2 active copies, intermediate metabolizers (IMs) with 1 inactive and 1 reduced activity copy and poor metabolizers (PMs) with 2 inactive copies of the enzyme [27]. As the enzyme function in PMs is hampered, the analgesic effect in this group is weaker and slower due to lower plasma levels of active metabolite M1 [29]. Unconverted tramadol concentrations tend to be higher, which in turn increases the risk related to increased monoamine transmission [14, 27]. On the contrary, patients from the first group (UMs) exhibit greater than average enzyme function. Tramadol is rapidly and extensively converted to its active metabolite M1, plasma concentrations of O-desmethyltramadol are relatively high, and opioid effects, sedation, as well as the risk of opioid toxicity in UMs are most pronounced [14, 26, 27]. The prevalence of the types mentioned varies among ethnicities. Ultra-rapid metabolizers constitute up to 20% of Iran, Saudi Arabia, Egypt and Northeast African populations; large numbers were found also among Ashkenazi Jews and Ethiopians, while among North American and Middle European Caucasians individuals with potentiated tramadol metabolism constitute 1–5% of the population [26, 30, 31]. Reduced enzyme activity is observed in even 20% of African Americans, 10% of Caucasians and 2% of Asians [30].

## SIDE EFFECTS

Usually, tramadol is well tolerated, but, like all drugs, it exhibits adverse effects [16]. The most common side effects encountered,

regardless of the administration route, include nausea (6.1%), dizziness (4.6%), fatigue (2.4%), sweating (1.9%), vomiting (1.7%), and dry mouth (1.6%) [15, 16]. Adverse effects tend to occur during the initial treatment rather than maintenance doses of the medicine [32]. Hypotension and orthostatic hypotension occasionally occur after (especially early) intravenous injection in the mechanism of peripheral vasodilatation [15]. Xerostomia, not uncommon after tramadol administration, is the result of direct inhibition of the cholinergic receptors M1 and M3 responsible for salivation by the drug [24]. Recently, high doses of tramadol have been observed to cause oxidative damage and apoptosis in oral tissues and salivary glands in rats, and it is possible that a similar process occurs in humans [33]. The potency of the analgesic action of tramadol is lower than that of morphine, but on the other hand, with weaker opioid agonism the risk of respiratory depression and dependency is also less pronounced [9, 33]. Similarly, the opioid side effects of tramadol (constipation, nausea, and vomiting) tend to be more attenuated and acceptable than those of classical opioid agents [17]. However, in the case of ultra-rapid metabolism, concomitant use of other depressants, and overdose, the risk of respiratory depression exists and should not be ignored [14, 27]. The danger of this serious effect of opioid toxicity is the reason for naloxone administration in every case of tramadol overdose [16]. The potential for tramadol abuse and dependency compared to classical opioid agents is less pronounced, but, again, not negligible [16]. In particular, antidepressant and antianxiety properties, along with possible euphoric effects, contribute to the addictive potential of the drug [26]. The risk increases with chronic administration and a history of substance abuse [16]. Tramadol lowers the seizure threshold. The proposed mechanism of this side effect and the enhancement of serotonergic transmission is gamma-aminobutyric acid (GABA) receptor antagonism. Both the drug itself and its active metabolite inhibit GABA A receptors at high concentrations [27]. The risk is most significant in patients with an existing seizure disorder or a history of previous seizures; therefore, the drug is relatively contraindicated in patients with a history of epilepsy and is also not suitable for use with other agents that lower the seizure threshold as well [19, 27]. Caution should be paid also to tramadol administration in patients with head injuries [15]. The highest seizure rate has been observed in cases of tramadol overdose, abuse, and chronic use [27]. Similarly, the drug's negative impact on the endocrine system, i.e. hypoglycaemia, is a dose-dependent effect, which occurs more likely in cases of overdose [27, 34, 35]. Symptoms related to monoaminergic transmission tend to be pronounced, especially in PMs or concomitant use of agents that stimulate monoaminergic transmission or block microsomal enzymes responsible for tramadol demethylation [36]. Patients can present with mild hypertension and cardiac palpitation [27]. Serotonin transmission enhancement except for sweating may lead to serotonin syndrome and be partially responsible for the risk of seizures [15, 30]. The most dangerous non-opioid side effect of tramadol – serotonin syndrome can be life-threatening [37]. Serotonin syndrome in a tramadol-treated patient usually is a result of the concomitant use of the drug together with other serotonergic

agents, especially selective serotonin reuptake inhibitors (SSRI) antidepressants or atypical antipsychotics [19, 27, 30]. The risk is especially high in PMs, who tend to have higher plasma levels of (+)-tramadol [27]. Symptoms usually develop within 24 h of initiation, addition or overdose of serotonin medications, affect distinct patient's systems and can differ in intensity [38]. Signs of a mental status change include agitation, anxiety, restlessness, disorientation, and excitement [38]. Among neuromuscular abnormalities are tremor, clonus, hyperreflexia, and nystagmus. Neurological examination will reveal bilateral Babinski's sign together with muscular rigidity in such patients [36, 38]. Serotonin toxicity also manifests itself as an autonomic dysfunction that is responsible for hypertension, hyperthermia, diaphoresis, shivering, and cardiac arrhythmias. Pupils are dilated and can be unreactive. Diarrhoea may be present together with vomiting [38]. Symptoms of serotonin syndrome are shown in Table 1. Management begins with a prompt diagnosis and is generally supportive, consisting of discontinuation of all serotonergic agents, in some cases administration of serotonergic antagonists, and sedation with benzodiazepines, used with special caution when tramadol is administered [36, 38].

**TABLE 1.** Symptoms of serotonin syndrome divided according to their intensity

Level of intensity	Symptoms present at clinical examination*
<b>Mild</b>	hypertension (mild), tachycardia, mydriasis, diaphoresis (excessive sweating), shivering, tremor, myoclonus, hyperreflexia, irritability, sleep disturbance
<b>Moderate</b>	as above (hypertension may be more intense) and: hyperthermia up to 40°C, gastro-intestinal hyperactivity (up to diarrhoea), agitation, pressured speech, hypervigilance, nystagmus
<b>Severe</b>	hyperthermia exceeding 41°C, vital signs instability, delirium, muscle rigidity – together with trismus, severe hypertension and tachycardia. Additionally, in the most severe cases, possible complications are: rhabdomyolysis, arrhythmias, respiratory arrest

\* Note that seizures are possible at any stage of serotonin syndrome severity.

## INTERACTIONS

Practitioners prescribing tramadol should be aware of potential interactions between the medicine and other commonly used drugs and substances. Extreme caution should be paid

to agents that combined with the drug may cause additive central nervous system (CNS) depression, increase the risk of seizures or may cause serotonin syndrome [14]. In the first group, one has to mention the older generation of antihistaminic drugs, hypnotics and sedatives together with opioids, both medical and illicit [14]. Practitioners must not forget about the most common depressant and advise against the drinking of alcoholic beverages during tramadol therapy [32]. The risk of seizures increases when tramadol is combined with bupropion, fluoroquinolone antimicrobials, and lithium [14]. CYP3A4 inducers, like carbamazepine, foster the process of breaking down tramadol to N-desmethyltramadol (M2) – a metabolite that elevates the risk of seizure and exhibits no analgesic properties – therefore concomitant use should be avoided [13]. Drugs enhancing serotonin transmission, used in psychiatry, are commonly and justifiably associated with the risk of serotonin syndrome, especially when used with other serotonergic medicines like tramadol. Other, less obvious, agents potentiating serotonergic transmission, that should not be used with tramadol, include over-the-counter antitussive dextromethorphan and popular illicit party drug “ecstasy/molly” (3,4-methylenedioxymethamphetamine – MDMA) [39]. Setron antiemetics, like ondansetron, are sometimes listed in the literature as agents that, when used in combination with tramadol, pose a risk of serotonin transmission enhancement up to serotonin syndrome [30, 36]. The mechanism of the antiemetic action of setrons is based on 5HT-3 receptors antagonism; the drugs compete with tramadol at CYP2D6 enzyme also as the result reducing the production of active tramadol metabolite.

In clinical practice, a reduction in the analgesic action of tramadol by 5HT-3 antagonists is more commonly encountered than serotonin syndrome [37]. Furthermore, the analgesic effect of tramadol can be limited by the co-administration of drugs like metoprolol, propranolol from the beta-adrenolytic group, a proton pump inhibitor (PPI) omeprazole and dopaminergic antagonist metoclopramide – used as antiemetic due to impact of these agents on tramadol metabolism [13]. The substances that may exhibit potentially significant interactions with tramadol in clinical practice are listed in Table 2.

## CONTRAINDICATIONS

Tramadol cannot be administered to every patient as it is obviously contraindicated in those who have had a hypersensitivity reaction to any opioid. Although the risk of respiratory depression after tramadol administration is lower in comparison with typical opioids, it is not negligible. Therefore, its use should be avoided in patients with a history of severe respiratory depression, or bronchial asthma, without the necessary equipment in the office to treat these conditions [32]. Gastrointestinal obstruction is another contraindication for the administration of this medication [32]. Despite promising reports on outcomes, safety concerns restrict tramadol's use in paediatric population and it is generally agreed that the drug should not be used in patients under the age of 12 [32, 40]. In the case of adolescents under the age of 18, the medication should not be given if they have had a history of tonsillectomy or adenoidectomy [32].

TABLE 2. Tramadol interactions that are significant in the clinical practice

<b>Agents that may cause additive central nervous system depression when combined with tramadol</b>	benzodiazepines (alprazolam, clonazepam, diazepam, lorazepam, midazolam), buspirone, ethanol, gabapentin, hydroxyzine, opioid drugs (e.g. codeine <sup>1</sup> , methadone, heroin), ramelteon, risperidone, Z-drugs (eszopiclone, zaleplon, zolpidem)
<b>Agents that may increase the risk of seizures when combined with tramadol</b>	bupropion, carbamazepine, fluoroquinolone antimicrobials (ciprofloxacin, levofloxacin, moxifloxacin), lithium
<b>Agents that may increase the risk of serotonin syndrome when combined with tramadol</b>	dextromethorphan <sup>2</sup> , lysergic acid diethylamide (LSD), methylene blue, 3,4-methylenedioxymethamphetamine (MDMA, “ecstasy”, “molly”), monoamine oxidase inhibitors (MAOIs) <sup>3</sup> , Panax ginseng, selective serotonin reuptake inhibitors – SSRIs (citalopram, escitalopram, fluoxetine, paroxetine, sertraline), serotonin–norepinephrine reuptake inhibitors – SNRIs (duloxetine, venlafaxine), sibutramine, St. John's wort ( <i>Hypericum perforatum</i> ), trazodone, tricyclic antidepressants – TCAs (amitriptyline, clomipramine, desipramine, imipramine, nortriptyline), triptans used in migraine treatment (sumatriptan, zolmitriptan), vortioxetine

<sup>1</sup> Note that codeine is available as an over-the-counter (OTC) drug in compound analgesic and antitussive formulations; <sup>2</sup> Antitussive drug available OTC also in formulations; <sup>3</sup> A break of at least 2 weeks is necessary before starting tramadol administration in patients who were treated with an MAOI



Similarly, obstructive sleep apnoea, obesity and severe lung disease are the conditions in which tramadol administration may increase the risk of breathing problems, which is why American Academy of Paediatric Dentistry and the Food and Drug Administration recommend against the use of tramadol in adolescents with these disorders [41]. Tramadol is capable of crossing the placental barrier [38]. In animal models, the drug has not been proven to possess teratogenic properties, but, because similar research in humans is lacking, tramadol administration in pregnancy remains controversial [41, 42]. Chronic use or abuse of the drug by pregnant women, especially in the third trimester, may bring withdrawal symptoms to their offspring after birth [41]. Small amounts of the medicine and its metabolites have been found in breast milk [40]. Single administration is without clinical significance and in such a situation it is not necessary to stop breastfeeding [18]. The drug may be used with caution for a short time in the lowest effective doses with close monitoring of a patient and her child [41]. The longer use poses a risk of adverse reactions in infants and is not recommended [43]. Due to the risk of accumulation, a dose reduction by half and an increase in dosage intervals are required in patients with severe hepatic or renal dysfunction. Lower doses may also be needed in older adults [41]. Suicidal ideation and the patient's history of substance abuse are contraindications for tramadol prescription [14].

## TRAMADOL FORMULATIONS

Currently, various formulations of tramadol for different applications are available, including solutions for intravenous, intramuscular, or subcutaneous injections, drops, capsules, immediate and sustained-release tablets for oral use, and rectal suppositories [26]. Clinical studies have revealed that, also in oral surgery, the intravenous route is more effective than the oral route, although the latter way is usually preferred by patients [17]. When administered parenterally, tramadol has about  $\frac{1}{10}$  the potency of morphine [26]. To minimise possible side effects, like transient haemodynamic instability, i.v. injections should be given slowly over 2–3 min in an appropriate dose titrated to the intensity of pain and patient response [15]. After oral administration, tramadol is rapidly absorbed, with an onset of action within 1 h, for capsules, tramadol action usually starts in 20–40 min, while in the case of oral drops, the onset is even more rapid. The peak effect is usually achieved within 2 h [15, 26]. Tramadol instant-release oral preparations possess a similar level of bioavailability and should be administered 3–4 times a day, in recommended doses of 50–100 mg, not exceeding 400 mg a day [15, 19, 26]. The absorption rate after oral administration is equal to 95% and bioavailability is about 70% [9]. After multiple oral administrations, the drug bioavailability increases [11]. The immediate-release formulations are no longer advised for use as an “as needed” medication; instead, the indication is the management of pain that has less than a week duration [32]. Sustained-release formulations prolong the effective therapeutic time by controlling the blood

concentration of the drug, enhancing patient compliance, and decreasing the need for frequent administration, thus reducing the risk of habit formation [44]. Extended-release formulations are the therapeutic choice for pain that lasts longer than a week [32]. They are usually administered twice a day, in doses of 100–200 mg (as in the case of other tramadol pharmaceutical forms the max. daily dose is 400 mg), the onset of action after oral administration occurs in 60 min, peak plasma concentrations are achieved within 4–5 h, with a half-life equal to 10–11 h [26]. The clinical efficacy of rectally administered tramadol is controversial and the benefits over oral formulations are doubted, therefore suppositories are usually not recommended [45]. Tramadol preparations currently available in Poland are listed in Table 3.

General administration of plain tramadol in dental practice is seldom used; however, it can be an effective strategy of pre-emptive analgesia. A single oral dose of 100 mg given 60 min before performing the procedure of inferior alveolar nerve blocks (IANB) in patients experiencing symptomatic irreversible pulpitis of mandibular teeth improves the efficacy of local anaesthesia and diminishes ailments after endodontic treatment [46].

## TRAMADOL COMBINATIONS

Not always a combination of tramadol with another medication brings unwanted effects; however, due to concerns about the risk of increased toxicity and serotonin syndrome, treatment regimens for tramadol should be carefully designed and justified based on 3 important factors:

- specific mechanism of action of a combination of tramadol and drug,
- adverse effects of each drug,
- pain category-specific targets [47].

Multimodal (or “balanced”) analgesia represents an approach to postoperative pain prevention where analgesic drugs that act at different sites within the central and peripheral nervous systems are used [48]. The rationale for balanced analgesia is to provide sufficient pain relief through additive or synergistic effects, with a concomitant reduction of side effects due to the resulting lower doses of individual drugs [49]. Management of acute pain following surgery using a multimodal approach is recommended by the American Society of Anaesthesiologists whenever possible [50]. In clinical practice, a multimodal approach is the reason for the effective and safe combining of tramadol with analgesics with different mechanisms of action. With the exemption of a single oral dose before the dental procedures, where post-operative pain of greater intensity is expected, generally administered combined tramadol formulations are preferred over the plain ones in the management of moderate to severe pain in dentistry and oral surgery [10, 46].

Fixed dose combinations of tramadol with acetaminophen and tramadol with dexketoprofen have reached the market [16].

TABLE 3. Tramadol formulations currently available in Poland

Formulation	Form	Dose	Trade names
Single tramadol hydrochloride formulations	solution for injections	50 mg/mL (ampules 1 mL)	Poltram 50, Tramadol Krka, Tramal
		100 mg/2 mL (ampules 2 mL)	Poltram 100, Tramadol Krka, Tramal
	oral drops	100 mg/mL	Poltram, Tramadol Krka, Tramadol Synteza
	capsules	50 mg	Poltram
	hard capsules	50 mg	Tramadol Aurovitas, Tramadol Krka, Tramadol Synteza, Tramal
	tablets	50 mg	Tramadol Vitabalans
	extended-release tablets	50 mg	Tramal Retard
		100 mg	Poltram Retard 100, Tramadol Krka, Tramal Retard
		150 mg	Poltram Retard 150, Tramadol Krka, Tramal Retard
		200 mg	Poltram Retard 200, Tramadol Krka, Tramal Retard
	extended-release coated tablets	100 mg	Tramudin
	suppositories	100 mg	Tramal
Compound formulations: tramadol hydrochloride and acetaminophen (paracetamol)	tablets	37.5 mg of tramadol hydrochloride +325 mg of paracetamol	Exbol
	coated tablets	37.5 mg of tramadol hydrochloride +325 mg of acetaminophen	Doreta, Padolten, Poltram Combo, Tramadol +Paracetamol Genoptim, Tramadol +Paracetamol Medreg, Tramapar, Zaldiar
		75 mg of tramadol hydrochloride +650 mg of acetaminophen	Doreta, Palgotal, Poltram Combo Forte
	extended-release tablets	75 mg of tramadol hydrochloride +650 mg of acetaminophen	Doreta SR
	effervescent tablets	37.5 mg of tramadol hydrochloride +325 mg of acetaminophen	Zaldiar Effervescent
	coated tablets	75 mg of tramadol hydrochloride +25 mg of dexketoprofen	Skudexa

In comparison with tramadol alone, the compounds formulations of the drug with acetaminophen (paracetamol) or NSAIDs exhibit better efficacy in acute perioperative pain management and are used successfully in dentoalveolar surgery also [10, 17]. Such formulations are a valuable help for practitioners, because both NSAIDs and acetaminophen, when added to tramadol, allow obtaining additive synergistic analgesic effect [6].

The combination of tramadol and acetaminophen was proved to be superior to either medication alone with respect to pain relief, time of onset and duration of action [17]. Its use in dentistry is limited to the management of pain with mechanic compound, like ailments after tooth extraction [3]. With some caution, tramadol/paracetamol formulations, due to certain anti-inflammatory properties of the first drug, may be used as

alternatives to NSAIDs when NSAID administration is contraindicated [51]. Enhancement of anti-inflammatory action, however, encourages practitioners to choose tramadol combined with an NSAID. Preparations of tramadol and dexketoprofen, available also in Poland, are a valuable help in pain management, especially useful in dentistry [52]. The combination represents a comprehensive multimodal approach to moderate-to-severe acute pain that encompasses central analgesic action, peripheral analgesic effect and anti-inflammatory activity, together with a good tolerability profile [53]. The effect is characterized by rapid onset and long-lasting analgesia [54]. The pronounced anti-inflammatory action of the formulation favours its use in clinical situations where expected acute pain is related to a lesion and consequent mild inflammatory response, for example in the third molar surgical extraction, and results in a superior analgesic effect compared to the tramadol/acetaminophen combination [55, 56].

In recent years, combinations of tramadol and other agents were brought under research both as compound formulations and simple co-administration of 2 agents in dental pain management. Of interest are tramadol combinations with flurbiprofen, ibuprofen, celecoxib and lysine clonixinate. Tramadol (100 mg loading dose and then 100 mg every 6 h) and flurbiprofen (100 mg loading dose and then 50 mg every 6 h) administered with causal treatment in emergency endodontic patients were more effective than either of the drugs administered alone in the same doses in symptomatic pulpitis pain management [57]. The dosing regimen in this study remains a matter of debate, given the questionable analgesic synergy between an NSAID and tramadol when a maximal daily dose of the latter is used. Tramadol 50 mg and ibuprofen 200 mg, given together orally every 8 h, provided better post-operative pain management and attenuation of inflammation after third molar extraction compared to the higher doses of either of the agents administered alone (100 mg and 400 mg, respectively) [58]. Analgesia with pronounced anti-inflammatory action is likely to be expected after the combination of tramadol and selective cyclooxygenase-2 (COX-2) inhibitors. Practitioners should not forget about the elevated risk of thromboembolic events related to the use of selective COX-2 inhibitors and avoid administering these agents to patients with existing intrinsic risk of cardiovascular disease [59]. Celecoxib, a preferable COX-2 inhibitor, would be an interesting candidate for co-administration with tramadol; however, it reduces CYP2D6 activity, hampers the process of tramadol demethylation to M1 thus limiting the analgesic action of this atypical opioid [13]. In order to overcome this challenge, a different formula was proposed. Co-crystal of tramadol-celecoxib (CTC), a first-in-class analgesic co-crystal comprising racemic tramadol hydrochloride and celecoxib in a supramolecular network, has recently been shown in pre-clinical and phase 1 studies to modify the physicochemical and pharmacokinetic properties of both agents, optimizing these properties compared with their administration alone or in free combination [60, 61]. Promising outcomes were brought by trials of novel formulations in acute moderate-to-severe pain in medicine and oral surgery [62, 63]. Tramadol with lysine

clonixinate is another noteworthy combination [49, 64]. Clonixine is an anthranilic acid derivative, and its lysine salt exhibits a mechanism of action similar to NSAIDs blocking COX-1 and COX-2 enzymes, thus lowering the level of proinflammatory prostaglandins. In clinical practice, the agent is used to treat chronic arthritic conditions and soft tissue disorders associated with pain and inflammation [65]. The drug is not available in Poland. In a trial conducted by Perez-Urizar et al., the combination of lysine clonixinate and tramadol (125 mg of lysine clonixinate + 25 mg of tramadol, every 8 h) was superior to that of a standard dose of 50 mg tramadol alone for postoperative pain treatment following the concomitant surgical extraction of 2 partial or fully impacted lower third molars. In comparison with tramadol alone, the combination exhibited a faster onset of action, exhibited more pronounced anti-inflammatory properties and reduced the risk of trismus [49].

Tramadol in drops with midazolam was proven to be effective before multiple dental extractions in general anaesthesia in children [64]. Due to the risk of CNS depression, however, such a combination is not a recommended strategy in ambulatory care, especially in children and fragile patients [13].

## SUMMARY

Tramadol hydrochloride is an atypical opioid agent exhibiting an unusual mechanism of analgesia. In the management of pain encountered in dentistry and oral surgery, tramadol is not a drug of choice, being restricted to cases with the pain of moderate to severe intensity. Especially useful are formulations with NSAIDs, showing that tramadol should not be underestimated as a valuable tool in dental practice.

## REFERENCES

1. Thota L, Bansal R, Thota G, Chikkanna MK, Shanab H, Kumari VV. Efficacy of routinely used analgesics in management of pulpal pain postoperatively a clinical study. *J Pharm Bioallied Sci* 2021;13(Suppl 1):S684-7.
2. Pasternak M, Woroń J. Ostry ból endodontyczny. *Ból* 2020;21(1):39-45.
3. Pasternak M, Woroń J. Postępowanie w bólu poekstrakcyjnym. *Ból* 2020;21(1):47-52.
4. Pergolizzi JV, Magnusson P, LeQuang JA, Gharibo C, Varrassi G. The pharmacological management of dental pain. *Expert Opin Pharmacother* 2020;21(5):591-601.
5. Pasternak M, Woroń J. Rola znieczulenia miejscowego w uśmierzaniu bólu śródzabiegowego w praktyce stomatologicznej. *Ból* 2021;22(1):24-35.
6. Jakubów P, Branko J. Leczenie bólu w stomatologii. In: Jabłecka A, Krzemiński TF, editors. *Podstawy farmakologii klinicznej, alergie, interakcje leków oraz wybrane problemy w stomatologii*. Lublin: Czelej; 2005. p. 75-96.
7. Singgih MF, Huldani, Achmad H, Sukmana BI, Carmelita AB, Putra AP, et al. A review of nonsteroidal anti-inflammatory drugs (NSAIDs) medications in dentistry: uses and side effects. *Sys Rev Pharm* 2020;11(5):293-8.
8. Hachimi-Idrissi S, Dobiáš V, Hautz WE, Leach R, Sauter TC, Sforzi I, et al. Approaching acute pain in emergency settings; European Society for Emergency Medicine (EUSEM) guidelines – part 2: management and recommendations. *Intern Emerg Med* 2020;15(7):1141-55.
9. Mutschler E, Geisslinger G, Kroemer HK, Ruth P, Schäfer-Korting M. Analgetyki (leki przeciwbólowe). In: Mutschler E, Geisslinger G, Kroemer HK, Ruth P, Schäfer-Korting M. *Mutschler. Farmakologia i toksykologia*. Podręcznik. 2nd ed. Wrocław: MedPharm Polska; 2010. p. 217-88.

10. Kaczmarzyk T, Goszcz A, Grodzińska L, Stypułkowska J, Woroń J, Zaleska M. Farmakoterapia bólu w chirurgii stomatologicznej i szczękowo-twarzowej. In: Kaczmarzyk T, Goszcz A, Grodzińska L, Stypułkowska J, Woroń J, Zaleska M. Współczesna farmakoterapia w schorzeniach chirurgicznych jamy ustnej i tkanek okolicznych. Kraków: Wydawnictwo Uniwersytetu Jagiellońskiego; 2006. p. 171-213.
11. Bravo L, Mico JA, Berrococo E. Discovery and development of tramadol for the treatment of pain. *Expert Opin Drug Discov* 2017;12(12):1281-91.
12. WHO model list of essential medicines. Geneva: World Health Organization; 2017.
13. Woroń J, Korbut R. Ambulatoryjne leczenie tramadolem – spojrzenie farmakologa. *Gal Gaz Lek* 2020;4:21-2.
14. Donaldson M, Goodchild JH. Tramadol: what have we learned in the last 25 years? *Gen Dent* 2021;69(4):14-8.
15. Shipton EA. Tramadol – present and future. *Anaesth Intensive Care* 2000;28(4):363-74.
16. Barakat A. Revisiting tramadol: a multi-modal agent for pain management. *CNS Drugs* 2019;33(5):481-501.
17. Cillo JE. Peri-operative pain management in maxillofacial surgery. In: Ferneini E, Bennett JD, editors. Perioperative assessment of the maxillofacial surgery patient. Cham: Springer; 2018. p.145-60. doi: 10.1007/978-3-319-58868-1\_11.
18. Dobrogowski J, Wordliczek J, Woroń J. Opioidowe leki przeciwbólowe w farmakoterapii bólu. In: Dobrogowski J, Wordliczek J, Woroń J, editors. Farmakoterapia bólu. Poznań: Termedia Wydawnictwa Medyczne; 2014. p. 61-104.
19. Schumacher MA, Basbaum AJ, Naidu RK. Opioid agonists & antagonists. In: Katzung BG, Trevor AJ, editors. Basic & clinical pharmacology. 13th ed. San Francisco: McGraw-Hill Education; 2015. p. 531-51.
20. Schuh CM, Bens B, Aguayo S. Potential novel strategies for the treatment of dental pulp-derived pain: pharmacological approaches and beyond. *Front Pharmacol* 2019;10:1068.
21. Olszanecki R. Immunofarmakologia. In: Olszanecki R, Wołkow P, Jawień J. Farmakologia. 2nd ed. Warszawa: PZWL Wydawnictwo Lekarskie; 2019. p. 184-210.
22. Saeed I, La Caze A, Hollmann MW, Shaw PN, Parat MO. New insights on tramadol and immunomodulation. *Curr Oncol Rep* 2021;23(11):123.
23. Raffa RB, Friderichs E, Reimann W, Shank RP, Codd EE, Vaught JL, et al. Complementary and synergistic antinociceptive interaction between the enantiomers of tramadol. *J Pharmacol Exp Ther* 1993;267(1):331-40.
24. Minami K, Sudo Y, Miyano K, Murphy RS, Uezono Y.  $\mu$ -Opioid receptor activation by tramadol and O-desmethyiltramadol (M1). *J Anesth* 2015;29(3):475-9.
25. Zebala JA, Searle SL, Webster LR, Johnson MS, Schuler AD, Maeda DY, et al. Desmetramadol has the safety and analgesic profile of tramadol without its metabolic liabilities: Consecutive randomized, double-blind, placebo- and active comparator-controlled trials. *J Pain* 2019;20(10):1218-35.
26. Ogbemudia B, Qu G, Henson C, Esfandiary L, Przkora R, Victor S. Tramadol use in perioperative care and current controversies. *Curr Pain Headache Rep* 2022;26(3):241-6.
27. Nakhaee S, Hoyte C, Dart RC, Askari M, Lamarine RJ, Mehrpour O. A review on tramadol toxicity: mechanism of action, clinical presentation, and treatment. *Forensic Toxicol* 2021;39(2):293-310.
28. Subrahmanyam V, Renwick AB, Walters DG, Young PJ, Price RJ, Tonelli AP, et al. Identification of cytochrome P-450 isoforms responsible for cis-tramadol metabolism in human liver microsomes. *Drug Metab Dispos* 2001;29(8):1146-55.
29. Saiz-Rodríguez M, Valdez-Acosta S, Borobia AM, Burgueño M, Gálvez-Múgica MÁ, Acero J, et al. Influence of genetic polymorphisms on the response to tramadol, ibuprofen, and the combination in patients with moderate to severe pain after dental surgery. *Clin Ther* 2021;43(5):e86-e102.
30. Terman G. Is Tramadol an Opioid or a Nonopioid Analgesic? Yes! Update! 2020;10. <https://wmc.wa.gov/sites/default/files/public/Newsletter/IsTramadolAnOpioid.pdf> (14.12.2022)
31. Llerena A, Naranjo MEG, Rodrigues-Soares F, Penas-Lledó EM, Fariñas H, Tarazona-Santos E. Interethnic variability of CYP2D6 alleles and of predicted and measured metabolic phenotypes across world populations. *Expert Opin Drug Metab Toxicol* 2014;10(11):1569-83.
32. Dhesi M, Maldonado KA, Maani CV. Tramadol. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022.
33. Hassabou NF, Elseweidy MM. Histopathological changes in submandibular gland and dorsal tongue of experimental rats due to prolonged tramadol intake focusing on novel modulatory effect of 10-dehydrogingerdione. *Arch Oral Biol* 2021;130:105223. doi: 10.1016/j.archoralbio.2021.105223.
34. World Health Organization. WHO Expert Committee on Drug Dependence: thirty-sixth report. WHO technical report series; No. 991. Geneva: World Health Organization; 2017. p. 45-6.
35. Cronin T, Smith LF. Tramadol-induced hypoglycaemia. *Postgrad Med J* 2018;94(1108):121. doi: 10.1136/postgradmedj-2017-135217.
36. Hassamal S, Miotto K, Dale W, Danovitch I. Tramadol: understanding the risk of serotonin syndrome and seizures. *Am J Med* 2018;131(11):1382-e1382.e6.
37. Stevens AJ, Woodman RJ, Owen H. The effect of ondansetron on the efficacy of postoperative tramadol: a systematic review and meta-analysis of a drug interaction. *Anaesthesia* 2015;70(2):209-18.
38. Beakley BD, Kaye AM, Kaye AD. Tramadol, pharmacology, side effects, and serotonin syndrome: a review. *Pain Physician* 2015;18(10):395-400.
39. Baldo BA, Rose MA. The anaesthetist, opioid analgesic drugs, and serotonin toxicity: a mechanistic and clinical review. *Br J Anaesth* 2020;124(1):44-62.
40. Bozkurt P. Use of tramadol in children. *Paediatr Anaesth* 2005;15(12):1041-7. doi: 10.1111/j.1460-9592.2005.01738.x.
41. Useful medications for oral conditions. In: American Academy of Pediatric Dentistry. The reference manual of pediatric dentistry. 2021-2022. Chicago (Ill): American Academy of Pediatric Dentistry; 2022. p. 612-8.
42. Médecins Sans Frontières. Essential drugs – practical guidelines. 2022. <https://medicalguidelines.msf.org/sites/default/files/pdf/guideline-339-en-2022-12-15.pdf> (15.12.2022).
43. U.S. Food and Drug Administration. Drug Safety Communication: FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women. <https://www.fda.gov/media/104268/download> (14.12.2022).
44. Vazzana M, Andreani T, Fanguero J, Faggio C, Silva C, Santini A, et al. Tramadol hydrochloride: pharmacokinetics, pharmacodynamics, adverse side effects, co-administration of drugs and new drug delivery systems. *Biomed Pharmacother* 2015;70:234-8.
45. le Roux PJ, Coetzee JF. Tramadol today. *Curr Opin Anesthesiol* 2000;13(4):457-61.
46. Elnaghy AM, Elshazli AH, Badr AE, Elsaka SE. Effect of preoperative tramadol, ibuprofen, ibuprofen/acetaminophen on the anaesthetic efficacy of inferior alveolar nerve block in patients with symptomatic irreversible pulpitis. *Aust Endod J* 2022. doi: 10.1111/aej.12642.
47. Mao J, Gold MS, Backonja MM. Combination drug therapy for chronic pain: a call for more clinical studies. *J Pain* 2011;12(2):157-66.
48. White PF. Multimodal analgesia: its role in preventing postoperative pain. *Curr Opin Investig Drugs* 2008;9(1):76-82.
49. Perez-Urizar J, Martínez-Rider R, Torres-Roque I, Garrocho-Rangel A, Pozos-Guillen A. Analgesic efficacy of lysine clonixinate plus tramadol versus tramadol in multiple doses following impacted third molar surgery. *Int J Oral Maxillofac Surg* 2014;43(3):348-54.
50. Elvir-Lazo OL, White PF. The role of multimodal analgesia in pain management after ambulatory surgery. *Curr Opin Anaesthesiol* 2010;23(6):697-703. doi: 10.1097/ACO.0b013e32833fad0a.
51. Medve RA, Wang J, Karim R. Tramadol and acetaminophen tablets for dental pain. *Anesth Prog* 2001;48(3):79-81.
52. Woroń J, Wordliczek J. Połączenie tramadolu z deksketoprofenem w praktyce klinicznej – postęp w leczeniu bólu. *Lekarz POZ* 2017;3(1):61-7.
53. Varrassi G, Hanna M, Macheras G, Montero A, Montes Perez A, Meissner W, et al. Multimodal analgesia in moderate-to-severe pain: a role for a new fixed combination of dexketoprofen and tramadol. *Curr Med Res Opin* 2017;33(6):1165-73. doi: 10.1080/03007995.2017.1310092.
54. Moore RA, Gay-Escoda C, Figueiredo R, Tóth-Bagi Z, Dietrich T, Milleri S, et al. Dexketoprofen/tramadol: randomised double-blind trial and confirmation of empirical theory of combination analgesics in acute pain. *J Headache Pain* 2015;16:541.
55. Fornasari D, Allegri M, Gerboni S, Fanelli G. A “novel” association to treat pain: tramadol/dexketoprofen. The first drug of a “new pharmacological class”. *Acta Biomed* 2017;88(1):17-24.
56. Hanna M, Montero A, Perrot S, Varrassi G. Tramadol/dexketoprofen analgesic efficacy compared with tramadol/paracetamol in moderate to severe postoperative acute pain: subgroup analysis of a randomized, double-blind, parallel group trial – DAVID study. *Pain Ther* 2021;10(1):485-503.



57. Doroschak AM, Bowles WR, Hargreaves KM. Evaluation of the combination of flurbiprofen and tramadol for management of endodontic pain. *J Endod* 1999;25(10):660-3.
58. El-Sharrawy EA, El-Hakim IE, Sameeh E. Attenuation of C-reactive protein increases after exodontia by tramadol and ibuprofen. *Anesth Prog* 2006;53(3):78-82.
59. Olszanecki R. Niesteroidowe leki przeciwzapalne. In: Olszanecki R, Wołkow P, Jawień J. *Farmakologia*. 2nd ed. Warszawa: PZWL Wydawnictwo Lekarskie; 2019. p. 156-66.
60. Almansa C, Mercè R, Tesson N, Farran J, Tomàs J, Plata-Salamán CR. Co-crystal of tramadol hydrochloride–celecoxib (CTC): a novel API–API co-crystal for the treatment of pain. *Cryst Growth Des* 2017;17(4):1884-92.
61. Gascon N, Almansa C, Merlos M, Miguel Vela J, Encina G, Morte A, et al. Co-crystal of tramadol–celecoxib: preclinical and clinical evaluation of a novel analgesic. *Expert Opin Investig Drugs* 2019;28(5):399-409.
62. Langford R, Morte A, Sust M, Cebrecos J, Vaqué A, Ortiz E, et al. Efficacy and safety of co-crystal of tramadol–celecoxib (CTC) in acute moderate-to-severe pain after abdominal hysterectomy: A randomized, double-blind, phase 3 trial (STARDOM2). *Eur J Pain* 2022;26(10):2083-96.
63. López-Cedrún J, Videla S, Burgueño M, Juárez I, Aboul-Hosn S, Martín-Granizo R, et al. Co-crystal of tramadol–celecoxib in patients with moderate to severe acute post-surgical oral pain: a dose-finding, randomised, double-blind, placebo-and active-controlled, multicentre, phase II trial. *Drugs R D* 2018;18(2):137-48.
64. Yengopal V. What's new for the clinician? Excerpts from and summaries of recently published papers. *S Afr Dent J* 2020;75(4):214-7.
65. Saber A, Kassir AR, Naaman N, Mokbel N, Semaan LB, Dagher M. Comparison of the analgesic efficacy of two medications in patients receiving dental implants: a randomized controlled trial. *Curr Res Dent* 2021;12(1):71-6.