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Review

Tramadol as an analgesic for mild to moderate cancer pain

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Abstract:
In most cancer patients, pain is successfully treated with pharmacological measures such as opioid analgesics alone or opioid analgesics combined with adjuvant analgesics (co-analgesics). Opioids for mild-to-moderate pain (formerly called weak opioids) are usually recommended in the treatment of cancer pain of moderate intensity. There is a debate whether the second step of the WHO analgesic ladder, which, in Poland, is composed of opioids such as tramadol, codeine, dihydrocodeine (DHC), is still needed for cancer pain treatment. One of the most interesting and useful drugs in this group is tramadol. Its unique mechanism of action, analgesic efficacy and profile of adverse effects are responsible for its successful use in patients with different types of acute and chronic pain, including neuropathic pain. The aim of this article is to summarize the data regarding pharmacodynamics, pharmacokinetics, possible drug interactions, adverse effects, dosing guidelines, equipotency with other opioid analgesics and clinical studies comparing efficacy, adverse reactions and safety of tramadol to other opioids in cancer pain treatment.

Key words:
analgesics, cancer pain, opioids, pain treatment, tramadol

Introduction

Tramadol ((1RS,2RS)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-cyclo-hexanol) is a synthetic opioid from the aminocyclohexanol group, an analgesic with opioid agonist properties that acts on the neurotransmission of noradrenalin and serotonin [13, 31, 83]. The drug was developed in Germany by Grünenthal in 1962, entering West Germany in 1977, Poland in 1992, the US in 1995 and the UK in 1997. In comparison with typical opioid agonists such as morphine, pethidine and the partial agonist buprenorphine, tramadol rarely causes respiratory depression [33, 107] or physical dependence [81].

Tramadol possesses opioid agonist activity and activates the spinal pain inhibitory system. Tramadol can be administered orally, subcutaneously (*sc*), intravenously (*iv*), intramuscularly (*im*), rectally and spinally. In patients with postoperative pain of moderate or severe intensity, tramadol administered *iv* or *im* is equivalent to the analgesic potency of pethidine [35] and pentazocine (oral route) [41]. In patients with postoperative pain of moderate intensity, tramadol analgesia (when administered *iv* in doses of 50–150 mg) is equivalent to the analgesic efficacy of morphine in doses of 5–15 mg [33], although during epidural administration, tramadol possesses 1/30 of the analgesic efficacy of morphine [2, 16]. Tramadol's main adverse reactions are nausea, dizziness, sedation, dry mouth

and sweating. Respiratory depression has been observed in a small percentage of patients after *iv* tramadol administration [33, 107]. Intravenous tramadol administration during childbirth does not cause respiratory depression in neonates [35]. Tolerance and physical dependence during tramadol treatment of up to 6 months are not significant, but the possibility of physical dependence during long-term treatment cannot be completely excluded [81]. Experimental and clinical trials indicate that tramadol is an effective analgesic, with little influence on the respiratory center, suggesting that it may be successfully used in the acute and chronic pain treatment of moderate and, in some cases, severe intensity. In experimental studies, tramadol has little immunosuppressive effect [59], possesses antidepressant activity [37] and is as effective as pethidine in the prophylaxis of post-anesthetic shivering [67].

Pharmacodynamics and pharmacokinetics

Tramadol possesses low affinity for opioid receptors, with Ki values from 2.1 to 57.6 μmol/l, and a lack of selectivity for μ, κ or δ opioid receptors [31]. Tramadol has moderate affinity to μ opioid receptor and a weaker affinity for δ and κ receptors. Tramadol affinity to μ receptors is about 10 times weaker than codeine, 60 times weaker than dextropropoxyphene and 6,000 times weaker than morphine. Tramadol in concentrations of 10–100 μmol/l does not bind significantly to α_2-adrenergic, 5-HT_2, NMDA or benzodiazepine receptors [83]. The active metabolite O-desmethyltramadol (M1) possesses a higher affinity to the μ opioid receptor than tramadol and displays analgesic activity.

The second mode of analgesic action of tramadol is its influence on the pain descending inhibitory system [13]. It consists mainly of two pathways. The first originates from periaqueductal grey matter (PAG) in the midbrain, with synapses in the nucleus raphe magnus (RM), from which fibers project to the spinal cord. The neurotransmitter released in this pathway is serotonin (5-HT). The second main pathway originates from the locus coeruleus in the pons, which has projections to the spinal cord. The neurotransmitter released in this pathway is noradrenaline , which inhibits pain responses in the spinal cord through an α-adrenergic mechanism [89]. PAG, RM in medulla oblongata and dorsal horns in the spinal cord possess significant amounts of endogenous opioid peptides and opioid receptors. Activation of the descending pain inhibitory system is connected with the stimulation of interneurons, which inhibits transmission of painful stimuli in synapses in the dorsal horn of the spinal cord by the action of endogenous opioids. The mechanism of analgesic action of tramadol involves the activation of both the descending serotonergic and noradrenergic pathways [22, 82].

Tramadol also displays anti-inflammatory effects in a rat experimental model [5]. Another mode of tramadol action is a local anesthetic effect that is comparable to the effect of ondansetron in alleviating pain caused by propofol injection [65]. Tramadol is a racemic mixture of (+) and (–) enantiomers. Research regarding tramadol enantiomers has revealed that (–)tramadol is approximately 10 times more potent than (+)tramadol for inhibiting noradrenaline uptake [22], and (+)tramadol is approximately 4 times stronger than (–)tramadol for inhibiting 5-HT uptake [84]. Both enantiomers act synergistically toward improving analgesia but do not increase adverse effects.

After a single orally administered 100-mg dose, tramadol is rapidly absorbed; the maximal serum concentration of the drug is achieved within approximately 2 h [55]. The mean bioavailability of tramadol after a single oral dose is 68% [57] and is much higher than the bioavailability of morphine, which is lower and more variable [88]. Tramadol bioavailability increases to approximately 90–100% during multiple oral administrations, which is due to the saturation of the liver first pass effect. The mean total bioavailability of tramadol was 100% after *im* administration and 78% after rectal administration. The volume of distribution (Vd) after oral and *iv* administration in young, healthy, male volunteers was 306 L and 203 L, respectively, indicating a high affinity of tramadol for tissues. Approximately 20% of tramadol binds to serum proteins and crosses the placenta; the concentration in the serum of umbilical veins is 80% of the concentration in the mother's veins [42]. During oral tramadol treatment for post-Caesarian pain (400 mg/day for 2–4 days), tramadol's mean relative infant dose was 2.88%, and no behavioral adverse effects appeared in exposed infants [36].

Tramadol is mainly metabolized by the cytochrome P-450 enzyme system in the liver and is excreted by the kidneys. Tramadol undergoes biotransformation in the liver, initially by the phase I reactions (mainly O- and N-demethylation) and later by the phase II reac-

tions (mainly conjugation of O- and N-demethylated compounds) [18, 58]. Eleven metabolites are produced in the first phase reactions, and twelve metabolites are produced in the second phase; the main metabolite is M1 [23, 113]. It possesses analgesic activity and has a higher affinity to mu opioid receptors than the parent compound [30, 88]; (+)M1 has 300–400 times greater affinity to μ opioid receptors than tramadol [25] and (–)M1 mainly inhibits noradrenalin reuptake [106]. Apart from M5 (which possess weaker analgesic activity compared to M1) and M1, other metabolites are pharmacologically inactive. Mono-O-demethylation leading to M1 production is possible by the polymorphic CYP2D6 enzyme (sparteine oxygenase) of cytochrome P-450 in the liver, which is inhibited by the quinidine-selective inhibitor of this enzyme [73].

The elimination half-life is approximately 5–6 h for tramadol and approximately 8 h for M1 [40]. During oral administration of tramadol, approximately 90% of the drug is excreted by the kidneys and 10% is excreted in feaces [58]. Patients with renal impairment (creatinine clearance < 79 ml/min) have decreased excretion of tramadol and M1 compared to healthy individuals with normal renal function (creatinine clearance > 100 ml/min) [56]. In patients with advanced cirrhosis, there is a decrease in tramadol metabolism with a concomitant decrease in hepatic clearance and increase in blood serum levels [94]. In these patients, the observed elimination half-life is 2.5 times longer.

The impact of CYP2D6 polymorphism on tramadol analgesia. Possible drug interactions

Polymorphism of the CYP2D6 gene may cause attenuation of tramadol analgesia in poor metabolizers (PM) in 7–10% of the Caucasian population that is connected with the formation of a negligible amount (+) M1, a potent μ opioid agonist [80]. In a prospective study, Stamer et al. [96] investigated whether the PM genotype has an impact on tramadol response in 300 postoperative patients who were treated with a 1-ml bolus dose of a combination of tramadol 20 mg/ml, dipyrone 200 mg/ml and metoclopramide 0.4 mg/ml *via* patient-controlled analgesia (PCA) after titration to an individual loading dose. Patients classified as PM (n = 30) needed higher loading doses of tramadol than extensive metabolizers (EM) (n = 241) (144.7 ± 22.6 and 108.2 ± 56.9 mg, respectively, $p < 0.001$). The percentage of non-responders was significantly higher in the PM group (46.7% *vs.* 21.6%, respectively, $p < 0.005$), and more patients from the PM group required rescue analgesia in the recovery room (43.3% *vs.* 21.6%, $p < 0.02$).

In another prospective study, Stamer et al. [98] investigated the impact of the CYP2D6 genotype and CYP2D6 inhibitors on plasma levels of tramadol and M1. There were 174 patients, 170 of whom received tramadol 3 mg/kg intravenously for postoperative analgesia. Blood samples were taken after 30, 90 and 180 min. Concentrations of M1 differed between the different genotypes (PM, IM (intermediate metabolizers), EM and UM (ultra-rapid metabolizers)). The median (1/3 quartile) areas under the concentration time curves for (+)M1 were 0 (0/11.4), 38.6 (15.9/75.3), 66.5 (17.1/118.4), and 149.7 (35.4/235.4) ng × h/ml for PM, IM, EM and UM, respectively ($p < 0.001$). Medications inhibiting CYP2D6 that were administered with tramadol decreased (+)M1 concentrations ($p < 0.01$). In the PM group, non-response rates to tramadol treatment increased fourfold compared to the other genotypes ($p < 0.001$).

Changes in the analgesic activity of tramadol during administration with some adjuvants were observed in a study performed in rats. Tramadol with midazolam and tramadol with haloperidol rendered better analgesia than tramadol alone, which can be explained by σ receptor involvement in the case of haloperidol [10]. Tramadol with levomepromazine and tramadol with metoclopramide attenuated tramadol analgesia, most likely in connection with the antidopaminergic activity of these compounds. Tramadol with hyoscine buthylbromide did not change its analgesic effect. These results were achieved in tail flick tests in rats and cannot easily be extrapolated to humans; however, they indicate the possibility of modification of tramadol analgesia by some adjuvants [70]. It should also be noted that administration of tramadol with metoclopramide and with levomepromazine may decrease nausea and vomiting, although these combinations also increase sedation [75, 76]. In clinical studies performed in patients with postoperative pain, the addition to tramadol diclofenac [110], ketamine or magnesium [105] and the addition of tramadol to morphine [108] resulted in better analgesia.

Tramadol metabolism through the CYP2D6 enzyme of cytochrome P-450 in the liver can be a cause

of possible interactions with drugs that inhibit this enzyme [74]. Cimetidine and ranitidine are commonly used drugs that have this effect. Combining SSRIs (fluoxetine, paroxetine and, to a lesser extent, sertraline, which all inhibit CYP2D6) with tramadol may cause symptoms of serotonin syndrome because SSRIs, apart from inhibiting tramadol metabolism, increase the level of serotonin in the central nervous system (CNS); because of this, they should not be co-administered with tramadol. Serotonin syndrome may also appear with concomitant MAO inhibitors, olanzapine, risperidone and venlafaxine. On the other hand, mianserin and mirtazapine do not influence serotonin levels and do not inhibit CYP2D6 [21, 63, 87].

Inhibition of tramadol metabolism may attenuate analgesia because (+)M1 possesses significant opioid analgesic activity. The attenuation of tramadol analgesia can be caused by concomitant administration of ondansetron ($5HT_3$ receptor selective antagonist). It is associated with blockage of spinal serotonin receptors and competitive inhibition of CYP2D6 by ondansetron [1]. Tramadol analgesia is impaired by concomitant administration of carbamazepine due to the acceleration of tramadol and M1 metabolism [28]. Concomitant administration of tricyclic antidepressants, which have a similar mode of action as tramadol, increases the risk of seizures. Tramadol should be avoided in patients with a history of epilepsy. However, tramadol administered alone does not influence the possibility of epileptic fits [24]. In rats and mice, concomitant administration of tramadol and pindolol, a β-adrenoceptor blocker and $5HT_{1A/1B}$ receptor antagonist, enhances analgesia [86].

Adverse effects

The most common adverse effects of tramadol are nausea, vomiting, dizziness, fatigue, sweating, dry mouth, drowsiness and orthostatic hypotension. In a summary of data from phase II–IV and post-marketing studies, as well as from spontaneous reports including over 21,000 patients, the frequency of side effects was estimated to be 1–6% [14]. In an open study of 7,198 patients with chronic pain, adverse effects were noted in 16.8% of patients: 68.9% of patients had mild adverse effects, 22.1% had adverse effects of severe intensity, and there was no data for 9% of patients. The most frequent adverse effects were unspecific CNS irritation and signs of coordination disorders (7.1%), dizziness (5.3%), nausea (4.8%), sedation (2.4%), dry mouth (2.2%) and vomiting (0.8%). At least some of the adverse effects might have been evoked by tramadol's interaction with concomitant drugs, which were administered to 45% of patients receiving tramadol [15]. In a post-marketing study, controlled release tramadol was administered to 3,153 patients with chronic pain of different origins; adverse effects were noted in 6.5% of patients, with the most frequent effects being nausea (3.4%), dizziness (1.5%) and vomiting (1.1%). No serious adverse effects were observed in this study [69]. Compared to other opioids, tramadol has little influence on GI tract motility. Tramadol has a minor delaying effect on colonic transit but no effect on upper GI transit or gut smooth muscle tone [109]. In contrast to morphine, tramadol at a dose of 1 mg/kg does not delay gastric emptying in humans [68]. In contrast to other opioids such as buprenorphine and pentazocine, tramadol has no effect on the sphincter of Oddi [100]. Tramadol treatment is less costly in comparison to morphine [19] and positively influences patients' quality of life [49].

Respiratory depression is rare during chronic tramadol use; however, some experimental data regarding the use of high doses of tramadol in cats (4 mg/kg) suggests such a possibility [103]. In clinical practice, respiratory depression was observed during cancer pain treatment with tramadol in patients with renal impairment [3]. This is related to the accumulation of the active metabolite (M1), which has a longer elimination half-life than the parent compound (8 h) and binds to μ opioid receptors. Respiratory depression is connected to the opioid mode of tramadol action; if it does occur, naloxone should be administered intravenously. A report of respiratory depression in a patient treated with tramadol for postoperative abdominal pain (renal carcinoma) who suffered from renal impairment (creatinine clearance 30 ml/min) and had a UM genotype was depicted. Because the symptom appeared over 10 h after the first tramadol dose, the cause was thought to be accumulation of M1; the symptom disappeared after an intravenous naloxone bolus was administered (0.4 mg). Authors do not recommend tramadol administration in patients with UM genotypes and renal impairment. The UM genotype is thought to be present in approximately 5% of people in North America and Middle Europe, 7–12% of people in the Mediterranean, 21% of people in Saudi Arabia and 29% of people in Ethiopia [99].

Tramadol intoxication is rare; symptoms of overdose may appear at a dose of 25 mg/kg. In rats, however, the LD_{50} (the dose causing death in 50% of those receiving the drug) is 300–350 mg/kg for oral administration and 50–100 mg/kg for *iv* administration [64]. Overdose symptoms are muscle spasm, seizures, cardiac and respiratory depression, miosis and vomiting. In this situation, naloxone should be administered *iv* either as a bolus or as a continuous infusion [42]. There are reports of intentional tramadol intoxications; ingestion of a dose over 5 g caused death due to cardiopulmonary arrest [90]. The potential risk of abuse and physical dependence is low in comparison to other opioids, such as morphine. In a study performed in opiate abusers, tramadol was identified as an opiate only at a high dose (300 mg) but did not produce morphine-like effects, such as liking or miosis [81]. The low abuse potential of tramadol was confirmed by experimental study in rats. Morphine produced conditioned place preference and very strong locomotor sensitization while tramadol and meptazinol produced only conditioned place preference [104]. In the US, where tramadol is a non-scheduled drug, the frequency of abuse is 1 case per 100,000 patients treated with tramadol; 97% of abuse cases occur in individuals with a history of substance abuse [11]. Additional evidence for low physical dependence is a mild intensity of withdrawal symptoms during naloxone administration [4].

Tramadol formulations and administration routes. Dosing guidelines and equipotency with other opioids

In clinical practice, tramadol is usually administered orally (the preferred route); however, in patients with severe nausea and vomiting, confusion and swallowing difficulties, the drug can be given *sc via* a butterfly needle. Other possible routes of tramadol administration include *iv*, *im*, rectal and spinal. Tramadol can be administered *sc* or *iv* from one syringe in a mixture with metoclopramide, hyoscine buthylbromide, haloperidol, levomepromazine and midazolam. Analytical studies confirmed the stability and lack of dissolution of analyzed compounds within 48 h [79].

Titration of tramadol dose should be performed carefully, to avoid and diminish adverse effects [77]. A prescription of prophylactic antiemetic when starting tramadol treatment by the oral route is recommended to avoid nausea and vomiting, such as haloperidol 1 mg b.i.d. or metoclopramide 10 mg t.i.d.; the latter, however, inhibits CYP2D6 and may theoretically attenuate tramadol analgesia [17]. The most convenient formulation of tramadol is drops (10 drops = 25 mg), although normal-release capsules (50 mg) can be also used, especially for dose titration. The starting single dose is usually 25–50 mg, but in older, cachectic patients as well as in cases of renal or hepatic impairment, a smaller starting dose of 12.5–25 mg is recommended. A dose titration against pain is usually performed with 25–50% dose increments. Another possibility is to start treatment with modified-release formulations; however, with this approach, the starting single dose is usually higher (50–100 mg b.i.d.).

In Poland, several modified-release tablets are available in doses of 100, 150 and 200 mg, along with controlled release tablets of 100 mg, which may be divided into two parts each containing 50 mg of tramadol without controlled release system interference, where this allows for mild dose titration. Another possibility is the administration of modified-release capsules (50, 100, 150, 200 mg), which contain multiple units (microcapsules) that can be poured out and then swallowed without controlled release system disturbance [12]. This may be especially useful for patients with dysphagia who are fed by a nasogastric tube. Pharmacokinetic comparison of controlled release capsules and tablets (both 100 mg) showed similar AUC (infinity). However, capsules possess a better profile compared to tablets, as a lower cmax (148.6 *vs*. 183.2 μg/ml), a later time to reach cmax (5.9 *vs*. 4.9 h) and a longer half-life duration (13.4 *vs*. 10.4 h) were observed. A smaller intra- and inter-subject variability in plasma concentration during the first 2.5 and 3 h after administration are produced by capsules ($p < 0.05$) [39].

In an open study, starting tramadol treatment with controlled release capsules of 50 mg twice daily, with a subsequent increase after 7 days to 100 mg twice daily, was compared to beginning treatment with controlled release capsules of 100 mg twice daily. There was less frequent occurrence of at least one adverse effect (18.4% *vs.* 30.4%, $p < 0.001$) and lower frequency of nausea and vertigo in the 50-mg group ($p < 0.001$). The percentage of patients who interrupted tramadol treatment because of adverse effects was significantly lower in the 50-mg (5.6%) than in the 100-mg group (12.6%, $p < 0.001$). ANOVA revealed that the risk of

safety-related treatment cessations was 2.3 times higher in the 100-mg group. Both treatments rendered equally effective analgesia [101]. Controlled release formulations are also convenient for long-term administration. Modified release tablets (150, 200, 300, 400 mg) for once daily administration showed comparable pharmacokinetics, tolerability and efficacy compared to normal release capsules [6]. Special attention should be paid when administering tramadol *iv*, as adverse effects (orthostatic hypotension, seizures, nausea and vomiting) may be more intense; administration of a smaller dose or slowing the bolus infusion rate for a few minutes is recommended [91].

The alternative route to oral is rectal administration [66]. Currently in Poland, only a single high-dose (100 mg) tramadol formulation is available in suppositories. The dose for oral and rectal routes is the same as when changing from the oral to *sc* route during chronic administration. Although Grünenthal GmbH company recommends a maximal daily dose of 400 mg tramadol, similar to German authors [27] own experience indicates that the maximal daily dose of tramadol should not exceed 600 mg [48]. In few patients with strong pain, daily doses even higher than 600 mg were given, rendering effective analgesia and good treatment tolerance [47]. If tramadol analgesia is ineffective, a change to a strong opioid (analgesic for moderate-to-severe pain) is recommended. The relative potency of tramadol to morphine is about 1/5 to 1/10 for the oral route and about 1/10 for the *sc* and *iv* routes. However, experimental data [81] and studies in patients with postoperative pain indicate that tramadol-to-morphine potency for the *sc* route is about 1/20 [32] and about 1/12 for the *iv* route [97].

When daily doses of 400–600 mg tramadol are ineffective, the drug should be substituted with opioids for strong pain. The starting dose of oral morphine is usually 40–60 mg per day (single dose of immediate-release 10 mg every 4–6 h or controlled-release tablet 20–30 mg every 12 h). For a *sc* route, a dose of 20 mg morphine per day (single dose of approximately 4 mg) is usually recommended. When substituting tramadol with oral controlled release oxycodone, a dose of 20–30 mg per day seems to be appropriate, but there is very limited experience with this opioid in Poland [45]. In patients not responding to a full dose of tramadol (400–600 mg per day), oral methadone may be started at a daily dose of 9–15 mg (3–5 mg every 8 h) [46]. When switching from tramadol to TTS (transdermal therapeutic system) fentanyl, one patch of 25 µg/h is usually recommended [60]. In cases of tramadol substitution with TTS buprenorphine, one patch of 35 µg/h is administered (Tab. 1) [34, 95].

Tab. 1. Relative potency of oral tramadol to other opioids (oral route unless indicated), based on [32, 34, 45, 46, 54, 60, 95, 97], modified

Analgesic	Potency ratio to tramadol	Duration of action[1] (h)
Codeine	1:1	3–6
Dihydrocodeine (DHC)	10:6	3–6
Pethidine*	1:1	2–4
Morphine	10:1 (oral) 20:1 (*sc*, *iv*)	3–6
Oxycodone	20:1(oral) 40:1 (*sc*, *iv*)	4–5
Methadone	50:1**	8–12
Hydromorphone***	75:1	4–5
Buprenorphine (sublingual)	800:1	6–12
Buprenorphine TTS (transdermal)	1000:1[2]	72–96
Fentanyl TTS (transdermal)	1000:1[3]	48–72

[1]Duration of action of immediate-release oral preparations (IR). Opioids available in Poland in controlled-release oral formulations (CR): DHC and oxycodone (both CR only), tramadol and morphine (both IR and CR), methadone (IR only, long plasma half-life). * Not recommended for chronic cancer and non-malignant pain. ** For equivalent daily doses of oral morphine to 100 mg; with higher doses, the ratio is larger, i.e., methadone analgesic effect is stronger. *** Currently not available in Poland. [2]If tramadol is ineffective, one patch of 35 µg/h (0.8 mg/24 h) is recommended. [3]When tramadol is ineffective, one patch of 25 µg/h (0.6 mg/24 h) is recommended; in patients with severe cachexia, hepatic and renal failure, one patch of 12.5 µg/h (0.3 mg/24 h) may be administered *sc* – subcutaneous route, *iv* – intravenous route, TTS – transdermal therapeutic system

Clinical studies comparing tramadol with other opioids in patients with cancer and osteoarthritis pain

Open, non-comparative, clinical studies demonstrated tramadol analgesia and acceptable toxicity in patients with cancer pain [15, 43, 47, 52, 61, 62, 69, 71, 78, 85]. Comparative tramadol trials with other opioids in patients with cancer and osteoarthritis pain are reviewed (Tab. 2).

Osipova et al. [72] compared tramadol (119 patients) with controlled release morphine (CRM, 26 patients). The time of treatment was 1–3 months. In

Tab. 2. Tramadol comparative studies in patients with cancer pain [7, 9, 27, 44, 54, 72, 102, 112] and osteoarthritis pain [38, 111]

Author/ref./study design	No of pts	Daily doses (mg)	Duration	Analgesic efficacy (% of pts)		
				Good	Satisfactory	Inadequate
Osipova et al. [72]	T 21[1]	314	4–12 weeks	100		
nrand, nb, p	T 98[2]	368		89		11
	M26[2]	69–96		96	4	
Wildersmith et al. [112]	T 20	330–390	4 days, no	80		20
rand, db, crossover	M 20	91–101	washout	100		
				T less n and c		
Tawfik et al. [102]	T 26	217–232	8 weeks	88		
db, p, rand	M 27	50–71		100		
Grond et al. [27]	T 810	300–600	23.497 days	74	10	16
nrand, nb, p	M 848	10–60	24.695 days	78	7	15
Leppert [44]	T 20	200–600	5 weeks	Similar in NC	M better in NP	
rand, nb, p	M 20	20–270				
Brema et al. [9]	T 68	100–400	6 months	56.9		43.1
rand, nb, p	B 63	0.2–0.8		45.5		54.5
Bono and Cuffari [7]	T 60	300	7 days,	Similar analg,		
rand, crossover	B 60	0.6	1 day washout	T better tolerated		
Karlsson and Berggren [38]	T 65	150–400	12 weeks	Similar analg		
rand, nb, p	TB 69	5–20 μg/h		and adv effects		
Wildersmith et al. [111]	T 30	191–220	4 weeks	Similar analg		
rand, p	DHC 30	121–136		T more adv effects		
				DHC more c		
Leppert and Majkowicz [54]	T 30	200–600	1 week,	DHC better analg	DHC less n, bet GQL	
rand, crossover, nb	DHC 30	120–360	no washout		T less c and d	

ref. – reference number, pts – patients, nrand – non randomized, nb – non-blind, rand – randomized, db – double blind, p – parallel. [1] Patients with moderate pain intensity. [2] Patients with strong pain intensity. T – tramadol, M – morphine, B – buprenorphine, TB – transdermal buprenorphine, DHC – dihydrocodeine, NC – nociceptive pain, NP – neuropathic pain, analg – analgesia, adv effects – adverse effects, n – nausea, c – constipation, d – drowsiness, bet GQL – better global quality of life

the tramadol group, very good or good analgesia was achieved in all 21 patients with moderate pain. From the 98 patients with strong pain that were treated with tramadol, very good analgesia was observed in 39% of patients, good analgesia was observed in 50%, and insufficient or poor analgesia was observed in 11%. In 9 patients, a naloxone precipitation test was performed; no (8 patients) or marginal (1 patient) signs of abstinence syndrome were found. Tramadol adverse effects were marginal, with no changes in cardiovascular or respiratory parameters and no signs of tolerance. In the CRM group, all 26 patients suffered from severe pain. Better analgesia was achieved than with tramadol; analgesia was very good in 65% of patients, good in 31% of patients and satisfactory in 4% of patients. However, in patients treated with CRM, adverse effects were more frequent and often appeared before analgesia. In 6 patients, severe adverse effects such as deep sedation, fatigue, inability of food intake and urine retention appeared, which demanded therapeutic interventions and CRM dose decrease, which caused pain recurrence. In these patients, CRM was substituted with immediate release morphine or buprenorphine, which had better treatment tolerance. Negative impact of morphine on respiratory parameters and analgesia duration was less

pronounced after a 50% decrease in single dose. Authors stated that a significant increase in mean daily doses of CRM suggests a tolerance for analgesia; they recommend tramadol as basic analgesic for the treatment of moderate or severe cancer pain.

Wilder-Smith et al. [112] performed a randomized, cross-over, double blind study comparing oral tramadol with morphine (M) water solution in 20 patients with severe cancer pain. At the beginning, patients received both drugs in solution: tramadol 50 mg or M 16 mg every 4 hours, followed by doses titrated to pain control. All patients received prophylaxis for constipation, and all but 2 patients treated with M and 1 patient treated with tramadol received sustained-release metoclopramide in a dose of 20 mg b.i.d. to avoid nausea. After 4 days of treatment, which was cross over date pain intensity in both groups was similar. However, significantly less intense nausea and constipation were noted in the tramadol group. According to authors on the basis of drug consumption, equianalgesic doses of M and tramadol administered orally are 1:4. The trial was prematurely finished in 4 patients receiving tramadol because of inadequate analgesia and in 3 patients receiving M because of adverse effects (nausea, vomiting, dizziness, disorientation). In conclusion, analgesia during tramadol administration appeared later, but adverse effects were less intense than during M treatment, which suggests a need for further long-term tramadol studies.

Tawfik et al. [102] compared oral tramadol with CRM in 64 patients with severe cancer pain in a randomized, double-blind study. Tramadol administration resulted in good analgesia for less severe pain intensity, while CRM was preferred for severe pain intensity. A good analgesic effect was achieved in the first two weeks of treatment (trial time was 8 weeks) in 88% of patients receiving tramadol and 100% of patients receiving CRM. The main adverse effects during tramadol therapy were fatigue (15%), nausea (8%) and sweating (8%); adverse effects during CRM treatment constipation (35%), rash (14%) and drowsiness (14%). Daily doses of tramadol were increased from 217 to 232 mg (7%), and daily doses of CRM were increased from 50.4 to 71.1 mg (41%). Authors indicated minimal tolerance during tramadol treatment.

Grond et al. [27] performed a retrospective study comparing analgesic efficacy and safety of high daily tramadol doses (300 mg or higher) with small daily doses of M less than or equal to 60 mg administered orally without randomization and blinding. Both analgesics were used when daily doses of tramadol 250 mg with non-opioids were ineffective. Tramadol was administered to 810 patients for 23,497 days, 848 patients were treated with M for 24,695 days. Mean daily doses of tramadol were 428 mg (range: 300–600 mg) and 42 mg (range: 10–60 mg) for M. Mean pain intensity in visual analogue scale (VAS) was 27 ± 21 mg and 26 ± 20 for tramadol and M, respectively. Analgesia was good in 74% and 78%, satisfactory in 10% and 7%, unsatisfactory in 16% and 15% of patients treated with tramadol and M, respectively (differences were not significant). Constipation, neuropsychological symptoms and pruritus were more frequent in the M group. Antiemetics, laxatives, neuroleptics and steroids were more frequently prescribed for patients treated with M. Authors concluded that tramadol could be used in cancer pain treatment if non-opioids are not effective alone and that high doses of tramadol are safe and effective.

Brema et al. [9], in a multicenter, randomized study, compared the efficacy and safety of tramadol and buprenorphine (B) in patients with cancer pain that was not responsive to NSAIDs. Tramadol was given to 68 patients in controlled release tablets of 100 mg every 8–12 h up to 400 mg/day, and 63 patients received one B tablet of 0.2 mg sublingually every 6–8 h. The patients were treated for up to 6 months. In cases of poor pain relief, paracetamol was additionally administered in doses up to 4 g/day. Pain was assessed by 6-step verbal scale. During the first 2 weeks, patients filled daily diaries recording pain intensity (VAS), pain relief and quality of sleep (verbal scales). Performance status (PS) was assessed by the Karnofsky scale, and quality of life (QL) was assessed by Spitzer's Index QL. Mean tramadol and B treatment times were 57.7 and 50.9 days, respectively. In the tramadol group, 98.4% of patients reported severe and unbearable pain before therapy. After the first week, 48.4% reported the same level of pain; after 2 weeks, severe or unbearable pain was reported in 43.1% of patients. For the B group, these numbers were in 92%, 66.7% and 54.5%, respectively. Tramadol was a more effective analgesic ($p < 0.05$) in the first week. During the 4 h after the first tramadol dose, pain intensity decreased by over 50%; pain decreased by 41.7% after the first B dose (patient diaries). Analgesic effects were maintained for 2 weeks. Tramadol was more active after 6 days ($p < 0.05$). Quality of sleep improved in both groups. After 14 days, PS did not change in the tramadol group, but it inconsidera-

bly decreased in the B group ($p < 0.05$). Well-being and Spitzer's Index QL did not change during the first weeks for both groups. Beneficial analgesia with both drugs was maintained, and PS and Spitzer's Index QL changed similarly in both groups. After 14 days and after treatment completion, both patients and physicians assessed tramadol significantly higher than B. Both drugs were well tolerated. Adverse effects appeared in 25% of patients in the tramadol group and in 25.4% of patients in the B group and caused therapy cessation in 8.8% of patients in the tramadol and 11.1% of patients of the B group. The most frequent adverse reactions in both groups were nausea and vomiting, drowsiness, constipation and dizziness; symptoms were usually mild or moderate and disappeared without treatment, after therapy or after analgesic dose reduction.

Bono and Cuffari [7] compared tramadol and B in a randomized, cross-over trial in 60 patients with advanced cancer. Both drugs were administered for one week with a 24-h wash-out period before switching drugs. Tramadol was administered orally at a dose of 300 mg/day. B was administered sublingually at a dose of 0.6 mg/day. Both analgesics were effective, but after 2 days of treatment, tramadol caused significantly better analgesia ($p < 0.05$) and was a better analgesic ($p < 0.05$); thus, tramadol therapy had higher acceptance ($p < 0.01$). Tramadol was better tolerated than B and caused less frequent and milder adverse effects; only one patient ceased tramadol treatment, but 18 withdrew from B because of adverse effects.

Wilder-Smith et al. [111], in an open, randomized, clinical parallel group design, compared tramadol and dihydrocodeine (DHC) (both in controlled release formulations) in 60 patients with severe pain from osteoarthritis who were not responding to NSAIDs. The study duration was 4 weeks. Tramadol was administered to 30 patients with a starting dose of 100 mg twice daily, and DHC was administered to 30 patients at a dose of 60 mg b.i.d.; doses were titrated by immediate-release tramadol and DHC, respectively. Thirty patients responding to NSAIDs alone formed the control group. Inclusion criteria were pain intensity equal to or greater than 3 on a verbal scale (0 – no pain, 4 – unbearable pain). Before and during the study, pain was assessed at rest and upon movement. Electrical sensation and pain thresholds over the osteoarthritic joint and at a distant location and GI transit times were assessed before and during treatment. Both drugs decreased pain intensity at rest and upon movement from over 3 to 1 or lower (verbal scale), but tramadol rendered better analgesia at rest ($p < 0.04$). Mean daily doses in the first and 28th day of the trial were 209 mg (range: 198–220 mg) and 203 mg (range: 191–206 mg) for tramadol, 129 mg (range: 122–136 mg) and 130 mg (range: 121–134 mg) for DHC. More adverse effects were observed in the tramadol group ($p < 0.04$). Frequency of defecation was lower and stools were harder in the DHC group. Oroceacal transit time remained unchanged and was similar to controls with both analgesics. Colonic transit times increased significantly during DHC treatment. Electrical sensation and pain thresholds were lower pre-treatment in both groups than in controls and increased during treatment. These analgesic effects were more marked in the tramadol group for pain at a site distant from the osteoarthritic joint. In conclusion, both controlled-release tramadol and DHC in combination with NSAIDs rendered rapid and effective analgesia for strong osteoarthritic pain. Minimal dose titration was required and adverse effects were minor. Tramadol interfered less with intestinal function and showed slighty better analgesia than DHC.

Karlsson and Berggren [38] compared controlled-release tramadol in daily doses of 150–400 mg (tablet strengths: 75, 100, 150 and 200 mg, administered twice daily) with low-dose buprenorphine patches (TB: 5, 10 and 20 μg/h) administered weekly in patients with moderate-to-severe chronic osteoarthritis pain of the hip and/or knee, equal to or greater than 4 on the 11 Box Scale (BS) during the screening week while using paracetamol in doses 4 g/day. The trial period was 12 weeks, and paracetamol was used as a rescue medication. A total of 134 patients were randomized (69 received TB, and 65 patients were treated with tramadol). Both drugs resulted in significant pain relief, with a mean change in BS of –2.26 and –2.09 for TB and tramadol, respectively. The efficacy of TB was not inferior to controlled-release tramadol. Adverse effects appeared in 88.4% of patients treated with TB and in 78.5% patients treated with tramadol; 14.5% and 29.2% patients, respectively, withdrew from the study due to adverse effects. The most frequent adverse effects in the TB group were nausea (30.4%), constipation (18.8%) and dizziness (15.9%); in the tramadol group, they were nausea (24.6%), fatigue (18.5%) and pain (12.3%). Over 70% of patients in each group would prefer future treatment with TB. In conclusion, both analgesics were effective and well tolerated.

In a retrospective study, analgesia and adverse effects of tramadol (54 patients) and small doses of M (42 patients), administered orally in moderate, strong and very strong nociceptive cancer pain, were compared [51]. Similar analgesia had been achieved in moderate, strong and very strong cancer pain as well as in visceral, bone and somatic from soft tissue pain. Daily doses of M were 30–200 mg (mean 77.50 mg); daily doses for tramadol were 50–600 mg (mean 321.02 mg), which indicated similar calculations of equianalgesic doses of oral M to tramadol as in the Wilder-Smith et al. study (1:4) [112]. A lower frequency of adverse effects (nausea and vomiting, constipation, urine retention) was found in the tramadol group.

Analgesic efficacy and adverse effects of tramadol and equianalgesic doses of M were assessed in a retrospective study, which was composed of 305 patients with cancer pain (moderate, strong or very strong on a verbal scale or at least 4 on a numerical scale of 0–10) that demanded opioids [50]. Of the two drugs, 154 patients were given tramadol, and 151 patients were given M; both drugs were administered by an oral route in immediate-release forms (tramadol in drops or capsules, M in water solution). Analgesic efficacy was assessed before and after 4 days of the treatment. Adverse effects were assessed by a verbal scale. Daily doses of 50–700 mg tramadol (mean 296.82 ± 136.67 mg) and 16-140 mg M (mean 68.45 ± 31.36 mg) were given. The duration of treatment was 7–351 days (mean 51.57 ± 58.53) for tramadol and 7–495 days (mean 52.10 ± 65.74) for M. In both groups, good analgesia was achieved, expressed as a significant decrease in pain intensity. However, M provided superior analgesia. In 48 (31.17%) patients, it was necessary to substitute for tramadol by M. More frequent adverse effects were observed in the M group (nausea, vomiting, constipation and difficulties in passing urine; all had significant differences).

In an open, prospective, randomized study of 40 opioid-naive patients with moderate, strong or very strong pain (verbal scale) or at least 45 on VAS, tramadol (20 patients) or M (20 patients) were administered [44]. During the first 7 days, pain was stabilized by immediate-release tramadol (drops, capsules) or M (water solution). After 7 days, if satisfactory pain relief was achieved and appropriate daily doses were used (tramadol 150–600 mg, M 20–200 mg), patients were switched to slow-release tramadol 100, 150 or 200-mg tablets or sustained-release M tablets (10, 30, 60 or 100 mg) or capsules (10, 30, 60 or 100 mg) for 28 days. Analgesic efficacy, adverse effects and QL by QLQ C 30 were evaluated. Pain was assessed weekly by VAS and a verbal scale, and adverse effects were assessed by a verbal scale. Treatment time was 3–310 days (mean 87.15 ± 78.23) for tramadol and 5–502 days (mean 100.05 ± 102.67) for M. Daily doses were 200–600 mg (mean 322.22 ± 116.60) for tramadol and 20–270 mg (123.5 ± 78.15) for M. In both groups, satisfactory analgesia was achieved. However, in patients with neuropathic pain, there was a trend toward better analgesia in the M group (significant difference in VAS after the first week). In both groups, 80% of patients preferred treatment with the slow-release forms of tramadol and M. There were more frequent adverse effects in the M group (drowsiness, difficulties in passing water, sweating and dizziness; all differences were significant). QL results revealed better global QL and less fatigue after 35 days of tramadol treatment. In conclusion, tramadol and small doses of M (up to 270 mg/day) are effective and safe for cancer pain treatment at home, but small doses of M are more effective for treating neuropathic pain.

In an open, prospective, randomized cross-over study, 30 patients with nociceptive (visceral or somatic) cancer pain that was treated previously with non-opioids received tramadol (15 patients) or DHC (15 patients) in controlled-release tablets for 7 days; the drugs were then switched and administered for the next 7 days without a wash-out period [54]. Analgesia was assessed by VAS; adverse effects were assessed by a modified ESAS (Edmonton Symptom Assessment System) with two additional scales for constipation and vomiting. Starting doses were 100 mg for tramadol and 60 mg for DHC, both twice daily and titrated to satisfactory analgesia; the maximal daily doses were 600 mg and 360 mg, respectively. In both groups, a decrease in pain intensity, better analgesia and better global QL during DHC treatment were achieved. At study completion, 19 patients preferred DHC, 4 patients preferred tramadol, and 7 assessed both drugs as equally effective. Patients on DHC reported less dyspnoea in the first 7 days, more constipation and a trend toward more drowsiness in the second week, more activity in the first week and better sensation of well being during both weeks; tramadol caused more nausea during both weeks. No differences in appetite or vomiting were observed. In the first week, patients in the DHC group were less anxious and less depressed. Serious adverse effects (respiratory de-

pression, allergy for drugs) were not observed. In conclusion, tramadol and DHC in controlled-release tablets are effective analgesics in nociceptive cancer pain. More constipation in DHC group suggests the need for prophylactic use of laxatives, whereas more nausea in the tramadol group is an indication for prophylactic antiemetic administration. Equianalgesic single doses of tramadol to DHC (according to a 10:6 ratio) rendered satisfactory analgesia.

Conclusions

Common use of tramadol is related to the availability of controlled-release tablets (100, 150 and 200 mg tablets) and controlled-release 50 mg capsules, the latter allow for mild dose titration. The effectiveness and safety of tramadol controlled-release formulations were confirmed in post-marketing studies of chronic non-malignant pain [38, 39, 69] and in cancer patients [78] as well as in Poland [52]. Tramadol substituted nearly completely for codeine at the second step of the WHO analgesic ladder in cancer pain treatment in Poland [48, 53]. The alternative drug for tramadol is DHC, available only in controlled-release tablets in doses of 60, 90 and 120 mg in Poland [54].

Tramadol may be safely combined with non-opioids, especially with paracetamol, with an improvement in analgesia but no increasing toxicity [20]. A combined preparation of tramadol (37.5 mg) and paracetamol (325 mg) is now available. The important advantage of tramadol is less constipation compared to codeine, DHC, morphine and oxycodone. In contrast to codeine and DHC, tramadol is available in Poland in ampoules for *sc* and *iv* administration and in suppositories [66]. It is easily obtainable and prescribed without any limits on normal receipts. Tramadol may be recommended for patients with moderate and in some cases severe nociceptive and neuropathic pain [8, 92, 93]. Tramadol may be particularly useful for patients who are more sensitive to the adverse effects of strong opioids, (e.g., sedation, fatigue, constipation). In clinical practice, this group is usually made up of older patients and patients with GI tumors; tramadol may be considered as an alternative to DHC and small doses of strong opioids such as morphine, oxycodone, hydromorphone, transdermal fentanyl or transdermal buprenorphine [26]. The mixed mode of tramadol analgesia (opioid component and monoamine reuptake blockade) predisposes this analgesic to the treatment of patients with a neuropathic pain component.

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