Tramadol: Does it have a role in cancer pain management?

Eric E. Prommer, MD

ABSTRACT

Tramadol (Ultram, Ortho-McNeil Pharmaceutical, Inc., Raritan, NJ) is considered a Step 2 analgesic under the World Health Organization's guidelines for the treatment of patients with cancer pain. It is a centrally acting analgesic that has affinity for opioid receptors and influences the action of norepinephrine and serotonin at the synapse. This dual mechanism of analgesia makes it unique among Step 2 agents. It is metabolized by CYP2D6, which increases the potential for drug interactions. Unlike other opioids, it does not cause respiratory depression. Tramadol has been studied in cancer pain and neuropathic pain. It compares well with low-dose morphine as an analgesic. The purpose of this review is to critically examine the pharmacodynamics, pharmacology, drug interactions, and adverse effects of the drug, and, based on the data presented, discuss the drug's role in cancer care.

Key words: tramadol, cancer pain, neuropathic pain, analgesia, pharmacology

INTRODUCTION

Pain is one of the most common and incapacitating symptoms experienced by patients with advanced cancer. Current treatment is based on the World Health Organization (WHO)'s concept of an "analgesic ladder," which involves a stepwise approach to the use of analgesic drugs.[1] Medication potency increases at each step of the WHO ladder, from nonopioid (Step 1; e.g., aspirin and nonsteroidal anti-inflammatory drugs) through weak (Step 2) opioids (e.g., codeine) plus a nonopioid, to strong opioids (Step 3; e.g., morphine) plus a nonopioid analgesic.[2] Tramadol (Figure 1) is considered a Step 2 analgesic under the WHO guidelines for the treatment of patients with cancer pain.[3] Tramadol is a centrally acting analgesic that possesses a dual mechanism of analgesia.[1] It is a racemic compound that has affinity for opioid receptors and also affects the actions of norepinephrine and serotonin at the synapse.[4]

PHARMACODYNAMICS

Tramadol and its chief metabolite (M1) are racemic compounds.[5] The parent compound, the enantiomers of the parent compound, and the enantiomers of the chief metabolite all have different affinities for opioid receptors and have different effects on adrenergic and serotonergic metabolism at the synapse.[6]

Opioid receptor interaction

Tramadol has low affinity for opioid receptors. Comparatively speaking, its affinity for μ-opioid receptors is several thousand-fold less than that of morphine and 10-fold less than that for codeine.[6] The parent compound and its enantiomers have no interaction with the δ-opioid receptor and have an extremely weak interaction with the κ-opioid receptor.[5] Of the metabolites, the + enantiomer of the M1 metabolite has the highest affinity to μ-opioid receptors (Ki 153).[5] The preceding suggests that the relative contributions of tramadol and M1 to human analgesia depend on the plasma concentrations of each compound.

Interaction with the monoaminergic system

It is well known that analgesia can be achieved centrally and peripherally by interference with a variety of neurotransmitter systems (nonopioid mechanisms).[7] Pain control is subject to descending modulation by brainstem groups such as the locus coeruleus/subcoeruleus and the raphe complex, containing noradrenaline (NA) and serotonin (5-HT), respectively.[8] Tramadol has effects on the serotonin and noradrenergic systems.[9] The ability to interfere with the monoaminergic system occurs at concentrations at which it binds to μ-opioid receptors.[10] Interestingly, tramadol has strong structural similarities to the antidepressant venlafaxine, which has effects on NA and 5-HT at the synapse.[11]

Noradrenergic effects

Enantiomers of tramadol and its chief metabolite act differently on the noradrenergic system. In locus coeruleus brain slices, racemic tramadol and its (+)- and (-)-enantiomers significantly increased stimulated norepinephrine

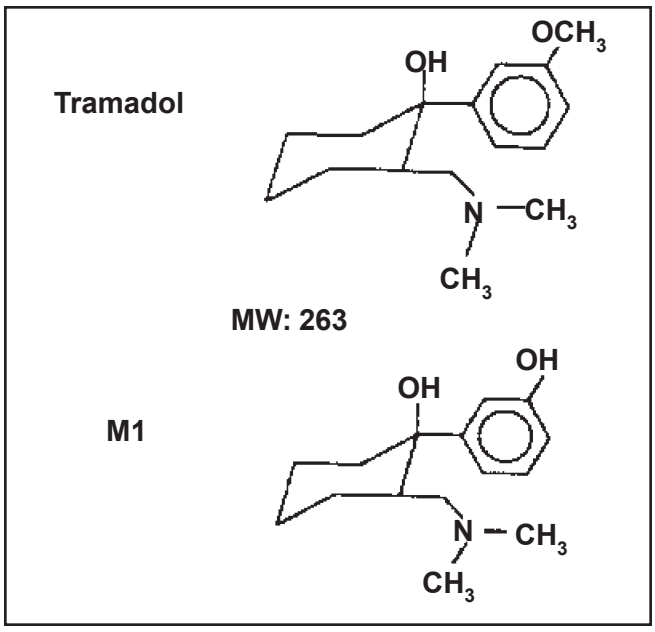

Figure 1. Structure of tramadol and M1 metabolite.

efflux.[12] However, only (-)-tramadol blocked norepinephrine reuptake. The chief metabolite M1 also affects the noradrenergic system. The (+)-M1 metabolite causes NA release, whereas the (-)-M1 metabolite blocks NA uptake.[13] Clinically, administration of α2-adrenoceptor antagonists such as yohimbine can affect the analgesia of tramadol.[14]

Effect on serotonergic pathway

The parent compound, its enantiomers, the chief metabolite, and its enantiomers have different effects on 5-HT at the synapse. Studies involving the actions of (+/-)-tramadol, (+)-tramadol, (-)-tramadol, and O-desmethyltramadol (M1 metabolite) in dorsal raphe nucleus brain slices have revealed that racemic tramadol and its (+)-enantiomer significantly block 5-HT uptake and increase stimulated 5-HT efflux.[7] The (-)-enantiomer of tramadol and its metabolite, M1, are inactive.[7]

Other receptor interactions

Tramadol inhibits muscarinic type-3 receptor function, which primarily mediates smooth muscle contraction and glandular secretion.[15] Tramadol has no effect on arachidonic acid metabolism and does not interact with nonsteroidal anti-inflammatory drugs.[16]

PHARMACOKINETICS/ROUTES OF ADMINISTRATION

Tramadol has been administered orally, rectally, intravenously, intramuscularly, subcutaneously, and via regional anesthesia.[17] The intravenous and rectal forms are unavailable in the United States. In the United States, the immediate-release form is available as tablets and is marketed as Ultracet (conjugated to acetaminophen, Ortho-McNeil Pharmaceutical, Inc.) and Ultram (tramadol immediate release, Ortho-McNeil Pharmaceutical, Inc.). In Europe, the immediate-release form is available in capsules and as an elixir.[18] A fast-release orodispersible tramadol tablet that can be taken without liquids has been developed.[19] A sustained-release form, in capsules, is available in Europe.[20] The sustained-release product available in the United States is in tablet form.

Tramadol is well absorbed orally, with an absolute bioavailability of 75 percent, and has a volume of distribution of approximately 2.7 L per kg.[21] It is only 20 percent bound to plasma proteins. Tramadol is characterized by extensive tissue distribution (apparent volume of distribution, approximately 3 L per kg). The observed plasma half-lives are 6.3 and 7.4 hours for tramadol and M1, respectively.[21] The clearance of tramadol is moderately high (600 mL per min).[22] The t_{max} value for both enantiomers of tramadol occurs two hours after administration, and that for the active (+)-M1 metabolite occurs after three hours.[14] Analgesia for racemic tramadol and the M1 metabolite in humans begins within approximately one hour after administration and reaches a peak in approximately two to three hours. Onset of analgesia for the long-acting form occurs at a median time of five hours.[23] In general, both enantiomers of tramadol and M1 follow a parallel time course in the body after single and multiple doses, although small differences (approximately 10 percent) exist in the absolute amount of each enantiomer present.[21] Steady-state plasma concentrations of both tramadol and M1 are achieved within two days with q.i.d. dosing. Oral administration of tramadol hydrochloride tablets with food does not significantly affect its rate or extent of absorption. Tramadol is extensively metabolized after oral administration. Sixty percent of the drug is excreted as metabolites. Elimination is primarily by the hepatic route and partly by the renal route (up to 30 percent of the dose as unchanged drug).[22] After rectal administration of tramadol suppositories, the extent of absolute bioavailability is equal to that of an oral administration of tramadol.[24]

METABOLISM

While cytochromes CYP2D6, CYP3A4, and CYP2B6 are involved in the metabolism of tramadol, the chief cytochrome responsible for metabolism is CYP2D6. Other metabolic pathways involved in the metabolism of tramadol are O-demethylation, N-demethylation, cyclohexyl oxidation, oxidative N-dealkylation, dehydration, and conjugation.[25] These pathways lead to multiple metabolites, of which only one, M1, is of clinical significance. The formation of M1 that results from the

Table 1. Adverse effects of tramadol	
Adverse effect	**Frequency (percent)**
Dizziness/vertigo	26
Nausea	24
Constipation	24
Headache	18
Somnolence	16
Vomiting	9
Pruritus	8
Central nervous system stimulation	7
Sweating	6
Asthenia	6
Dyspepsia	5
Diarrhea	5
Dry mouth	5
Adapted from package insert.	

O-demethylation of tramadol is catalyzed by human hepatic CYP2D6.[26] Patients with dysfunctional CYP2D6 are unable to form M1 (5 to 10 percent white, 18 percent African American, 1 percent Asian).[27,28] The AUC for M1 is significantly decreased in these patients. There is a correlation between the number of functional alleles and the ratio of tramadol to M1.[28] Hui-Chen et al. found the values of C_{max} for the enantiomers of trans-T and M1, and AUC_{0-8} for (-)-trans T, (+)-M1, and (-)-M1 were higher in women than in men.[31]

DRUG INTERACTIONS

Dependence of the metabolism of tramadol on CYP2D6 (and to a lesser extent CYP3A4) for the formation of its chief metabolite leads to concerns that interactions with drugs that inhibit this cytochrome may lead to clinically significant toxicities or alterations in analgesic properties. Important drugs used in palliative care that are metabolized by CYP2D6 are codeine, oxycodone, hydrocodone, haloperidol, tricyclic antidepressants, risperidone, and phenothiazines.[29] Important inhibitors of CYP2D6 are quinidine, fluoxetine, and its metabolite norfluoxetine.[29] In vitro studies involving liver microsomes suggest that inhibitors of CYP2D6 such as fluoxetine and its metabolite norfluoxetine,[30] as well as amitriptyline and quinidine,[22] can inhibit the metabolism of tramadol to various degrees, suggesting that concomitant administration of these compounds could result in increases in tramadol concentrations and decreased concentrations of M1.[22] The actual pharmacological impact of these alterations in terms of either efficacy or safety is unknown. Therefore, until further information is available, caution should be used when tramadol is administered with other drugs that inhibit CYP2D6.

A major interaction of clinical importance can occur when tramadol is given with selective serotonin reuptake inhibitors and monoamine oxidase inhibitors. This can result in the serotonin syndrome. The serotonin syndrome is characterized by a symptom triad of altered mental status, neuromuscular abnormalities, and autonomic dysfunction; the absence of hyperthermia and rigidity as well as the presence of a normal creatine phosphokinase level distinguish it from the neuroleptic malignant syndrome.[32] The serotonin syndrome has been reported when tramadol has been administered concomitantly with venlafaxine,[33] citalopram,[34] sertraline,[35] fluoxetine,[36] paroxetine,[37] and monoamine oxidase inhibitors such as phenelzine and isoniazid.[38,39] Not surprisingly, it also has occurred with newer antidepressants such as mirtazapine.[40] The overall incidence of the serotonin syndrome is rare, but should be watched for when other serotonin-modifying drugs are given.

Administration of α-adrenergic blockers can decrease the duration of analgesia of tramadol.[14] Administration of serotonin inhibitors such as ondansetron has lead to increased tramadol requirements, probably by blocking spinal 5-HT (3) receptors.[41] Carbamazepine causes a significant increase in tramadol metabolism, presumably through metabolic induction by carbamazepine, which is metabolized via CYP34A.[21] Patients receiving chronic carbamazepine doses of up to 800 mg daily may require up to twice the recommended dose of tramadol.[21] Case reports of Coumadin potentiation by tramadol have not been substantiated.[42,43]

Table 2. Adverse effects of tramadol versus morphine (frequency)		
Adverse effect	**Morphine**	**Tramadol**
Nausea/vomiting	15 to 30 percent	24 percent
Constipation	40 to 70 percent	24 percent
Sedation	20 to 60 percent	16 percent
Cognitive failure	Mild common; severe unknown	Unknown
Myoclonus	With high doses	Not reported
Pruritus	2 to 10 percent	8 percent

Table 3. Tramadol and chronic malignant pain			
Author	**Number of patients**	**Intervention**	**Outcome**
Tawfik, 1990[66]	32	Patients treated with tramadol (mean dosage, 217 mg per day) or with sustained-release morphine (mean dosage, 50 mg per d) for up to eight weeks	Morphine produced better analgesia but was associated with more intensive adverse effects; crossover study of 20 patients suggests same analgesic efficacy as morphine but fewer adverse effects
Osipova, 1991[67]	124 (cancer patients)	98 patients receiving tramadol (mean dosage, 368 mg per day) and 26 patients receiving sustained-release morphine (mean dosage, 69 to 96 mg per day) for relief of severe cancer pain	Morphine produced better analgesia but was associated with more intensive adverse effects
Wilder-Smith, 1994[49]	20 (cancer patients)	Doses of oral solutions of tramadol or morphine were individually titrated in a double-blind, randomized, crossover study; crossover was after day four	Pain intensity was similar with morphine and with tramadol; relative potency of 4:1 with oral dosing; adverse effects per person were lower on the fourth day with tramadol with respect to nausea and constipation
Bono, 1997[68]	60 (44 men, 16 women; average age, 61.4 years; controlled crossover trial with randomized sequences; severity of pain measured before and during the four hours after taking study drugs)	Tramadol was prescribed at the daily dosage of 300 mg orally, and buprenorphine at 0.6 mg per day as a sublingual preparation	Buprenorphine and tramadol had a similar analgesic effect, although tramadol had a quicker onset of action
Brema, 1996[69]	131 (adults with neoplastic pain no longer responsive to nonsteroidal anti-inflammatory drugs)	Tramadol (one 100 mg slow-release tablet every eight to 12 hours), or buprenorphine (one sublingual 0.2 mg tablet every six to eight hours); mean treatment period was 58 days for tramadol and 51 for buprenorphine	Similar pain control acutely for both drugs; superior pain control for tramadol after one week
Grond, 1999[60]	1,658 (cancer pain, retrospective study)	810 patients received oral tramadol for a total of 23,497 days, and 848 patients received oral morphine for a total of 24,695 days	Constipation, neuropsychological symptoms, and pruritus were observed significantly more frequently with low-dose morphine; pain intensity did not differ between arms
Petzke, 2001[20]	146 (moderate-to-severe cancer pain and insufficient pain relief from nonopioid analgesics)	Treated with slow-release tramadol for initial dose finding and as long-term treatment; immediate-release tramadol and a standard nonopioid analgesic (1,000 mg naproxen daily) were provided for treatment of breakthrough pain	Number of patients with good/complete pain relief increased from 43 percent after week one to 71 percent after week six, with maximum daily dosages of tramadol up to 650 mg; most (70 percent) still needed less than 400 mg tramadol per day; common adverse effects such as fatigue, dizziness, and constipation decreased in frequency; other adverse events such as nausea, vomiting, and sweating did not change

Table 4. Tramadol and neuropathic pain				
Author	**Type of trial**	**Number of patients**	**Intervention**	**Outcome**
Harati, 1998[61]	Double-blind, randomized, controlled trial	131 with painful diabetic neuropathy	Treated with tramadol (n = 65) or placebo (n = 66), administered as identical capsules in divided doses four times daily	Tramadol, at an average dosage of 210 mg per day, was more effective than placebo for pain control
Boureau, 2003[62]	Multicenter, randomized, double-blind, parallel-group study	127 with post-therapeutic neuralgia	The dosage of tramadol could be increased from 100 mg per day to 400 mg per day compared with placebo	Better pain relief (via pain measurement over time) over six weeks; tramadol versus placebo
Sindrup, 1999[63]	Double-blind, placebo-controlled and crossover	45 with painful polyneuropathy and allodynia	Tramadol slow-release tablets, titrated to 200 to 400 mg per day, versus placebo	Pain, paraesthesia, and touch-evoked pain levels were lower with tramadol than with placebo, as were ratings of allodynia (0 vs. 4, p = 0.012)

ADVERSE EFFECTS

Common adverse effects with frequencies greater than 5 percent are listed in Table 1. The incidence of adverse effects is higher in the clinical trial data than in outpatient postmarketing surveillance.[44]

Central nervous system

Central nervous system (CNS) adverse effects are common and include drowsiness, dizziness, headache, and agitation.[21] Headache with tramadol differs from that of other opioids and may be related to serotonin blockade. Rare CNS adverse effects include mania[45] and musical hallucinations.[46] Seizures have occurred after the first therapeutic dose of tramadol. However, seizures have occurred when other factors predisposing to seizures are present, such as concomitant administration of other medications that lower the seizure threshold, patients with a history of epilepsy, and other patients at risk for seizures.[47] Tramadol may cause or exacerbate cognitive impairment in patients older than 75 years.[48]

Gastrointestinal

The most frequent adverse gastrointestinal effects in clinical trials of tramadol were nausea (24 percent), vomiting (9 percent), and constipation (24 percent); however, postmarketing surveillance suggests a lower incidence (4.2 percent and 0.5 percent, respectively) for nausea and vomiting.[21,44] Tramadol has less effect on colonic transit time than morphine.[49] There is no effect of intravenous tramadol on bile duct sphincter.[50]

Genitourinary

Urinary retention or urinary frequency has been reported in up to 5 percent of patients taking therapeutic doses of tramadol.[51]

Respiratory

Tramadol was not associated with respiratory depression and does not suppress the hypoxic ventilatory response.[52]

Other adverse effects

Diaphoresis has been reported in up to 20 percent of patients treated with oral or parenteral tramadol.[4] Fatigue as well as skin reactions have been reported with tramadol use.[20,53] Tramadol has been associated with exacerbation of attacks of acute porphyria.[54] A small percentage (0.1 percent) of the administered dose passes into breast milk.[55]

COMPARISON WITH MORPHINE

Table 2 compares the adverse effects of morphine with those of tramadol. In contrast with morphine, tramadol has not been shown to cause myoclonus or hyperalgesia. Although it reportedly causes less histamine release, pruritus can still occur (Table 1).[56] Tramadol is not associated with respiratory depression and does not suppress hypoxic ventilatory response.[52] Tramadol may be less immunosuppressive than morphine.[57] Tramadol has minimal cardiovascular adverse effects.[22]

Table 5. Cost comparison of Step 2 opioids		
Drug	**Average wholesale price (generic)**	**Average wholesale price (trade name)**
Ultram 50 mg	$0.84	$1.25
Ultracet	$1.07	$1.14
Codeine 30 mg	$0.35	–
Tylenol #3	$0.05	$0.36
Tylenol #4	$0.08	$0.80
Vicodin	$0.45	$0.84
Oxycodone 5 mg	$1.14	–

Withdrawal has been reported with chronic use of tramadol, but because of the drug's weak interaction with opioid receptors, it is considered a nonhabit- and nondependence-forming analgesic and is not classified as a controlled substance by the US Food and Drug Administration.[58,59] Surveillance studies and case reports suggest that abstinence symptoms can occur. In most cases, the withdrawal symptoms consisted of classic opioid withdrawal, but in some cases were accompanied by withdrawal symptoms not normally observed in opiate withdrawal, such as hallucinations, paranoia, extreme anxiety, panic attacks, confusion, and unusual sensory experiences such as numbness and tingling in one or more extremities. These cases were more likely to occur after abrupt cessation of intake, especially when the compound had been taken for more than one year. Therefore, patients should be advised of such an effect whenever they decide to stop intake or their physician is planning to switch them to another medication. To avoid abstinence symptoms, doses should be slowly tapered.[59]

TRAMADOL FOR CANCER PAIN

Table 3 reviews the studies involving tramadol and cancer pain. Grond and colleagues[60] compared the efficacy and safety of high dosages of oral tramadol (= 300 mg per day) with low dosages of oral morphine (= 60 mg per day). Patients were included in this nonblinded and nonrandomized study if the combination of a nonopioid analgesic and up to 250 mg per day of oral tramadol was inadequate. The average dosage of tramadol was 428 ± 101 mg per day (range, 300 to 600 mg per day); the average dosage of morphine was 42 ± 13 mg per day (range, 10 to 60 mg per day). The mean pain intensity was similar between the two study groups. Constipation, neuropsychological symptoms, and pruritus were observed significantly more frequently with low-dose morphine; other symptoms had similar frequencies in both groups.

In a study of patients with moderate to severe cancer pain and insufficient pain relief from nonopioid analgesics, Petzke and colleagues[20] examined slow-release tramadol for initial dose findings and as a long-term treatment. Immediate-release tramadol was provided for the treatment of breakthrough pain, in addition to oral Naprosyn 500 mg twice a day. Ninety of 146 patients (62 percent) completed the six-week trial. Average and maximal pain intensity decreased from day one to day four. The number of patients with good and complete pain relief increased from 43 percent after week one to 71 percent after week six. The maximum daily dosages of tramadol were up to 650 mg. However, 70 percent of the patients still needed less than 400 mg tramadol per day in week six. The frequency of some common adverse effects of opioids such as fatigue, dizziness, and constipation, decreased during the six weeks. The frequency of other adverse events such as nausea, vomiting, and sweating did not change. Slow-release tramadol provided fast and efficient pain relief in almost two-thirds of patients during initial dose finding and during long-term treatment.

TRAMADOL FOR NEUROPATHIC PAIN

Table 4 summarizes the studies involving tramadol and neuropathic pain. Tramadol was better than placebo for pain control in diabetic neuropathy and postherpetic neuralgia.[61,62] In patients with polyneuropathy, Sindrup found tramadol to be effective for allodynia.[63] Harati found that use of tramadol in diabetic neuropathy was associated with improved quality of life.[61] There are no data available for neuropathic pain in the cancer setting.

PHARMACOECONOMICS

The average wholesale price of Ultram (tramadol 50 mg) is $1.21 per tablet. The price of generic tramadol is $0.84. The cost of Ultracet is $1.07. Table 5 compares the cost of tramadol with other Step 2 agents.

SCHEDULE OF ADMINISTRATION

The oral dosage of tramadol is one or two 50-mg tablets up to four times daily; maximum dosage is eight tablets per day. The fixed combination of tramadol/acetaminophen is available as tablets containing 37.5/325 mg with a recommended dosage of two tablets every four to six hours. The extended-release formulation of tramadol hydrochloride (tramadol ER), given as 100 mg twice daily, is considered therapeutically equivalent to the immediate-release formulation of 50 mg administered four times daily. If kidney (creatinine clearance below 30 mL per min) or hepatic function is severely impaired, some dosage reduction (approximately by 50 percent) or extension of the dosage interval should be considered.[22]

The relative potency of tramadol to morphine is approximately 1:5 to 1:4 for the oral route and about 1:10 for the subcutaneous and intravenous routes.[64] The oral dose in pediatric patients is of 1 to 2 mg per kg every four to six hours.[65]

DISCUSSION

Tramadol is a centrally acting analgesic with a dual mechanism of action. As a Step 2 agent, it has affinity for opioid receptors and has a potent metabolite with strong affinity for the μ-opioid receptor. It is also unique in that part of its mechanism of action also involves effects on the uptake/release of serotonin/norepinephrine at the synapse. This makes it more versatile than the currently available Step 2 agents and potentially useful for neuropathic pain. Clinical trials suggest efficacy in neuropathic pain and equivalency with low-dose morphine in cancer pain. The study comparing tramadol with low doses of morphine was nonblinded and nonrandomized. Adverse effects were comparable or better than those of low-dose morphine. Offsetting the increased versatility of the drug is the potential for drug interactions because of its dependence on CYP2D6 for metabolism. The drug appears to have a ceiling effect, whereupon adverse effects occur at increased frequency. For now, it represents an option for patients with pain not responsive to nonopioid analgesics. Superiority over low-dose Step 3 agents requires further testing in randomized clinical trials.

Eric E. Prommer, MD, Assistant Professor of Medicine, UCLA School of Medicine, Division of Hematology/Oncology, and VIP Palliative Care Program, Greater Los Angeles Healthcare, Los Angeles, California.

REFERENCES

1. Hanks GW, Conno F, Cherny N, et al.: Morphine and alternative opioids in cancer pain: The EAPC recommendations. *Br J Cancer.* 2001; 84(5): 587-593.
2. O'Brien T, Mortimer PG, McDonald CJ, et al.: A randomized crossover study comparing the efficacy and tolerability of a novel once-daily morphine preparation (MXL capsules) with MST Continus tablets in cancer patients with severe pain. *Palliat Med.* 1997; 11(6): 475-482.
3. Reig E: Tramadol in musculoskeletal pain—A survey. *Clin Rheumatol.* 2002; 21 Suppl 1: S9-S11.
4. Lee CR, McTavish D, Sorkin EM: Tramadol. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in acute and chronic pain states. *Drugs.* 1993; 46(2): 313-340.
5. Lai J, Ma SW, Porreca F, et al.: Tramadol, M1 metabolite and enantiomer affinities for cloned human opioid receptors expressed in transfected HN9.10 neuroblastoma cells. *Eur J Pharmacol.* 1996; 316(2-3): 369-372.
6. Raffa RB: A novel approach to the pharmacology of analgesics. *Am J Med.* 1996; 101(1A): 40S-46S.
7. Bamigbade TA, Davidson C, Langford RM, et al.: Actions of tramadol, its enantiomers and principal metabolite, O-desmethyltramadol, on serotonin (5-HT) efflux and uptake in the rat dorsal raphe nucleus. *Br J Anaesth.* 1997; 79(3): 352-356.
8. Millan MJ: Descending control of pain. *Prog Neurobiol.* 2002; 66(6): 355-474.
9. Raffa RB, Friderichs E, Reimann W, et al.: Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an "atypical" opioid analgesic. *J Pharmacol Exp Ther.* 1992; 260(1): 275-285.
10. Garrido MJ, Sayar O, Segura C, et al.: Pharmacokinetic/pharmacodynamic modeling of the antinociceptive effects of (+)-tramadol in the rat: Role of cytochrome P450 2D activity. *J Pharmacol Exp Ther.* 2003; 305(2): 710-718.
11. Hopwood SE, Owesson CA, Callado LF, et al.: Effects of chronic tramadol on pre- and post-synaptic measures of monoamine function. *J Psychopharmacol.* 2001; 15(3): 147-153.
12. Halfpenny DM, Callado LF, Hopwood SE, et al.: Effects of tramadol stereoisomers on norepinephrine efflux and uptake in the rat locus coeruleus measured by real time voltammetry. *Br J Anaesth.* 1999; 83(6): 909-915.
13. Garrido MJ, Valle M, Campanero MA, et al.: Modeling of the in vivo antinociceptive interaction between an opioid agonist, (+)-O-desmethyltramadol, and a monoamine reuptake inhibitor, (-)-O-desmethyltramadol, in rats. *J Pharmacol Exp Ther.* 2000; 295(1): 352-359.
14. Desmeules JA, Piguet V, Collart L, et al.: Contribution of monoaminergic modulation to the analgesic effect of tramadol. *Br J Clin Pharmacol.* 1996; 41(1): 7-12.
15. Minami K, Ogata J, Horishita T, et al.: Intramuscular tramadol increases gastric pH during anesthesia. *Can J Anaesth.* 2004; 51(6): 545-548.
16. Buccellati C, Sala A, Ballerio R, et al.: Tramadol anti-inflammatory activity is not related to a direct inhibitory action on prostaglandin endoperoxide synthases. *Eur J Pain.* 2000; 4(4): 413-415.
17. Acalovschi I, Cristea T, Margarit S, et al.: Tramadol added to lidocaine for intravenous regional anesthesia. *Anesth Analg.* 2001; 92(1): 209-214.
18. Leppert W, Luczak J: The role of tramadol in cancer pain treatment—A review. *Support Care Cancer.* 2005; 13(1): 5-17.
19. Tagarro I, Vauzelle-Kervroedan F, Diez MC: Pharmacokinetic assessment of a fast-release orodispersible tramadol tablet compared to a conventional tramadol capsule. *Arzneimittelforschung.* 2004; 54(5): 293-297.
20. Petzke F, Radbruch L, Sabatowski R, et al.: Slow-release tramadol for treatment of chronic malignant pain—An open multicenter trial. *Support Care Cancer.* 2001; 9(1): 48-54.
21. Ortho-McNeil Phamaceutical, Inc.: Product insert, Ultram, 2000.
22. Klotz U: Tramadol—The impact of its pharmacokinetic and pharmacodynamic properties on the clinical management of pain. *Arzneimittelforschung.* 2003; 53(10): 681-687.
23. Malonne H, Sonet B, Streel B, et al.: Pharmacokinetic evaluation of a new oral sustained release dosage form of tramadol. *Br J Clin Pharmacol.* 2004; 57(3): 270-278.
24. Lintz W, Barth H, Osterloh G, et al.: Pharmacokinetics of tramadol and bioavailability of enteral tramadol formulations. 3rd Communication: Suppositories. *Arzneimittelforschung.* 1998; 48(9): 889-899.
25. Wu WN, McKown LA, Liao S: Metabolism of the analgesic drug ULTRAM (tramadol hydrochloride) in humans: API-MS and MS/MS characterization of metabolites. *Xenobiotica.* 2002; 32(5): 411-425.
26. Subrahmanyam V, Renwick AB, Walters DG, et al.: Identification of cytochrome P-450 isoforms responsible for cis-tramadol metabolism in human liver microsomes. *Drug Metab Dispos.* 2001; 29(8): 1146-1155.

27. Poulsen L, rendt-Nielsen L, Brosen K, et al.: The hypoalgesic effect of tramadol in relation to CYP2D6. *Clin Pharmacol Ther.* 1996; 60(6): 636-644.
28. Levo A, Koski A, Ojanpera I, et al.: Post-mortem SNP analysis of CYP2D6 gene reveals correlation between genotype and opioid drug (tramadol) metabolite ratios in blood. *Forensic Sci Int* 2003; 135(1): 9-15.
29. Bernard SA, Bruera E: Drug interactions in palliative care. *J Clin Oncol.* 2000; 18(8): 1780-1799.
30. Jin SM, Liu HC: [Gender-related differences in metabolism of the enantiomers of trans tramadol and trans O-demethyltramadol in rat liver microsomes]. *Yao Xue Xue Bao.* 2004; 39(8): 581-585.
31. Hui-Chen L, Yang Y, Na W, et al. Pharmacokinetics of the enantiomers of trans-tramadol and its active metabolite, trans-O-demethyltramadol, in healthy male and female chinese volunteers. *Chirality.* 2004 ;16(2): 112-118.
32. Sternbach H: The serotonin syndrome. *Am J Psychiatry.* 1991; 148(6): 705-713.
33. Venlafaxine + tramadol: Serotonin syndrome. *Prescrire Int.* 2004; 13(70): 57.
34. Mahlberg R, Kunz D, Sasse J, et al.: Serotonin syndrome with tramadol and citalopram. *Am J Psychiatry.* 2004; 161(6): 1129.
35. Mittino D, Mula M, Monaco F: Serotonin syndrome associated with tramadol-sertraline coadministration. *Clin Neuropharmacol.* 2004; 27(3): 150-151.
36. Kesavan S, Sobala GM: Serotonin syndrome with fluoxetine plus tramadol. *J R Soc Med.* 1999; 92(9): 474-475.
37. Lantz MS, Buchalter EN, Giambanco V: Serotonin syndrome following the administration of tramadol with paroxetine. *Int J Geriatr Psychiatry.* 1998; 13(5): 343-345.
38. Calvisi V, Ansseau M: [Clinical case of the month. Mental confusion due to the administration of tramadol in a patient treated with MOAI]. *Rev Med Liege.* 1999; 54(12): 912-913.
39. de Larquier A, Vial T, Brejoux G, et al.: [Serotoninergic syndrome after combining tramadol and iproniazid]. *Therapie.* 1999; 54(6): 767-768.
40. Houlihan DJ: Serotonin syndrome resulting from coadministration of tramadol, venlafaxine, and mirtazapine. *Ann Pharmacother.* 2004; 38(3): 411-413.
41. Arcioni R, della RM, Romano S, et al.: Ondansetron inhibits the analgesic effects of tramadol: A possible 5-HT (3) spinal receptor involvement in acute pain in humans. *Anesth Analg.* 2002; 94(6): 1553-1557.
42. Sabbe JR, Sims PJ, Sims MH: Tramadol-warfarin interaction. *Pharmacotherapy.* 1998; 18(4): 871-873.
43. Boeijinga JK, van ME, van den ER, et al.: Is there interaction between tramadol and phenprocoumon? *Lancet.* 1997; 350(9090): 1552-1553.
44. Cossmann M, Kohnen C, Langford R, et al.: [Tolerance and safety of tramadol use. Results of international studies and data from drug surveillance]. *Drugs.* 1997; 53 Suppl 2: 50-62.
45. Gonzalez-Pinto A, Imaz H, De Heredia JL, et al.: Mania and tramadol-fluoxetine combination. *Am J Psychiatry.* 2001; 158(6): 964-965.
46. Meseguer RV, Navarro LV: [Auditive and visual hallucinations secondary to tramadol administration]. *Ann Med Intern.* 2003; 20(9): 493.
47. Gardner JS, Blough D, Drinkard CR, et al.: Tramadol and seizures: A surveillance study in a managed care population. *Pharmacotherapy.* 2000; 20(12): 1423-1431.
48. Dworkin RH, Backonja M, Rowbotham MC, et al.: Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. *Arch Neurol* 2003; 60(11): 1524-1534.
49. Wilder-Smith CH, Hill L, Osler W, et al.: Effect of tramadol and morphine on pain and gastrointestinal motor function in patients with chronic pancreatitis. *Dig Dis Sci.* 1999; 44(6): 1107-1116.
50. Staritz M: Pharmacology of the sphincter of Oddi. *Endoscopy.* 1988; 20 Suppl 1: 171-174.
51. Meyboom RH, Brodie-Meijer CC, Diemont WL, et al.: Bladder dysfunction during the use of tramadol. *Pharmacoepidemiol Drug Saf.* 1999; 8 Suppl 1: S63-S64.
52. Warren PM, Taylor JH, Nicholson KE, et al.: Influence of tramadol on the ventilatory response to hypoxia in humans. *Br J Anaesth.* 2000; 85(2): 211-216.
53. Ghislain PD, Wiart T, Bouhassoun N, et al.: [Toxic dermatitis caused by tramadol]. *Ann Dermatol Venereol.* 1999; 126(1): 38-40.
54. Lambrecht RW, Gildemeister OS, Williams A, et al.: Effects of selected antihypertensives and analgesics on hepatic porphyrin accumulation: Implications for clinical porphyria. *Biochem Pharmacol.* 1999; 58(5): 887-896.
55. Kmetec V, Roskar R: HPLC determination of tramadol in human breast milk. *J Pharm Biomed Anal.* 2003; 32(4-5): 1061-1066.
56. Barth H, Giertz H, Schmal A, et al.: Anaphylactoid reactions and histamine release do not occur after application of the opioid tramadol. *Agents Actions.* 1987; 20(3-4): 310-313.
57. Sacerdote P, Bianchi M, Gaspani L, et al.: The effects of tramadol and morphine on immune responses and pain after surgery in cancer patients. *Anesth Analg.* 2000; 90(6): 1411-1414.
58. Freye E, Levy J: Acute abstinence syndrome following abrupt cessation of long-term use of tramadol (Ultram): A case study. *Eur J Pain.* 2000; 4(3): 307-311.
59. Senay EC, Adams EH, Geller A, et al.: Physical dependence on Ultram (tramadol hydrochloride): Both opioid-like and atypical withdrawal symptoms occur. *Drug Alcohol Depend.* 2003; 69(3): 233-241.
60. Grond S, Radbruch L, Meuser T, et al.: High-dose tramadol in comparison to low-dose morphine for cancer pain relief. *J Pain Symptom Manage.* 1999; 18(3): 174-179.
61. Harati Y, Gooch C, Swenson M, et al.: Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. *Neurology.* 1998; 50(6): 1842-1846.
62. Boureau F, Legallicier P, Kabir-Ahmadi M: Tramadol in postherpetic neuralgia: A randomized, double blind, placebo-controlled trial. *Pain.* 2003; 104(1-2): 323-331.
63. Sindrup SH, Andersen G, Madsen C, et al.: Tramadol relieves pain and allodynia in polyneuropathy: A randomised, double-blind, controlled trial. *Pain.* 1999; 83(1): 85-90.
64. Hopkins D, Shipton EA, Potgieter D, et al.: Comparison of tramadol and morphine via subcutaneous PCA following major orthopaedic surgery. *Can J Anaesth.* 1998; 45: 435-442.
65. Finkel JC, Rose JB, Schmitz ML, et al.: An evaluation of the efficacy and tolerability of oral tramadol hydrochloride tablets for the treatment of postsurgical pain in children. *Anesth Analg.* 2002; 94(6): 1469-1473.
66. Tawfik MO, Elborolossy K, Nasr F: Tramadol hydrochloride in the relief of cancer pain: a double blind comparison against sustained release morphine. *Pain.* 1990; (suppl 5): S377.
67. Osipova NA, Novikov GA, Beresnev VA, et al.: Analgesic effect of tramadol in cancer patients with chronic pain: A comparison with prolonged-action morphine sulfate. *Curr Ther Res.* 1991; 50: 812-821.
68. Bono AV, Cuffari S: [Effectiveness and tolerance of tramadol in cancer pain. A comparative study with respect to buprenorphine] [French]. *Drugs.* 1997; 53(suppl 2): 40-49.
69. Brema F, Pastorino G, Martini MC, et al.: Oral tramadol and buprenorphine in tumour pain. An Italian multicentre trial. *Int J Clin Pharmacol Res.* 1996; 16(4-5): 109-116