

Clinical Pharmacology of Tramadol

Stefan Grond and Armin Sablotzki

Department of Anesthesia, Martin-Luther-University, Halle-Wittenberg, Germany

Contents

Abstract	880
1. Pharmacokinetic Properties	881
1.1 Pharmaceutical Formulations	881
1.2 Absorption	881
1.3 Sustained-Release Preparations	881
1.4 Distribution	884
1.5 Metabolism and Elimination	884
1.6 Influence of Cytochrome P450 on Biotransformation	888
1.7 Stereoselective Pharmacokinetic Properties	889
1.8 Pharmacokinetic-Pharmacodynamic Modelling	891
1.9 Effect of Age and Impaired Renal and Hepatic Function	892
1.10 Drug Interactions	893
2. Pharmacodynamic Properties	893
2.1 Mechanism of Action	893
2.2 Analgesic Effects	894
2.3 Effects on Respiration	895
2.4 Haemodynamic Effects	895
2.5 Gastrointestinal Effects	896
2.6 Effects on Immune System	896
3. Therapeutic Efficacy in Acute Pain	896
3.1 Postoperative Pain	896
3.1.1 Oral Administration	896
3.1.2 Rectal Administration	897
3.1.3 Intramuscular Administration	897
3.1.4 Intravenous Administration	900
3.1.5 Patient-Controlled Analgesia	901
3.1.6 Regional Administration	902
3.2 Other Acute Pain Syndromes	902
3.2.1 Trauma	902
3.2.2 Abdominal Pain	903
3.2.3 Labour	903
3.3 Place of Tramadol in Acute Pain	903
4. Chronic Pain	906
4.1 Cancer Pain	906
4.1.1 Sustained-Release	907
4.2 Chronic Non-Cancer Pain	909
4.2.1 Sustained-Release	910
4.3 Neuropathic Pain	910
4.4 Place of Tramadol in Chronic Pain	911
5. Tolerability	912
6. Conclusions	915

Abstract

Tramadol, a centrally acting analgesic structurally related to codeine and morphine, consists of two enantiomers, both of which contribute to analgesic activity via different mechanisms. (+)-Tramadol and the metabolite (+)-*O*-desmethyl-tramadol (M1) are agonists of the μ opioid receptor. (+)-Tramadol inhibits serotonin reuptake and (-)-tramadol inhibits norepinephrine reuptake, enhancing inhibitory effects on pain transmission in the spinal cord. The complementary and synergistic actions of the two enantiomers improve the analgesic efficacy and tolerability profile of the racemate.

Tramadol is available as drops, capsules and sustained-release formulations for oral use, suppositories for rectal use and solution for intramuscular, intravenous and subcutaneous injection. After oral administration, tramadol is rapidly and almost completely absorbed. Sustained-release tablets release the active ingredient over a period of 12 hours, reach peak concentrations after 4.9 hours and have a bioavailability of 87–95% compared with capsules. Tramadol is rapidly distributed in the body; plasma protein binding is about 20%.

Tramadol is mainly metabolised by *O*- and *N*-demethylation and by conjugation reactions forming glucuronides and sulfates. Tramadol and its metabolites are mainly excreted via the kidneys. The mean elimination half-life is about 6 hours.

The *O*-demethylation of tramadol to M1, the main analgesic effective metabolite, is catalysed by cytochrome P450 (CYP) 2D6, whereas *N*-demethylation to M2 is catalysed by CYP2B6 and CYP3A4. The wide variability in the pharmacokinetic properties of tramadol can partly be ascribed to CYP polymorphism. *O*- and *N*-demethylation of tramadol as well as renal elimination are stereoselective. Pharmacokinetic-pharmacodynamic characterisation of tramadol is difficult because of differences between tramadol concentrations in plasma and at the site of action, and because of pharmacodynamic interactions between the two enantiomers of tramadol and its active metabolites.

The analgesic potency of tramadol is about 10% of that of morphine following parenteral administration. Tramadol provides postoperative pain relief comparable with that of pethidine, and the analgesic efficacy of tramadol can further be improved by combination with a non-opioid analgesic. Tramadol may prove particularly useful in patients with a risk of poor cardiopulmonary function, after surgery of the thorax or upper abdomen and when non-opioid analgesics are contraindicated.

Tramadol is an effective and well tolerated agent to reduce pain resulting from trauma, renal or biliary colic and labour, and also for the management of chronic pain of malignant or nonmalignant origin, particularly neuropathic pain. Tramadol appears to produce less constipation and dependence than equianalgesic doses of strong opioids.

Tramadol hydrochloride (tramadol), (1*R*S,2*R*S)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-cyclohexanol hydrochloride, is a centrally acting analgesic that is structurally related to codeine and morphine. It was first synthesised in 1962 and has been available for pain treatment in Germany since 1977.^[1] Tramadol has a low incidence of adverse

effects, particularly of respiratory depression, constipation and abuse potential,^[2] and has never been a scheduled drug.^[3] Therefore it became the most frequently prescribed opioid in Germany.

The registration of tramadol in the UK (1994), the US (1995) and then many other countries required extensive additional preclinical and clinical

research and increased international interest. Recent studies have confirmed the unique and unusual pharmacodynamic profile of this opioid, which is attributable to tramadol being a racemate. Both enantiomers and their metabolites contribute to the analgesic activity by means of different mechanisms.^[4,5] These include binding to opioid receptors and blockade of both norepinephrine and serotonin reuptake. This duality of action has prompted the classification of tramadol by the US FDA as a nontraditional centrally acting analgesic.

1. Pharmacokinetic Properties

1.1 Pharmaceutical Formulations

Tramadol is available in various pharmaceutical forms. Ampoules contain 50mg (1mL) or 100mg (2mL) of tramadol in a solution for intravenous, intramuscular or subcutaneous injection. Immediate-release (IR) formulations, which normally require oral administration four to six times daily, are capsules (50mg), soluble tablets (50mg to be dissolved in 50mL of water), drops (50mg = 0.5mL = 20 drops or four actuations of the pump) and suppositories (100mg). Several sustained-release (SR) formulations have been developed, which provide the opportunity for administration only twice daily. SR tablets (100, 150 and 200mg) are based on a hydrophilic matrix system in which tramadol is evenly distributed. On contact with the gastrointestinal fluid, the outer layer of the tablet swells gradually and forms a retarding gel layer. SR capsules (100, 150 and 200mg) contain multiple pellets of 1mm in diameter consisting of a neutral core layered with tramadol and a membrane that controls the release. In addition, a two-phase SR tablet contains 25mg of tramadol for IR and 75mg of tramadol for SR.

1.2 Absorption

The pharmacokinetic properties of tramadol are summarised in table I. After oral administration, tramadol is absorbed almost completely and quite rapidly after a lag time of 0.2 hours for drops^[6,7] and 0.5 hours for capsules.^[8] Peak plasma concentrations (C_{max}) are attained within 1.2 hours after oral administration of drops^[6,7] and within 1.6–1.9 hours after oral administration of capsules.^[8,9] There are

no available pharmacokinetic data on soluble tablets, but rapid absorption, similar to that of drops, can be expected.

Following a single oral dose of 100mg, C_{max} is approximately 300 $\mu\text{g/L}$.^[6-9,11] Plasma concentration and area under the concentration-time curve (AUC) increase linearly over the dose range 50–400mg.^[7,10] The extent of oral absorption of tramadol is almost 100% and the bioavailability is 70% following a single dose.^[8,20-22] The difference between absorption and bioavailability is attributed to the 20–30% first-pass metabolism.^[6,8,21,22] Following multiple oral administration of tramadol 100mg four times daily, C_{max} is 16% higher and AUC is 36% higher than after a single 100mg dose, indicating that oral bioavailability increases to approximately 90–100% on multiple oral administration, possibly due to saturated first-pass hepatic metabolism.^[12,23] The bioavailability of drops with ethanol is about the same as that of drops without ethanol.^[7] Oral administration of tramadol 100mg following a high-fat breakfast results in a 17% higher C_{max} and a 10% higher AUC than the corresponding values in fasted volunteers.^[24] This increase of the bioavailability by food was not considered clinically relevant.^[21,22]

After rectal administration of suppositories 100mg, tramadol absorption begins within a few minutes (0–22 minutes).^[11] A C_{max} of 294 $\mu\text{g/L}$ is reached within 3.3 hours.^[11] The absolute bioavailability (77%) is higher than that after oral administration, probably due to a reduced first-pass metabolism after rectal administration.^[11]

Tramadol is rapidly and almost completely absorbed after intramuscular injection.^[17] C_{max} of 166 $\mu\text{g/L}$ is reached 0.75 hours after intramuscular injection of 50mg.^[17] Intramuscular injection and intravenous infusion over 30 minutes are bioequivalent with respect to the extent of systemic availability.^[17] C_{max} values of 355–369 $\mu\text{g/L}$ are reached 0.9 and 1.1 hours after intramuscular injections of 100mg.^[18] The pharmacokinetic properties of subcutaneous tramadol, which is effective in post-operative pain,^[25] have not been examined.

1.3 Sustained-Release Preparations

SR tablets and capsules provide stable plasma concentrations when administered at 12-hour inter-

Table I. Pharmacokinetic properties of tramadol

Population (n)	Route and dose (mg)	t _{max} (h)	C _{max} (µg/L)	AUC _{0-∞} (µg • h/L)	t _{1/2β} (h)	CL (mL/min)	Reference
Volunteers (4)	PO (100)		260 (4h)	2194	5.1		10
Volunteers (4)	PO (200)		575 (3.5h)	4924	5.9		
Volunteers (3)	PO (300)		930 (4h)	8599	5.7		
Volunteers (3)	PO (400)		1220 (4.7h)	10 473	5.3		
Volunteers (10)	PO, capsules (100)	1.9	290	2488	5.1	710	8
Volunteers (8)	PO, ethanol drops (100)	1.2	308	2390	5.5	742	6
Volunteers (12)	PO, drops (50)	1.2	136	875	5.0	837	7
Volunteers (10)	PR, suppository (100)	3.3	294	2933	5.7		11
Volunteers (18)	PO (100) [single dose]	1.6	308	2649	5.6	110 ^a	12
Volunteers (18)	PO (100) [qid, 1 week] ^b	2.3	592	3679	6.7	73 ^a	
Volunteers (12)	PO, capsules (100)	1.6	274	2177	5.9		13
Volunteers (12)	PO, SR tablets (100)	4.9	141	2119	5.7		
Volunteers (12)	PO, capsules (100) [bid, 5 days] ^c	1.9	414	2970			
Volunteers (12)	PO, SR tablets (100) [bid, 5 days] ^d	3.5	293	2656			
Volunteers (12)	PO, SR capsules (50)	5.3	70	1039	6.0		14
Volunteers (12)	PO, SR capsules (100)	5.9	137	2060	6.2		14
Volunteers (12)	PO, SR capsules (200)	4.9	277	3952	5.6		14
Fasting (24)	PO, SR capsules (200)	6.7	294	5293	7.2		15
Nonfasting (24)	PO, SR capsules (200)	7.0	305	5266	6.8		
Fasting (24)	PO, IR capsules (200)	2.0	640	5826	6.1		
Fasting (24)	PO, SR tablets (200)	4.5	375	5517	6.2		
Volunteers (24)	PO, IR capsules (50) [qid, 3 days]		321	5167			16
Volunteers (24)	PO, SR capsules (100) [bid, 3 days]		274	5168			
Volunteers (10)	IV (100)		409 (2h)	3709	5.2	467	8
Volunteers (8)	IV (100)		394 (2h)	3490	5.2	487	6
Volunteers (10)	IV (100)		418 (2h)	3775	5.7	447	11
Volunteers (12)	IV over 30 min (50)	0.52	287	1233	5.0	594	7
Volunteers (12)	IV over 30 min (50)	0.54	305	1332	5.5	596	17
Volunteers (12)	IM (50)	0.75	293	1353	5.5	613	
Volunteers (12)	IM (100)	0.9	355	3160			18
Volunteers (12)	IM (100)	1.1	369	3250			
65–75 years (12)	PO, capsules (100)	2.0	324	2508	6.1	793	19
>75 years (8)	PO, capsules (100)	2.1	415	3854	7.0	491	19
Renal insufficiency ^e (21)	IV (100)		894	7832	10.8	280	19
Hepatic impairment ^f (12)	PO, capsules (100)	1.9	433	7848	13.3	271	19

Continued next page

Table I. Contd

Population (n)	Route and dose (mg)	t _{max} (h)	C _{max} (µg/L)	AUC _∞ (µg • h/L)	t _{1/2β} (h)	CL (mL/min)	Reference
Cimetidine ^a 3 days (12)	PO, capsules (100)	1.5	364	3526	7.2	521	19
Carbamazepine ^h 12 days (7)	PO, capsules (100)	1.0	150	528	2.5	3809	19

a Renal clearance.
b Multiple doses, 100mg qid for 1 week.
c Multiple doses, 100mg capsule every 12 hours for 5 days.
d Multiple doses, 100mg capsule every 12 hours for 5 days.
e Renal insufficiency with a creatinine clearance of 30–80 mL/min in five patients, 10–30 mL/min in seven patients, 5–10 mL/min in four patients and <5 mL/min in five patients.
f Alcohol-induced liver cirrhosis.
g Pretreatment with cimetidine 2 × 400mg for 3 days.
h Pretreatment with carbamazepine 2 × 400mg for 12 days.

AUC_∞ = area under the concentration-time curve from time zero to infinity; **bid** = twice daily; **CL** = total clearance; **C_{max}** = maximum plasma concentration; **IM** = intramuscular; **IR** = immediate-release; **IV** = intravenous; **PO** = oral; **PR** = rectal; **qid** = four times daily; **SR** = sustained-release; **tm_{max}** = time to maximum plasma concentration; **t_{1/2β}** = terminal elimination half-life.

vals. SR tablets (100, 150 and 200mg) release 100% of the active ingredient over a 12-hour period *in vitro*.^[13] The absolute bioavailability of SR tablets is 67.3% relative to the intravenous reference formulation, indicating bioequivalence of SR tablets and IR capsules (95.1%, 90% CI 87.8, 103.0%).^[13] The time to C_{max} (t_{max}) of 4.9 ± 0.8 hours for the SR tablets (compared with 1.6 ± 0.5 hours for IR capsules), the C_{max} of 141.7 ± 40.4 µg/L (274.1 ± 75.3 µg/L) and the mean absorption time of 4.70 ± 0.90 hours (1.09 ± 0.56 hours) reflect the slow-release properties of the SR tablets (table I).^[13]

At steady state (after 48 hours of twice-daily administration), bioavailability of the SR tablet is 87.4% (90% CI 81.3, 94.0%) relative to IR capsules administered with the same regimen.^[13] The peak-trough fluctuation in plasma concentrations at steady state is reduced from 121% with the IR capsule to 66% with the SR tablet.^[13] The extent of relative bioavailability of tramadol SR tablets after a lipid-rich meal (postprandial/fasting administration) is 105.1% (90% CI 99.0, 111.5%) and within the range of 80–125%.^[13] Food intake has a slight influence on rate of absorption, as shown by the shorter t_{max} and higher C_{max}, indicating that food causes a slight reduction in the retarding effect.^[13]

The pharmacokinetic properties of SR capsules are similar to those of SR tablets. Single doses of 50, 100 and 200mg of tramadol as SR capsules produce plasma concentrations above half of C_{max} (half-value duration) for 12.8, 12.9 and 13.0 hours, respectively.^[14] There is a direct linear relationship between the administered dosage and the achieved concentration (table I).^[14] Compared with IR capsules, bioavailability is only slightly diminished, whereas C_{max} is markedly reduced and t_{max} increased (table I).^[15] Compared with SR tablets 200mg, SR capsules 200mg show 95% of the AUC, 77% of the C_{max} and 118% of the half-value duration (table I), indicating enhanced retardation at almost identical bioavailability.^[15] Food intake has no influence on plasma concentrations after administration of tramadol 200mg as SR capsules.^[15] At steady state (reached after approximately 48 hours), the bioavailability of the SR capsule 100mg every 12 hours is 100% relative to IR capsules 50mg every 6 hours.^[16] The peak-trough fluctuation in plasma

concentrations at steady state is reduced from 86% with the IR capsule to 57% with the SR capsule.^[16]

The two-phase tablet of tramadol (25mg IR plus 75mg SR) produces a faster increase in plasma concentration than an IR capsule of tramadol 50mg and an SR tablet of tramadol 100mg.^[26] About 2.5 hours after administration of the two-phase tablet, the concentrations become lower than those after the SR tablet of tramadol 100mg.

For subcutaneous, intramuscular or intrathecal administration, a tramadol depot system composed of monoolein and water has been developed.^[27] In rats, intramuscular administration provides stable pain relief for more than 10 hours.^[27] Further investigations of this novel depot system will be of interest.

1.4 Distribution

Tramadol is rapidly distributed in the body, with a distribution half-life in the initial phase of 6 minutes, followed by a slower distribution phase with a half-life of 1.7 hours.^[23] The high total distribution volume of 306L after oral and 203L after parenteral administration indicates high tissue affinity; plasma protein binding is about 20%.^[8,23] After intravenous injection of tramadol 100mg, plasma concentrations of 612, 553, 483 and 409 µg/L were measured after 0.25, 0.5, 1 and 2 hours.^[8] In a rodent model, tramadol was particularly distributed into the lungs, spleen, liver, kidneys and brain.^[21]

Brain peak concentrations of tramadol occur 10 minutes after oral administration, and those of its major active metabolite *O*-desmethyl-tramadol (M1) 20–60 minutes after oral administration.^[28] In mice, the ratio tramadol/M1 in plasma was 0.5–1.0 throughout the measurements, whereas the ratio in brain was about ten at 10 minutes and about two from 20 to 50 minutes.^[28] In rats, the ratio tramadol/M1 in plasma was 0.5–1.5, whereas the ratio in brain was about 15 at 10 minutes and about 4–7 thereafter.^[28] There appears to be preferential brain versus plasma distribution of tramadol over M1 in mice and rats.

Tramadol passes the placental barrier, with umbilical venous plasma concentrations being 80% of maternal concentration.^[29] Very small amounts (0.1%) of tramadol and M1 are excreted in breast

milk, and have been detected within 16 hours after administration.^[22]

1.5 Metabolism and Elimination

Tramadol is mainly excreted via the kidneys (approximately 90%); the residual activity of a radioactively labelled dose of tramadol was recovered in the faeces.^[30] In a study involving nine cholecystectomised patients, only 1% of tramadol and its metabolites were eliminated via biliary excretion.^[10] At 30 minutes after intramuscular administration of tramadol 50mg, tramadol concentrations in saliva and urine considerably exceeded the plasma concentration.^[17] The C_{max} in saliva and urine occurred at nearly the same time as in plasma, and thereafter the plasma and saliva concentrations and the renal excretion rates decreased almost in parallel.^[17] The saliva concentrations were 7- to 8-fold and the urine concentrations 43- to 46-fold higher than the corresponding plasma concentrations.^[17] The mean elimination half-life is about 5–6 hours (table I).^[6-12,17] The mean total clearance of tramadol was 467 mL/min (approximately 28 L/h) and 710–742 mL/min (approximately 43–44 L/h) following intravenous and oral administration, respectively.^[6,8]

The main metabolic pathways of tramadol, *N*- and *O*-demethylation (phase I reactions) and conjugation of *O*-demethylated compounds (phase II reactions), were described 20 years ago.^[30] Eleven metabolites were known, five arising by phase I reactions (M1 to M5) and six by phase II reactions (glucuronides and sulfates of M1, M4 and M5). Tramadol is metabolised much more rapidly in animals than in humans: 1% and 25–30% of an oral dose, respectively, are excreted unchanged in the urine.^[30] In all species, M1 and M1 conjugates, M5 and M5 conjugates, and M2 are the main metabolites, whereas M3, M4 and M4 conjugates are only formed in minor quantities (table II).^[30] In a study where a 50mg oral dose of tramadol was given to 104 volunteers, mean values for tramadol, M1 and M2 excretion in 24-hour urine were 12%, 15% and 4% of the administered dose, respectively.^[31] However, great interindividual differences were observed in two humans after oral administration of either 1.06 or 1.25 mg/kg of ¹⁴C-labelled tramadol.^[30] One volunteer produced mainly M1, M5, M1 conjugates and M5 conjugates, whereas the other produced

Table II. Excretion of unchanged tramadol and its metabolites in the urine of humans, dogs and rats receiving oral tramadol, and metabolites found in human hepatic microsomes^[30,31,33,34]

Analyte	Chemical structure ^[30,33,34]	Percentage of each analyte found								
		human ^a	human ^b	dog ^c	rat ^d	human ^e	human ^f	hepatic ^g	rat ^h	dog ⁱ
Tramadol		25	32	1	0.9	12	>10	82	2	2
M1	<i>O</i> -Desmethyl-tramadol	10	5	2	9	15	>10	5	13	6
M2	<i>N</i> -Desmethyl-tramadol	2	31	5	17	4	>10	6	13	6
M3	<i>N,N</i> -Didesmethyl-tramadol	ND	0.8	2	10		5–10	ND	9	4
M4	<i>O,N,N</i> -Tridesmethyl-tramadol	0.1	0.8	4	2		<2	<0.5	<2	<2
M5	<i>O,N</i> -Didesmethyl-tramadol	13	6	10	14		5–10	<0.5	5	6
M6	4-Hydroxycyclohexyl-tramadol						2–5	3	<2	3
M7	4-Hydroxycyclohexyl- <i>N</i> -desmethyl-tramadol						<2	ND	<2	3
M8	4-Hydroxycyclohexyl- <i>N,N</i> -didesmethyl-tramadol						<2	ND	<2	<2
M9	4-Oxocyclohexyl-tramadol						<2	ND	<2	<2
M10	Dehydrated tramadol						<2	ND	<2	<2
M11	2-Formyl-1-(3-methoxyphenyl)cyclohexanol						<2	ND	<2	<2
M12	Tramadol glucuronide						<2	ND		
M13	M1 glucuronide						2–5	ND	7	<2
M14	M4 glucuronide						<2	ND	<2	<2
M15	M5 glucuronide						2–5	ND	10	7
M16	M6 glucuronide						2–5	ND	<2	8
M17	M7 glucuronide						<2	ND	<2	7
M18	M8 glucuronide						<2	ND	ND	<2
M19	Tramadol sulfate						<2	ND		
M20	M1 sulfate						2–5	ND		
M21	M4 sulfate						2–5	ND		
M22	M5 sulfate						5–10	ND		
M23	M6 sulfate						<2	ND		
M24	M7 sulfate								ND	<2
M25	Acetyl-M2								<2	<2
M26	Dehydro-M3								<2	<2
M27	Dehydro-M11								<2	<2
M28	Alcoholic metabolite								<2	<2
M29	Carboxylic acid								<2	<2
M30	M29 glucuronide								ND	<2
M31	Tramadol N-oxide						ND	2	ND	ND

Continued next page

Table II. Contd

Analyte	Chemical structure ^[30,33,34]	Percentage of each analyte found								
		human ^a	human ^b	dog ^c	rat ^d	human ^e	human ^f	hepatic ^g	rat ^h	dog ⁱ
M32	Hydroxy-M1					ND	<1	ND	ND	ND
M33	Dehydrated M31					ND	<2			
M13 or M20	M1 conjugates	15	8	12	11					
M14 or M21	M4 conjugates	0.8	0.2	6	4					
M15 or M22	M5 conjugates	15	6	33	14					
	Unknown	18	11	25	20					
a	Urine (0–72h) of humans (n = 1) after oral tramadol 1.25 mg/kg. ^[30]									
b	Urine (0–72h) of humans (n = 1) after oral tramadol 1.06 mg/kg. ^[30]									
c	Urine (0–72h) of dogs (n = 3) after oral tramadol 10.5 mg/kg. ^[30]									
d	Urine (0–72h) of rats (n = 5) after oral tramadol 30 mg/kg. ^[30]									
e	Urine (0–24h) of humans (n = 104) after oral tramadol 50mg. ^[31]									
f	Urine (4–12h) of humans (n = 3) after oral tramadol 100mg. ^[33]									
g	Human liver microsomal fraction incubated with tramadol 10 mg/L. ^[33]									
h	Urine (0–24h) of rats (n = 4) after oral tramadol 50 mg/kg. ^[34]									
i	Urine (0–24h) of dogs (n = 2) after oral tramadol 20 mg/kg. ^[34]									

ND = not detected.

mainly M2 (table II).^[30] In contrast to the above-mentioned studies involving Caucasians, the biotransformation of tramadol appears to be remarkably reduced in African subjects.^[32] In 10 Nigerian volunteers, about 96% of tramadol was excreted unchanged in the urine after oral administration of 100mg.^[32] There is a need to investigate racial variations in the metabolism of tramadol in more detail.

In a recent study, a total of 23 metabolites, consisting of 11 phase I metabolites (M1 to M11) and 12 conjugates (seven glucuronides, five sulfates), were profiled in the urine of male volunteers after oral tramadol 100mg.^[33] These metabolites were formed via the following six metabolic pathways: *O*-demethylation, *N*-demethylation, cyclohexyl oxidation, oxidative *N*-dealkylation, dehydration and conjugation.^[33] The previously known metabolites (M1 to M5)^[30] were confirmed as major metabolic products (table II). Six additional phase I metabolites (M6 to M11) resulted from newly identified pathways and had not previously been reported. M12 to M18 were identified as glucuronides and M19 to M23 as sulfates, of which M13 to M15 and M20 to M23 had previously been reported as M1, M4 and M5 conjugates.^[30] Additional phase I metabolites (M25 to M29) and phase II metabolites (M24 and M30) have been identified in rats or dogs, but not in humans (table II).^[33,34]

The *in vitro* metabolism of tramadol has been studied in a human liver microsomal fraction incubated with tramadol 10 mg/L.^[33] Unchanged tramadol (82% of the sample) plus eight metabolites (M1, M2, M4, M5 and M6, plus M31, M32 and M33, which were not found in urine) were identified (table II).^[33] Of the 26 identified metabolites in humans, seven (M12, M19 to M23 and M33) have not been found in the rat or dog.^[34]

The metabolism of tramadol to M1 is slow in humans (table III). After oral or rectal administration of tramadol 100mg, the t_{max} of M1 is about 1.4 hours longer than that of tramadol and the C_{max} of M1 is no more than 18–26% of that of tramadol.^[12,35] After multiple oral doses or administration of SR capsules, the time to reach C_{max} of tramadol and M1 was similar.^[12,36] After single and multiple oral administration of tramadol, the AUC for M1 was about 25% of that of the parent com-

Table III. Pharmacokinetic properties of M1 and tramadol after administration of tramadol

Study	Population (n)	Administration	Analyte	t _{max} (h)	C _{max} (μg/L)	AUC _∞ (μg • h/L)	t _{1/2β} (h)	CL (mL/min)
Liao et al. ^[12]	Volunteers (18)	PO, 100mg (single dose)	Tramadol	1.6	308	2649	5.6	110 ^a
			M1	3.0	55	722	6.7	188 ^a
		PO, 100mg (qid, 1 week) ^b	Tramadol	2.3	592	3679	6.7	73 ^a
			M1	2.4	110	835	7.0	134 ^a
Thurauf et al. ^[36]	Volunteers (20)	PO (SR capsules), 100mg	Tramadol	4.8	160	1402 ^c		
			M1	4.7	73	618 ^c		
		PO (SR capsules), 200mg	Tramadol	4.4	295	2599 ^c		
			M1	5.4	143	1201 ^c		
Nobilis et al. ^[35]	Volunteers (24)	PR (suppositories) ^d , 100mg	Tramadol	2.5	796 ^e	9510 ^f	9.1	
			M1	4.0	214 ^e	3590 ^f		
		PR (suppositories) ^d , 100mg	Tramadol	2.7	879 ^e	10 410 ^f	8.5	
			M1	4.0	230 ^e	3960 ^f		
Murthy et al. ^[37]	Children (9)	IV, 2 mg/kg	Tramadol	0.19	1079	5738	6.4	6.1 ^g
			M1	4.9	64	1172	10.6	
	Children (5)	Caudally, 2 mg/kg	Tramadol	0.55	709	4774	3.7	6.6 ^g
			M1	6.4	40	556	5.4	

a Renal clearance.

b Multiple doses, 100mg qid for 1 week.

c AUC₁₂.

d Two different pharmaceutical formulations.

e nmol/L.

f AUC₃₂ (μmol • h/L).

g mL/min/kg.

AUC_x = area under the concentration-time curve from time zero to x hours; **AUC_∞** = area under the concentration-time curve from time zero to infinity; **C_{max}** = maximum plasma concentration; **CL** = total clearance; **IV** = intravenous; **PO** = oral; **PR** = rectal; **qid** = four times daily; **SR** = sustained-release; **t_{max}** = time to maximum plasma concentration; **t_{1/2β}** = terminal elimination half-life.

pound and the elimination half-life of M1 was 6.7 and 7.0 hours, respectively, which is not substantially different from that of tramadol.^[12]

The pharmacokinetic properties of other metabolites have not been investigated in detail. It has been reported that the biological half-lives of the metabolites are similar to that of the parent substance, diminishing the likelihood of accumulation of metabolites after multiple administration.^[23] Like tramadol, all metabolites are almost completely excreted via the kidneys; from a quantitative point of view, biliary excretion of these components is negligible.^[30]

The *N*-oxide of tramadol is a prodrug for tramadol.^[38] Although tramadol *N*-oxide has no direct pharmacodynamic effects, it produces dose-related long-lasting antinociception in the mouse and rat.^[39] Tramadol concentrations were essentially the same after administration of either tramadol or tramadol *N*-oxide to mice, suggesting complete conversion.^[39] In contrast to the rapid attainment of C_{max} and rapid decline in tramadol plasma concentration after tramadol administration, tramadol concentrations increase more gradually and were maintained for a longer period after administration of tramadol *N*-oxide.^[39] Therefore, tramadol *N*-oxide could offer the clinical benefits of an extended duration of action and a 'blunted' plasma concentration spike, possibly leading to an improved adverse effect profile.^[39]

1.6 Influence of Cytochrome P450 on Biotransformation

In vitro investigations suggest that the *O*-demethylation of tramadol to metabolite M1 is catalysed by the liver enzyme cytochrome P450 (CYP) 2D6, because this biotransformation is inhibited by quinidine, a selective CYP2D6 inhibitor.^[40,41] In addition, good correlations were obtained between M1 formation and dextromethorphan *O*-demethylase, a marker for CYP2D6, in human liver microsome preparations.^[41] The gene encoding for CYP2D6 is known to show polymorphism and the existence of different alleles results in functionally different enzymes.^[42] Phenotypically, 90–95% of Caucasians are 'extensive metabolisers' and the remainder are 'poor metabolisers' of CYP2D6 probe substrates such as debrisoquine and sparteine.

M1 production in microsomes prepared from the liver of a poor metaboliser was markedly reduced.^[43] After administration of tramadol 2 mg/kg, the plasma concentration of (+)-M1 ranged from 10 to 100 µg/L in extensive metabolisers, whereas in poor metabolisers plasma concentrations of (+)-M1 were below or around the detection limit of 3 µg/L.^[44] Furthermore, poor metabolisers had inferior analgesic effects, because tramadol interacts with µ opioid receptors predominantly by way of M1.^[44]

In a study of 104 healthy volunteers, poor metabolisers of sparteine exhibited a 5-fold higher tramadol/M1 plasma concentration ratio than extensive metabolisers.^[31] Furthermore, there was a highly significant correlation between sparteine oxidation and tramadol *O*-demethylation in extensive metabolisers.^[31]

However, the biotransformation of tramadol varies within the phenotypic population of extensive metabolisers depending on the genotype of CYP2D6.^[45] In 13 children, there was only a modest correlation between tramadol/M1 plasma concentration ratio and CYP2D6 activity, as determined by dextromethorphan urinary metabolite ratio; however, when subjects were segregated based on the number of functional CYP2D6 alleles, a much stronger relationship was observed for subjects with two functional alleles, with essentially no relationship evident in those individuals with one functional allele.^[45] Further evaluation of these data suggested that the CYP2D6-mediated metabolite (M1) is formed to a lesser extent, and the formation of the non-CYP2D6 product (M2) is more pronounced, in subjects with one versus two functional alleles.^[45]

The importance of the CYP2D6 genotype for the biotransformation of tramadol has been emphasised by a study in Malaysian subjects.^[46] Compared with 5–10% of Caucasians, only 1% of Asians are homozygous for mutant CYP2D6 alleles such as CYP2D6*3, *4 or *5, which results in no functional protein being formed.^[46] Despite this low frequency of poor metabolisers in the Asian population, they carry a high frequency (51%) of the CYP2D6*10 allele, which is relatively rare in Caucasian populations.^[46] This mutation leads to an unstable enzyme with lower metabolic activity. Of 30 healthy Malaysians, all being extensive metabolisers, those who were homozygous for CYP2D6*10 had a longer

plasma half-life of tramadol than subjects in the heterozygous or normal groups (7.2, 10.0 and 12.1 hours, respectively).^[46] When these patients were screened for the presence of other alleles as well, the pharmacokinetic parameters were even better explained: tramadol half-lives were 6.6 hours for CYP2D6*1/*1, 7.4 hours for CYP2D6*1/*9 and CYP2D6*1/*10, 7.5 hours for CYP2D6*1/*4 and CYP2D6*1/*5, 8.5 hours for CYP2D6*10/*10 and CYP2D6*10/*17 and 21.5 hours for CYP2D6*4/*10 and CYP2D6*5/*10.^[46]

Investigations in human liver microsomes have shown differences between the kinetics of *O*- and *N*-demethylation.^[41] Although M1 is the major metabolite formed at low tramadol substrate concentrations, M2 formation predominates at high substrate concentrations.^[41] The biphasic kinetics of both M1 and M2 formation indicate the participation of more than one CYP isoform in these pathways of tramadol metabolism.^[41] In the presence of low CYP2D6 concentrations or when the *O*-demethylation of tramadol is inhibited, a metabolic switch in favour of enhanced *N*-demethylation can be observed.^[22,47] *In vivo*, however, there was no correlation between CYP2D6 activity, determined by sparteine oxidation, and tramadol *N*-demethylation.^[31]

In vitro, the *N*-demethylation of tramadol to metabolite M2 is catalysed by cDNA-expressed human CYP2B6 and CYP3A4.^[41] In addition, M2 formation was inhibited by the CYP3A4 inhibitor troleanomycin to 33–44% of control, and good correlations were obtained between M2 formation and (*S*)-mephenytoin *N*-demethylase, a marker for CYP2B6, in human liver microsomes.^[41]

Based on the observations that CYP2D6 primarily catalyses tramadol *O*-demethylation (M1 formation), whereas CYP2B6 and CYP3A4 primarily catalyse tramadol *N*-demethylation (M2 formation), CYP2D6 would be expected to participate in M5 formation from M2.^[41] In addition, CYP2B6 and CYP3A4 would be expected to participate in M1 metabolism to M5, and M2 metabolism to M3.^[41] Additional studies, using M1 and M2 as substrates, are required to fully elucidate the CYP isoforms involved in M3 and M5 formation. Further *in vitro* and *in vivo* studies should investigate the influence of CYP isoforms on the formation of the remaining tramadol metabolites.

The wide variability in the pharmacokinetic properties of tramadol can partly be ascribed to CYP polymorphism. Because fluctuations in the concentrations of tramadol and its pharmacodynamically active metabolites have impact on the therapeutic response and toxicity of tramadol, genotypic and phenotypic characterisation of individuals and populations becomes increasingly important to predict enzyme activity, individualise drug therapy and thus maximise safety and efficacy.

1.7 Stereoselective Pharmacokinetic Properties

Tramadol is administered as a racemic mixture of two enantiomers, (+)-tramadol and (–)-tramadol, that are essentially metabolised by the liver producing (+)-metabolites and (–)-metabolites, respectively. Several *in vitro* and *in vivo* studies have shown that the metabolism and distribution of tramadol are stereoselective. So far, no study has investigated whether interconversion of the enantiomers of tramadol or its metabolites occurs.

In vitro, *O*- and *N*-demethylation of tramadol were both demonstrated to be stereoselective.^[40] The *O*-demethylation of tramadol, leading to M1, was determined to be 2-fold greater for the (–)-enantiomer than for the (+)-enantiomer.^[40] On the other hand, *N*-demethylation, leading to M2, was considerably faster after incubation of the (+)-enantiomer compared with the (–)-enantiomer.^[40] Since *O*-demethylation is the preferred biotransformation of tramadol in most subjects, higher plasma concentrations of (+)-tramadol and (–)-M1 compared with (–)-tramadol and (+)-M1, respectively, can be expected *in vivo*.

To study the stereoselectivity of renal clearance, isolated kidneys of rats were perfused with tramadol and M1.^[48] The renal clearance of the enantiomers of both compounds was stereoselective, (–)-tramadol and (+)-M1 being preferentially eliminated. In addition, the *O*-demethylation of tramadol was stereoselective in the kidneys, (–)-tramadol being preferentially metabolised.^[48]

The distribution of tramadol in the central nervous system of rats is also stereoselective.^[49] At 1 hour after intraperitoneal administration of tramadol 17 mg/kg, concentrations of (+)-tramadol were

Table IV. Stereoselective pharmacokinetic properties of tramadol and M1 after administration of tramadol

Reference	Population (n)	Administration	Analyte	t _{max} (h)	C _{max} (µg/L)	AUC _∞ (µg • h/L)	t _{1/2β} (h)	CL (mL/min)
Campanero et al. ^[52]	Volunteers (12)	IV over 30 min, 100mg	(+)-Tramadol			1815	5.5	423 ^a
			(-)-Tramadol			1348	4.6	554 ^a
			(+)-M1			515	9.1	1513 ^a
			(-)-M1			501	9.0	1500 ^a
Ceccato et al. ^[53]	Volunteers (30)	PO, 100mg	(+)-Tramadol	1.8	323	2784 ^b		
			(-)-Tramadol	1.8	290	2227 ^b		
			(+)-M1	2.1	61	697 ^b		
			(-)-M1	2.1	81	761 ^b		
Liu et al. ^[54]	Volunteers (12)	PO (SR tablets), 100mg (bid, 5 days)	(+)-Tramadol	4.2	164	2482	7.8	
			(-)-Tramadol	3.4	144	1911	6.2	
			(+)-M1	3.8	18	162		
			(-)-M1	3.4	23	179		

a mL/h/kg.

b AUC₃₆.

AUC₃₆ = area under the concentration-time curve from time zero to 36 hours; AUC_∞ = area under the concentration-time curve from time zero to infinity; bid = twice daily; CL = total clearance; C_{max} = maximum plasma concentration; IV = intravenous; PO = oral; SR = sustained-release; t_{max} = time to maximum plasma concentration; t_{1/2β} = terminal elimination half-life.

higher than those of (-)-tramadol and concentrations of (-)-M1 were higher than those of (+)-M1 in plasma, cerebrospinal fluid and cerebral cortex.^[49] Tramadol and M1 concentrations of both enantiomers were the highest in cerebral cortex and the lowest in cerebrospinal fluid.^[49] At 1 hour after intraperitoneal administration of M1 5 mg/kg, the concentrations of (+)-M1 were higher than those of (-)-M1 in plasma, cerebrospinal fluid and cerebral cortex, which was different from the results after intraperitoneal administration of tramadol.^[49] The concentrations of both enantiomers of M1 were the highest in cerebral cortex and the lowest in cerebrospinal fluid.^[49] Following intravenous infusion of (+)-M1 or (-)-M1 in rats, the pharmacokinetics of both substrates were similar and could best be described by a two-compartment model.^[50] There was no pharmacokinetic interaction between the two compounds.^[51]

Following an intravenous infusion of tramadol 100mg over 10 minutes to 12 human volunteers, at all times of the observation period (10 minutes to 24 hours) plasma concentrations, AUC and elimination half-life of (+)-tramadol were greater than those of (-)-tramadol (table IV).^[52] On the other hand, (+)-M1 concentrations were lower than (-)-M1 concentrations between 10 minutes and 8 hours after infusion, but greater at 12 and 24 hours.^[52]

After oral administration of tramadol 200mg, t_{max} was identical for (+)-tramadol and (-)-tramadol, as well as for (+)-M1 and (-)-M1 (table IV).^[53] The C_{max} and AUC values of (+)-tramadol were greater than those for (-)-tramadol, and those of (-)-M1 were greater than those of (+)-M1 (table IV).^[53] Another study investigated the stereoselective pharmacokinetics of tramadol after multiple oral doses of SR tablets 100mg.^[54] (+)-Tramadol was shown to be absorbed more completely, but eliminated more slowly. At steady state, the plasma concentrations of (+)-tramadol were higher than those of (-)-tramadol at every sampling timepoint, and those of (-)-M1 were higher than those of (+)-M1 at most sampling timepoints. A time-dependent increase of the (+)/(-)-tramadol ratio and the (-)/(+)-M1 ratio was observed during the 32-hour sampling period. Although the (+)/(-)-tramadol ratios were similar among the 12 subjects (range 1.19–1.48), the (-)/(+)-M1 ratios were very different (range

0.89–1.90). It needs to be determined whether the pharmacokinetic stereoselectivity of the enantiomers of M1 is caused by different levels of protein binding, different rates of renal clearance and/or polymorphism of CYP2D6.

Analysis of the enantiomers of tramadol and its metabolites in the urine of volunteers has confirmed that a stereoselective metabolism of tramadol clearly occurs. After oral administration of tramadol 100mg, 16% of the dose was excreted within 30 hours in the urine as unchanged tramadol, 16% as M1, 2% as M2 and 15% as M5.^[55] For all compounds, a time-dependent increase of the initial enantiomeric ratio was observed during the study period.^[55] The enantiomeric ratios [(+)/(–) for tramadol; not determined if (+)/(–) or (–)/(+) for metabolites] were 1.22 for tramadol, 1.48 for M1, 2.29 for M2 and 2.19 for M5.^[55] This is in good agreement with the results of other investigations, which also showed a higher excretion of the (+)-enantiomer.^[56–58] In addition, a 4- to 5-fold higher excretion of the (–)-enantiomers of two phase II metabolites, *O*-demethyl-tramadol glucuronide (M13) and *N,O*-didemethyl-tramadol (M15), was observed after oral administration of tramadol 100 or 150mg to volunteers.^[58,59]

1.8 Pharmacokinetic- Pharmacodynamic Modelling

Pharmacokinetic-pharmacodynamic studies are used to describe and predict the time course of the *in vivo* effect in different scenarios. For tramadol, interpretation of the pharmacokinetic-pharmacodynamic relationship is difficult because of: (i) a delay of effect resulting from transport from plasma to central nervous system; (ii) potential development of tolerance; and (iii) pharmacodynamic interactions among the two enantiomers of tramadol and its active metabolites.^[50] So far, only two animal studies have investigated the pharmacokinetic-pharmacodynamic relationships of tramadol.^[50,51]

The first pharmacokinetic-pharmacodynamic study investigated the pharmacokinetic properties and the antinociceptive and respiratory effects of the two main metabolites of tramadol, (+)-M1 and (–)-M1, in rats.^[50] The pharmacokinetics of both compounds were considered similar and were well described with multicompartment models. (+)-

M1 2 mg/kg was enough to achieve 100% antinociception without respiratory depression. Antinociceptive response elicited by (+)-M1 could be adequately described by a standard pharmacokinetic-pharmacodynamic model. In addition, the results indicated the development of tolerance for the antinociceptive effects of (+)-M1. The administration of doses of (+)-M1 higher than 2.5 mg/kg elicited dose-dependent respiratory depression. However, doses of (–)-M1 up to 8 mg/kg showed neither antinociception nor respiratory effects.^[50]

The second pharmacokinetic-pharmacodynamic study investigated the interactions between (+)-M1 and (–)-M1 in rats.^[51] The pharmacokinetic parameters of both enantiomers infused together were similar to those obtained when both compounds were administered alone; no pharmacokinetic interaction between (+)- and (–)-M1 was found. Although (–)-M1 alone showed no antinociception,^[50] it caused potentiation of the antinociceptive effect elicited by (+)-M1. This phenomenon has successfully been modelled by using a noncompetitive interaction model, including an effect compartment to account for the opioid effect of (+)-M1 and an indirect response model accounting for the release of norepinephrine by (+)-M1 and inhibition of norepinephrine reuptake by (–)-M1.^[51,60]

In humans, no pharmacokinetic-pharmacodynamic modelling has been performed so far. Two studies investigated the analgesic effect of SR tramadol in 20 volunteers with an experimental pain model.^[36,61] In both studies, the antinociceptive effects did not correlate with changes in pharmacokinetics. The authors concluded that these discrepancies might be based on differences between tramadol concentrations in plasma and at the site of action.

Another approach was the determination of 'minimum effective' plasma concentrations during intravenous patient-controlled analgesia (PCA) for post-operative pain. Venous blood samples were taken immediately before a patient's demand, i.e. at the point in time at which the patient was just becoming dissatisfied with analgesia.^[62–64] The determined mean minimum effective concentrations varied depending on the study conditions, and were 298 µg/L in a study where patients received at least 5 µg/kg fentanyl intraoperatively,^[64] 590 µg/L in a study

where patients received no opioids whatsoever besides tramadol^[62] and 916 µg/L in a study where tramadol PCA was combined with a continuous infusion of tramadol at 12 mg/h independent of the demands.^[63] The range of minimum effective concentrations was rather broad in all of these three studies – 20–986 µg/L,^[64] 65–2169 µg/L^[62] and 272–1900 µg/L.^[63] The relative parenteral opioid potency derived from minimum effective concentrations in postoperative pain treatment was calculated to be 0.05 : 1 for tramadol compared with morphine.^[65]

The minimum effective concentrations of M1 (84 and 36 µg/L) were only 12–14% of those of tramadol.^[62,64] Plasma concentrations did not rise from the initial to the final blood sample (tramadol, 250 vs 208 µg/L; M1, 30 vs 34 µg/L),^[65] indicating that accumulation or acute tolerance does not develop during short postoperative use of tramadol.

During intravenous PCA using (+)-tramadol, tramadol racemate and (–)-tramadol, the mean plasma concentrations of tramadol were 470, 590 and 771 µg/L, and those of M1 were 57, 84 and 96 µg/L, respectively.^[62] The finding that the minimum effective concentrations of tramadol and M1 in the (+)-tramadol group were lower than those in the (–)-tramadol group confirms that (+)-tramadol or (+)-M1 are more potent analgesics than the (–)-enantiomers.^[62] Stereoselective analysis showed that the concentrations of (+)-tramadol and (+)-M1 were lower in the tramadol racemate group than in the (+)-tramadol group; this finding suggests that a potentiation in the analgesic effect elicited by (+)-tramadol or (+)-M1 is caused by (–)-tramadol or (–)-M1 in humans.^[62]

The concentrations described as ‘minimum effective’ in these studies,^[62-64] however, are not really ‘minimum effective’ because no quantitative data are available for the roles of tramadol, M1 and other metabolites in the analgesic effect of tramadol.^[62] In addition, all studies demonstrated a great inter- and intraindividual variability in postoperative plasma concentrations and could not fix narrow analgesic threshold concentrations.^[62]

Proper pharmacokinetic-pharmacodynamic characterisation of tramadol in humans, which implies the administration of (+)-tramadol, (–)-tramadol, (+)-M1 and/or (–)-M1 and use of enantioselective

analytical methods to quantify plasma concentrations of each of the important and active components, is required to allow better understanding of tramadol effects.

1.9 Effect of Age and Impaired Renal and Hepatic Function

The pharmacokinetics of tramadol are not age-dependent (table I). Only one study has investigated the pharmacokinetic properties of tramadol in children (table I).^[37] After intravenous injection of tramadol 2 mg/kg in nine children aged 1–7 (median 2.4) years, the mean plasma concentrations of tramadol and M1 were only slightly higher than those in adults.^[37] None of the pharmacokinetic variables calculated was significantly different from those in healthy adult volunteers.^[37] As *O*-demethylation of tramadol is carried out by CYP, which usually reaches adult levels by 1 year of age, it is not surprising that the M1/tramadol plasma concentration ratio after intravenous injection was similar to that in adults.^[37] The AUC value in five children aged 6–12 (median 6.0) years after caudal administration was only 17% lower than after intravenous injection, demonstrating that there is extensive systemic absorption of tramadol after caudal administration.^[37]

Only one study has investigated the pharmacokinetic properties of tramadol in older subjects (table I).^[19] There were no clinically relevant differences in pharmacokinetic properties between healthy adult volunteers aged <65 years and volunteers aged >65–75 years. However, elimination may be prolonged in patients >75 years of age.^[19]

Since tramadol and its main pharmacologically active metabolite M1 are eliminated both metabolically and renally, the terminal half-life may be prolonged in hepatic or renal function disorders. However, the prolongation of the elimination half-life is relatively slight, as long as one of the two excretion organs is virtually intact.^[19] In patients with severe liver cirrhosis, the elimination half-life of tramadol was extended to a mean of about 13 hours; extreme values reached up to 22 hours.^[19] In addition, the renal clearance of unchanged tramadol increases in patients with liver cirrhosis.^[66] Since it is not yet known whether patients with liver cirrhosis experience sufficient pain relief after recommended doses

of tramadol, and because of the potential for delayed elimination and accumulation, it appears advisable to consider alternative drugs in this setting until more information becomes available.^[66]

In patients with renal failure whose creatinine clearance was <5 mL/min the mean elimination half-life of tramadol was about 11 hours; extreme values reached about 19 hours.^[19] The administration of tramadol 50mg four times daily on a haemodialysis-free day resulted in a t_{max} of 3 hours and an elimination half-life of 6.4 hours, both being comparable to those in healthy subjects.^[67] However, total clearance (151 mL/min) and volume of distribution (83L) were decreased, and thus the C_{max} increased (478 μ g/L).^[67] Therefore, the doses and intervals of tramadol should be adjusted in patients with severe renal impairment.

Dialysis appears not to have a significant effect on tramadol concentrations. The total amount of tramadol and M1 removed during a 4-hour dialysis period (haemodialysis, intermittent or continuous haemofiltration, peritoneal dialysis) was <7% of the administered dose.^[10] However, a case report described a 55% extraction ratio during haemodialysis and recommended that tramadol administration should be performed after the session of haemodialysis.^[67]

1.10 Drug Interactions

An interaction study with cimetidine, a typical enzyme inhibitor, showed that previous administration of cimetidine 400mg twice daily for 3 days resulted in an increase of tramadol AUC (27%) and elimination half-life (20%),^[19] an effect that was not considered to require dosage adjustment.^[10]

Investigations on the interaction with carbamazepine 400mg twice daily for 12 days as a typical enzyme inducer showed that tramadol C_{max} (51%), AUC (26%) and elimination half-life (54%) were reduced.^[19] Therefore, an increase in tramadol dosage should be considered in patients with previous or concomitant carbamazepine treatment.

There is no interaction between tramadol and coumarin anticoagulants.^[68]

2. Pharmacodynamic Properties

2.1 Mechanism of Action

Tramadol has a weak affinity for the μ opioid receptor. A second, non-opioid, mechanism is suggested by: (i) lack of naloxone reversibility; (ii) lack of significant naloxone-induced withdrawal; (iii) production of mydriasis (rather than miosis); and (iv) attenuation of its antinociceptive or analgesic effect by non-opioid (i.e. serotonin or adrenergic) antagonists.^[69]

Tramadol possesses only a modest affinity for μ opioid receptors and no affinity for δ or κ opioid receptors.^[4] The affinity of tramadol for μ opioid receptors is approximately 10-fold less than that of codeine and 6000-fold less than that of morphine, an affinity that by itself does not seem sufficient to contribute to the analgesic action of tramadol (table V). The metabolite M1 binds with about 300-fold higher affinity than the parent compound, but still with much lower affinity than morphine.^[60,70,71] The increase in subjective and objective pain thresholds induced by tramadol is, in contrast to that of other opioids, only partially blocked by the opioid antagonist naloxone.^[72] Therefore, the activation of μ

Table V. Relative activity for inhibition of opioid receptor binding or monoamine uptake^[5,73]

Drug	K_i (μ mol/L)					
	opioid receptor affinity			uptake inhibition		
	μ	δ	κ	norepinephrine	serotonin	
(\pm)-Tramadol	2.1	57.6	42.7	0.78	0.9	
(+)-Tramadol	1.3	62.4	54.0	2.51	0.53	
(-)-Tramadol	24.8	213	53.5	0.43	2.35	
(+)-M1	0.0034					
Morphine	0.00034	0.092	0.57	IA	IA	
Imipramine	3.7	12.7	1.8	0.0066	0.021	

IA = inactive; K_i = inhibition constant.

opioid receptors appears to be only one of the components of the mechanism of action of tramadol.

In addition to its opioid actions, tramadol inhibits the neuronal reuptake of norepinephrine and serotonin (5-hydroxytryptamine, 5-HT).^[4] These monoamine neurotransmitters are involved in the antinociceptive effects of descending inhibitory pathways in the central nervous system. The α_2 -adrenoceptor antagonist yohimbine and the serotonin antagonist ritanserin block the antinociceptive effects of tramadol,^[72] but not those of morphine.^[4] The reuptake inhibition of the non-opioid system requires the same range of concentrations as the inhibition of the opioid system (table V), suggesting that both mechanisms are active *in vivo*.

Tramadol is a racemate of 50% (+)-enantiomer and 50% (-)-enantiomer.^[74] (+)-Tramadol has a 2-fold higher affinity for the μ opioid receptor than the racemate (table V).^[5] Of the metabolites, (+)-M1 has the highest affinity for the μ opioid receptor, being about 700-fold more potent than (\pm)-tramadol.^[73] Another metabolite with a higher affinity than (\pm)-tramadol for the μ opioid receptor is (\pm)-M5.^[73] The intravenous administration of M1, but not of M5, produced strong antinociceptive effects.^[71] However, a pronounced effect was seen after direct administration of M5 into the brain ventricle, indicating that M5 does not penetrate the blood-brain barrier because of its high polarity.^[71] Therefore *in vivo*, (+)-M1 appears to be responsible for the μ opioid-derived analgesic effect of tramadol.

(\pm)-Tramadol inhibits the neuronal reuptake of serotonin; the (+)-enantiomer is about 4-fold more potent than the (-)-enantiomer.^[75] In addition, (\pm)-tramadol and its (+)-enantiomer, but not the (-)-enantiomer and M1, increase serotonin efflux.^[76] Whereas one study suggests that an enhancement of serotonin release contributes to its actions,^[77] another study indicates that tramadol is only a serotonin reuptake blocker and not a serotonin releaser.^[78] Furthermore, the serotonergic pathway is responsible for the antinociceptive effect of tramadol in the formalin test, and this effect is mediated by 5-HT₂ receptors.^[79]

Tramadol enhances extraneuronal norepinephrine levels in the spinal cord by competitive interference with the norepinephrine reuptake mechanism.^[80] The site of interference is the norepinephrine transporter function.^[81]

The effect on norepinephrine efflux was smaller than the effect on norepinephrine uptake.^[82] (-)-Tramadol is a more potent blocker of norepinephrine reuptake than is (+)-tramadol or M1.^[82,83]

These findings led to the hypothesis that tramadol produces its antinociception in animals and analgesia in humans by a multimodal mechanism.^[69] (+)-M1 acts as a μ opioid agonist, (+)-tramadol inhibits serotonin reuptake and (-)-tramadol inhibits norepinephrine reuptake. The activity of the individual enantiomers at either the opioid or monoamine uptake sites is low when compared with such reference compounds as morphine for the opioid sites and imipramine for the uptake sites (table V).^[69]

In rats, the measured effective dose to produce 50% antinociception (ED₅₀) of racemic tramadol was lower than the theoretical value calculated if the contributions of the enantiomers were simply additive.^[5] Thus, combined as a racemate, the enantiomers of tramadol act in a synergistic manner and are more efficacious. It is of great interest that less-than-synergistic interactions have been observed for adverse events, i.e. in the rotarod test and the colonic propulsive motility test.^[5] The severity of adverse events seen with the racemate is reduced because these effects predominate with one or the other of the enantiomers and, in part, they antagonise each other.

2.2 Analgesic Effects

In healthy volunteers undergoing experimental pain, oral tramadol 100mg and intravenous tramadol 2 mg/kg provided analgesia superior to that of placebo.^[84,85] Analgesia peaked at 3 hours and lasted for about 6 hours.^[84] Tramadol-induced analgesia was only partly antagonised by the opioid antagonist naloxone.^[84,86] The combination of naloxone and the α_2 -adrenoceptor antagonist yohimbine abolished the analgesic effects of tramadol.^[72] Furthermore, ondansetron, a selective 5HT₃ receptor antagonist, reduced the analgesic effects of tramadol in post-operative pain.^[87,88] These data point to the synergy of monoaminergic modulation and opioid agonism in tramadol-induced analgesia in humans.

Tramadol interacts with μ opioid receptors predominantly by way of its metabolite (+)-M1.^[44] In

extensive sparteine metabolisers, the analgesic effects of tramadol were superior to those in poor metabolisers.^[44] Therefore, the formation of (+)-M1 by CYP2D6 is important for the analgesic effect of tramadol.

Three studies investigated the extent of analgesia contributed by the enantiomers of tramadol in humans.^[89-91] In healthy volunteers, oral (+)-tramadol was associated with an immediate rapid increase in the pain threshold that could be inhibited by naloxone.^[91] (-)-Tramadol and the racemate both induced antinociceptive effects of a similar magnitude that were not affected by naloxone.^[91] Following orthopaedic surgery, intravenous administration of up to 150mg of (+)-tramadol, (-)-tramadol or the racemate were superior to placebo, but inferior to morphine (up to 15mg).^[90] Whereas (+)-tramadol and morphine had the highest rate of adverse events, tramadol racemate had the lowest rate.^[90] In a randomised double-blind study, 98 patients recovering from major gynaecological surgery were treated with intravenous PCA.^[89] Of patients treated with (+)-tramadol, racemate or (-)-tramadol, 67%, 48% and 38%, respectively, were considered responders regarding the primary criterion of efficacy, and 82%, 76% or 41% with respect to the secondary criterion. Nausea and vomiting were the most frequently reported adverse effects and were most often seen with (+)-tramadol. Taking into account both efficacy and adverse events, the racemate seems to be superior to either enantiomer alone.^[89,90]

Lehmann performed multiple identical studies using different opioids in intravenous PCA and calculated equipotent dose ratios from hourly opioid consumption and retrospective pain score.^[65] The equipotent dose ratio of tramadol compared with morphine was between 6.3 : 1 and 10.2 : 1.^[65]

In a pooled analysis of 18 single-dose studies on oral tramadol, nine in dental extraction pain (1594 patients) and nine in postsurgical pain (1859 patients), tramadol 50mg showed similar analgesic efficacy to codeine 60mg, and tramadol 100mg was the optimal single dose for acute pain.^[92] Because tramadol has a higher oral bioavailability than morphine, an equipotent dose ratio of 4 : 1 for oral tramadol compared with oral morphine should be expected.

2.3 Effects on Respiration

Tramadol, as a μ opioid agonist, influences respiration but is unlikely to produce clinically relevant respiratory depression at the recommended dosage. In healthy volunteers, tramadol reduces total ventilatory CO₂ sensitivity by acting at μ opioid receptors in the brainstem,^[93] but does not depress the hypoxic ventilatory response.^[94] Furthermore, tramadol exhibited a minimum effect on respiration and breathing pattern when given as a 150mg bolus plus a subsequent 3-hour steady infusion of 250mg.^[95]

In spontaneously breathing anaesthetised patients, tramadol 0.6 mg/kg had no effects on end-tidal CO₂ concentration, minute volume and respiratory rate, whereas equianalgesic doses of oxycodone or pethidine produced respiratory depression.^[96,97] In children under halothane anaesthesia, intravenous tramadol 1 or 2 mg/kg caused significantly less respiratory depression than intravenous pethidine 1 mg/kg.^[98]

2.4 Haemodynamic Effects

Tramadol has no clinically relevant haemodynamic effects. In healthy volunteers, blood pressure and heart rate were only very slightly and transiently elevated following intravenous tramadol 100mg.^[99] A bolus of 150mg plus a subsequent 3-hour steady infusion of 250mg did not have any clinically significant effects on haemodynamics in volunteers, but an increase in plasma epinephrine levels was noted.^[95] During artificial ventilation with oxygen and nitrous oxide before the start of surgery, intravenous tramadol 0.75 and 1.5 mg/kg caused a minor increase in systemic and pulmonary blood pressure.^[100] Intravenous tramadol 0.6 mg/kg and oxycodone 0.04 mg/kg had no significant effect on heart rate in spontaneously breathing patients during halothane anaesthesia.^[101]

No major effects on heart rate, mean pulmonary artery pressure, pulmonary capillary wedge pressure, stroke volume index and total peripheral resistance were observed in 57 circulatory risk patients prior to major vascular surgery following equipotent doses of morphine, fentanyl, alfentanil, tramadol and nalbuphine.^[102] Furthermore, tramadol 50mg administered intravenously produced no significant change in heart rate and blood pressure in patients

with myocardial infarction or unstable angina pectoris.^[103]

2.5 Gastrointestinal Effects

Tramadol, in contrast to other μ receptor agonists, has only a minor delaying effect on gastrointestinal transit. In healthy volunteers, tramadol 1 mg/kg did not delay gastric emptying.^[104] In another study, tramadol 1.25 mg/kg had a measurable but smaller inhibitory effect on gastric emptying compared with morphine and codeine.^[105] In a double-blind crossover study of ten healthy volunteers, tramadol 50mg and placebo solutions were given four times daily for 10 days.^[106] In this longer-term study, tramadol had a minor delaying effect on colonic transit but no effect on upper gastrointestinal transit or gut smooth muscle tone.

In patients with pancreatitis, orocecal transit time was unchanged after 5 days of tramadol, but increased with morphine.^[107] Gastrointestinal motility was also evaluated after abdominal hysterectomies in 50 patients who were randomised to receive double-blinded postoperative 48-hour infusions of morphine or tramadol.^[108] Orocecal and colonic transit times increased after operation with both morphine and tramadol, but gastric emptying was prolonged only with morphine. Whereas pentazocine causes spasm of the bile duct sphincter, tramadol, buprenorphine and saline showed no such effect.^[109]

2.6 Effects on Immune System

In rats, tramadol has an immunological profile different from that of morphine, which is known to suppress both natural killer cell activity and T lymphocyte proliferation at subanalgesic doses.^[110] Tramadol significantly depressed T lymphocyte function at analgesic doses, but did not modify the activity of natural killer cells, which mediate cytotoxicity against tumour cells and are important in immune defence against viral infection.^[110]

Another study demonstrated immunostimulatory properties of tramadol.^[111] In contrast to morphine, tramadol increased natural killer cell activity in normal non-operated rats and was able to prevent surgery-induced suppression of natural killer cell activity.^[111] Furthermore, tramadol given before and

after surgery blocked the enhancement of lung metastasis induced by surgery in rats.^[111]

After surgery in cancer patients, analgesic doses of tramadol, in contrast to morphine, returned the surgery-induced depression of T lymphocyte proliferation to basal levels.^[112] In addition, tramadol enhanced the activity of natural killer cells.^[112]

3. Therapeutic Efficacy in Acute Pain

Extensive studies reviewed previously^[22,65] have demonstrated the analgesic efficacy and tolerability of orally, intramuscularly or intravenously administered tramadol in acute pain. Although tramadol has been used in post-traumatic, obstetric, and renal or biliary colic pain, most studies have investigated postoperative pain (table VI). In a meta-analysis that included, for methodical reasons, only three of 36 controlled trials on postoperative pain, an odds ratio of 0.4 (95% CI -0.60, 0.86) demonstrated the analgesic efficacy of tramadol compared with placebo and morphine.^[113]

3.1 Postoperative Pain

3.1.1 Oral Administration

A meta-analysis of published and unpublished data has demonstrated clear analgesic efficacy of single-dose oral tramadol.^[142] In postsurgical pain, oral tramadol 50, 100 and 150mg had number needed to treat (NNT) of 7.1, 4.8 and 2.4, respectively, compared with aspirin 650mg plus codeine 60mg (3.6) and paracetamol (acetaminophen) 650mg plus propoxyphene 100mg (4.0).^[142] This means that one in every 2.4–7.1 patients would experience at least 50% pain relief with tramadol, but would not have done so with placebo.

Two of these single-dose studies have been published in detail, but present contradicting results.^[118,119] Oral tramadol 75 or 150mg was significantly more effective than placebo and a combination of paracetamol 650mg and propoxyphene 100mg in 161 patients following caesarean section.^[119] Stubhaug et al.,^[118] however, found no difference in analgesic efficacy between tramadol 50 or 100mg and placebo on the first day after total hip replacement in 144 patients, but significantly more emetic episodes after tramadol. The good test sensitivity of the latter study was confirmed by the active

control (paracetamol 1000mg plus codeine 60mg) being superior to tramadol and placebo. Explanations for the discrepancy between these two studies are that baseline pain intensity was obviously higher in the study of Stubhaug et al.^[118] and that pain following hip surgery is somatic whereas pain following caesarean section also includes visceral pain. Thus, a single oral dose of tramadol does not seem to be adequate in severe pain following orthopaedic surgery. Multiple doses of oral tramadol 50–200mg, however, provided effective analgesia on the day after prolapsed intervertebral disc repair in 80 patients with severe pain, with no difference in pain relief or adverse events to oral pentazocine 50–200mg.^[116]

The analgesic efficacy of oral single-dose tramadol can be increased by combination with a non-opioid analgesic. A meta-analysis of seven randomised, double-blind, placebo-controlled trials compared the combination of tramadol 75 or 112.5mg plus paracetamol 650 or 975mg with its components in postoperative pain.^[143] Combination analgesics (tramadol plus paracetamol) had significantly better NNTs than the components alone and a similar rate of adverse events.

Oral tramadol has also been demonstrated to be effective following surgery in children. Oral tramadol 1.5 mg/kg provided postoperative analgesia superior to that of placebo in 60 children undergoing extraction of six or more teeth.^[144] In another study, 81 postsurgical patients 7–16 years of age received oral tramadol 1 or 2 mg/kg for postoperative analgesia when they were ready to convert from morphine PCA to oral analgesics.^[145] The 2 mg/kg group required approximately half as much rescue analgesia as did the 1 mg/kg group. Adverse events were similar between the two treatment groups. In a single-blind study of children aged 11 years and older, oral tramadol delivered the same analgesic efficacy as oral diclofenac for post-tonsillectomy pain relief.^[146]

Oral tramadol is a suitable analgesic in patients undergoing day surgery, because the lack of respiratory depressant effect allows its use after discharge from hospital. In a double-blind, multicentre study, 111 patients were treated with oral tramadol 100–400 mg/day after discharge from groin surgery and 117 patients were treated with oral codeine/

paracetamol 16/1000 mg/day.^[114] Prior to discharge, the patients received pre-, intra- and postoperatively, either tramadol 100mg or fentanyl intravenously. Tramadol provided analgesic efficacy superior to that of fentanyl plus codeine/paracetamol. In a double-blind study of 91 gynaecological patients, oral tramadol 100mg administered pre- and postoperatively provided similar analgesic efficacy compared with oral naproxen 500mg administered pre- and postoperatively.^[117] Well-being improved significantly in the tramadol group compared with the naproxen group. In another double-blind study, postoperative administration of tramadol 50–100mg every 4–6 hours provided efficacy similar to that of a combination of paracetamol/codeine 500/30mg or paracetamol/dextropropoxyphene 325/32.5mg in 68 patients who underwent laparoscopic surgery.^[115]

3.1.2 Rectal Administration

The use of rectal tramadol administration was investigated in only one study of 40 patients.^[147] There was no difference in pain scores at rest and during movement between tramadol suppositories 100mg or paracetamol/codeine suppositories 1000/20mg every 6 hours, but the incidence of nausea and vomiting was significantly higher in the tramadol-treated group (84% vs 31%).

3.1.3 Intramuscular Administration

Early studies in 1981 demonstrated the analgesic effects of single-dose intramuscular tramadol 50–100mg.^[120,123] Several recent studies have confirmed that repeated intramuscular administration of tramadol can provide effective and well tolerated postoperative analgesia comparable to that obtained with morphine, pentazocine and ketorolac.^[112,121,124,126,127] In contrast, multiple intramuscular injections of codeine 60mg provided better analgesia than tramadol 50 or 75mg after craniotomy.^[125] In addition, tramadol 75mg was associated with increased sedation, nausea and vomiting.^[125] A potential explanation for this discrepancy could be that pain after craniotomy is less responsive to serotonin and norepinephrine reuptake inhibition, which is part of the mechanism of action of tramadol.

The intramuscular administration of tramadol 150mg also improved lung function in 20 patients receiving dipyron 2g every 6 hours intravenously following laparoscopic cholecystectomy^[122] and in-

Table VI. Controlled trials of tramadol in postoperative pain

Study	Type of surgery	Study design	n	Analgesic drug	Dosage (mg/day)	Analgesic efficacy
Oral administration						
Bamigbade et al. ^[114]	Groin	db	228	Tramadol	100–400	T > C/P
Crichton et al. ^[115]	Laparoscopy	db	68	Codeine/paracetamol	16–64/1000–4000	T = C/P = DP/P
				Tramadol	50–400	
				Codeine/paracetamol	30–240/500–4000	
Kupers et al. ^[116]	Orthopaedic	db	160	Dextropropoxyphene/paracetamol	32.5–260/325–2600	T = PE
				Tramadol	50	
				Pentazocine	50	
Peters et al. ^[117]	Gynaecological	db	91	Tramadol	150–200	T > N
Stubhaug et al. ^[118]	Orthopaedic	db, sd	144	Naproxen	750–1000	C/P > T = PL
				Tramadol	50 or 100	
				Codeine/paracetamol	60/1000	
Sunshine et al. ^[119]	Section	db, sd	161	Placebo		T > PR/P > PL
				Tramadol	75 or 150	
				Propoxyphene/paracetamol	100/650	
Intramuscular administration						
Alon et al. ^[120]	General	db, sd	60	Tramadol	50	T < B
Colletti et al. ^[121]	Nasal	nb	77	Buprenorphine	0.3	T = K
				Tramadol	100–400	
de La Pena et al. ^[122]	Laparoscopic cholecystectomy	db, sd	20	Ketorolac	30–90	T > P
				Tramadol	50	
Fassolt ^[123]	General	db, sd	75	Placebo		T = PE
				Tramadol	100	
Gritti et al. ^[124]	Abdominal	nb	70	Pentazocine	30	T = M
				Tramadol	100–600	
Jeffrey et al. ^[125]	Craniotomy	db	75	Morphine	10–60	T < C
				Tramadol	50	
				Tramadol	75	
Lanzetta et al. ^[126]	Orthopaedic	nb	48	Codeine	60	T = K
				Tramadol	100–400	
				Ketorolac	30–90	
Magrini et al. ^[127]	Various	nb	50	Tramadol	300	T > PE
				Pentazocine	90	

Continued next page

Table VI. Contd

Study	Type of surgery	Study design	n	Analgesic drug	Dosage (mg/day)	Analgesic efficacy
Sacerdote et al. ^[112]	Abdominal	db, sd	30	Tramadol Morphine	100 10	T = M
Intravenous administration						
Bloch et al. ^[128]	Thoracotomy	db	89	Tramadol (+ morphine PCA) Morphine epidural (+ morphine PCA) Placebo (+ morphine PCA)	150 + 350/24h 2 + 0.2/h	T = ME > PL
Dejonckheere et al. ^[129]	Thyroidectomy	db	80	Tramadol Propacetamol	1.5 mg/kg 2000	T > PP
Driessen et al. ^[130]	Vaginal hysterectomy	nb, sd	27	Tramadol Buprenorphine Pentazocine	50 0.3 30	T < PE < B
Houmes et al. ^[131]	Gynaecological	db	150	Tramadol Morphine	50–150 5–15	T = M
Manji et al. ^[132]	Cardiac	nb	56	Tramadol Alfentanil	100–600 12.5 µg/kg/h	T = A
Olle et al. ^[133]	Abdominal hysterectomy	db	76	Tramadol Ketorolac	400 120	T > K
Putland and McCluskey ^[134]	Laparoscopy	db, sd	60	Tramadol	1.5 mg/kg	T > K
Ranucci et al. ^[135]	Cardiac	db	60	Ketorolac Tramadol Ketorolac Propacetamol	10 200 60 2000	T = K > PP
Sellin et al. ^[136]	Cardiac	db	100	Tramadol Morphine	360–600 24 + 2 prn	T = M
Stankov et al. ^[137]	Urological	db, sd	100	Tramadol Dipyrone	100 2500	T < D
Striebel et al. ^[138]	Vaginal hysterectomy	db	60	Tramadol/dipyrone Tramadol/ibuprofen	400/5000 400/585	T/D = T/I
Torres et al. ^[139]	Abdominal hysterectomy	db	151	Tramadol Dipyrone	100–400 1000–8000	T = D
Tryba and Zenz ^[140]	Orthopaedic	db	60	Tramadol Morphine Clonidine	50–100 5–10 0.15–0.3	T = M = CL
Vickers and Paravicini ^[141]	Abdominal	db	523	Tramadol Morphine	100–650 5–60	T = M

A = alfentanil; **B** = buprenorphine; **C** = codeine; **CL** = clonidine; **D** = dipyrone; **db** = double-blind; **DP** = dextropropoxyphene; **I** = ibuprofen; **K** = ketorolac; **M** = morphine; **ME** = morphine epidural; **N** = naproxen; **nb** = nonblind; **P** = paracetamol; **PCA** = patient-controlled analgesia; **PE** = pentazocine; **PL** = placebo; **PP** = propacetamol; **PR** = propoxyphene; **prn** = as needed; **sd** = single dose; **T** = tramadol; **>** indicates superior to; **=** indicates equivalent to; **<** indicates inferior to.

tramuscular administration of tramadol 100mg could improve postoperative immune suppression.^[112]

3.1.4 Intravenous Administration

In an early study, a single intravenous bolus injection of tramadol 50mg was inferior to buprenorphine 0.3mg for pain relief after vaginal hysterectomy.^[130] The authors suggested that tramadol doses >50mg might be necessary in many patients. In two other studies, two or three intravenous bolus doses of tramadol 50mg provided acceptable analgesia, which was similar to the effects of morphine 5mg.^[131,140] In a double-blind randomised study involving 523 patients, the analgesic efficacy of tramadol (up to 650 mg/day) was compared with that of morphine (up to 60 mg/day) given as repeated intravenous boluses as required to control pain following abdominal surgery.^[141] Responder rates reached 72.6% with tramadol and 81.2% with morphine, and the treatments were statistically equivalent.

In two double-blind comparative studies, continuous intravenous infusion of tramadol 12 mg/h showed a trend towards better pain relief than with intermittent intravenous bolus doses of tramadol 50mg following abdominal surgery.^[148,149] Although total consumption of tramadol was more than 30% higher with the continuous infusion, the rate of adverse events was not increased.^[148,149] Two other studies demonstrated that continuous infusion of tramadol, titrated to the patient's requirements, provides adequate analgesia after cardiac surgery, comparable with the effects of alfentanil or morphine infusion.^[132,136] In two recent studies, the addition of a tramadol infusion to morphine PCA improved analgesia and reduced morphine requirements after abdominal or thoracic surgery.^[128,150] No differences were found with regard to nausea or sedation after abdominal surgery.^[150] For the management of post-thoracotomy pain, 90 patients received, in addition to morphine PCA, either intravenous tramadol (150mg bolus followed by infusion, total 450 mg/day), epidural morphine (2mg, then 0.2 mg/h) or nothing.^[128] Pain scores at rest and on coughing were lower in the tramadol and epidural morphine groups than in the placebo (only PCA morphine) group. The authors concluded that an intraoperative

bolus of tramadol followed by an infusion was as effective as epidural morphine and avoided the necessity of placing a thoracic epidural catheter.

The continuous intravenous infusion of tramadol 0.25 mg/kg/h was also shown to be a simple and well tolerated procedure following urological surgery in children.^[151]

Several studies have compared the efficacy of intravenous tramadol with that of non-opioid analgesics. A single dose of tramadol 1.5 mg/kg provides a better quality of analgesia than that with propacetamol 2g during the first 6 hours after thyroidectomy.^[129] In an observer-blind randomised study, single intravenous doses of tramadol 100mg produced less pain relief after abdominal or urological surgery than intravenous dipyrone, which possesses spasmolytic effects.^[137] Another study used an intravenous loading dose immediately after abdominal hysterectomy followed by intravenous maintenance infusion and on-demand boluses up to a maximum of either dipyrone 8 g/day or tramadol 500 mg/day.^[139] Both drugs showed similar efficacy for early pain, but tramadol caused nausea and vomiting more frequently. An intravenous bolus of tramadol 1.5 mg/kg was more effective than ketorolac 10 mg/kg following laparoscopic sterilisation in 60 patients.^[134] No difference in either the incidence or severity of nausea and vomiting was observed between the two groups. In 76 women undergoing abdominal hysterectomies, the intravenous injection of tramadol 100mg every 6 hours provided more effective pain relief than that with ketorolac 30mg, but was associated with a high incidence of postoperative vomiting.^[133] A randomised trial was aimed at investigating the effectiveness of intravenous ketorolac 60mg, propacetamol 2g and tramadol 200mg for the management of postoperative pain in early extubated cardiac surgical patients.^[135] There was a significantly higher rate of patients with severe pain in the propacetamol group. Patients treated with tramadol had a higher arterial partial pressure of CO₂, which was not clinically relevant and can be explained by the relatively high dose of 200mg.

The infusion of a fixed combination of tramadol and non-opioids, which is very popular in Germany, has been investigated in only one controlled study.^[138] This study compared a tramadol/dipyrone

infusion (400mg/5g in 500mL) with a tramadol infusion (400mg in 500mL) in combination with rectal ibuprofen 585mg.^[138] In 60 patients recovering from vaginal hysterectomy, satisfactory pain reduction occurred rather late, although 60% of the 500mL was administered within 60 minutes. The authors concluded that neither regimen could be recommended for fast onset of adequate analgesia. Another fixed combination, tramadol 600mg and ketorolac 180mg diluted to a volume of 96mL and intravenously infused at a constant rate of 2 mL/h, was investigated in 585 patients following major abdominal surgery.^[152] Supplementary tramadol 100–300 mg/day was injected on request. The average pain intensity (verbal numeric scale 0–10) was below 3 at rest and below 4 on movement, which was interpreted as good quality of pain relief by the authors of this uncontrolled trial.^[152]

Intravenous tramadol reduces not only postoperative pain but also postoperative shivering. Several double-blind controlled studies demonstrate that intravenous tramadol 0.7–2.5 mg/kg can prevent the severity and prevalence of postanaesthetic shivering in a dose-dependent manner.^[132,153-156] Tramadol 1 mg/kg was superior to pethidine 0.5 mg/kg.^[153] Furthermore, intravenous tramadol reduced shivering during regional anaesthesia of obstetric patients in two controlled double-blind studies.^[157,158]

In an early double-blind study on the intraoperative use of tramadol, 65% of the patients receiving tramadol were aware of intraoperative music whereas patients in the placebo group were amnesiac.^[159] Therefore, tramadol was not recommended as the sole agent for intraoperative analgesia. Several recent studies on the intraoperative use of tramadol in combination with volatile or intravenous anaesthetics have shown no clinically relevant lightening of anaesthetic depth.^[160-164] Preoperative administration of morphine 10mg was more effective than tramadol 100mg as an intraoperative analgesic, but there was no difference in the postoperative pain treatment.^[160] Other studies demonstrated that intravenous tramadol administered at wound closure provided postoperative analgesia superior to that with placebo^[161,162] and similar to that with intravenous^[163] or epidural^[164] morphine.

Several studies have investigated the intravenous injection of tramadol 0.5–3 mg/kg at induction of anaesthesia in children.^[165-169] In adenoidectomy and/or tonsillectomy, pre-emptive tramadol provided posterior analgesia superior to that with placebo^[165,167,169] or propacetamol.^[166] Tramadol 3 mg/kg was inferior to pethidine 1.5 mg/kg and nalbuphine 0.3 mg/kg in tonsillo-adenoidectomy,^[169] and tramadol 1 mg/kg was inferior to fentanyl 2 µg/kg/h in paediatric neurosurgery.^[168]

Intravenous tramadol is also effective in preventing the pain of propofol injection.^[170,171] The combination of tramadol with lidocaine for intravenous regional anaesthesia had only a limited benefit and cannot be recommended.^[172-175]

3.1.5 Patient-Controlled Analgesia

PCA allows the patients to self-administer small bolus doses of a potent analgesic in a running intravenous infusion.^[176] Whenever the patients feel that pain relief is necessary, they can activate an electronically controlled infusion pump that dispenses a preprogrammed amount of analgesic. A controlled study of 20 patients undergoing gynaecological operations compared tramadol PCA (loading dose 3 mg/kg, demand dose 30mg, lock-out time 5 minutes, concurrent infusion 5 mg/h) and tramadol continuous infusion (loading dose 3 mg/kg, continuous infusion 0.35 mg/kg/h).^[177] PCA ensured adjustment of the medication to the individual demand, whereas continuous infusion provided better analgesia after sleeping periods.^[177]

Table VII summarises the controlled trials of PCA with tramadol, demonstrating its feasibility in postoperative pain. Most studies compared tramadol with other opioids, used a tramadol demand dose of 10–50mg and investigated pain following abdominal or orthopaedic surgery. In the only placebo-controlled study of intravenous PCA, tramadol and morphine proved to be efficacious.^[178] Of 180 patients recovering from abdominal surgery, 68%, 75% and 18% of patients treated with tramadol, morphine and placebo, respectively, were assessed as responders. In five PCA studies comparing intravenous tramadol and morphine, the equipotent dose ratio was between 9 : 1 and 19 : 1.^[160,179-182] Another study compared tramadol and morphine via subcutaneous PCA following major orthopaedic

surgery in 40 patients.^[25] Both drugs provided effective analgesia; the mean consumption in the first 24 hours was 792mg of tramadol and 42mg of morphine. Whereas tramadol is associated more frequently with nausea and vomiting, morphine has a higher risk of respiratory depression.^[25,179-182]

Double-blind PCA studies comparing tramadol with other opioids reported an equipotent dose ratio of 5 : 1 for tramadol : nalbuphine, 979 : 1 for tramadol : fentanyl, 1.1–1.2 : 1 for tramadol : pethidine and 8 : 1 for tramadol : oxycodone.^[63,183,184,190,191]

Several studies have investigated methods to reduce the rate of nausea during tramadol PCA. Administering the loading dose of tramadol during surgery decreases the risk of nausea/vomiting and improves the quality of tramadol PCA in the relief of postoperative pain.^[192] A tramadol and droperidol combination is superior to tramadol alone for postoperative PCA.^[193] It provides a similar quality of analgesia with less nausea and vomiting and without an increase in sedation. When ondansetron was administered for antiemetic prophylaxis, the tramadol requirement during PCA was increased.^[88]

The analgesic effect of tramadol in postoperative PCA can further be improved by a combination with non-opioid analgesics. The combination of tramadol and dipyrone was superior to piritramide.^[185] A further study included 101 post-hysterectomy patients who, at the time of analgesia request, received tramadol 100mg or dipyrone 1.2g alone, or combined in 1 : 1, 1 : 0.3 or 1 : 3 ratio.^[187] After 15 minutes, they received the same treatment by PCA. When drugs were combined in a 1 : 1 ratio, synergy was present for the analgesic effects, but also for adverse events; all other treatments were additive. Tramadol PCA in combination with intravenous propacetamol 2g four times daily provided analgesia superior to that of tramadol monotherapy.^[186] Another randomised double-blind study compared PCA with tramadol and PCA with a mixture of tramadol plus lysine acetylsalicylate (a soluble aspirin) in 50 adult patients who had undergone major orthopaedic surgery.^[188] Total tramadol consumption was significantly less and patients were more alert in the aspirin group. One study of PCA has compared tramadol with non-opioid analgesics.^[189] According to patient global assessment, 72% of patients in the tramadol group assessed analgesia as excellent or very good,

compared with 58% with ketorolac, 50% with clonixin and 55% with dipyrone.

3.1.6 Regional Administration

Only a few studies are available on epidural tramadol,^[194-197] a mode of administration for which tramadol is not registered. Two placebo-controlled studies demonstrated that epidural tramadol 50 and 100mg provided adequate postoperative analgesia after caesarean delivery.^[194,198] After abdominal surgery, epidural tramadol 100mg produced better pain relief than tramadol 50mg or 10mL of 0.25% buprenorphine^[196] and was not different from morphine 4mg.^[197] However, ineffective analgesia from epidural tramadol 50 and 100mg was reported in patients undergoing total knee replacement.^[195]

Tramadol 1–2 mg/kg has also administered caudally in children for postoperative analgesia.^[199-203] Caudal tramadol 2 mg/kg provided reliable postoperative analgesia similar to that with caudal morphine 0.03 mg/kg in children who were undergoing herniorrhaphy.^[199] Although in two studies tramadol was less effective than caudal bupivacaine 0.2–0.25%,^[200,203] one study reported comparable effects.^[201] In another study, lower pain scores were seen with caudal bupivacaine 0.25% in the immediate postoperative period, whereas caudal tramadol caused a significantly lower pain score in the late postoperative period.^[202] The combination of both drugs improved the analgesic action of bupivacaine in only one^[200] of three studies.^[200,201,203]

Prompted by the success of intra-articular morphine, tramadol 10mg was used intra-articularly after arthroscopic knee surgery in a double-blind study and provided effective pain relief, although morphine 1mg was more effective.^[204] Another study demonstrated that the admixture of tramadol 100mg with mepivacaine 1% for brachial plexus block provided a pronounced prolongation of blockade without adverse effects.^[205]

3.2 Other Acute Pain Syndromes

3.2.1 Trauma

Several reports describe positive experiences with tramadol for orthopaedic trauma,^[206] winter sports injuries^[207] and use in the prehospital situation by ambulance paramedics.^[208] A double-blind study found no difference in the efficacy of tramadol

100–200mg and morphine 5–20mg administered intravenously for the management of pain in 105 trauma patients in the prehospital situation.^[209] In a controlled trial, intravenous tramadol 1 mg/kg, propacetamol 20 mg/kg and diclofenac 1 mg/kg were equally efficacious for emergency analgesic treatment of 131 patients.^[210] In the piritramide group (0.25 mg/kg), significantly more adverse effects were noted.

3.2.2 Abdominal Pain

Parenteral tramadol in emergency department patients with abdominal pain in the right lower quadrant resulted in pain reduction without concurrent normalisation of abdominal examination findings indicative of acute appendicitis.^[211] Several controlled studies have demonstrated the efficacy of tramadol in colic pain.^[212-216] In renal and biliary colic pain, intravenous dipyrone 2.5g was superior to tramadol 100mg and butylscopolamine 20mg.^[214,215] In another study, tramadol 100mg was as effective as dipyrone 2.5g for ureteric colic.^[216] In acute renal colic pain, intravenous pethidine 50mg was superior to tramadol 50mg^[212] and intramuscular ketorolac 30mg was as effective as subcutaneous tramadol 1 mg/kg.^[213]

3.2.3 Labour

Elbourne and Wiseman^[217] searched the Cochrane Library in 1997 and assessed 16 randomised trials comparing the effects of different currently used opioids administered intramuscularly in labour for women who requested systemic analgesia. They found no evidence of a difference between pethidine and tramadol in terms of pain relief, interval to delivery, or instrumental or operative delivery. There appeared to be more adverse effects such as nausea, vomiting and drowsiness with pethidine.

Intramuscular tramadol 100mg, but not 50mg, provided pain relief equivalent to that with pethidine 75mg.^[218] With pethidine, adverse effects were more frequent and respiratory function of the neonates was significantly lower. Another study found no differences in analgesic efficacy, incidence of adverse effects, umbilical cord blood gases or Apgar scores between tramadol 100mg and pethidine 50mg.^[219] Other authors confirmed that tramadol resulted in analgesia equivalent to that with pethidine without respiratory depression in mothers

and neonates.^[29,220-223] Intravenous tramadol 50–100mg in the first stages of labour produced respiratory depression in only 7% of neonates, compared with 31% in the pethidine group.^[224] This study is unusual with regard to the high rate of respiratory depression in both groups. Tramadol suppositories have also been recommended for obstetrical analgesia.^[225]

3.3 Place of Tramadol in Acute Pain

The treatment of acute pain is not only important for the well-being of patients, it also reduces the risk of complications such as pneumonia, cardiac infarction or thromboembolism and may improve the outcome.^[226] Besides regional analgesia, which is invasive and only suitable for selected patients, the administration of opioids is the most common approach to treat postoperative pain.

Tramadol provides adequate analgesia in acute pain, being superior to placebo and comparable with various opioid and non-opioid analgesics in the majority of studies (table VI and table VII). Therefore, tramadol can be recommended as a basic analgesic for the treatment of moderate-to-severe acute pain.

Intravenous infusion or intravenous PCA are indicated in severe pain following surgery. Although intramuscular tramadol is effective, the injection is painful and systemic absorption might be delayed in the early postoperative period; therefore, oral or intravenous administration may be preferred. Drops or capsules are a good choice when enteral administration is possible after surgery, particularly in day case surgery. Further indications for systemic tramadol include postanaesthetic shivering, post-traumatic pain, labour pain and colic pain. In addition, oral and intravenous tramadol appears to be an effective and well tolerated analgesic agent in children with postoperative pain. The good analgesic effects achieved by caudal administration can be explained by extensive systemic absorption,^[37] and no advantages over systemic administration can be expected.

In contrast to the majority of studies (table VI and table VII), tramadol did not equal the analgesic efficacy of other drugs in all circumstances. A single dose of tramadol was not different from placebo in a

Table VII. Controlled trials of patient-controlled analgesia with tramadol in postoperative pain

Study	Surgery [duration of PCA (h)]	Drug	n	Loading dose (mg)	Infusion rate (mg/h)	Demand dose (mg) [lock-out (min)]	Mean cumulative dose (mg)	Analgesic efficacy (relative potency)
Alon et al. ^[183]	Abdominal hysterectomy (5)	Tramadol	20	50	25	25 (30)	373	T = N (1 : 5)
		Nalbuphine	20	10	5	5 (30)	73	
Hackl et al. ^[63]	Cholecystectomy (6)	Tramadol	7	0	12	20	412	T = F (1 : 979)
		Fentanyl	10	0	0.054	0.009	0.53	
Lehmann et al. ^[184]	Various (18)	Tramadol	40	0	1.15	9.6 (1)	203	T = PE (1 : 1.2)
		Pethidine	40	0	1.15	9.6 (1)	175	
Likar et al. ^[185]	Orthopaedic (24)	Tramadol/dipyrone	18	164/1090	0	10/50 (6)	267/1335	T/D > PI
		Tramadol/dipyrone	19	72/482	0	5/25 (6)	256/1275	
		Piritramide	21	7.5	0	1.5 (6)	44	
		Piritramide	20	4.5	0	0.75 (6)	37	
Migliorini et al. ^[186]	Orthopaedic (24)	Tramadol	35	0	10	50 (15)	489	T < T/PP
		Tramadol + propacetamol 2g qid	35	0	10	50 (15)	426	
Montes et al. ^[187]	Abdominal hysterectomy (24)	Tramadol	21	100	0	20 (15)	NR	T/D (1 : 1) > T = D = T/D (1 : 0.3) = T/D (0.3 : 1)
		Dipyrone	21	1200	0	240 (15)	NR	
		Tramadol/dipyrone (1 : 1)	20	50/600	0	10/120 (15)	NR	
		Tramadol/dipyrone (1 : 0.3)	19	75/300	0	15/60 (15)	NR	
		Tramadol/dipyrone (0.3 : 1)	20	25/900	0	5/180 (15)	NR	
Naguib et al. ^[160]	Laparoscopy (24)	Tramadol	50	100	0	16 (5)	248	T = M (1 : 13)
		Morphine	50	10	0	1.6 (5)	20	
Ng et al. ^[179]	Abdominal (48)	Tramadol	19	0	0	10 (5)	9.8/h	T = M (1 : 9)
		Morphine	19	0	0	1 (5)	1.1/h	
Pang et al. ^[180]	Orthopaedic (48)	Tramadol	40	285	0	30 (10)	868	T = M (1 : 19)
		Morphine	40	13	0	1 (10)	46	
Pang et al. ^[188]	Orthopaedic (48)	Tramadol	25	2.5 mg/kg	0		923 (T)	T < T/AS
		Tramadol/aspirin	25	1.25/12.5 mg/kg	0		614 (T)	
Rodriguez et al. ^[189]	Abdominal hysterectomy (24)	Tramadol	40	30	15	15 (NR)	NR	T = K = D > CL

Continued next page

Table VII. Contd

Study	Surgery [duration of PCA (h)]	Drug	n	Loading dose (mg)	Infusion rate (mg/h)	Demand dose (mg) [lock-out (min)]	Mean cumulative dose (mg)	Analgesic efficacy (relative potency)
		Ketorolac	40	10	5	5 (NR)	NR	
		Clonixin	40	30	15	15 (NR)	NR	
		Dipyrone	40	660	330	330 (NR)	NR	
Silvasti et al. ^[161]	Breast (36)	Tramadol	25	51	0	450 µg/kg (5)	677	T = M (1 : 11)
		Morphine	18	6	0	45 µg/kg (5)	61	
Silvasti et al. ^[160]	Maxillofacial (24)	Tramadol	27	38	0	300 µg/kg (5)	200	T = O (1 : 8)
		Oxycodone	25	3	0	30 µg/kg (5)	26	
Stamer et al. ^[162]	Abdominal (48)	Tramadol	60	145	0	20 (5)	650	T = M > PL (1 : 12)
		Morphine	60	12	0	2 (5)	62	
		Placebo	60	17mL	0	1mL (5)	97mL	
Vickers et al. ^[161]	Abdominal (24)	Tramadol	20	0	0	20 (5–10)	624	T = PE (1 : 1.1)
		Pethidine	10	0	0	20 (5–10)	606	

AS = aspirin; CL = clonixin; D = dipyrone; F = fentanyl; K = ketorolac; M = morphine; N = nalbuphine; NR = not reported; O = oxycodone; PCA = patient-controlled analgesia; PE = pethidine; PI = piritramide; PL = placebo; PP = propacetamol; qid = four times daily; T = tramadol; > indicates superior to; = indicates equivalent to; < indicates inferior to.

study of severe pain following orthopaedic surgery,^[118] and tramadol was less effective than codeine after craniotomy,^[125] less effective than dipyrone after abdominal urological surgery,^[137] less effective than pethidine or nalbuphine after tonsillo-adenoidectomy in children,^[169] and less effective than fentanyl in paediatric neurosurgery.^[168] The discrepancy in the results can mainly be attributed to different baseline pain intensity, different type of pain, different criteria of efficacy, and different doses and potencies of the active drug control. These results emphasise that the analgesic efficacy of tramadol should be monitored, as that of any other opioid, and that the dosage requires titration up to individual need by repeated oral administration, repeated injections, adaptation of a continuous infusion or intravenous PCA.

The analgesic efficacy of tramadol can be increased by combination with non-opioid analgesics such as paracetamol, dipyrone or ketorolac.^[143,152,186-188] Following a suggestion of Krimmer et al.,^[227] an infusion of a fixed combination of tramadol 300–400mg and dipyrone 2.5–5g in 500mL of saline over 12–30 hours is frequently used in Germany.^[65] Despite the widespread application of this simple-to-use combination, which is usually given in general wards without close supervision, no controlled studies investigating the risk/benefit ratio of such combinations are available. If tramadol at dosages of 400–600 mg/day provides no adequate pain relief, administration of a stronger opioid, such as morphine, is necessary and useful.^[150]

Nausea and vomiting are typical adverse effects with opioids. Although some studies found that tramadol is associated with an increased risk,^[118,125,147,179,181] others reported no difference in the incidence of nausea and vomiting between tramadol and other opioids.^[114,116,124,127,132,160] The rate of postoperative nausea and vomiting, however, depends only partly on the type of opioid; other major factors include dose, time and mode of opioid administration, pain intensity, type of surgery, type of anaesthesia and history of motion sickness. The rate of nausea and vomiting can be reduced by prophylactic administration of antiemetics, but unfortunately droperidol has been withdrawn and ondansetron reduces the analgesic efficacy of tramadol. There is lack of evidence whether triflupromazine,

dimenhydrinate, metoclopramide or other antiemetics have a better risk/benefit ratio in combination with tramadol. One study showed that nausea and vomiting with tramadol occurred more frequently during the 15 minutes after the initial injection of the loading dose than during the PCA period, when boluses were infused over 2 minutes.^[178] The authors concluded that a slower injection could avoid some nausea and vomiting. This hypothesis is in agreement with personal experiences of many doctors, but has not been investigated. Another approach to reduce the rate of postoperative nausea and vomiting is to inject the first tramadol bolus intraoperatively at wound closure.^[162,163,192]

Tramadol demonstrates similar analgesia to that of several non-opioid analgesics (table VI). Although it is associated with a higher risk of typical opioid adverse effects, such as nausea, it may prove particularly beneficial in patients in whom non-opioid analgesics are not appropriate, including patients predisposed to peptic ulcers, with haemorrhagic disorders, hypertension and renal insufficiency.^[22]

The most important advantage of tramadol over morphine and other opioids is its minimal effect on respiratory function.^[25,97,131,141,179-182,191,228] Therefore, tramadol is a very good choice for children, in day-surgery, in normal wards without close supervision, in labour pain and in traumatic pain. In addition, tramadol improves lung function after laparoscopy^[122] and thoracotomy;^[128] in the latter study it was similar to epidural morphine. Patients with an increased risk of respiratory dysfunction, such as the elderly, smokers, those with pre-existing cardiopulmonary disease and those after surgery of the thorax or upper abdomen causing a decreased residual reserve, are expected to benefit particularly from this advantage. Further studies comparing equianalgesic doses of different opioids and carefully assessing adverse events are needed to confirm the influence of tramadol on postoperative convalescence in these situations.

Another advantage of tramadol is its low gastrointestinal inhibition.^[108] Tramadol is, therefore, expected to improve gastrointestinal recovery from abdominal surgery and reduce the risk of postoperative paralysis and ileus compared with other opioids.

Recently, tramadol was shown to have positive effects on immune system function.^[110,112,229] Therefore, tramadol might be a better choice than morphine, particularly in patients with compromised immunity or cancer. Further studies are required to confirm these preliminary results.

4. Chronic Pain

Chronic pain requires regular administration of analgesics. Only studies on the oral administration of tramadol over a period of at least 1 week can investigate its utility in the treatment of chronic pain. Therefore, single-dose studies and studies on parenteral administration have not been included in the following discussion. The controlled studies have been summarised in table VIII. In a meta-analysis, which, for methodical reasons, included only two of six controlled trials on cancer pain and three of ten controlled trials on chronic non-cancer pain, odds ratios of 0.49 (95% CI -0.36, 0.8) and 0.57 (95% CI 0.23, 0.9), respectively, demonstrated the analgesic efficacy of tramadol compared with placebo and morphine.^[113]

4.1 Cancer Pain

Three noncomparative studies have demonstrated the efficacy of oral tramadol in cancer pain.^[232,250,251] Of 30 patients with different malignant diseases, 86% had excellent or adequate pain relief after the administration of tramadol up to 200 mg/day.^[250] In another study, 51 cancer patients were treated with oral or intramuscular tramadol 300 mg/day for periods of 2 weeks to 14 months.^[251] Eighty-three percent of patients with bone pain and 62% of patients with visceral pain, but only 33% of patients with neuropathic pain, reported good analgesia. In another open study, tramadol was used in 294 cancer patients in whom non-opioids alone failed to provide sufficient analgesia.^[232] As recommended by the WHO, tramadol was combined with non-opioid analgesics and co-analgesics where appropriate. Patients were treated with oral tramadol at 4-hour intervals at a dosage of between 250 and 600 mg/day for an overall period of 8227 days (mean 28 days). If pain could not be controlled with the maximum daily dosage of 600mg, a strong opioid was started (70% of patients). Tramadol was stopped

because of adverse events in only 4% of patients. On 78% of the treatment days, patients had no or only mild pain.

The effectiveness and tolerability of tramadol in the treatment of cancer pain has been confirmed in several studies comparing tramadol with morphine or buprenorphine (table VIII). A nonrandomised study compared 810 patients receiving high-dosage tramadol 300–600 mg/day for a total of 23 497 days with 848 patients receiving low-dosage morphine 10–60 mg/day for a total of 24 695 days.^[252] The analgesic efficacy was good in 74% and 78% of patients receiving tramadol and morphine, respectively. Constipation, neuropsychiatric symptoms and pruritus were observed more frequently with morphine. This lower rate of typical opioid adverse effects can be explained by the multiple modes of action of tramadol. The recommended maximum dose of tramadol is 400 mg/day. Tramadol, however, is a pure agonist (with a low affinity) at μ opioid receptors and no ceiling effect has been determined. The above data demonstrate that tramadol dosages up to 600 mg/day are effective and well tolerated in the treatment of cancer pain. Higher dosages have not been investigated, although a further enhancement of the analgesic effects would be expected. They cannot be recommended because of a potentially increasing risk of specific and nonspecific adverse effects, such as seizures.

Osipova et al.^[233] compared 98 patients receiving tramadol (mean dosage 368 mg/day [stable dose throughout the study]) and 26 patients receiving SR morphine (mean dosage increased from 69 mg/day to 96 mg/day during the study) for relief of severe cancer pain. Tramadol was effective and well tolerated during a study period of 1–3 months in all patients with moderate pain and in 89% of the patients with severe pain. Morphine produced excellent to good analgesic efficacy in all patients, but was associated with more intense adverse effects. Similar results were observed by Tawfik et al.^[234] investigating 32 patients being treated with tramadol (mean dosage 217 mg/day) and 32 patients treated with SR morphine (mean dosage 50 mg/day) for up to 8 weeks. Adequate pain relief was obtained with tramadol in 58–88% and with morphine in 67–100% of the patients. Insufficient analgesia was more frequent in the tramadol group, but tramadol caused

fewer adverse effects. In a double-blind, randomised, crossover trial (2 × 4 days), 20 patients were treated with oral solutions of tramadol (mean dosage 375 mg/day) and morphine (mean dosage 101 mg/day).^[235] Tramadol had the same efficacy but produced less nausea and constipation than morphine. Examination of doses used revealed a tendency to greater tolerance development with morphine than with tramadol.^[233,234]

To compare the analgesic effect and tolerability of tramadol 300 mg/day and buprenorphine 0.6 mg/day, 60 cancer patients were treated orally in a controlled crossover trial (2 × 1 week).^[230] Buprenorphine and tramadol had a similar analgesic effect; the incidence of adverse effects such as constipation and respiratory depression was lower with tramadol. Only one patient discontinued tramadol compared with 18 using buprenorphine. The final assessment was significantly in favour of tramadol as regards efficacy and patient acceptability.

4.1.1 Sustained-Release

SR formulations are given at intervals of 8–12 hours and are, therefore, of special interest for the treatment of chronic pain. An open noncomparative study proved the analgesic efficacy of SR tramadol with administration every 12 hours to patients with moderate-to-severe cancer pain.^[253] Of 146 patients, 62% completed the 6-week trial period; 20% discontinued because of adverse events, 9% because of inadequate pain relief, 3% because of both reasons and 6% because of other reasons. The number of patients with good and complete pain relief increased from 43% after week 1 to 71% after week 6 with daily dosages of tramadol up to 650mg. Most patients (86%) experienced adverse events during the study period. Nausea and vomiting were most frequently reported, but were judged to be clearly related to the study medication in <25% of patients. In a multicentre trial of 131 cancer patients over a period of up to 6 months, levels of efficacy and acceptability were better with tramadol (one 100mg SR tablet every 8–12 hours) than with buprenorphine (one sublingual 0.2mg tablet every 6–8 hours).^[231] Adverse reactions were reported in 25% of patients taking tramadol and in 26% taking buprenorphine. Serious symptoms arose more fre-

Table VIII. Controlled trials of oral tramadol in chronic pain

Study	Type of pain	Study design	n	Duration	Analgesic drug	Dosage (mg/day)	Analgesic efficacy	Adverse events
Cancer pain								
Bono and Cuffari ^[230]	Cancer	db, co	60	2 × 1wk	IR tramadol Buprenorphine	300 0.6	T = B	T < B
Brema et al. ^[231]	Cancer	no	131	1–6mo	SR tramadol Buprenorphine	200–300 0.6–0.8	T > B	T = B
Grond et al. ^[232]	Cancer	no	1658	1–967d	IR or SC tramadol IR morphine	300–600 10–60	T = M	T < M
Osipova et al. ^[233]	Cancer	no	124	4–12wk	IR tramadol SR morphine	368 69–96	T < M	T < M
Tawfik et al. ^[234]	Cancer	db	64	8wk	IR tramadol SR morphine	217 50	T < M	T < M
Wilder-Smith et al. ^[235]	Cancer	db, co	20	2 × 4d	IR tramadol IR morphine	375 101	T = M	T < M
Chronic pain								
Adler et al. ^[236]	Osteoarthritis	db,	279	1mo	SR tramadol IR tramadol	150–400 150–400	SR-T = IR-T	SR-T = IR-T
Bird et al. ^[237]	Osteoarthritis	db, co	40	2 × 2wk	IR tramadol Pentazocine	200 150	T > PE	T < PE
Goroll ^[238]	Chronic	db	84	1wk	IR tramadol Tilidine/naloxone	prn prn	T > TI/N	NR
Jensen and Ginsberg ^[239]	Osteoarthritis	db	264	2wk	IR tramadol	300	T > D	T > D
Pavelka et al. ^[240]	Osteoarthritis	db, co	60	2 × 4wk	Dextropropoxyphene IR tramadol Diclofenac	300 164 87	T = DI	T > DI
Rauck et al. ^[241]	Chronic	db	390	4wk	IR tramadol Paracetamol/codeine	244 1407/140	T = P/C	T = P/C
Roth ^[242]	Osteoarthritis	db	63	13d	IR tramadol + NSAID Placebo + NSAID	250	T > PL	NR
Schnitzler et al. ^[243]	Low back	db	254	4wk	IR tramadol Placebo	200–400	T > PL	T > PL
Silverfield et al. ^[244]	Osteoarthritis	db	308	10d	IR tramadol/paracetamol + NSAID Placebo + NSAID	150–300/ 1300–2600	T/P > PL	T/P > PL
Sorge and Stadler ^[245]	Low back	db	205	3wk	SR tramadol	200	SR-T = IR-T	SR-T = IR-T

Continued next page

Table VIII. Contd

Study	Type of pain	Study design	n	Duration	Analgesic drug	Dosage (mg/day)	Analgesic efficacy	Adverse events
Wilder-Smith et al. ^[246]	Osteoarthritis	db	60	1mo	IR tramadol SR tramadol SR dithydrocodeine	200 200 120	T > DC	T < DC
Neuropathic pain								
Göbel and Stadler ^[247]	Postherpetic neuralgia	ra	35	6wk	IR tramadol	Up to 600	T = CL	T = CL
Harati et al. ^[248]	Diabetic neuropathy	db	131	42d	Clomipramine IR tramadol Placebo	Up to 100 210	T > PL	T > PL
Sindrup et al. ^[249]	Polyneuropathy	db, co	45	2 × 4wk	SR tramadol Placebo	200–400	T > PL	T > PL

B = buprenorphine; **C** = codeine; **CL** = clomipramine; **co** = crossover; **d** = days; **D** = dextropropoxyphene; **db** = double-blind; **DC** = dithydrocodeine; **DI** = diclofenac; **IR** = immediate-release; **M** = morphine; **mo** = months; **N** = naloxone; **no** = nonrandomised open; **NR** = not reported; **P** = paracetamol; **PE** = pentazocine; **PL** = placebo; **prn** = as needed; **ra** = randomised; **SC** = subcutaneous; **SR** = sustained-release; **T** = tramadol; **TI** = tilidine; **wk** = weeks; > indicates superior to; = indicates equivalent to; < indicates inferior to.

quently in the buprenorphine group (19% vs 10%).

4.2 Chronic Non-Cancer Pain

Several studies have demonstrated the effectiveness of oral tramadol in the treatment of chronic pain of nonmalignant origin (table VIII). In a double-blind study involving 264 osteoarthritis patients, oral treatment with tramadol 300mg was compared with oral dextropropoxyphene 300mg.^[239] Pain relief was superior with tramadol; at the end of the second week, 72% of tramadol-treated patients and 53% of dextropropoxyphene-treated patients had symptom improvement during daily activities. Tramadol was associated with a higher incidence of adverse effects, especially nausea, dizziness and vomiting, which led to more withdrawals from the study. However, in view of reports of fatal overdoses with dextropropoxyphene,^[254] the authors concluded that tramadol should be preferred for chronic pain.

Bird et al.^[237] found lower pain scores and less morning stiffness in 40 patients with osteoarthritis who received tramadol 200mg compared with those treated with pentazocine 150mg in a double-blind crossover study (2 × 2 weeks). Adverse events were reported by 53% of patients taking tramadol and 78% of those taking pentazocine. Patients rated overall efficacy higher for tramadol than for pentazocine.

The analgesic efficacy of oral tramadol drops was superior to that of tilidine/naloxone drops in a double-blind study in patients with various chronic pain conditions.^[238] Unfortunately, pain aetiology was not mentioned in this report.

Another double-blind crossover study (2 × 4 weeks) compared diclofenac and tramadol in 60 patients with painful osteoarthritis.^[240] The dosage of tramadol (50–100mg up to three times daily) and diclofenac (25–50mg up to three times daily) could be individually titrated by the patients. Both tramadol (mean dosage 164 mg/day) and diclofenac (mean dosage 87 mg/day) improved pain intensity and functional parameters, and there was no difference between the groups. More patients reported adverse events with tramadol than with diclofenac (20% vs 3%).

In a 4-week, double-blind study, tramadol was compared with a combination of paracetamol and codeine in 390 patients >65 years of age who had a variety of malignant and nonmalignant pain conditions.^[241] Patients were allowed to titrate the dosage according to pain intensity. There was a tendency for better pain relief with tramadol (mean dosage 244 mg/day) than with paracetamol/codeine (mean dosage 1407/140 mg/day), but the difference was not significant. Nausea, constipation, dizziness and somnolence were the most common adverse events, with no differences between the groups.

In a study of patients with chronic low back pain, 380 subjects were treated with tramadol up to 400 mg/day.^[243] Of these, 254 entered a double-blind study with tramadol 200–400 mg/day or placebo. The discontinuation rate because of therapeutic failure was 21% in the tramadol group and 51% in the placebo group. There were better scores on the visual analogue pain scale, the McGill Pain Questionnaire and the Roland Disability Questionnaire among tramadol patients compared with placebo patients.

Roth^[242] investigated the efficacy of tramadol in 63 osteoarthritis patients who experienced breakthrough pain while taking a NSAID. In addition to their stable daily NSAID regimen, patients were randomised to a 13-day double-blind phase of adjunctive therapy with tramadol 50–100mg every 4–6 hours as needed, or placebo. The time to exit from the study because of insufficient pain relief tended to be longer in the tramadol group. Patients' overall assessment and investigator's rating of global improvement were significantly better with tramadol.

In 308 patients with osteoarthritis achieving inadequate pain relief from traditional NSAIDs or cyclooxygenase (COX)-2-selective inhibitors, the addition of tramadol/paracetamol tablets to existing therapy was investigated in a double-blind placebo-controlled study.^[244] Supplementation with one or two tramadol/paracetamol (37.5/325mg) tablets four times daily was superior to placebo on the patients' and physicians' overall assessments.

Two studies demonstrated that a slower titration rate of tramadol can improve its tolerability in patients who previously discontinued therapy because of nausea and/or vomiting.^[255,256]

4.2.1 Sustained-Release

In experimental pain, SR tramadol was effective for 12 hours and produced fewer adverse effects than the standard formulation, presumably because high peak concentrations did not occur.^[36,61] An open noncomparative study investigated the efficacy of SR tramadol in 1893 patients with chronic pain.^[257] Daily dosages of between 1 × 100mg and 3 × 100mg were administered for a period of 4 weeks. Efficacy was assessed as very good by 46% of patients and good by 42% of patients.

A randomised, double-blind study compared the analgesic efficacy and tolerability of tramadol SR tablets and IR capsules in patients with chronic low back pain, of whom 103 received tramadol SR (2 × 100 mg/day) and 102 received tramadol IR (4 × 50 mg/day) over 3 weeks.^[245] There was no difference in pain relief between tramadol SR and IR (59% vs 59% of patients with sufficient pain relief). Adverse events were reported at a similar rate in both groups (54% vs 53%). These results confirmed the equivalence with regard to efficacy and tolerability of twice daily administration of tramadol SR compared with four-times-daily administration of tramadol IR. Another study compared SR tablets once daily (1 × 150–400 mg/day) with IR capsules (3 × 50mg up to 4 × 100 mg/day) in 279 patients with osteoarthritis.^[236] There was no difference between treatments and both produced good pain control and a similar adverse event profile; 49% of SR tramadol recipients and 52% of IR tramadol recipients withdrew, mostly because of adverse events.

Wilder-Smith et al.^[246] compared analgesia and adverse effects of tramadol (2 × 100 mg/day) and dihydrocodeine (2 × 60 mg/day), both in long-acting formulations, in 60 osteoarthritis patients with strong pain refractory to treatment with NSAIDs. During the treatment period of 1 month, the dihydrocodeine dosage was increased to 180 mg/day in five patients and the tramadol dosage to 300 mg/day in two patients. The pain intensity at rest, but not during movement, was significantly lower with tramadol. The frequency of defecation was lower and stools were harder with dihydrocodeine.

4.3 Neuropathic Pain

For a long time, neuropathic pain has been considered to be unresponsive to opioids. Most authors

now agree that opioids may be effective on such pain provided that sufficient dosages are achieved.^[258,259] The monoaminergic effect of tramadol, although substantially weaker, is similar to that of the tricyclic antidepressants commonly used in neuropathic pain. Therefore, tramadol is an interesting alternative to strong opioids in the treatment of neuropathic pain. The antinociceptive efficacy of tramadol was demonstrated in experimental models of neuropathic pain.^[260,261] Several clinical studies have demonstrated the analgesic efficacy of tramadol in neuropathic pain, but more controlled trials are required. In postmarketing surveillance of SR tramadol, 485 of 7710 documented patients had only neuropathic pain.^[262] Patients were treated over a period of 4 weeks with a mean tramadol dosage of 205 mg/day; 83% reported excellent or good, 12% adequate and 5% inadequate pain relief.

In an open study, 35 patients with postherpetic neuralgia were randomised to oral tramadol up to 600 mg/day or clomipramine up to 100 mg/day with or without levomepromazine 100 mg/day.^[247] Ten patients on tramadol and 11 patients on clomipramine completed the 6-week treatment phase. Nine of ten patients in the tramadol group and six of 11 patients in the clomipramine group rated their analgesia as excellent, good or satisfactory. The incidence of adverse events was similar in both groups (77% vs 83%).

A total of 131 patients with painful diabetic neuropathy were treated with oral tramadol or placebo in a randomised, double-blind study over 42 days.^[248] Tramadol, at an average dosage of 210 mg/day, was significantly more effective, whereas nausea, constipation and headache were reported more frequently. Patients in the tramadol group scored significantly better in physical and social functioning ratings than patients in the placebo group. A total of 117 patients (56 former tramadol and 61 former placebo) entered an open-label extension of up to 6 months and received tramadol 50–400 mg/day.^[263] Mean pain relief scores (2.4 vs 2.2) were similar after 30 days in the former placebo and former tramadol groups, respectively, and were maintained for the duration of the study. Four patients discontinued therapy because of ineffective pain relief; 13 patients discontinued because of adverse events.

A randomised, double-blind, placebo-controlled, crossover study investigated tramadol in painful polyneuropathy during two treatment periods of 4 weeks' duration.^[249] After baseline observations, 45 patients were assigned to tramadol SR tablets (200 mg/day titrated up to 400 mg/day) or placebo. Thirty-four patients completed the study. Their ratings for pain (median 4 vs 6), paraesthesia (4 vs 6) and touch-evoked pain (3 vs 5) were lower on tramadol than on placebo. Tramadol was associated with a higher rate of adverse events (82% vs 35%). The investigators concluded that tramadol appears to relieve both ongoing pain symptoms and the key neuropathic pain feature allodynia in polyneuropathy.

The above studies demonstrate that tramadol can relieve neuropathic pain. Further crossover studies would be useful to compare the efficacy of tramadol with that of other opioids in different types of neuropathic pain. Of most importance are long-term studies demonstrating effectiveness and tolerability of tramadol over several months compared with anticonvulsants, antidepressants or antiarrhythmics.

4.4 Place of Tramadol in Chronic Pain

Many patients with chronic pain are inadequately treated and suffer needlessly. Opioids are often withheld because of irrational fears of respiratory depression, dizziness, confusion, addiction and tolerance. However, adequate use of opioids according to the guidelines of the WHO has been shown to be an efficacious, well tolerated and simple method for cancer pain relief until death.^[264] Because of these good results, opioids are indicated not only in most patients with cancer pain, but also in a subgroup of patients with chronic pain of nonmalignant origin.

The regular administration of oral analgesics is the mainstay of cancer pain treatment.^[265] Depending on pain intensity, analgesics are selected 'by the ladder', switching from non-opioids (WHO step 1) to weak opioids (step 2) and then to strong opioids (step 3). Analgesics are combined with co-analgesics (e.g. antidepressants, anticonvulsants, corticosteroids) to treat special pain conditions, or with adjuvants (e.g. antiemetics, laxatives) against other symptoms. The effectiveness and feasibility of the WHO guidelines have been demonstrated in several clinical studies.^[266,267]

The distinction between weak and strong opioids, made by the WHO for practical purposes, is arbitrary and does not reflect pharmacological differences. In contrast with strong opioids, the weak opioids listed in the WHO guidelines^[265] (codeine, dihydrocodeine, dextropropoxyphene, standardised opium and tramadol) have a maximum recommended dosage and are not scheduled in many countries. The maximum dosages were chosen from experience that higher dosages are associated with progressively more adverse effects, notably nausea and vomiting, that outweigh any extra analgesic effect, but have not been formally determined in clinical studies.

Due to lack of alternatives in many countries, codeine was regarded as the standard drug among the weak opioids. Codeine is a prodrug of morphine and has, therefore, the same efficacy and adverse effect profile as low doses of morphine. For this reason, there have been continuous demands to abolish WHO step 2 and to initiate early therapy with low doses of morphine.^[268] However, the three-step analgesic ladder of the WHO has an important political and educational impact and should not be altered.^[269]

Tramadol can be recommended as a well tolerated and efficacious drug for step 2 of the WHO guidelines for cancer pain management. Compared with morphine, tramadol is more freely available and offers pain relief to many patients who would otherwise receive no opioids at all or at a later time. Furthermore, several comparative trials suggest that tramadol has a better adverse effect profile than other opioids, although long-term studies comparing equianalgesic dosages of tramadol and other opioids are required for confirmation. The incidence of nausea can be reduced by antiemetics or careful dosage titration. If cancer pain cannot be controlled by adequate dosages of tramadol, morphine or other strong opioids are required.

The oral administration of SR formulations has the advantage of continuous pain relief and better compliance. In many cancer patients, the combination of tramadol with non-opioid analgesics and adjuvants can improve efficacy and safety. When oral administration is not longer possible, tramadol can be given subcutaneously.

Tramadol, particularly the SR formulation, may also be used for long-term treatment of chronic pain of nonmalignant origin, either alone or in combination with non-opioid analgesics. Many studies have demonstrated its effectiveness in pain from osteoarthritis. Special advantages are expected in neuropathic pain.

5. Tolerability

Safety data for tramadol have recently been summarised by Cossmann et al.^[270] They considered information from phase II to IV clinical studies and postmarketing surveillance studies, covering safety data from a total of more than 21 000 patients. The most frequent adverse events were nausea (6.1%), dizziness (4.6%), drowsiness (2.4%), tiredness/fatigue (2.3%), sweating (1.9%), vomiting (1.7%) and dry mouth (1.6%). Adverse events that occurred in <1% but >0.1% of patients were somnolence, hypotension, flush, stomach upset, constipation, nausea plus vomiting, sedation, circulatory failure, sleep disorder, pruritus, abdominal pain, diarrhoea, tachycardia and local irritation. Other events occurring in <0.1% of patients were not shown, because more than 150 descriptive terms were involved.^[270]

The profile for single-dose or short-term (<24 hours) administration (6011 patients) is quite similar, qualitatively and quantitatively, to that for long-term administration (15 211 patients), as shown in figure 1.^[270]

The incidence of most adverse events, in particular nausea, was higher in controlled trials than in postmarketing surveillance studies (table IX). This is not unexpected, because controlled studies are performed under more stringent conditions.^[270] In addition, most controlled studies involved postoperative use and had been carried out in hospitals, whereas the postmarketing surveillance studies were all in outpatients.^[270] The incidence of adverse events depends also on the mode of administration (table IX). Following parenteral administration, relatively high initial plasma concentrations are attained, particularly when an injection is administered too rapidly.

Qualitatively, the profile of adverse effects of tramadol corresponds to that known for opioids,

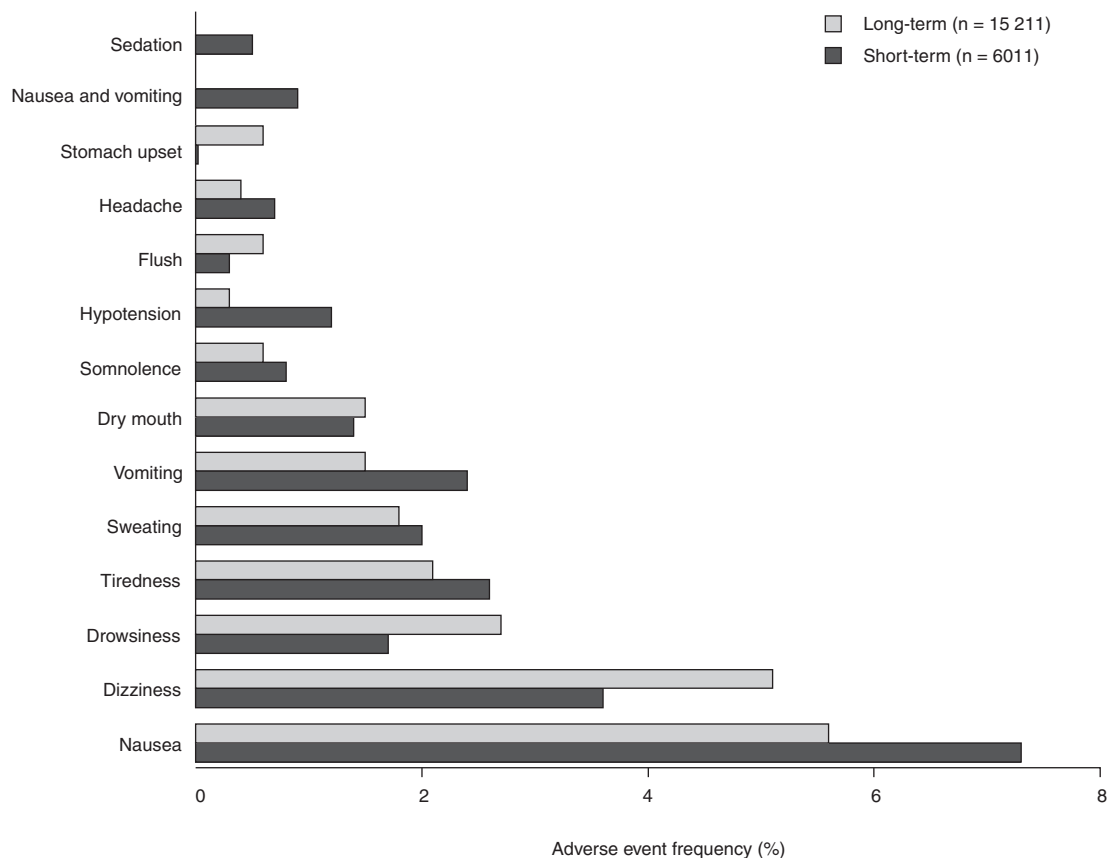


Fig. 1. Frequency of adverse events in clinical trials and postmarketing surveillance studies of tramadol (reproduced from Cossmann et al.,^[270] with permission).

although there are some essential differences. Several long-term trials have shown that the rate of constipation^[232-235] and nausea^[233,235] was lower for tramadol than for morphine. In postoperative pain, some studies found that tramadol is associated with an increased risk of nausea and vomiting,^[118,125,147,179,181] whereas others reported no difference between tramadol and other opioids.^[114,116,124,127,132,160] Of particular significance, tramadol had less respiratory depressant potential than morphine,^[25,131,141,179-182] buprenorphine,^[97,130] oxycodone,^[228] pethidine^[98,191] and nalbuphine.^[271] The use of tramadol in postoperative pain, however, is not completely free from problems, as two case reports describe respiratory depression.^[272,273] A patient with undiagnosed hyperthyroidism developed

respiratory depression after an infusion of tramadol 600mg following abdominal surgery.^[273] He recovered completely after repeated doses of naloxone. Although faster metabolism could be expected in hyperthyroid patients, no explanation is available for this mishap. Another patient with impaired renal function became respiratory insufficient during treatment with tramadol 400 mg/day.^[272] He also recovered completely following naloxone infusion. A few cases of respiratory depression have been reported to the spontaneous reporting system of Grünenthal GmbH.^[270] In the cases where the cause could be attributed to tramadol, mainly high parenteral doses of up to 1000mg had been administered, or the patients had considerably compromised function.

Table IX. Incidence of adverse events with tramadol observed in controlled trials and postmarketing surveillance studies, classified by route of administration (reproduced from Cossmann et al.,^[270] with permission)

Adverse event	Patients experiencing event (%)							
	short-term administration					long-term administration		
	PO (n = 352)	IM (n = 546)	IV (n = 759)	PCA (n = 140)	PMS ^a (n = 3536)	PO (n = 799)	PMS ^b (n = 13 129)	
Nausea	3.1	17.8	16.2	20.7	4.2	21.4	4.8	
Dizziness	1.7	2.9	3.2	6.4	4.4	18.7	4.6	
Drowsiness	0.3	10.3	3.6			8.5	1.1	
Tiredness	5.7	3.3	6.9		1.9	5.9	2.1	
Sweating	1.1	4.6	3.6	15.0	0.8	7.9	0.8	
Vomiting	2.6	7.0	6.2	11.4	0.5	9.6	1.0	
Dry mouth	3.1	1.3	2.8	14.3	0.7	4.3	1.5	

a Parenteral.

b Oral or parenteral.

IM = intramuscular; IV = intravenous; PCA = patient-controlled analgesia; PMS = postmarketing surveillance; PO = oral.

In their review, Cossmann et al.^[270] presented data from the spontaneous reporting system reflecting the time period 1977–93, in which more than one billion single dose units were distributed. The most frequently documented adverse effects in formal studies, namely nausea, vomiting, dizziness, drowsiness, tiredness, sweating and dry mouth, were noted infrequently in spontaneous reports, since these adverse effects are usually recognised as typical of opioids and described in the product information.^[270] There have been some spontaneous reports of allergic and anaphylactic reactions, but the incidence was lower than 0.1%, corresponding to the generally accepted knowledge that the incidence of these reactions is low with opioids. Most of the reports dealt with psychiatric disorders, mainly dependence and abuse, and central and peripheral nervous system disorder, mainly seizures.

In a cohort of 9218 adult tramadol users, fewer than 1% had a presumed incident seizure.^[274] Risk was highest among those aged 25–54 years, those with more than four tramadol prescriptions, and those with history of alcohol abuse, stroke, or head injury. A case-control study among users was conducted to validate incident seizure outcomes from medical records.^[274] Only eight cases were confirmed and all had cofactors associated with increased seizure risk. Experimental data from rats confirm that a pre-existing lowered seizure threshold increases the risk of tramadol-induced seizures.^[275] An evaluation of a General Practice

Research Database identified 21 cases of idiopathic seizures in 11 383 subjects.^[276] Three patients were exposed to tramadol, ten to other opioids, three to both tramadol and other opioids, one to other analgesics, and four to no analgesics. The risk of idiopathic seizures was similarly elevated in each analgesic exposure category compared with non-users, suggesting that the risk for patients taking tramadol was not increased compared with other analgesics.^[276]

Tramadol has a low abuse potential and is not classified as a controlled drug. Epidemiological data collected in Germany over 14 years through the substance abuse warning system indicates that tramadol abuse is less common than abuse of dihydrocodeine or codeine, despite much greater use of tramadol.^[3] Most of the patients were abusing other drugs or alcohol at the same time as abusing tramadol.^[3] After approval of tramadol as a non-scheduled drug in 1995, a postmarketing surveillance programme was started in the US.^[277] The data for 3 years show that the reported rate of abuse has been low. Although a period of experimentation seemed to occur in the first 18 months after its introduction, which reached a peak rate of approximately two cases per 100 000 patients exposed, the reported rate of abuse has significantly declined, reaching levels of less than one case per 100 000 patients in the second 18 months. The overwhelming majority of abuse cases (97%) have been found

to occur among individuals with a history of substance abuse.^[277]

Further evidence for the low abuse potential of tramadol comes from a double-blind placebo controlled study in volunteers who were previous addicts.^[278] Morphine 15 and 30mg produced typical subjective effects, opioid identification and miosis. Tramadol 75 and 150mg was not different from placebo. Although tramadol 300mg was identified as an opioid, it produced no other morphine-like effects and was not liked. These observations were confirmed in a study involving volunteers enrolled in a methadone maintenance programme.^[279] Tramadol 100 and 300mg neither produced morphine-like effects nor precipitated a withdrawal syndrome; its subjective, behavioural and physiological effects were not different from those of placebo.

Overdose of tramadol is associated with neurological toxicity; cardiovascular toxicity has not been reported.^[280] Prospective data from seven poisons centres in the US indicate that the most common symptoms of tramadol overdose are lethargy (30%), nausea (14%), tachycardia (13%), agitation (10%), seizures (8%), coma (5%), hypertension (5%) and respiratory depression (2%). In case reports describing tramadol toxicity, most patients received concomitant medications or alcohol.^[281-285]

6. Conclusions

Tramadol offers an important alternative to other opioids, because the complementary and synergistic actions of the two enantiomers (opioid and reuptake inhibitor of norepinephrine and serotonin) enhance its analgesic effects and improve its tolerability profile. The analgesic efficacy of tramadol has been demonstrated in different acute and chronic pain syndromes, being comparable with that of various other opioid and non-opioid analgesics. Unlike other opioids, tramadol has no clinically relevant effects on respiration, is associated with a low incidence of constipation, shows positive effects on immune system function and has a low potential for abuse and dependence. In addition, tramadol is not scheduled in most countries. It is a further advantage of tramadol that the best mode of administration can be selected for the individual patient and the specific situation, because drops, capsules and SR preparations for oral administration, suppositories and for-

mulations for intramuscular, intravenous and subcutaneous injection are available. Tramadol has proved to be an effective and well tolerated analgesic in the treatment of acute and chronic pain.

Tramadol can be recommended as a basic analgesic for the treatment of moderate-to-severe acute pain. The most frequent adverse event is nausea. Tramadol is particularly useful in patients with poor cardiopulmonary function, including the elderly, the obese, smokers, and after surgery of the thorax or upper abdomen, in situations with an increased risk of respiratory depression, including labour pain, paediatric surgery, day-case surgery and general wards without close supervision, in patients in whom non-opioid analgesics need to be used with caution and in patients with compromised immunity or cancer.

Tramadol can be recommended as an opioid for step 2 of the WHO guidelines for cancer pain treatment. Because IR preparations should be administered every 4 (up to 6) hours, SR preparations that can be administered every 8–12 hours are preferred. Tramadol can be combined with non-opioid analgesics or adjuvants. If tramadol at dosages up to 600 mg/day is not adequate, morphine or other opioids of step 3 are required. Tramadol can also be recommended in the treatment of chronic pain of nonmalignant origin, such as osteoarthritis or neuropathic pain. Further crossover studies would be useful to compare the efficacy of tramadol with that of other opioids in different types of chronic pain. Of most importance are long-term studies aiming to demonstrate the effectiveness and tolerability of tramadol over several months.

Acknowledgements

The authors thank Grünenthal GmbH for providing data on file on sustained-release tramadol. Dr S. Grond is the principal investigator of several clinical studies from Grünenthal GmbH, Mundipharma GmbH and Janssen-Cilag GmbH, and presents clinical lectures on behalf of these companies.

References

1. Schenck EG, Arend I. The effect of tramadol in an open clinical trial [in German]. *Arzneimittel Forschung* 1978; 28 (1a): 209-12
2. Radbruch L, Grond S, Lehmann KA. A risk-benefit assessment of tramadol in the management of pain. *Drug Saf* 1996; 15 (1): 8-29

3. Keup W. Missbrauchsmuster bei Abhängigkeit von Alkohol, Medikamenten und Drogen: Frühwarnsystem-Daten für die Bundesrepublik Deutschland 1976-1990. Freiburg: Lambertus, 1993
4. Raffa RB, Friderichs E, Reimann W, et al. Opioid and non-opioid components independently contribute to the mechanism of action of tramadol, an 'atypical' opioid analgesic. *J Pharmacol Exp Ther* 1992; 260 (1): 275-85
5. Raffa RB, Friderichs E, Reimann W, et al. Complementary and synergistic antinociceptive interaction between the enantiomers of tramadol. *J Pharmacol Exp Ther* 1993; 267 (1): 331-40
6. Lintz W, Barth H, Becker R, et al. Pharmacokinetics of tramadol and bioavailability of enteral tramadol formulations. 2nd communication: drops with ethanol. *Arzneimittel Forschung* 1998; 48 (5): 436-45
7. Lintz W, Becker R, Gerloff J, et al. Pharmacokinetics of tramadol and bioavailability of enteral tramadol formulations. 4th communication: drops (without ethanol). *Arzneimittel Forschung* 2000; 50 (2): 99-108
8. Lintz W, Barth H, Osterloh G, et al. Bioavailability of enteral tramadol formulations. 1st communication: capsules. *Arzneimittel Forschung* 1986; 36 (8): 1278-83
9. Stadler T. Eckdaten zur Pharmakokinetik der Retardtablette Tramal long 100. Aachen: Grünenthal GmbH, 1994
10. Raffa RB, Nayak RK, Liao S, et al. The mechanism (s) of action and pharmacokinetics of tramadol hydrochloride. *Rev Contemp Pharmacother* 1995; 6: 485-97
11. Lintz W, Barth H, Osterloh G, et al. Pharmacokinetics of tramadol and bioavailability of enteral tramadol formulations. 3rd communication: suppositories. *Arzneimittel Forschung* 1998; 48 (9): 889-99
12. Liao S, Hill JF, Nayak RK. Pharmacokinetics of tramadol following single and multiple oral doses in man [abstract]. *Pharm Res* 1992; 9 Suppl.: 308
13. Data on file, Grünenthal GmbH
14. Schulz HU, Raber M, Schurer M, et al. Pharmacokinetic properties of tramadol sustained release capsules. 1st communication: investigation of dose linearity. *Arzneimittel Forschung* 1999; 49 (7): 582-7
15. Raber M, Schulz HU, Schurer M, et al. Pharmacokinetic properties of tramadol sustained release capsules. 2nd communication: investigation of relative bioavailability and food interaction. *Arzneimittel Forschung* 1999; 49 (7): 588-93
16. Raber M, Schulz HU, Schurer M, et al. Pharmacokinetic properties of tramadol sustained release capsules. 3rd communication: investigation of relative bioavailability under steady state conditions. *Arzneimittel Forschung* 1999; 49 (7): 594-8
17. Lintz W, Beier H, Gerloff J. Bioavailability of tramadol after i.m. injection in comparison to i.v. infusion. *Int J Clin Pharmacol Ther* 1999; 37 (4): 175-83
18. Chao CK, Yu LL, Su LL, et al. Bioequivalence study of tramadol by intramuscular administration in healthy volunteers. *Arzneimittel Forschung* 2000; 50 (7): 636-40
19. Lintz W. Aktuelle pharmakokinetische Ergebnisse zu Tramal. Stolberg: Grünenthal GmbH, 1991
20. Lintz W. Overall summary on pharmacokinetics of tramadol in man. Aachen: Grünenthal GmbH, 1992
21. Bamigbade TA, Langford RM. The clinical use of tramadol hydrochloride. *Pain Rev* 1998; 5: 155-82
22. Scott LJ, Perry CM. Tramadol: a review of its use in perioperative pain. *Drugs* 2000; 60 (1): 139-76
23. 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): 313-40
24. Liao S, Hill JF, Stubbs R. The effect of food on the bioavailability of tramadol [abstract]. *Pharm Res* 1992; 9 Suppl.: 308
25. 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 (5 Pt 1): 435-42
26. Tramundin SL® product information. Limburg: Mundipharma GmbH, 1998
27. Malonne H, Fontaine J, Moes A. *In vitro/in vivo* characterization of a tramadol HCl depot system composed of monoolein and water. *Biol Pharm Bull* 2000; 23 (5): 627-31
28. Tao Q, Stone DJ, Borenstein MR, et al. Differential tramadol and O-desmethyl metabolite levels in brain vs plasma of mice and rats administered tramadol hydrochloride orally. *J Clin Pharm Ther* 2002; 27 (2): 99-106
29. Husslein P, Kubista E, Egarter C. Obstetrical analgesia with tramadol: results of a prospective randomized comparative study with pethidine [in German]. *Z Geburtshilfe Perinatol* 1987; 191 (6): 234-7
30. Lintz W, Erlacin S, Frankus E, et al. Biotransformation of tramadol in man and animal [in German]. *Arzneimittel Forschung* 1981; 31 (11): 1932-43
31. Paar WD, Poche S, Gerloff J, et al. Polymorphic CYP2D6 mediates O-demethylation of the opioid analgesic tramadol. *Eur J Clin Pharmacol* 1997; 53 (3-4): 235-9
32. Ogunleye DS. Investigation of racial variations in the metabolism of tramadol. *Eur J Drug Metab Pharmacokinet* 2001; 26 (1-2): 95-8
33. 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): 411-25
34. Wu WN, McKown LA, Gauthier AD, et al. Metabolism of the analgesic drug, tramadol hydrochloride, in rat and dog. *Xenobiotica* 2001; 31 (7): 423-41
35. Nobilis M, Kopecky J, Kvetina J, et al. High-performance liquid chromatographic determination of tramadol and its O-desmethylated metabolite in blood plasma: application to a bioequivalence study in humans. *J Chromatogr A* 2002; 949 (1-2): 11-22
36. Thurauf N, Fleischer WK, Liefhold J, et al. Dose dependent time course of the analgesic effect of a sustained-release preparation of tramadol on experimental phasic and tonic pain. *Br J Clin Pharmacol* 1996; 41 (2): 115-23
37. Murthy BV, Pandya KS, Booker PD, et al. Pharmacokinetics of tramadol in children after i.v. or caudal epidural administration. *Br J Anaesth* 2000; 84 (3): 346-9
38. Wu WN, McKown LA, Codd EE, et al. *In vitro* metabolism of the analgesic agent, tramadol-N-oxide, in mouse, rat, and human. *Eur J Drug Metab Pharmacokinet* 2002; 27 (3): 193-7
39. Raffa RB, Haslego ML, Maryanoff CA, et al. Unexpected antinociceptive effect of the N-oxide (RWJ 38705) of tramadol hydrochloride. *J Pharmacol Exp Ther* 1996; 278 (3): 1098-104
40. Paar WD, Frankus P, Dengler HJ. The metabolism of tramadol by human liver microsomes. *Clin Invest* 1992; 70 (8): 708-10
41. 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): 1146-55
42. Lledo P. Variations in drug metabolism due to genetic polymorphism: a review of the debrisoquinidine/sparteine type. *Drug Invest* 1993; 5: 19-34
43. Collart L, Luthy C, Dayer P. Multimodal analgesic effect of tramadol [abstract]. *Clin Pharmacol Ther* 1993; 53: 223

44. Poulsen L, Arendt-Nielsen L, Brosen K, et al. The hypoalgesic effect of tramadol in relation to CYP2D6. *Clin Pharmacol Ther* 1996; 60 (6): 636-44
45. Abdel-Rahman SM, Leeder JS, Wilson JT, et al. Concordance between tramadol and dextromethorphan parent/metabolite ratios: the influence of CYP2D6 and non-CYP2D6 pathways on biotransformation. *J Clin Pharmacol* 2002; 42 (1): 24-9
46. Gan SH, Ismail R, Wan Adnan WA, et al. Correlation of tramadol pharmacokinetics and CYP2D6*10 genotype in Malaysian subjects. *J Pharm Biomed Anal* 2002; 30 (2): 189-95
47. Hamm S, von Unruh GE, Paar WD, et al. Isotope effects during metabolism of (\pm)-tramadol isoptomers by human liver microsomes. *Istopenpraxis Environ Health Stud* 1994; 30: 99-110
48. Liu HC, Zhang XJ, Yang YY, et al. Stereoselectivity in renal clearance of trans-tramadol and its active metabolite, trans-O-demethyltramadol. *Acta Pharmacol Sin* 2002; 23 (1): 83-6
49. Liu HC, Wang N, Liu CS, et al. Distribution of enantiomers of trans-tramadol and trans-O-demethyltramadol in central nervous system of rats. *Acta Pharmacol Sin* 2001; 22 (10): 871-5
50. Valle M, Garrido MJ, Pavon JM, et al. Pharmacokinetic-pharmacodynamic modeling of the antinociceptive effects of main active metabolites of tramadol, (+)-O-desmethyltramadol and (-)-O-desmethyltramadol, in rats. *J Pharmacol Exp Ther* 2000; 293 (2): 646-53
51. 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): 352-9
52. Campanero MA, Calahorra B, Valle M, et al. Enantiomeric separation of tramadol and its active metabolite in human plasma by chiral high-performance liquid chromatography: application to pharmacokinetic studies. *Chirality* 1999; 11 (4): 272-9
53. Ceccato A, Vanderbist F, Pabst JY, et al. Enantiomeric determination of tramadol and its main metabolite O-desmethyltramadol in human plasma by liquid chromatography-tandem mass spectrometry. *J Chromatogr B Biomed Sci Appl* 2000; 748 (1): 65-76
54. Liu HC, Liu TJ, Yang YY, et al. Pharmacokinetics of enantiomers of trans-tramadol and its active metabolite, trans-O-demethyltramadol, in human subjects. *Acta Pharmacol Sin* 2001; 22 (1): 91-6
55. Rudaz S, Veuthey JL, Desiderio C, et al. Simultaneous stereoselective analysis by capillary electrophoresis of tramadol enantiomers and their main phase I metabolites in urine. *J Chromatogr A* 1999; 846 (1-2): 227-37
56. Elsing B, Blaschke G. Achiral and chiral high-performance liquid chromatographic determination of tramadol and its major metabolites in urine after oral administration of racemic tramadol. *J Chromatogr* 1993; 612 (2): 223-30
57. Kurth B, Blaschke G. Achiral and chiral determination of tramadol and its metabolites in urine by capillary electrophoresis. *Electrophoresis* 1999; 20 (3): 555-63
58. Soetebeer UB, Schierenberg MO, Schulz H, et al. Direct chiral assay of tramadol and detection of the phase II metabolite O-demethyl tramadol glucuronide in human urine using capillary electrophoresis with laser-induced native fluorescence detection. *J Chromatogr B Biomed Sci Appl* 2001; 765 (1): 3-13
59. Overbeck P, Blaschke G. Direct determination of tramadol glucuronides in human urine by high-performance liquid chromatography with fluorescence detection. *J Chromatogr B Biomed Sci Appl* 1999; 732 (1): 185-92
60. Frink MC, Hennies HH, Englberger W, et al. Influence of tramadol on neurotransmitter systems of the rat brain. *Arzneimittel Forschung* 1996; 46 (11): 1029-36
61. Hummel T, Roscher S, Pauli E, et al. Assessment of analgesia in man: tramadol controlled release formula vs tramadol standard formulation. *Eur J Clin Pharmacol* 1996; 51 (1): 31-8
62. Grond S, Meuser T, Uragg H, et al. Serum concentrations of tramadol enantiomers during patient-controlled analgesia. *Br J Clin Pharmacol* 1999; 48 (2): 254-7
63. Hackl W, Fitzal S, Lackner F, et al. Comparison of fentanyl and tramadol in pain therapy with an on-demand analgesia computer in the early postoperative phase [in German]. *Anaesthesist* 1986; 35 (11): 665-71
64. Lehmann KA, Kratzenberg U, Schroeder-Bark B, et al. Post-operative patient-controlled analgesia with tramadol: analgesic efficacy and minimum effective concentrations. *Clin J Pain* 1990; 6 (3): 212-20
65. Lehmann KA. Tramadol for the management of acute pain. *Drugs* 1994; 47 Suppl. 1: 19-32
66. Tegeger I, Lotsch J, Geisslinger G. Pharmacokinetics of opioids in liver disease. *Clin Pharmacokinet* 1999; 37 (1): 17-40
67. Izzedine H, Launay-Vacher V, Abbara C, et al. Pharmacokinetics of tramadol in a hemodialysis patient. *Nephron* 2002; 92 (3): 755-6
68. Boeijinga JK, van Meegen E, van den Ende R, et al. Lack of interaction between tramadol and coumarins. *J Clin Pharmacol* 1998; 38 (10): 966-70
69. Raffa RB, Friderichs E. The basic science aspect of tramadol hydrochloride. *Pain Rev* 1996; 3: 249-71
70. Hennies HH, Friderichs E, Schneider J. Receptor binding, analgesic and antitussive potency of tramadol and other selected opioids. *Arzneimittel Forschung* 1988; 38 (7): 877-80
71. Kögel B, Englberger W, Hennies HH, et al. Involvement of metabolites in the analgesic action of tramadol [abstract]. 9th World Congress of Pain; 1999 Aug 22-27; Vienna, 523
72. Desmeules JA, Piguat V, Collart L, et al. Contribution of monoaminergic modulation to the analgesic effect of tramadol. *Br J Clin Pharmacol* 1996; 41 (1): 7-12
73. Gillen C, Haurand M, Kobelt DJ, et al. Affinity, potency and efficacy of tramadol and its metabolites at the cloned human mu-opioid receptor. *Naunyn Schmiedebergs Arch Pharmacol* 2000; 362 (2): 116-21
74. Frankus E, Friderichs E, Kim SM, et al. On separation of isomers, structural elucidation and pharmacological characterization of 1-(m-methoxyphenyl)-2-(dimethylaminomethyl)-cyclohexan-1-ol [in German]. *Arzneimittel Forschung* 1978; 28 (1a): 114-21
75. Driessen B, Reimann W. Interaction of the central analgesic, tramadol, with the uptake and release of 5-hydroxytryptamine in the rat brain *in vitro*. *Br J Pharmacol* 1992; 105 (1): 147-51
76. 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): 352-6
77. Reimann W, Schneider F. Induction of 5-hydroxytryptamine release by tramadol, fenfluramine and reserpine. *Eur J Pharmacol* 1998; 349 (2-3): 199-203
78. Gobbi M, Mennini T. Release studies with rat brain cortical synaptosomes indicate that tramadol is a 5-hydroxytryptamine uptake blocker and not a 5-hydroxytryptamine releaser. *Eur J Pharmacol* 1999; 370 (1): 23-6
79. Oliva P, Aurilio C, Massimo F, et al. The antinociceptive effect of tramadol in the formalin test is mediated by the serotonergic component. *Eur J Pharmacol* 2002; 445 (3): 179-85

80. Reimann W, Hennies HH. Inhibition of spinal noradrenergic uptake in rats by the centrally acting analgesic tramadol. *Biochem Pharmacol* 1994; 47 (12): 2289-93
81. Sagata K, Minami K, Yanagihara N, et al. Tramadol inhibits norepinephrine transporter function at desipramine-binding sites in cultured bovine adrenal medullary cells. *Anesth Analg* 2002; 94 (4): 901-6
82. 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): 909-15
83. Driessen B, Reimann W, Giertz H. Effects of the central analgesic tramadol on the uptake and release of noradrenaline and dopamine *in vitro*. *Br J Pharmacol* 1993; 108 (3): 806-11
84. Collart L, Luthy C, Favario-Constantin C, et al. Duality of the analgesic effect of tramadol in humans [in German]. *Schweiz Med Wochenschr* 1993; 123 (47): 2241-3
85. Parth P, Madler C, Morawetz RF. Characterization of the effect of analgesics on the assessment of experimental pain in man. Pethidine and tramadol in a double-blind comparison [in German]. *Anaesthesist* 1984; 33 (5): 235-9
86. Collart L, Luthy C, Dayer P. Partial inhibition of tramadol antinociceptive effect by naloxone in man [abstract]. *Br J Clin Pharmacol* 1993; 35: 73P
87. Arcioni R, della Rocca M, 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): 1553-7
88. De Witte JL, Schoenmaekers B, Sessler DI, et al. The analgesic efficacy of tramadol is impaired by concurrent administration of ondansetron. *Anesth Analg* 2001; 92 (5): 1319-21
89. Grond S, Meuser T, Zech D, et al. Analgesic efficacy and safety of tramadol enantiomers in comparison with the racemate: a randomised, double-blind study with gynaecological patients using intravenous patient-controlled analgesia. *Pain* 1995; 62 (3): 313-20
90. Wiebalck A, Zenz M, Tryba M, et al. Are tramadol enantiomers for postoperative pain therapy better suited than the racemate: a randomized, placebo- and morphine-controlled double blind study [in German]. *Anaesthesist* 1998; 47 (5): 387-94
91. Violand C, Desmeules J, Pignatelli V, et al. The antinociceptive effects of tramadol and its enantiomers [abstract]. *Schweiz Med Wochenschr* 1999; 129 (13 Suppl.): 32S
92. Sunshine A. New clinical experience with tramadol. *Drugs* 1994; 47 Suppl. 1: 8-18
93. Nieuwenhuijs D, Bruce J, Drummond GB, et al. Influence of oral tramadol on the dynamic ventilatory response to carbon dioxide in healthy volunteers. *Br J Anaesth* 2001; 87 (6): 860-5
94. 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): 211-6
95. Mildh LH, Leino KA, Kirvela OA. Effects of tramadol and meperidine on respiration, plasma catecholamine concentrations, and hemodynamics. *J Clin Anesth* 1999; 11 (4): 310-6
96. Tarkkila P, Tuominen M, Lindgren L. Comparison of respiratory effects of tramadol and oxycodone. *J Clin Anesth* 1997; 9 (7): 582-5
97. Tarkkila P, Tuominen M, Lindgren L. Comparison of respiratory effects of tramadol and pethidine. *Eur J Anaesthesiol* 1998; 15 (1): 64-8
98. Bosenberg AT, Ratcliffe S. The respiratory effects of tramadol in children under halothane anaesthesia. *Anaesthesia* 1998; 53 (10): 960-4
99. 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): 310-3
100. Muller H, Stoyanov M, Braehler A, et al. Hemodynamic and respiratory effects of tramadol during nitrous oxide-oxygen artificial respiration and in the postoperative period [in German]. *Anaesthesist* 1982; 31 (11): 604-10
101. Takacs AR. Ancillary approaches to toxicokinetic evaluations. *Toxicol Pathol* 1995; 23 (2): 179-86
102. Ellmayer S, Dick W, Otto S, et al. Different opioids in patients at cardiovascular risk: comparison of central and peripheral hemodynamic adverse effects [in German]. *Anaesthesist* 1994; 43 (11): 743-9
103. Rettig G, Kropp J. Analgesic effect of tramadol in acute myocardial infarct [in German]. *Ther Ggw* 1980; 119 (6): 705-7
104. Murphy DB, Sutton A, Prescott LF, et al. A comparison of the effects of tramadol and morphine on gastric emptying in man. *Anaesthesia* 1997; 52 (12): 1224-9
105. Crighton IM, Martin PH, Hobbs GJ, et al. A comparison of the effects of intravenous tramadol, codeine, and morphine on gastric emptying in human volunteers. *Anesth Analg* 1998; 87 (2): 445-9
106. Wilder-Smith CH, Bettiga A. The analgesic tramadol has minimal effect on gastrointestinal motor function. *Br J Clin Pharmacol* 1997; 43 (1): 71-5
107. 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): 1107-16
108. Wilder-Smith CH, Hill L, Wilkins J, et al. Effects of morphine and tramadol on somatic and visceral sensory function and gastrointestinal motility after abdominal surgery. *Anesthesiology* 1999; 91 (3): 639-47
109. Staritz M, Poralla T, Manns M, et al. Effect of modern analgesic drugs (tramadol, pentazocine, and buprenorphine) on the bile duct sphincter in man. *Gut* 1986; 27 (5): 567-9
110. Tsai YC, Won SJ. Effects of tramadol on T lymphocyte proliferation and natural killer cell activity in rats with sciatic constriction injury. *Pain* 2001; 92 (1-2): 63-9
111. Gaspani L, Bianchi M, Limiroli E, et al. The analgesic drug tramadol prevents the effect of surgery on natural killer cell activity and metastatic colonization in rats. *J Neuroimmunol* 2002; 129 (1-2): 18-24
112. 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): 1411-4
113. Savoia G, Loreto M, Scibelli G. Systemic review of trials on the use of tramadol in the treatment of acute and chronic pain [in Italian]. *Minerva Anestesiologica* 2000; 66 (10): 713-31
114. Bamigbade TA, Langford RM, Blower AL. Pain control in day surgery: tramadol vs standard analgesia. *Br J Anaesth* 1998; 80: 558-9
115. Crighton IM, Hobbs GJ, Wrench IJ. Analgesia after day case laparoscopic sterilisation: a comparison of tramadol with paracetamol/dextropropoxyphene and paracetamol/codeine combinations. *Anaesthesia* 1997; 52 (7): 649-52
116. Kupers R, Callebaut V, Debois V, et al. Efficacy and safety of oral tramadol and pentazocine for postoperative pain following prolapsed intervertebral disc repair. *Acta Anaesthesiol Belg* 1995; 46 (1): 31-7
117. Peters AA, Witte EH, Damen AC, et al. Pain relief during and following outpatient curettage and hysterosalpingography: a double blind study to compare the efficacy and safety of tramadol versus naproxen. *Cobra Research Group. Eur J Obstet Gynecol Reprod Biol* 1996; 66 (1): 51-6
118. Stubhaug A, Grimstad J, Brevik H. Lack of analgesic effect of 50 and 100mg oral tramadol after orthopaedic surgery: a randomized, double-blind, placebo and standard active drug comparison. *Pain* 1995; 62 (1): 111-8
119. Sunshine A, Olson NZ, Zigelboim I, et al. Analgesic oral efficacy of tramadol hydrochloride in postoperative pain. *Clin Pharmacol Ther* 1992; 51 (6): 740-6

120. Alon E, Schulthess G, Axhausen C, et al. A double-blind comparison of tramadol and buprenorphine in the control of postoperative pain [in German]. *Anaesthesist* 1981; 30 (12): 623-6
121. Colletti V, Carner M, Vincenzi A. Intramuscular tramadol versus ketorolac in the treatment of pain following nasal surgery: a controlled multicenter trial. *Curr Ther Res Clin Exp* 1998; 59: 608-18
122. de La Pena M, Togoers B, Bosch M, et al. Recovery of lung function after laparoscopic cholecystectomy: the role of postoperative pain. *Arch Bronconeumol* 2002; 38 (2): 72-6
123. Fassolt A. The analgesic effectiveness of Tramal (tramadol) 100mg for postoperative wound pain [in German]. *Schweiz Rundsch Med Prax* 1981; 70 (10): 435-40
124. Gritti G, Verri M, Launo C, et al. Multicenter trial comparing tramadol and morphine for pain after abdominal surgery. *Drugs Exp Clin Res* 1998; 24 (1): 9-16
125. Jeffrey HM, Charlton P, Mellor DJ, et al. Analgesia after intracranial surgery: a double-blind, prospective comparison of codeine and tramadol. *Br J Anaesth* 1999; 83 (2): 245-9
126. Lanzetta A, Vizzardi M, Letizia G. Intramuscular tramadol versus ketorolac in patients with orthopaedic and traumatic postoperative pain: a comparative multicenter trial. *Curr Ther Res Clin Exp* 1998; 59: 39-47
127. Magrini M, Rivolta G, Bolis C, et al. Analgesic activity of tramadol and pentazocine in postoperative pain. *Int J Clin Pharmacol Res* 1998; 18 (2): 87-92
128. Bloch MB, Dyer RA, Heijke SA, et al. Tramadol infusion for postthoracotomy pain relief: a placebo-controlled comparison with epidural morphine. *Anesth Analg* 2002; 94 (3): 523-8
129. Dejonckheere M, Desjeux L, Deneu S, et al. Intravenous tramadol compared to propacetamol for postoperative analgesia following thyroidectomy. *Acta Anaesthesiol Belg* 2001; 52 (1): 29-33
130. Driessen A, Grogass B, Glocke M. Vergleichende Untersuchungen zur postoperativen Schmerzbehandlung nach vaginalen Hysterektomien. *Anästhesth Intensivmed* 1984; 25: 26-9
131. Houmes RJ, Voets MA, Verkaaik A, et al. Efficacy and safety of tramadol versus morphine for moderate and severe postoperative pain with special regard to respiratory depression. *Anesth Analg* 1992; 74 (4): 510-4
132. Manji M, Rigg C, Jones P. Tramadol for postoperative analgesia in coronary artery bypass graft surgery [abstract]. *Br J Anaesth* 1997; 78 Suppl. 2: 44
133. Olle FG, Opisso JL, Oferli RF, et al. Ketorolac versus tramadol: comparative study of analgesic efficacy in the postoperative pain in abdominal hysterectomy. *Rev Esp Anesthesiol Reanim* 2000; 47 (4): 162-7
134. Putland AJ, McCluskey A. The analgesic efficacy of tramadol versus ketorolac in day-case laparoscopic sterilisation. *Anaesthesia* 1999; 54 (4): 382-5
135. Ranucci M, Cazzaniga A, Soro G, et al. Postoperative analgesia for early extubation after cardiac surgery: a prospective, randomized trial. *Minerva Anesthesiol* 1999; 65 (12): 859-65
136. Sellin M, Louvard V, Siesic JC. Postoperative pain: tramadol versus morphine after cardiac surgery [abstract]. *Br J Anaesth* 1998; 80 Suppl. 2: 41
137. Stankov G, Schmieder G, Lechner FJ. Observer-blind multicenter study with metamizole versus tramadol in postoperative pain. *Eur J Pain* 1995; 16: 56-63
138. Striebel HW, Hackenberger J. A comparison of a tramadol/metamizole infusion with the combination tramadol infusion plus ibuprofen suppositories for postoperative pain management following hysterectomy [in German]. *Anaesthesist* 1992; 41 (6): 354-60
139. Torres LM, Rodriguez MJ, Montero A, et al. Efficacy and safety of dipyrone versus tramadol in the management of pain after hysterectomy: a randomized, double-blind, multicenter study. *Reg Anesth Pain Med* 2001; 26 (2): 118-24
140. Tryba M, Zenz M. Wirksamkeit und Nebenwirkungen von Opioiden und alpha2-Adrenozeptor-agonisten in der Therapie postoperativer Schmerzen. *Schmerz* 1992; 6: 182-91
141. Vickers MD, Paravicini D. Comparison of tramadol with morphine for post-operative pain following abdominal surgery. *Eur J Anaesthesiol* 1995; 12 (3): 265-71
142. Moore RA, McQuay HJ. Single-patient data meta-analysis of 3453 postoperative patients: oral tramadol versus placebo, codeine and combination analgesics. *Pain* 1997; 69 (3): 287-94
143. Edwards JE, McQuay HJ, Moore RA. Combination analgesic efficacy: individual patient data meta-analysis of single-dose oral tramadol plus acetaminophen in acute postoperative pain. *J Pain Symptom Manage* 2002; 23 (2): 121-30
144. Roelofse JA, Payne KA. Oral tramadol: analgesic efficacy in children following multiple dental extractions. *Eur J Anaesthesiol* 1999; 16 (7): 441-7
145. 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): 1469-73
146. Courtney MJ, Cabraal D. Tramadol vs diclofenac for posttonsillectomy analgesia. *Arch Otolaryngol Head Neck Surg* 2001; 127 (4): 385-8
147. Pluim MA, Wegener JT, Ruprecht J, et al. Tramadol suppositories are less suitable for post-operative pain relief than rectal acetaminophen/codeine. *Eur J Anaesthesiol* 1999; 16 (7): 473-8
148. Hartjen K, Fischer MV, Mewes R, et al. Preventive pain therapy: preventive tramadol infusion versus bolus application in the early postoperative phase [in German]. *Anaesthesist* 1996; 45 (6): 538-44
149. Rud U, Fischer MV, Mewes R, et al. Postoperative analgesia with tramadol: continuous infusion versus repetitive bolus administration [in German]. *Anaesthesist* 1994; 43 (5): 316-21
150. Webb AR, Leong S, Myles PS, et al. The addition of a tramadol infusion to morphine patient-controlled analgesia after abdominal surgery: a double-blinded, placebo-controlled randomized trial. *Anesth Analg* 2002; 95 (6): 1713-8
151. Griessinger N, Rosch W, Schott G, et al. Tramadol infusion for pain therapy following bladder exstrophy surgery in pediatric wards [in German]. *Urologe A* 1997; 36 (6): 552-6
152. Pieri M, Meacci L, Santini L, et al. Control of acute pain after major abdominal surgery in 585 patients given tramadol and ketorolac by intravenous infusion. *Drugs Exp Clin Res* 2002; 28 (2-3): 113-8
153. Bhatnagar S, Saxena A, Kannan TR, et al. Tramadol for postoperative shivering: a double-blind comparison with pethidine. *Anaesth Intensive Care* 2001; 29 (2): 149-54
154. De Witte J, Deloof T, de Veylder J, et al. Tramadol in the treatment of postanesthetic shivering. *Acta Anaesthesiol Scand* 1997; 41 (4): 506-10
155. Mathews S, Al Mulla A, Varghese PK, et al. Postanaesthetic shivering: a new look at tramadol. *Anaesthesia* 2002; 57 (4): 394-8
156. Trekova N, Bunatian A, Zolicheva N. Tramadol hydrochloride in the management of postoperative shivering: a double-blind trial with placebo [abstract 264]. 9th World Congress on Pain; 1999 Aug 22-27; Vienna, 337
157. Chan AM, Ng KF, Tong EW, et al. Control of shivering under regional anesthesia in obstetric patients with tramadol. *Can J Anaesth* 1999; 46 (3): 253-8
158. Tsai YC, Chu KS. A comparison of tramadol, amitriptyline, and meperidine for postepidural anesthetic shivering in parturients. *Anesth Analg* 2001; 93 (5): 1288-92

159. Lehmann KA, Horrichs G, Hoeckle W. The significance of tramadol as an intraoperative analgesic: a randomized double-blind study in comparison with placebo [in German]. *Anaesthesist* 1985; 34 (11): 11-9
160. Naguib M, Seraj M, Attia M, et al. Perioperative antinociceptive effects of tramadol: a prospective, randomized, double-blind comparison with morphine. *Can J Anaesth* 1998; 45 (12): 1168-75
161. Naguib M, Attia M, Samarkandi AH. Wound closure tramadol administration has a short-lived analgesic effect. *Can J Anaesth* 2000; 47 (8): 815-8
162. De Witte J, Rietman GW, Vandenbroucke G, et al. Post-operative effects of tramadol administered at wound closure. *Eur J Anaesthesiol* 1998; 15 (2): 190-5
163. Coetzee JF, van Loggenberg H. Tramadol or morphine administered during operation: a study of immediate postoperative effects after abdominal hysterectomy. *Br J Anaesth* 1998; 81 (5): 737-41
164. James MF, Heijke SA, Gordon PC. Intravenous tramadol versus epidural morphine for postthoracotomy pain relief: a placebo-controlled double-blind trial. *Anesth Analg* 1996; 83 (1): 87-91
165. Viitanen H, Annala P. Analgesic efficacy of tramadol 2mg kg⁻¹ for paediatric day-case adenoidectomy. *Br J Anaesth* 2001; 86 (4): 572-5
166. Pendeville PE, Von Montigny S, Dort JP, et al. Double-blind randomized study of tramadol vs paracetamol in analgesia after day-case tonsillectomy in children. *Eur J Anaesthesiol* 2000; 17 (9): 576-82
167. Ozkose Z, Akcabay M, Kemaloglu YK, et al. Relief of posttonsillectomy pain with low-dose tramadol given at induction of anesthesia in children. *Int J Pediatr Otorhinolaryngol* 2000; 53 (3): 207-14
168. Chiaretti A, Viola L, Pietrini D, et al. Preemptive analgesia with tramadol and fentanyl in pediatric neurosurgery. *Childs Nerv Syst* 2000; 16 (2): 93-9
169. van den Berg AA, Montoya-Pelaez LF, Halliday EM, et al. Analgesia for adenotonsillectomy in children and young adults: a comparison of tramadol, pethidine and nalbuphine. *Eur J Anaesthesiol* 1999; 16 (3): 186-94
170. Wong WH, Cheong KF. Role of tramadol in reducing pain on propofol injection. *Singapore Med J* 2001; 42 (5): 193-5
171. Memis D, Turan A, Karamanlioglu B, et al. The prevention of propofol injection pain by tramadol or ondansetron. *Eur J Anaesthesiol* 2002; 19 (1): 47-51
172. Tan SM, Pay LL, Chan ST. Intravenous regional anaesthesia using lignocaine and tramadol. *Ann Acad Med Singapore* 2001; 30 (5): 516-9
173. Acalovschi I, Cristea T, Margarit S, et al. Tramadol added to lidocaine for intravenous regional anesthesia. *Anesth Analg* 2001; 92 (1): 209-14
174. Choyce A, Peng P. A systematic review of adjuncts for intravenous regional anesthesia for surgical procedures. *Can J Anaesth* 2002; 49 (1): 32-45
175. Langlois G, Estebe JP, Gentili ME, et al. The addition of tramadol to lidocaine does not reduce tourniquet and post-operative pain during iv regional anesthesia. *Can J Anaesth* 2002; 49 (2): 165-8
176. Lehmann KA. New developments in patient-controlled post-operative analgesia. *Ann Med* 1995; 27: 271-82
177. Jellinek H, Haumer H, Grubhofer G, et al. Tramadol in post-operative pain therapy: patient-controlled analgesia versus continuous infusion [in German]. *Anaesthesist* 1990; 39 (10): 513-20
178. Stamer UM, Maier C, Grond S, et al. Tramadol in the management of post-operative pain: a double-blind, placebo- and active drug-controlled study. *Eur J Anaesthesiol* 1997; 14 (6): 646-54
179. Ng KF, Tsui SL, Yang JC, et al. Increased nausea and dizziness when using tramadol for post-operative patient-controlled analgesia (PCA) compared with morphine after intraoperative loading with morphine. *Eur J Anaesthesiol* 1998; 15 (5): 565-70
180. Pang WW, Mok MS, Lin CH, et al. Comparison of patient-controlled analgesia (PCA) with tramadol or morphine. *Can J Anaesth* 1999; 46 (11): 1030-5
181. Silvasti M, Svartling N, Pitkanen M, et al. Comparison of intravenous patient-controlled analgesia with tramadol versus morphine after microvascular breast reconstruction. *Eur J Anaesthesiol* 2000; 17 (7): 448-55
182. Stamer UM, Grond S, Maier C. Responders and non-responders to post-operative pain treatment: the loading dose predicts analgesic needs. *Eur J Anaesthesiol* 1999; 16 (2): 103-10
183. Alon E, Atanassoff PG, Biro P. Intravenous postoperative pain management using nalbuphine and tramadol: a combination of continuous infusion and patient-controlled administration [in German]. *Anaesthesist* 1992; 41 (2): 83-7
184. Lehmann KA, Jung C, Hoeckle W. Tramadol und Pethidin zur postoperativen Schmerztherapie: eine Doppelblindstudie unter den Bedingungen der intravenösen on-demand Analgesie. *Eur J Pain* 1985; 6: 88-100
185. Likar R, Jost R, Mathiaschitz K. Postoperative patient-controlled analgesia using a low-tech PCA system. *Int J Acute Pain Manage* 1999; 2: 17-26
186. Migliorini F, Tropea F, Perciaccante L. Tramadol in PCA plus propacetamol is a good choice after orthopaedic surgery [abstract]. *Br J Anaesth* 1999; 82 Suppl. 1: 190
187. Montes A, Warner W, Puig MM. Use of intravenous patient-controlled analgesia for the documentation of synergy between tramadol and metamizol. *Br J Anaesth* 2000; 85 (2): 217-23
188. Pang W, Huang S, Tung CC, et al. Patient-controlled analgesia with tramadol versus tramadol plus lysine acetyl salicylate. *Anesth Analg* 2000; 91 (5): 1226-9
189. Rodriguez MJ, De La Torre MR, Perez-Iraola P. Comparative study of tramadol versus NSAIDs as intravenous continuous infusion for managing postoperative pain. *Curr Ther Res* 1993; 54: 375-83
190. Silvasti M, Tarkkila P, Tuominen M, et al. Efficacy and side effects of tramadol versus oxycodone for patient-controlled analgesia after maxillofacial surgery. *Eur J Anaesthesiol* 1999; 16 (12): 834-9
191. Vickers MD, O'Flaherty D, Szekely SM, et al. Tramadol: pain relief by an opioid without depression of respiration. *Anaesthesia* 1992; 47 (4): 291-6
192. Pang WW, Mok MS, Huang S, et al. Intraoperative loading attenuates nausea and vomiting of tramadol patient-controlled analgesia. *Can J Anaesth* 2000; 47 (10): 968-73
193. Ng KF, Tsui SL, Yang JC, et al. Comparison of tramadol and tramadol/droperidol mixture for patient-controlled analgesia. *Can J Anaesth* 1997; 44 (8): 810-5
194. Siddik-Sayyid S, Aouad-Maroun M, Sleiman D, et al. Epidural tramadol for postoperative pain after Cesarean section. *Can J Anaesth* 1999; 46 (8): 731-5
195. Grace D, Fee JP. Ineffective analgesia after extradural tramadol hydrochloride in patients undergoing total knee replacement. *Anaesthesia* 1995; 50 (6): 555-8
196. Delilkan AE, Vijayan R. Epidural tramadol for postoperative pain relief. *Anaesthesia* 1993; 48 (4): 328-31
197. Baraka A, Jabbour S, Ghabash M, et al. A comparison of epidural tramadol and epidural morphine for postoperative analgesia. *Can J Anaesth* 1993; 40 (4): 308-13
198. Pan AK, Mukherjee P, Rudra A. Role of epidural tramadol hydrochloride on postoperative pain relief in caesarean section delivery. *J Indian Med Assoc* 1997; 95 (4): 105-6
199. Ozcengiz D, Gunduz M, Ozbek H, et al. Comparison of caudal morphine and tramadol for postoperative pain control in chil-

- dren undergoing inguinal herniorrhaphy. *Paediatr Anaesth* 2001; 11 (4): 459-64
200. Senel AC, Akyol A, Dohman D, et al. Caudal bupivacaine-tramadol combination for postoperative analgesia in pediatric herniorrhaphy. *Acta Anaesthesiol Scand* 2001; 45 (6): 786-9
 201. Gunduz M, Ozcengiz D, Ozbek H, et al. A comparison of single dose caudal tramadol, tramadol plus bupivacaine and bupivacaine administration for postoperative analgesia in children. *Paediatr Anaesth* 2001; 11 (3): 323-6
 202. Batra YK, Prasad MK, Arya VK, et al. Comparison of caudal tramadol vs bupivacaine for post-operative analgesia in children undergoing hypospadias surgery. *Int J Clin Pharmacol Ther* 1999; 37 (5): 238-42
 203. Prosser DP, Davis A, Booker PD, et al. Caudal tramadol for postoperative analgesia in pediatric hypospadias surgery. *Br J Anaesth* 1997; 79 (3): 293-6
 204. Likar R, Mathiaschitz K, Burtcher M. Randomized, double-blind, comparative study of morphine and tramadol administered intra-articularly for postoperative analgesia following arthroscopic surgery. *Clin Drug Invest* 1995; 10 (1): 17-21
 205. Kapral S, Gollmann G, Waltl B, et al. Tramadol added to mepivacaine prolongs the duration of an axillary brachial plexus blockade. *Anesth Analg* 1999; 88 (4): 853-6
 206. Sommer F. Klinische Erfahrung mit dem Analgetikum Tramadol-HCl Erfahrungsbericht aus einer orthopädischen Praxis. *Extracta Med Pract* 1981; 2: 826-31
 207. Berghold F, Aufmesser H, Aufmesser W. Erstversorgung von Wintersportverletzungen: analgetische Wirksamkeit und Verträglichkeit von Tramadol. *Therapiewoche Österreich* 1991; 6: 173-84
 208. Ward ME, Radburn J, Morant S. Evaluation of intravenous tramadol for use in the prehospital situation by ambulance paramedics. *Prehospital Disaster Med* 1997; 12 (2): 158-62
 209. Vergnion M, Degesves S, Garcet L, et al. Tramadol, an alternative to morphine for treating posttraumatic pain in the prehospital situation. *Anesth Analg* 2001; 92 (6): 1543-6
 210. Hoogewijs J, Diltoer MW, Hlubloue I, et al. A prospective, open, single blind, randomized study comparing four analgesics in the treatment of peripheral injury in the emergency department. *Eur J Emerg Med* 2000; 7 (2): 119-23
 211. Mahadevan M, Graff L. Prospective randomized study of analgesic use for ED patients with right lower quadrant abdominal pain. *Am J Emerg Med* 2000; 18 (7): 753-6
 212. Eray O, Cete Y, Oktay C, et al. Intravenous single-dose tramadol versus meperidine for pain relief in renal colic. *Eur J Anaesthesiol* 2002; 19 (5): 368-70
 213. Nicolas Torralba JA, Rigabert Montiel M, Banon Perez V, et al. Intramuscular ketorolac compared to subcutaneous tramadol in the initial emergency treatment of renal colic [in Spanish]. *Arch Esp Urol* 1999; 52 (5): 435-7
 214. Stankov G, Schmieder G, Zerle G, et al. Double-blind study with dipyrone versus tramadol and butylscopolamine in acute renal colic pain. *World J Urol* 1994; 12 (3): 155-61
 215. Schmieder G, Stankov G, Zerle G, et al. Observer-blind study with metamizole versus tramadol and butylscopolamine in acute biliary colic pain. *Arzneimittel Forschung* 1993; 43 (11): 1216-21
 216. Primus G, Pummer K, Vuicsina F, et al. Tramadol versus metamizole in alleviating pain in ureteral colic [in German]. *Urologe A* 1989; 28 (2): 103-5
 217. Elbourne D, Wiseman RA. Types of intra-muscular opioids for maternal pain relief in labour. *Cochrane Database Syst Rev* 2000; (2): CD001237
 218. Viegas OA, Khaw B, Ratnam SS. Tramadol in labour pain in primiparous patients: a prospective comparative clinical trial. *Eur J Obstet Gynecol Reprod Biol* 1993; 49 (3): 131-5
 219. Kainz C, Joura E, Obwegeser R, et al. Effectiveness and tolerance of tramadol with or without an antiemetic and pethidine in obstetric analgesia [in German]. *Z Geburtshilfe Perinatol* 1992; 196 (2): 78-82
 220. Fieni S, Angeri F, Kaihura CT, et al. Evaluation of the peripartum effects of 2 analgesics: meperidine and tramadol, used in labor. *Acta Biomed Ateneo Parmense* 2000; 71 Suppl. 1: 397-400
 221. Li E, Weng L. Influence of dihydroetorphine hydrochloride and tramadol on labor pain and umbilical blood gas. *Zhonghua Fu Chan Ke Za Zhi* 1995; 30 (6): 345-8
 222. Prasertsawat PO, Herabuty Y, Chaturachinda K. Obstetric analgesia: comparison between tramadol, morphine and pethidine. *Curr Ther Res* 1986; 40: 1022-8
 223. Bitsch M, Emmrich J, Hary J, et al. Obstetrical analgesia with tramadol [in German]. *Fortschr Med* 1980; 98 (16): 632-4
 224. Suvonnakote T, Thitadilok W, Atisook R. Pain relief during labour. *J Med Assoc Thai* 1986; 69 (11): 575-80
 225. Bredow V. Use of tramadol versus pethidine versus denaverine suppositories in labor: a contribution to noninvasive therapy of labor pain [in German]. *Zentralbl Gynakol* 1992; 114 (11): 551-4
 226. Liu S, Carpenter RL, Neal JM. Epidural anesthesia and analgesia. *Anesthesiology* 1995; 82 (6): 1474-506
 227. Krimmer H, Pfeiffer H, Arbogast R, et al. Combined infusion analgesia: an alternative concept in postoperative pain therapy [in German]. *Chirurg* 1986; 57 (5): 327-9
 228. Tarradell R, Pol O, Farre M, et al. Respiratory and analgesic effects of meperidine and tramadol in patients undergoing orthopedic surgery. *Methods Find Exp Clin Pharmacol* 1996; 18 (3): 211-8
 229. Novikov IA, Kon'kov S, Shumilov EI. Immunity state of oncological patients during long-term treatment with Tramal [in Russian]. *Anesteziol Reanimatol* 1994; (3): 12-3
 230. Bono AV, Cuffari S. Effectiveness and tolerance of tramadol in cancer pain: a comparative study with respect to buprenorphine. *Drugs* 1997; 53 Suppl. 2: 40-9
 231. 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): 109-16
 232. Grond S, Zech D, Lynch J, et al. Tramadol: a weak opioid for relief of cancer pain. *Pain Clinic* 1992; 5 (4): 241-7
 233. 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 (6): 812-21
 234. Tawfik MO, Elborolossy K, Nasr F. Tramadol hydrochloride in the relief of cancer pain: a double blind comparison against sustained release morphine [abstract]. *Pain* 1990; Suppl. 5: S377
 235. Wilder-Smith CH, Schimke J, Osterwalder B, et al. Oral tramadol, a mu-opioid agonist and monoamine reuptake-blocker, and morphine for strong cancer-related pain. *Ann Oncol* 1994; 5 (2): 141-6
 236. Adler L, McDonald C, O'Brien C, et al. A comparison of once-daily tramadol with normal release tramadol in the treatment of pain in osteoarthritis. *J Rheumatol* 2002; 29 (10): 2196-9
 237. Bird HA, Hill J, Stratford M. A double blind cross-over study comparing the analgesic efficacy of tramadol with pentazocine in patients with osteoarthritis. *J Drug Dev Clin Pract* 1995; 7: 81-8
 238. Goroll D. Tropfenform eines stark wirksamen Analgetikums in der Doppelblindprüfung. *Med Klin* 1983; 78: 173-5

239. Jensen EM, Ginsberg F. Tramadol versus dextropropoxyphene in the treatment of osteoarthritis. *Drug Invest* 1994; 8 (4): 211-8
240. Pavelka K, Peliskova Z, Stelikova H. Intraindividual differences in pain relief and functional improvement in osteoarthritis with diclofenac or tramadol. *Clin Drug Invest* 1998; 16 (6): 1-9
241. Rauck RL, Ruoff GE, McMillen JI. Comparison of tramadol and acetaminophen with codeine for long-term pain management in elderly patients. *Curr Ther Res Clin Exp* 1994; 55 (12): 1417-31
242. Roth SH. Efficacy and safety of tramadol HCl in breakthrough musculoskeletal pain attributed to osteoarthritis. *J Rheumatol* 1998; 25 (7): 1358-63
243. Schnitzer TJ, Gray WL, Paster RZ, et al. Efficacy of tramadol in treatment of chronic low back pain. *J Rheumatol* 2000; 27 (3): 772-8
244. Silverfield JC, Kamin M, Wu SC, et al. Tramadol/acetaminophen combination tablets for the treatment of osteoarthritis flare pain: a multicenter, outpatient, randomized, double-blind, placebo-controlled, parallel-group, add-on study. *Clin Ther* 2002; 24 (2): 282-97
245. Sorge J, Stadler T. Comparison of the analgesic efficacy and tolerability of tramadol 100mg sustained-release tablets and tramadol 50mg capsules for the treatment of chronic low back pain. *Clin Drug Invest* 1997; 14 (3): 157-64
246. Wilder-Smith CH, Hill L, Spargo K, et al. Treatment of severe pain from osteoarthritis with slow-release tramadol or dihydrocodeine in combination with NSAIDs: a randomised study comparing analgesia, antinociception and gastrointestinal effects. *Pain* 2001; 91 (1-2): 23-31
247. Göbel H, Stadler T. Treatment of post-herpes zoster pain with tramadol: results of an open pilot study versus clomipramine with or without levomepromazine. *Drugs* 1997; 53 Suppl. 2: 34-9
248. 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): 1842-6
249. 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
250. Lenzhofer R, Moser K. Analgesic effect of tramadol in patients with malignant diseases [in German]. *Wien Med Wochenschr* 1984; 134 (8): 199-202
251. Rodriguez N, Rodriguez Pereira E. Tramadol in cancer pain. *Curr Ther Res* 1989; 46 (6): 1142-8
252. 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): 174-9
253. 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
254. Theilade P. Death due to dextropropoxyphene: Copenhagen experiences. *Forensic Sci Int* 1989; 40: 143-51
255. Ruoff GE. Slowing the initial titration rate of tramadol improves tolerability. *Pharmacotherapy* 1999; 19 (1): 88-93
256. Petrone D, Kamin M, Olson W. Slowing the titration rate of tramadol HCl reduces the incidence of discontinuation due to nausea and/or vomiting: a double-blind randomized trial. *J Clin Pharm Ther* 1999; 24 (2): 115-23
257. Frank M, Sturm M, Arnau H, et al. Quality of life and patient compliance during pain therapy: multicenter study using Tramundin retard [in German]. *Fortschr Med* 1999; 117 (10): 38-9
258. Attal N, Guirimand F, Brasseur L, et al. Effects of IV morphine in central pain: a randomized placebo-controlled study. *Neurology* 2002; 58 (4): 554-63
259. Grond S, Radbruch L, Meuser T, et al. Assessment and treatment of neuropathic cancer pain following WHO guidelines. *Pain* 1999; 79 (1): 15-20
260. Apaydin S, Uyar M, Karabay NU, et al. The antinociceptive effect of tramadol on a model of neuropathic pain in rats. *Life Sci* 2000; 66 (17): 1627-37
261. Tsai YC, Sung YH, Chang PJ, et al. Tramadol relieves thermal hyperalgesia in rats with chronic constriction injury of the sciatic nerve. *Fundam Clin Pharmacol* 2000; 14 (4): 335-40
262. Olligs J, Anderson A. Schmersybehandlung mit Tramadol Retard bei Neuropathie [abstract]. *Schmerz* 1997; Suppl. 1: 49
263. Harati Y, Gooch C, Swenson M, et al. Maintenance of the long-term effectiveness of tramadol in treatment of the pain of diabetic neuropathy. *J Diabetes Complications* 2000; 14 (2): 65-70
264. Grond S, Zech D, Schug SA, et al. Validation of World Health Organization guidelines for cancer pain relief during the last days and hours of life. *J Pain Symptom Manage* 1991; 6: 411-22
265. World Health Organization: Cancer pain relief. Geneva: World Health Organization, 1996
266. Mercadante S. Pain treatment and outcomes for patients with advanced cancer who receive follow-up care at home. *Cancer* 1999; 85 (8): 1849-58
267. Zech DF, Grond S, Lynch J, et al. Validation of World Health Organization guidelines for cancer pain relief: a 10-year prospective study. *Pain* 1995; 63: 65-76
268. Eisenberg E, Berkey CS, Carr DB, et al. Efficacy and safety of nonsteroidal antiinflammatory drugs for cancer pain: a meta-analysis. *J Clin Oncol* 1994; 12: 2756-65
269. Grond S, Meuser T. Weak opioids: an educational substitute for morphine? *Curr Opin Anaesthesiol* 1998; 11: 559-65
270. 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
271. Schaffer J, Piepenbrock S, Kretz FJ, et al. Nalbuphine and tramadol for the control of postoperative pain in children [in German]. *Anaesthesiol* 1986; 35 (7): 408-13
272. Barnung SK, Treschow M, Borgbjerg FM. Respiratory depression following oral tramadol in a patient with impaired renal function. *Pain* 1997; 71 (1): 111-2
273. Maier C, Kibbel K, Mercker S, et al. Postoperative pain therapy at general nursing stations: an analysis of eight year's experience at an anesthesiological acute pain service [in German]. *Anaesthesiol* 1994; 43 (6): 385-97
274. Gardner JS, Blough D, Drinkard CR, et al. Tramadol and seizures: a surveillance study in a managed care population. *Pharmacotherapy* 2000; 20 (12): 1423-31
275. Potschka H, Friderichs E, Loscher W. Anticonvulsant and proconvulsant effects of tramadol, its enantiomers and its M1 metabolite in the rat kindling model of epilepsy. *Br J Pharmacol* 2000; 131 (2): 203-12
276. Gasse C, Derby L, Vasilakis-Scaramozza C, et al. Incidence of first-time idiopathic seizures in users of tramadol. *Pharmacotherapy* 2000; 20 (6): 629-34
277. Cicero TJ, Adams EH, Geller A, et al. A postmarketing surveillance program to monitor Ultram (tramadol hydrochloride) abuse in the United States. *Drug Alcohol Depend* 1999; 57 (1): 7-22
278. Preston KL, Jasinski DR, Testa M. Abuse potential and pharmacological comparison of tramadol and morphine. *Drug Alcohol Depend* 1991; 27 (1): 7-17
279. Cami J, Lamas X, Farre M. Acute effects of tramadol in methadone-maintained volunteers. *Drugs* 1994; 47 Suppl. 1: 39-43

-
280. Spiller HA, Gorman SE, Villalobos D, et al. Prospective multicenter evaluation of tramadol exposure. *J Toxicol Clin Toxicol* 1997; 35 (4): 361-4
281. Mason BJ, Blackburn KH. Possible serotonin syndrome associated with tramadol and sertraline coadministration. *Ann Pharmacother* 1997; 31 (2): 175-7
282. Egberts AC, ter Borgh J, Brodie-Meijer CC. Serotonin syndrome attributed to tramadol addition to paroxetine therapy. *Int Clin Psychopharmacol* 1997; 12 (3): 181-2
283. Lantz MS, Buchalter EN, Giambanco V. Serotonin syndrome following the administration of tramadol with paroxetine. *Int J Geriatr Psychiatry* 1998; 13 (5): 343-5
284. Goeringer KE, Logan BK, Christian GD. Identification of tramadol and its metabolites in blood from drug-related deaths and drug-impaired drivers. *J Anal Toxicol* 1997; 21 (7): 529-37
285. Ripple MG, Pestaner JP, Levine BS, et al. Lethal combination of tramadol and multiple drugs affecting serotonin. *Am J Forensic Med Pathol* 2000; 21 (4): 370-4
-
- Correspondence and offprints: Dr *Stefan Grond*, Universitätsklinik für Anästhesiologie und Operative Intensivmedizin, Martin-Luther-Universität Halle-Wittenberg, Ernst-Grube-Str. 40, D-06097 Halle, Germany.
E-mail: Stefan.grond@medizin.uni-halle.de