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TRAMADOL

A Position Statement of the NSW Therapeutic Assessment Group Inc.

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EXECUTIVE SUMMARY

Tramadol is a centrally acting synthetic analgesic of the aminocyclohexanol group with opioid-like effects. Its mode of action is not completely understood but it appears to act by modifying transmission of pain impulses via inhibition of noradrenaline and serotonin re-uptake and also by weakly binding to mu-opioid receptors.

In Australia it is marketed under the trade name Tramal[®] and is available as capsules (50mg), sustained release tablets (100mg, 150mg, 200mg) and ampoules (100mg/2ml) for relief of moderate to severe pain.

On the basis of published evidence, tramadol appears to have reasonable dose related efficacy in comparison with other opioid analgesics, with a relative lack of respiratory depression, major organ toxicity or abuse potential.

Because of its side-effect profile in comparison with other analgesics, tramadol may have a role in patients who are intolerant of conventional opioid and other non-opioid analgesics, those who have pre-existing cardiopulmonary disease, such as the elderly or obese, and those in whom codeine use is inappropriate. In the acute and post-operative settings, it may have a place in multi-modal analgesia, where opioid and non-opioid drugs are given in combination to achieve analgesia, with a reduction in the incidence and severity of side effects.

Similarly, in chronic pain conditions, tramadol may be considered (as a single agent or in combination) where non-opioid analgesics have proven ineffective or where multimodal therapy might be advantageous in order to limit side-effects (eg where a reduction in NSAID dosage is desirable). The reduced constipating effect of tramadol compared with other opioids may be useful in patients with chronic cancer pain, although nausea may be a dose-limiting side-effect and sustained-release morphine is more effective in severe cancer pain. Because of its extended duration of effect, the sustained release formulation may provide convenience in ambulatory patients with chronic pain. However, studies of long-term use have not yet been reported and the potential for serious drug-drug interactions with tramadol should not be under-estimated.

As a single agent, tramadol's place in therapy is likely to be limited by both cost and tolerability (particularly nausea). In the majority of patients it offers few advantages at considerable additional cost. However, it may be a useful alternative to other analgesics in selected patients with moderate to severe pain.

1. BACKGROUND

Tramadol is a centrally acting, synthetic analgesic of the aminocyclohexanol group, which has opioid-like effects¹. It has been in clinical use in Europe since the late 1970s². Its mode of action is not completely understood but it appears to have a dual mechanism of action, which involves inhibition of re-uptake of serotonin (5-HT) and/or noradrenaline as well as weak affinity for opioid (μ) receptors³. Since tramadol does not affect prostaglandin synthesis, it does not have antipyretic or anti-inflammatory effects⁴.

In Australia, tramadol is marketed under the trade name Tramal[®] and is available as capsules (50mg), sustained-release tablets (100mg, 150mg, 200mg) and ampoules (100mg/2ml). It is approved for oral, intravenous (iv) and intramuscular (im) administration for relief of moderate to severe pain. (Government subsidy for the immediate and sustained-release formulations is limited to use for pain where aspirin and/or paracetamol alone are inappropriate or have failed.) In Australia it is not recommended for use in children¹, although in other countries, licence for use in children over the age of one year exists.⁵

Tramadol has high oral bioavailability³. Its absorption is not affected by food¹. The two oral dosage forms (50mg capsules 4 times daily and 100mg sustained-release tablets twice daily) have been reported to be equivalent in terms of analgesic efficacy and tolerability⁶.

Tramadol is extensively metabolised³. The production of the only known active metabolite, M1 (mono-o-desmethyltramadol) is dependent on the CYP2D6 isoenzyme of the cytochrome P-450 enzyme system and hepatic impairment results in decreased metabolism of both the parent compound and the active metabolite⁷. Patients who metabolise drugs poorly via CYP2D6 may obtain reduced benefit from tramadol due to reduced formation of M1¹. However, there is still measurable analgesia with tramadol in these patients⁵, in contrast to the complete lack of analgesic efficacy with codeine in such patients (7% of Caucasians are poor metabolisers)⁵. In such patients there may be an argument for using tramadol as an alternative to codeine⁸.

Tramadol causes a minor delay in colonic transit, but has no effect on upper gastrointestinal transit or gut smooth muscle tone^{9,10}. It has no significant effect on the Sphincter of Oddi or intrabiliary pressure and it has weak spasmolytic properties¹⁰.

The recommended dose for moderate to severe pain is 50-100mg every four to six hours (or 100-200mg twice daily for the sustained-release formulation), to a maximum daily dosage of 400mg for oral therapy or 600mg parenterally^{1,11}.

2. CLINICAL USE

Publications reporting the clinical use of tramadol are numerous. A number of reviews of the clinical use of tramadol have also been published^{5,7,10,12-17}.

2.1 Intra-operative and Post-operative Analgesia

2.1.1 Comparison with placebo

A pooled analysis of 9 single-dose, double-blind, randomised, placebo-controlled studies¹⁸ included a total of 1594 patients with post-operative pain following **caesarean section or general surgical procedures**. Analysis showed that analgesic efficacy of tramadol at doses equal to or greater than 50mg was superior to that of placebo (statistical value not reported). Likewise, pooled analysis of 9 double-blind, randomised studies involving 1859 patients with **dental extraction** pain evaluated single oral doses of tramadol ranging from 50mg to 200mg¹⁸. Analysis demonstrated a significantly greater efficacy for tramadol than for placebo at all doses evaluated. (The majority of these studies have not been published.) A subsequent meta-analysis of these 18 studies confirmed the effectiveness of tramadol in comparison with placebo and demonstrated a significant dose response¹⁹. Multi-dose studies have also demonstrated a superior effect of oral tramadol over placebo in both pain **after dental extraction** and pain after **orthopaedic surgery**¹⁸.

2.1.2 Comparison with morphine

Tramadol (up to 3 doses of 50mg iv) was compared with morphine (up to 3 doses of 5mg iv) over 6 hours in a double-blind, randomised study of 150 patients after **gynaecological surgery**²⁰. In those patients who reported moderate pain, the two drugs were equally effective. However, morphine was superior in patients starting with severe pain. Respiratory depression (as measured by oxygen desaturation) occurred in 13% of the morphine group but not at all in the tramadol group. Sedation and nausea were also more common in the morphine group.

In a multi-centre, double-blind, randomised study involving 523 patients²¹, the analgesic efficacy of tramadol and morphine given in repeated intravenous boluses as required to control post-operative pain over 24 hours **following abdominal surgery** was compared. There was no substantive difference in analgesia between tramadol (100mg iv then 100-125mg iv or im as needed) and morphine (5mg iv then 5-20mg iv or im as needed). The time between the first and second dose of study medication was longer in the tramadol group than in the morphine group, probably due to the lower comparative starting dose of morphine (5mg) compared with tramadol (100mg). However, the intervals between all subsequent doses were comparable. A high incidence of gastrointestinal adverse events were observed with both treatments, mostly consisting of nausea and symptoms such as dry mouth, vomiting, dyspepsia and hiccups. Constipation was not reported in either group. Similar efficacy has been observed in more recent studies in this surgical group.²²

Scott et al²³ reviewed the literature (since 1993) where effectiveness of tramadol in perioperative pain was assessed using standard visual analogue scales. On the basis of percentage change in pain scores from baseline, they concluded that tramadol effectively relieved moderate to severe postoperative pain associated with several types of surgery, including **abdominal, orthopaedic and cardiac surgery**. Pain scores with tramadol were reduced by approximately 57% within 4 to 6 hours, compared to a reduction of approximately 70% with morphine.

2.1.3. Comparison with pethidine

Tramadol was compared to pethidine in 30 patients undergoing **gynaecological surgery**²⁴. Using **patient controlled analgesia** during the first 24 hours post-operatively, tramadol was demonstrated to be of equivalent potency to pethidine. Mean 24 hour consumption of tramadol was 642mg (SD

190mg, range 180-840mg) and for pethidine 606mg (SD 172mg, range 360-780mg). The estimate of relative potency of tramadol to pethidine was 0.94 (95% CI: 0.72-1.17).

In a randomised study in 50 patients presenting for **caesarean section** under spinal anaesthesia with lignocaine²⁵, tramadol 1.5mg/kg was as effective as pethidine 1mg/kg intramuscularly. There was no significant difference in side effects between the two groups, including neonatal APGAR scores.

2.1.4. Comparison with NSAIDs

In comparative studies of tramadol and ketorolac in **nasal surgery**²⁶ and **orthopaedic surgery**²⁷, improvements in postoperative analgesia and quality of sleep were similar with intramuscular tramadol or ketorolac²³.

2.1.5. Comparison with oral analgesics: single-dose studies

The analgesic efficacy of single dose, orally administered tramadol 75mg or 150mg was compared in a double blind, placebo controlled trial with a combination of paracetamol 650mg and dextropropoxyphene napsylate 100mg in 161 patients with severe post operative pain after **caesarean section**²⁸. Both tramadol and the combination analgesic were statistically superior to placebo. Tramadol 150mg was significantly more effective than both tramadol 75mg and combination paracetamol/ dextropropoxyphene. No serious adverse effects were observed, but dizziness was more frequently reported with 150mg tramadol.

On the other hand, Stubhaug et al²⁹ compared oral tramadol 50mg or 100mg with a combination paracetamol/codeine analgesic (1000mg/60mg) or placebo in a single-dose study in 144 patients after **total hip replacement**. In this study the combination of paracetamol/codeine was superior to both doses of tramadol. There was no difference in efficacy between either dose of tramadol and placebo. Adverse effects were more common with tramadol than with the combination, particularly nausea.

Single oral doses of tramadol 75mg or 150mg have been compared with codeine phosphate 60mg and paracetamol/propoxyphene HCl (650mg/65mg) in 239 patients with pain after **dental extraction**³⁰. Tramadol 75mg was more effective than codeine. Although 150mg of tramadol was superior to the combination analgesic, 75mg of tramadol was not. In another double-blind, single dose parallel study in 206 patients after **dental extraction**³¹, tramadol 100mg was judged to be more effective than codeine 60mg but only tramadol 200mg was statistically so. (Both of these studies have been published in abstract form only.)

2.1.6 Paediatric Surgery

In **paediatric surgery** (in patients over the age of 12 months), tramadol has been used effectively for moderate to severe pain in im or iv doses of 1-2mg/kg⁵.

2.2 Other Acute Pain Syndromes

In randomised, double-blind comparisons of tramadol with pethidine or morphine in **obstetric analgesia**,^{32, 33} intramuscular tramadol 50mg to 100mg was generally equivalent to intramuscular pethidine 50mg to 100mg, and tramadol 100mg was equivalent to morphine 10mg. Tramadol

administered intramuscularly did not cause respiratory depression in neonates and caused significantly less maternal respiratory depression than pethidine.

Tramadol has been compared with morphine in patients with **post-traumatic musculoskeletal pain** in the pre-hospital setting³⁴. Intravenous tramadol 100mg was equivalent to 5-10mg morphine, with similar incidence of side effects and similar degree of patient satisfaction.

Repeat bolus doses of tramadol have been administered for analgesia, with some success, in patients with **acute myocardial infarction** and **unstable angina**. However, because of the accepted benefits of traditional opioids in these conditions, replacement with tramadol in this patient group is not recommended⁵.

2.3 Chronic Pain

Tramadol has been included as a step 2 analgesic in the second edition of the World Health Organisation's recommendations for treatment of cancer pain¹⁶.

Twenty **cancer patients** with strong pain unresponsive to previous pain treatment were randomised to receive oral tramadol or morphine solution in a randomised, double-blind, cross-over study³⁵. Doses were individually titrated and cross-over occurred on day 4. Pain scores were similar on day 4, although pain scores were higher in the tramadol group on days 1 and 2. There was a statistically significant reduction in side-effects (particularly nausea and constipation) with tramadol.

Efficacy and safety of high dose oral tramadol (300-600mg/day) compared with low dose oral morphine (10-60mg/day) was evaluated in a non-blinded, non-randomised study involving a total of 1658 patients with **cancer pain**³⁶. There was no significant difference in analgesic efficacy between the two groups. Antiemetics, laxatives, neuroleptics and steroids were prescribed significantly more frequently in the morphine group; the use of other adjuvants was similar in both groups. Constipation, neuropsychological symptoms and pruritus were observed significantly more frequently with low dose morphine. Other symptoms had similar frequencies in both groups.

Oral tramadol was evaluated in a double-blind study over a 4 week period in 390 patients over 65 years of age with **chronic pain due to a variety of conditions**³⁷. Patients were initially treated with either tramadol 50mg orally or paracetamol/codeine 300mg/30mg and were then allowed to titrate the dose according to pain severity to a total of eight capsules per day. Mean pre-treatment pain intensities were moderate for both groups. At the end of the study, average daily doses were 244mg of tramadol and 1,407mg/140.7mg of paracetamol/codeine. Both treatments were rated as good, very good or excellent by 55% of patients in each group. There was no significant difference in the incidence of adverse effects in each group, but adverse effects resulted in discontinuation in a significantly higher proportion of patients taking tramadol (18.8% vs 9.6%, $p < 0.05$).

Oral tramadol (100mg eighth hourly) was compared with a fixed dose combination of paracetamol/codeine (1000mg/60mg eighth hourly) in a randomised, double-blind cross-over study in 55 patients suffering from refractory **chronic back pain**³⁸. Efficacy was similar in the two arms. Although the combination analgesic was reported by the authors as better tolerated than tramadol, the difference was not statistically significant. A multicentre, randomised, double-blind, parallel-

group study compared the analgesic efficacy and tolerability of immediate release tramadol (50mg four times daily) and sustained-release tramadol (100mg twice daily) in 205 patients with **chronic refractory low back pain**. There was no difference in pain relief, the course of pain intensity or adverse events between the two groups⁶. Those continuing beyond the first week became more tolerant of the adverse effects.

The efficacy of tramadol in **osteoarthritis** has been evaluated in patients who experienced breakthrough pain while being treated with NSAIDs³⁹. After an open label phase, forty two patients were randomised to receive tramadol or placebo for a two week period; NSAID therapy was continued. Significantly more tramadol-treated patients completed the study. An average daily dosage of 245mg was significantly more effective than placebo in reducing the severity of pain at rest. In naproxen-responsive patients with painful osteoarthritis of the knee, the addition of tramadol 200mg/day allowed a significant reduction in NSAID dosage (by 78%) without compromising pain relief⁴⁰. Fifty eight percent were able to discontinue naproxen with the addition of tramadol.

Tramadol may have a role in treatment of **neuropathic pain** of diabetic or other origin and has been estimated to be similar in efficacy to tricyclic antidepressants in such conditions.⁴¹

Tramadol has been reported to be effective across a wide range of chronic pain conditions, including chronic pancreatitis, fibromyalgia, and scleroderma^{10, 17}. It should be noted, however, that controlled studies in chronic pain conditions have been of relatively short duration (4-8 weeks)⁴² and studies of longer-term use are required.

2.4 Indications other than analgesia

Case reports have been published which describe the use of tramadol (alone or in combination with antidepressants) for treatment of psychiatric disorders, including major depression^{43, 44}, Tourette's Syndrome⁴⁵, obsessive-compulsive disorder^{45, 46} and anorexia nervosa⁴⁷. While there is a theoretical basis for such use, no clinical trials in psychiatric indications have been published to date.

Tramadol in a dose of 1mg/kg appears to be more effective than pethidine 0.5mg/kg for the treatment of postoperative shivering, and is associated with fewer side-effects.⁴⁸

3. ADVERSE EFFECTS

The adverse effects of tramadol are similar to other opioids and include nausea, vomiting, constipation, headache, dizziness, dry mouth, sedation, asthenia, fatigue and sweating^{1, 49}. Less common effects include skin reactions and pruritus. Titrating the dose slowly may improve tolerability⁵⁰, and intra-operative loading may reduce post-operative nausea and vomiting⁵¹. With the exception of sweating, constipation and dry mouth, most adverse effects appear to decrease with prolonged use^{6, 52}.

Tramadol is unlikely to produce clinically relevant respiratory depression at recommended doses but respiratory depression may occur if recommended doses are exceeded¹². Bronchospasm has been noted with tramadol, but always with other implicated contributory factors⁵.

Tramadol appears to carry the same risk of urinary disorders (difficulty in micturition, urinary retention) as other opiates⁵³.

Seizures have been reported in patients taking tramadol at and above the recommended dose, particularly in the presence of other pro-convulsant drugs⁵. Data from the UK General Practice Research Database (1994-96) identified 17 cases of idiopathic seizures (11 definite, 6 possible) among the 10,916 patients treated with tramadol⁵⁴. The conclusion was that there was no increased risk of idiopathic incident seizures associated with exposure to tramadol alone. Nevertheless, tramadol should be avoided in epileptics and should be used with caution in patients on concomitant medications which lower seizure threshold, such as tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), major tranquillisers, fentanyl and especially pethidine.^{5, 16, 55, 56}

The abuse and/or dependence potential for tramadol is low, provided it is dosed within recommended ranges⁵⁷. However, reports of drug dependence and withdrawal have occurred¹⁶. Tramadol has very low affinity for opioid receptors (10 times less than codeine, 60 times less than propoxyphene and 6000 times less than that of morphine)¹². Low abuse potential has been confirmed in a randomised, double-blind, placebo-controlled, crossover trial comparing tramadol 75mg, 150mg and 300 mg with morphine 15mg and 30 mg and placebo in 12 volunteers who were previously registered drug addicts, but were currently non-opioid dependent⁵⁸. Effects were assessed on measures of subjective, behavioural and physiological response. The effects of tramadol 75mg and 150mg over 12 hours were not different from placebo. Although tramadol 300mg was identified as an opiate, it produced no other morphine like effects.

The opioid agonist and antagonist properties of tramadol were assessed in 6 male opioid dependent volunteers enrolled in a methadone maintenance program⁵⁹. Intramuscular tramadol 100mg and 300mg were compared with placebo in a double-blind fashion. Tramadol neither produced morphine-like effects, nor precipitated withdrawal signs and its effects were indistinguishable from placebo.

However, a number of case reports have been published which highlight the potential for dependence, abuse and withdrawal syndrome after long-term treatment^{57, 60-62}. Up until 2000, the FDA had received reports of 115 cases of patients developing abuse, dependence or withdrawal in association with tramadol use⁵⁷. Since marketing of tramadol in Australia, the Australian Drug Reaction Advisory Committee (ADRAC) has received 3 reports of drug withdrawal syndrome in association with tramadol. In all cases tramadol has been the sole suspected drug.

Although tolerance appears to develop to a much lesser extent with tramadol than with other opioids, tramadol does have weak dependence potential⁵. It should therefore be used with caution in at-risk patients¹¹.

3.1 Drug Interactions

Tramadol is contraindicated in patients who have taken monoamine oxidase inhibitors within the previous two weeks⁶³. Tramadol should be used with caution in combination with medications which lower seizure threshold.

A Serotonin Syndrome may occur with the concomitant administration of tramadol with selective serotonin reuptake inhibitors (SSRIs)⁶⁴⁻⁶⁷, moclobemide⁶⁸ (a reversible inhibitor of monoamine oxidase A), and the monoamine oxidase inhibitors iproniazid⁶⁹ (not available in Australia) or phenelzine⁷⁰. (Diagnosis of serotonin syndrome generally requires identification of at least three of the following clinical features⁷¹: mental status changes (confusion, hypomania), agitation, myoclonus, hyper-reflexia, diaphoresis, shivering, tremor, diarrhoea, incoordination and fever. This interaction is detailed further in a separate NSW TAG document⁷².) Tramadol should be used with caution in patients receiving any other serotonergic medications¹¹.

Concomitant administration of carbamazepine increases the metabolism of tramadol⁷. The interaction of tramadol with coumarin anticoagulants resulting in increased International Normalised Ratio (INR) has been reported⁷³, but not confirmed^{74, 75}.

Ondansetron has been reported to decrease the analgesic effectiveness of tramadol⁷⁶ and may not adequately prevent nausea associated with tramadol⁷⁷. The mechanism has been postulated to involve competition for CYP2D6 metabolism.⁷⁸

Tramadol is metabolised to M1 by the CYP2D6 isoenzyme of the cytochrome P-450 enzyme system. CYP2D6 metabolises a multitude of drugs including tricyclic anti-depressants, haloperidol, risperidone, flecainide, dextromethorphan and codeine⁷⁹. Drugs that selectively inhibit this isoenzyme (eg fluoxetine, paroxetine, quinidine, phenothiazines, antipsychotic agents) may cause increased concentrations of tramadol and decreased concentrations of M1¹. It has been suggested that this may result in reduced efficacy⁵, increased incidence of seizures⁸⁰ or manic symptoms⁸¹. The clinical significance of these interactions has not been fully investigated¹¹.

Concomitant administration of tramadol with cimetidine does not result in clinically significant changes in tramadol pharmacokinetics. Other drugs known to inhibit the CYP3A4 isoenzyme of P-450, such as ketoconazole and erythromycin, may inhibit the metabolism of tramadol and probably the metabolism of M1. Again, the clinical significance of this is unclear¹¹.

4. ECONOMIC ANALYSIS

A significant disadvantage of tramadol is its substantially higher acquisition cost compared with alternative analgesics⁴⁹. Duggan⁸² has argued that in comparison with morphine, acquisition costs for tramadol can be offset by a reduced need for treatments for constipation and a saving in nursing time otherwise spent on controlled (S8) drug activities. In his analysis, the total costs (in pounds Sterling) of treating postoperative pain with morphine (4 doses of 10mg) or tramadol (4 doses of 100mg) were £13.81 per patient per day for morphine and £10.99 per patient per day for tramadol. Cost items included drug acquisition, controlled drug activities, ward costs, anti-emetic treatment, escape analgesia and constipation treatment. Cost comparison with other agents was not reported. While the theoretical arguments appear reasonable, evidence of actual cost offsets in clinical practice was not provided.

Economic analysis in the Australian hospital environment has not been published. Simple costing on the basis of acquisition costs (price to NSW hospitals, September 2001) and typical daily dose schedules, provides the following comparative cost estimate:

Drug	Typical dosing schedule	Cost/day
Morphine	(10mg im/iv four times daily)	\$ 1.44
Codeine/paracetamol	(30mg/500mg oral four times daily)	\$ 0.19
Naproxen	(1000mg daily in divided doses)	\$ 0.30
Tramadol	(100mg im/iv four times daily)	\$ 5.96
Tramadol SR	(100mg oral twice daily)	\$ 0.91
Tramadol	(50mg oral four times daily)	\$ 0.64

A more accurate cost model would take account of a potential reduction in cost of constipation treatment with tramadol, although at an estimated hospital cost for laxatives of \$0.08 per day, offsets in drug costs are small. There may be a potential reduction in respiratory complications and NSAID-associated adverse events in some patients. However, cost models should also recognise the potential for additional anti-emetic treatment costs in many patients.

In the acute post-operative setting, tramadol may be used to replace codeine-based products, but these are typically associated with minimal gut effects in the short term and very few respiratory effects in the doses normally used.

Cost offsets because of reduced controlled drug activities are unlikely to be realised in most hospital situations, although there may be improved work flow in nursing units if recording is not required.

It is likely that widespread use of tramadol in the hospital setting would be associated with an overall increase in drug costs, with minimal benefits for the majority of patients.

5. RECOMMENDED INDICATIONS

On the basis of published evidence, tramadol appears to have reasonable dose related efficacy in comparison with other opioid analgesics, with a relative lack of respiratory depression, major organ toxicity or abuse potential¹⁶.

Because of its side-effect profile in comparison with other analgesics, tramadol may have a role in patients who are intolerant of conventional opioid and other non-opioid analgesics (such as those at risk of problematic constipation or biliary colic), those who have pre-existing cardiopulmonary disease (such as the elderly or obese), and those in whom codeine use is inappropriate.

In the acute and post-operative settings, because of its non-opioid analgesic effects, tramadol may have a particular place in multi-modal analgesia, where opioid and non-opioid drugs are given in combination to achieve analgesia, with a reduction in the incidence and severity of side effects⁸³.

Similarly, in chronic pain conditions, tramadol may be considered (as a single agent or in combination) where non-opioid analgesics have proven ineffective or where multimodal therapy might be advantageous in order to limit side-effects (eg where a reduction in NSAID dosage is desirable). The reduced constipating effect of tramadol compared with other opioids may be useful in patients with chronic cancer pain¹⁶, although nausea may be a dose-limiting side-effect¹⁷ and sustained-release morphine is more effective in severe cancer pain⁵. Because of its extended duration of effect, the sustained release formulation may provide convenience in ambulatory patients with chronic pain. However, studies of long-term use have not yet been reported and the potential for serious drug-drug interactions with tramadol should not be under-estimated.

As a single agent, tramadol's place in therapy is likely to be limited by both cost and tolerability (particularly nausea). In the majority of patients it offers few advantages at considerable additional cost. However, it may be a useful alternative to other analgesics in selected patients with moderate to severe pain.

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REFERENCES

1. CSL-Limited. Approved Product Information - Tramal, 1998.
2. Anonymous. Tramadol - a new oral analgesic. *Medical Letter on Drugs & Therapeutics*; 37:59-62.
3. Raffa RB, Nayak RK, Minn FL. The mechanism(s) of action and pharmacokinetics of tramadol hydrochloride. *Rev Contemp Pharmacother* 1995; 6:485-497.
4. Schnitzer TJ. Non-NSAID pharmacologic treatment options for management of chronic pain. *Am J Med* 1998; 105:45S-52S.
5. Bamigbade TA, Langford RM. The clinical use of tramadol hydrochloride. *Pain Reviews* 1998; 5:155-182.
6. 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; 14:157-164.
7. Lewis KS, Han NH. Tramadol: a new centrally acting analgesic. *Am J Health-Syst Pharm* 1997; 54:643-52.
8. Besson J-M, Vickers MD. Panel Discussion. In Proceedings of a satellite symposium associated with the 7th World Congress on pain. Paris, France 24 August 1993. *Drugs* 1994;

47:44-46.

9. Crighton IM, Martin PH, Hobbs GJ, Cobby TF, Fletcher AJP, Stewart PD. A comparison of the effects of intravenous tramadol, codeine, and morphine on gastric emptying in human volunteers. *Anesth Analg* 1998; 87:445-449.
10. Shipton EA. Tramadol - present and future. *Anaesth Intensive Care* 2000; 28:363-374.
11. CSL-Limited. Approved Product Information - Tramal SR. 2001.
12. 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; 46:313-340.
13. Budd K. Chronic Pain - Challenge and Response. *Drugs* 1994; 47:33-38.
14. Lehmann KA. Tramadol for the management of acute pain. *Drugs* 1994; 47:19-32.
15. Radbruch L, Grond S, Lehmann KA. A risk-benefit assessment of tramadol in the management of pain. *Drug Safety* 1996; 15:8-29.
16. Budd K, Langford R. Tramadol revisited (Editorial). *Brit J Anaesth* 1999; 82:493-95.
17. le Roux PJ, Coetzee JF. Tramadol today. *Current Opinion in Anesthesiology* 2000; 13:457-461.
18. Sunshine A. New clinical experience with tramadol. *Drugs* 1994; 47:8-18.
19. Moore RA, McQuay HJ. Single-patient data meta-analysis of 3453 postoperative patients: oral tramadol versus placebo, codeine and combination analgesics. *Pain* 1997; 69:287-294.
20. Houmes R-JM, Voets MA, Verkaaik A, Erdmann W, Lachmann B. Efficacy and safety of tramadol versus morphine for moderate and severe postoperative pain with special regard to respiratory depression. *Anesthesia and Analgesia* 1992; 74:510-514.
21. Vickers MD, Paravicini D. Comparison of tramadol with morphine for post-operative pain following abdominal surgery. *European Journal of Anaesthesiology* 1995; 13:265-271.
22. Gritti G, Verri M, Launo C, et al. Multicenter trial comparing tramadol and morphine for pain after abdominal surgery. *Drugs Exptl Clin Res* 1998; 24:9-16.
23. Scott LJ, Perry CM. Tramadol: a review of its use in perioperative pain. *Drugs* 2000; 60:139-176.
24. Vickers MD, O'Flaherty D, Szekely SM, Read M, Yoshizumi J. Tramadol: pain relief by an opioid without depression of respiration. *Anaesthesia* 1992; 47:291-296.
25. Ravishankar M, Parathasarathy S, Hemavarthy B, Saravanan P, Oumachigui A. Comparative evaluation of postoperative analgesia with tramadol and pethidine following caesarian section. *J Anaesth Clin Pharmacol* 1996; 12:125-128.
26. Colletti V, Carner M, Vincenzi A, al. e. Intramuscular tramadol versus ketorolac in the treatment of pain following nasal surgery: a controlled multicentre trial. *Curr Ther Res Clin Exp* 1998; 59:608-618.
27. Lanzetta A, Vizzardi M, Letizia G, al. e. Intramuscular tramadol versus ketorolac in patients with orthopedic and traumatologic postoperative pain: a comparative multicentre trial. *Curr Ther Res Clin Exp* 1998; 59:39-47.
28. Sunshine A, Olson NZ, Zigelboim I, DeCastro A, Minn FL. Analgesic oral efficacy of tramadol hydrochloride in postoperative pain. *Clin Pharmacol Ther* 1992; 61:740-746.
29. Stubhaug A, Grimstad J, Breivik 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 Reviews* 1995; 62:111-118.

30. Mehlish DR, Minn F, Brown P. Tramadol hydrochloride: efficacy compared to codeine sulphate, acetaminophen with dextropropoxyphene and placebo in dental extraction pain (Abstract), *Clin Pharmacol Ther*, 1990. Vol. 47.
31. Fricke JR, Minn F, Cunningham BD, Angelocci DL, Peteros-Nowak CA, al. e. Dose response in pain from oral surgery (Abstract). *Clin Pharmacol Ther* 1991; 49:182.
32. Viegas O, Khaw B, Ratnam S. Tramadol in labour pain in primiparous patients. A prospective comparative clinical trial. *European Journal of Obstetrics & Gynaecology and Reproductive Biology* 1993; 49:131-135.
33. Prasertsawat P, Herabutya Y, K C. Obstetric analgesia: comparison between tramadol, morphine and pethidine. *Curr Ther Res* 1986; 40:1022-1028.
34. Vergnion M, Degesves S, Gercet L, Mogatteaux V. Tramadol, an alternative to morphine for treating posttraumatic pain in the prehospital situation. *Anaesth Analg* 2001; 92:1543-1546.
35. Wilder-Smith CH, Schimke J, Osterwalder B, Senn HJ. Oral tramadol, a μ -opioid agonist and monoamine reuptake-blocker, and morphine for strong cancer-related pain. *Ann Oncol* 1994; 5:141-146.
36. Grond S, Radbruch L, Meuser T, Loick G, Sabatowski R, al. e. High-dose tramadol in comparison to low-dose morphine for cancer pain relief. *Journal of pain and Symptom Management* 1999; 18:174-179.
37. Rauck RL, Ruoff GE, McMillen JI. Comparison of tramadol and acetaminophen with codeine for long-term pain management in elderly patients. *Current Therapeutic Research* 1994; 55:1417-1431.
38. Muller FO, Odendaal CL, Muller FR, Raubenheimer J, Middle MV, al. e. Comparison of the efficacy and tolerability of a paracetamol/codeine fixed-dose combination with tramadol in patients with refractory chronic back pain. *Arzneimittelforschung(Drug Research)* 1998; 48:675-679.
39. Roth SH. Efficacy and safety of tramadol HCl in breakthrough musculoskeletal pain attributed to osteoarthritis. *J Rheumatol* 1998; 25:1358-1363.
40. Schnitzer MK, Olson WH. Tramadol allows reduction of naproxen dose among patients with naproxen-responsive osteoarthritis pain. *Arthritis and Rheumatism* 1999; 42:1370-1377.
41. Sindrup S, Jensen T. Pharmacologic treatment of pain in polyneuropathy. *Neurology* 2000; 55:915-920.
42. Katz WA. Pharmacology and clinical experience with tramadol in osteoarthritis. *Drugs* 1996; 52:39-47.
43. Shapira NA, Verduin ML, DeGraw JD. Treatment of refractory major depression with tramadol monotherapy (letter). *J Clin Psychiatry* 2001; 62:205-206.
44. Spencer C. The efficacy of intramuscular tramadol as a rapid-onset antidepressant. *Australian and New Zealand Journal of Psychiatry* 2000; 34:1032-1033.
45. Shapira NA, McConville BJ, Pagnucco ML, Norman AB, Keck PE. Novel use of tramadol hydrochloride in the treatment of Tourette's syndrome (letter). *J Clin Psychiatry* 1997; 58:174-175.
46. Goldsmith TD, Shapira NA, Keck PE. Rapid remission of OCD with tramadol hydrochloride. *Am J Psychiatry* 1999; 156:660-661.
47. Mendelson SD. Treatment of anorexia nervosa with tramadol (letter). *Am J Psychiatry* 2001; 158:963-964.

48. Bhatnagar S, Saxena A, Kannan TR, Junj J, Panigrahi M, Mishra S. Tramadol for postoperative shivering: a double-blind comparison with pethidine. *Anaesth Intensive Care* 2001; 29:149-154.
49. National Health and Medical Research Council. Acute pain management: scientific evidence: Commonwealth of Australia, 1999.
50. Ruoff GE. Slowing the initial titration rate of tramadol improves tolerability. *Pharmacotherapy* 1999; 19:88-93.
51. Pang WW, M.S. M, Huang S, Hung C-P, Huang M-H. Intraoperative loading attenuates nausea and vomiting of tramadol patient-controlled analgesia. *Can J Anesth* 2000; 47:968-973.
52. Wilder-Smith CH, Hill L, Spargo K, Kalla A. 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; 91:23-31.
53. Anonymous. Urinary disorders on tramadol. *Prescrire International* 2001; 10:152.
54. Jick H, Derby LE, Vasilakis C, Fife D. The risk of seizures associated with tramadol. *Pharmacotherapy* 1998; 18:607-611.
55. Buchanan N. Medications which may lower seizure threshold. *Australian Prescriber* 2001; 24:8-9.
56. Loadman J. Medications which may lower seizure threshold (letter). *Australian Prescriber* 2001; 24:51-52.
57. Leo RJ, Narendran R, DeGuiseppe B. Methadone detoxification of tramadol dependence. *Journal of Substance Abuse Treatment* 2000; 19:297-299.
58. Preston KL, Jasinski DR, Testa M. Abuse potential and pharmacological comparison of tramadol and morphine. *Drug and Alcohol Dependence* 1991; 27:7-17.
59. Cami J, Lamas X, Farre M. Acute effects of tramadol in methadone-maintained volunteers. *Drugs* 1994; 47:39-43.
60. Villamaman JCR, Blanco CA, Sanchez A, Carvajal A, Arias LM, Del Pozo JG. Withdrawal syndrome after long-term treatment with tramadol (letter). *British Journal of General Practice* 2000:406.
61. Thomas AN, Suresh M. Opiate withdrawal after tramadol and patient-controlled analgesia (letter). *Anaesthesia* 2000; 55:826-827.
62. Yates WR, Nguyen MD, Warnock JK. Tramadol dependence with no history of substance abuse. *Am J Psychiatry* 2001; 158:964.
63. Anonymous. Tramadol hydrochloride. *Australian Prescriber* 1998; 21:110.
64. Mason BJ, Blackburn KH. Possible serotonin syndrome associated with tramadol and sertraline coadministration. *Ann Pharmacother* 1997; 31:175-177.
65. Egberts ACG, ter Borgh J, Brodie-Meijer CCE. Serotonin syndrome attributed to tramadol addition to paroxetine therapy. *International Clinical Psychopharmacology* 1997; 12:181-182.
66. Lantz MS, Buchalter EN, Giambanco V. Serotonin syndrome following the administration of tramadol with paroxetine (letter). *International Journal of Geriatric Psychiatry* 1998; 13:343-345.
67. Kesevan S, Sobala GM. Serotonin syndrome with fluoxetine plus tramadol. *Journal of the Royal Society of Medicine* 1999; 92:474-475.

68. Hernandez AF, al. e. Fatal moclobemide overdose or death caused by serotonin syndrome? *J Forensic Sci* 1995; 40:128-130.
69. de Larquier A, al. e. [Serotonergic syndrome after combining tramadol and iproniazid (letter)]. *Therapie* 1999; 54:767-768.
70. Calvisi V, Anseau M. Mental confusion due to administration of tramadol in a patient treated by MAOI. *Revue Medicale de Liege* 1999; 54:912-913.
71. Sternbach H. The serotonin syndrome. *Am J Psychiatry* 1991; 148:705-713.
72. New South Wales Therapeutic Assessment Group. Tramadol Alert. TAGNet Bulletin. Sydney: NSW TAG, 2000.
73. Madsen H, Moller Rasmussen J, Broesen K. Interaction between tramadol and phenprocoumon. *Lancet*; 1997;350:637.
74. Boeijinga JK, van Meegan E, van den Ende R, Schook CE, Cohen AF. Is there interaction between tramadol and phenprocoumon. *Lancet* 1997; 350:1552.
75. Boeijinga JK, van Meegan E, van den Ende R, Schook CE, Cohen AF. Lack of interaction between tramadol and coumarins. *J Clin Pharmacol* 1998; 38:966-970.
76. De Witte JL, Schoenmaekers B, Sessler DI, Deloof T. The analgesic efficacy of tramadol is impaired by concurrent administration of ondansetron. *Anesth Analg* 2001; 92:1319-1321.
77. Broome IJ, Robb HM, Raj N, Girgis Y, Wardell GJ. The use of tramadol following day-case oral surgery. *Anaesthesia* 1999; 54:289-291.
78. Stamer U, Stuber F. Analgesic efficacy of tramadol if coadministered with ondansetron. *Anaesth Analg* 2001; 93:1623.
79. Richelson E. Pharmacokinetic interactions of antidepressants. *J Clin Psychiatry* 1998; 59:22-26.
80. Reus VI, Rawitscher L. Possible interaction of tramadol and antidepressants (letter). *Am J Psychiatry* 2000; 157:839.
81. Gonzalez-Pinto A, Imaz H, De Heredia JLP, Gutierrez M, Mico JA. Mania and tramadol-fluoxetine combination. *Am J Psychiatry* 2001; 158:964-965.
82. Duggan A. Pharmacoeconomic aspects of the use of tramadol hydrochloride. *Rev Contemp Pharmacother* 1995; 6:541-545.
83. Power I, Barratt S. Analgesic agents for the postoperative period: nonopioids. *Surgical Clinics of North America* 1999; 79:275-295.