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Pharmacology and Clinical Experience with Tramadol in Osteoarthritis

Warren A. Katz

University of Pennsylvania Health System, Presbyterian Medical Center, Philadelphia, Pennsylvania, USA

Summary

Tramadol is a centrally acting analgesic that has been shown to be effective in a variety of acute and chronic pain states. Unlike other centrally acting analgesics, it exerts a dual action by binding to the opioid receptor site in the central nervous system and by weakly inhibiting the reuptake of biogenic amines. Tramadol is rapidly and almost completely absorbed, with an onset of action occurring within 1 hour of oral administration. The recommended dosage is 50 to 100mg every 4 to 6 hours; however, regular administration is an alternative, particularly for chronic pain states such as osteoarthritis, where the use of the recently developed sustained release formulation may represent an important advantage. Published studies specifically evaluating the use of tramadol in this disease support its effectiveness. Nausea, drowsiness, constipation, dizziness, and sweating have been reported in association with tramadol use. Nausea occurs early in the course of administration, and may be reduced by slowly titrating the dose of tramadol against response. Tramadol would appear to be particularly useful in the elderly population affected by osteoarthritis because, unlike nonsteroidal anti-inflammatory drugs, it does not aggravate hypertension or congestive heart failure, nor does it have the potential to cause peptic ulcer disease. Compared with narcotics, tramadol does not induce significant respiratory depression, constipation, or have significant abuse potential.

The management of painful osteoarthritis calls for a comprehensive approach that may consist of pharmacological agents, physical medicine and rehabilitation, surgical intervention, minimally invasive techniques, patient education, and psychological support.[1] Pain is the common denominator for the majority of the estimated 18 million patients in the United States with this disease and is responsible for much of the associated disability. What percentage of patients with painful osteoarthritis seek medical care is not known, but a recent Harris poll indicated that 17% of the adult population in the US suffered from chronic pain.[2] Many (46%) had arthritis – osteoarthritis being the most common type of arthritis. Yet, the poll showed that approximately one-third of these felt that their pain caused work disability, and one-fifth were dissatisfied with pain medication.

Although optimal pain management is multidisciplinary, medications are the cornerstone of the therapeutic armamentarium in many patients. Analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), systemic or local corticosteroids, muscle relaxants, antidepressant drugs, anticonvulsants, and antihistamines are frequently used categories of drugs. Most acute and chronic musculoskeletal

pain is managed with analgesic agents ranging from weaker compounds containing aspirin or paracetamol to the reluctant use of strong narcotics such as codeine, morphine and pethidine, which is fraught with more common complications such as nausea, lightheadedness, sedation, and constipation. Addiction, dependence, tolerance and respiratory depression are less common but often adversely affect a physician's willingness to prescribe these drugs. Many physicians recommend paracetamol for mild pain because of its favourable benefit/risk ratio. A study by Bradley et al.[3] showed that the efficacy of paracetamol was equal to that of the NSAID, ibuprofen, in the treatment of osteoarthritis of the hip. Unquestionably, stronger narcotics are beneficial for relieving pain, but few physicians are willing to prescribe such drugs for chronic pain because of their adverse reactions. NSAIDs may be effective for mild to moderate musculoskeletal pain; yet, few pharmaceutical manufacturers have pursued indications other than osteoarthritis and rheumatoid arthritis for NSAIDs. Furthermore, there is growing concern about the high incidence of peptic ulcer disease caused by some NSAIDs, particularly when administered to the elderly.[4]

The availability of tramadol as an analgesic for the management of painful osteoarthritis represents a desirable therapeutic option.

1. Background

Grünenthal first introduced tramadol to the German market as a weak opioid in 1977,[5] and claimed that respiratory depression or other adverse effects associated with opioids were less pronounced with tramadol. Once released into the marketplace, the drug failed to become popular as an abuse agent.[6] Indeed, Keup[7] reported no significant abuse with tramadol, making it clearly different from other μ opioid receptor agonists. Tramadol has since been marketed in more than 70 countries, and over 40 million patients worldwide have used it. The drug has recently been marketed in the United States as Ultram®, for the management of moderate to moderately severe pain.

2. Mechanism of Action

Tramadol is a single-entity, centrally acting analgesic. Unlike other centrally acting analgesics such as codeine, hydrocodone, oxycodone, and morphine, tramadol has a dual mechanism of action at therapeutic doses. Like narcotics, tramadol binds to the μ opioid receptor site in the central nervous system, with a binding affinity 6000 times less than that of morphine. However, tramadol-mediated analgesia is only partially reduced by the opioid antagonist, naloxone, thus suggesting an important nonopioid mechanism of action.[8] It was subsequently appreciated that the known reuptake inhibitory effects on the monoamines noradrenaline (norepinephrine) and serotonin (5-hydroxytryptamine; 5-HT) contributed to the analgesic effects of tramadol by inhibiting pain transmission in the spinal cord.[9]

The drug is a racemic mixture; the (+) enantiomer has a weakly preferential effect at μ opioid receptors and in inhibiting the reuptake of serotonin, whereas the (–) enantiomer preferentially inhibits the reuptake of noradrenaline. These enantiomers act in a complementary and synergistic fashion to produce analgesia.[10] Mono-*O*-desmethyltramadol (M1), the one active metabolite of tramadol, has a greater opioid receptor affinity than the parent compound, but the contribution of the metabolite to the analgesic effect in humans appears minimal after a single oral dose. There are no studies that address the analgesic effect of multiple doses of M1, although there is no build-up of the compound with repeated doses (R.B. Raffa, personal communication).[11]

As noted above, tramadol has definite selectivity for the μ opioid receptor compared with the δ and κ opioid receptors. Codeine has 10 times greater affinity for the μ opioid receptor than tramadol. The reuptake inhibitory effects of tramadol on noradrenaline and serotonin are 100 to 1000 times weaker than those of imipramine.

3. Pharmacokinetics/ Pharmacodynamics

The pharmacokinetic profile of oral tramadol reflects its 75% bioavailability (rising to 100% with multiple administration), which is not significantly altered when the drug is administered with food.[11] Tramadol is rapidly and almost completely absorbed, with an onset of action occurring within 1 hour of oral administration. Peak serum concentrations are reached approximately 2 hours after administration, and steady-state concentrations are achieved within 2 days. Tramadol is only 20.2% bound to plasma proteins, so that drug interactions with highly protein-bound drugs would not be expected.[12,13] Tramadol is extensively metabolised by the liver; only the *O*-demethylated metabolite has pharmacological activity. The drug and its metabolites are eliminated primarily by the kidney (90%), with 30% of an oral dose excreted unchanged in the urine. The plasma terminal elimination half-life of tramadol is 6.3 hours after a single 100mg dose.[14]

Respiratory depression is uncommon with tramadol administration and has occurred only when the recommended dose has been considerably exceeded (overdose) or in conjunction with drugs that themselves depress respiration. In most studies there was no clinically significant change in heart rate or blood pressure.[15]

4. Dosage and Administration

The recommended tramadol dosage is 50 to 100mg every 4 to 6 hours, as needed.[16] Regular twice- and 3-times daily administration is an alternative, but the total daily dose should not exceed 400mg. Clinical experience has shown that initiating tramadol at a lower dosage for the first 2 or 3 days reduces the incidence of nausea (see below). Furthermore, regular administration seems to be more efficacious for the management of painful osteoarthritis (W.A. Katz, unpublished observations).

Elderly patients aged between 65 and 75 years may exhibit a prolonged elimination half-life compared with younger patients, and thus a slightly elevated serum tramadol concentration. Serum concentrations in patients aged more than 75 years may be further increased; therefore, in the US, it is recommended that the daily dose should not exceed 300mg in this population.[16]

Furthermore, tramadol should be administered with caution to patients with moderate to severe renal impairment.[16] In the US, the manufacturer recommends a tramadol dosage of 50 to 100mg every 12 hours. A standard tramadol dose can be administered to patients needing haemodialysis on the day of dialysis, because less than 7% of the total administered dose is removed during a 4-hour haemodialysis session. Similar warnings are given for patients with hepatic cirrhosis, because the terminal elimination half-life of tramadol increases by almost 3-fold in this population.[17]

5. Drug Interactions

As noted previously, since tramadol is minimally protein bound, it can be safely administered with highly protein-bound drugs such as anticoagulants and oral hypoglycaemic agents.[18] Coadministration of tramadol with cimetidine increases the terminal elimination half-life of tramadol; however, these changes are not clinically significant and do not necessitate an adjustment of the tramadol dose.[18]

Quinidine is a selective inhibitor of the isoenzyme cytochrome P450 2D6, which is responsible for the conversion of tramadol to its only active metabolite, *O*-desmethyltramadol. Yet, concomitant administration of oral tramadol and oral quinidine in humans had no effect on tramadol-induced analgesia.[8] This is in contrast to the situation with codeine, since codeine's analgesia is eliminated by the inhibition of its *O*-demethylation to morphine. Coadministration of carbamazepine resulted in a decrease in the half-life of tramadol.[18-20]

The effect of tramadol on the plasma concentration of monoamine oxidase (MAO) inhibitors has not been studied. Because tramadol inhibits the uptake of noradrenaline and serotonin, it should be used with caution in patients taking MAO inhibitors.[21] Indeed, according to the interna-

tional data sheets,[22] tramadol administration is contraindicated with concomitant MAO inhibitor use, or within 14 days of their discontinuation. Clinically, coadministration of tramadol with NSAIDs has produced additive analgesic effects, and in animal models clear synergy has been found between tramadol and a number of NSAIDs.[23]

6. Precautions

In contrast to traditional opioids, tramadol at the usual doses has rarely been associated with respiratory depression, but it should be administered cautiously in patients who are at risk.

7. Therapeutic Efficacy

In 1970, Sunshine and colleagues[24] reported the first clinical experience with tramadol in the US; 3 single dose levels of the drug (50, 100, or 150mg) were compared with dextropropoxyphene (65 or 130mg) and placebo in patients with postoperative fracture or musculoskeletal pain.[24] They determined that all active treatments were significantly superior to placebo and that tramadol at a dose of 150mg was significantly better than dextropropoxyphene. A follow-up study by Sunshine et al.[25] again compared the short term effect of tramadol at single doses of 75 and 150mg in various acute pain conditions. In a double-blind single dose study conducted in 161 patients with postcaesarean section pain, tramadol 75 and 150mg were found to be as effective as paracetamol 650mg plus dextropropoxyphene 100mg. Both treatments were superior to placebo. In a review of 17 other similar studies in patients with pain after surgery (n = 1594) or dental extraction (n = 1859), tramadol 100mg was the optimal single dose treatment for acute pain, and tramadol 50mg showed similar analgesic efficacy to that of codeine 60mg.[26]

Göbel and Stadler[27] reported the effect of tramadol on postherpetic neuralgia. 35 patients were randomised to treatment with either tramadol or clomipramine plus levomepromazine. The maximum daily dose of the former was 600mg, whereas the maximum dose of the latter was 100mg/100mg. 41.2% and 38.9% of patients in the tramadol and clomipramine plus levomepromazine groups, respectively, prematurely withdrew from the study. At the end of the 6-week study, 9 of 10 tramadol-treated patients and 6 of 11 control patients indicated satisfactory to excellent responses. This was the first study to show such effectiveness by a weak opioid in postherpetic neuralgia. The incidence of adverse effects of any kind was high in both groups, at 76.5% and 83.3%, respectively. Dry mouth was the most prevalent complaint in both groups.

A double-blind study comparing tramadol with paracetamol plus codeine in chronic nonmalignant pain revealed that tramadol provided analgesia comparable to that of the reference agents, although there were no statistically significant differences between the treatment groups.[28] Patients were instructed to take an initial dose of 2 capsules (i.e. tramadol 100mg or paracetamol 600mg/codeine 60mg) when they felt pain. The daily dose of tramadol did not significantly increase during the double-blind period when there was an option for increasing the dose, indicating that patients did not become tolerant to its analgesic effect. In these studies, there was little difference between the type of pain and the average daily dose of tramadol required, nor was there any significant increase in the dose for any particular pain state. These disorders included joint and connective tissue diseases, musculoskeletal diseases, and neuropathic diseases.

7.1 Experience in 'Breakthrough' Pain

The effect of tramadol in 42 patients with 'breakthrough' pain from osteoarthritis treated with NSAIDs has been evaluated. Half received the study drug for 14 days, the other half a placebo. 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 the pain at rest. The incidence of constipation, nausea, drowsiness, vertigo, and dizziness was greater in the study group,

but there were no serious adverse effects nor did tramadol affect laboratory values or blood pressure.[29]

Another recent study used a double-blind crossover design to compare the effect of tramadol 200mg/day and pentazocine 200mg/day in 40 patients with painful arthritis of the hip and/or knee, confirmed by radiological evidence. Total daily pain scores were lower for patients receiving tramadol than for those receiving pentazocine. Tramadol was more effective in terms of morning stiffness and the need for concomitant paracetamol. Overall preference scales indicated that 33% of patients rated tramadol as good or very good compared with 13% of controls. Changes in functional improvement were comparable in both the study and control groups. Compliance was better in the tramadol group: 68% of patients took at least 80% of their medication compared with 22% in the pentazocine group. The number of patients withdrawing from each group was similar. Nine patients taking tramadol withdrew because of a total of 24 adverse events, which included nausea (9), vomiting (5), dizziness (4), increased sweating (2), diarrhoea (2), headache (1), and increased salivation (1).[30]

Rousi and co-workers reported to the XIIth European Congress on Rheumatology in 1991 that, in 40 patients with osteoarthritis of the hip or knee, tramadol 50mg 3 times daily for 3 weeks was slightly more effective than dextropropoxyphene in relieving pain. The incidence of adverse effects, primarily opioid in nature, was similar in both the dextropropoxyphene and tramadol groups.[31]

In a randomised crossover clinical study of the analgesic efficacy and tolerability of tramadol versus diclofenac in 60 patients with osteoarthritis of the hip and/or knee, both drugs showed comparable efficacy after 4 weeks. The mean daily dose of tramadol was 164.8mg and that of diclofenac was 86.9mg. 20% of tramadol recipients reported adverse events compared with 3% of those receiving diclofenac; however, there were no serious adverse reactions in either group and both drugs were equally preferred by the same number of patients.[32]

7.2 Postmarketing Experience

In a phase IV postmarketing surveillance study in 13 802 patients with pain of various origins and with many formulations being used, Cossmann and Wilsmann[33-35] showed that a mean daily tramadol dose of 160mg (maximum total dose of 400mg) for up to 4 weeks produced overall 'satisfactory' pain relief in approximately 86% of patients. In this group, patients with contusions or crush injuries experienced the greatest relief (93.5% of patients), whereas patients complaining of headache/ migraine experienced the least effect (93% of patients). 82% of patients with rheumatic pain obtained a satisfactory analgesic effect. Numerous other studies have attested to the analgesic effect of tramadol in acute and chronic painful conditions.[36]

Uncontrolled clinical postmarketing experience in 32 patients with osteoarthritis of the hip, knee, or neck indicates that the majority of patients respond well to tramadol and that many responders become asymptomatic (W.A. Katz, personal observations). Tramadol can be effectively substituted for NSAIDs in some patients with osteoarthritis, apparently because the degree of inflammation is not great. Ortho-McNeil is currently analysing the results of a double-blind study of 293 patients with hip or knee osteoarthritis treated with ibuprofen 1200 to 2400mg, or tramadol 200 to 400mg daily. Both drugs demonstrated equivalent efficacy. The author has also observed that in 11 other patients tramadol was able to effectively replace an NSAID. Three of these patients could not tolerate most NSAIDs but did respond to and could tolerate tramadol. Some patients prefer to remain on both NSAIDs and tramadol for maximum pain relief. The issue of how long an analgesic such as tramadol can be administered to patients with chronic painful osteoarthritis has not been resolved.

8. Tolerability and Safety

In a study by Cossmann and Wilsmann,[35] adverse effects spontaneously reported by the patient

Table I. Incidence of adverse events of tramadol (> 0.1%) from controlled (C) and uncontrolled (UC) clinical trials and postmarketing surveillance (PMS) studies. Numbers of patients are given in parentheses. (From Cossmann & Kohnen.[38] Reprinted with permission.)

Adverse event	Acute administration							Multiple dose administration						
	C IV (759)	C IM (546)	UC IV/IM (678)	C PCA (140)	C oral (352)	PMS inj (3536)	total acute (6011)	UC all (1283)	C oral (799)	PMS all (7198)	PMS all (3068)	PMS all (2863)	total multiple (15 211)	**total (21 222)**
Nausea	16.2	17.8	4.1	20.7	3.1	4.2	7.3	4.8	21.4	5.5	5.4	2.3	5.6	**6.1**
Dizziness	3.2	2.9	0.7	6.4	1.7	4.4	3.6	0.9	18.7	5.4	4.8	2.6	5.1	**4.6**
Drowsiness	3.6	10.3	2.2		0.3		1.7	15.5	8.5	1.8		0.7	2.7	**2.4**
Tiredness/fatigue	6.9	3.3			5.7	1.9	2.6		5.9	2.1	3.3	0.8	2.1	**2.3**
Sweating	3.6	4.6	1.9	15.0	1.1	0.8	2.0	8.2	7.6	1.0	1.0	0.2	1.8	**1.9**
Vomiting	6.2	7.0	1.8	11.4	2.6	0.5	2.4	1.6	9.6	0.8	1.0	1.4	1.5	**1.7**
Dry mouth	2.8	1.3		14.3	3.1	0.7	1.4	0.3	4.3	2.2	1.2	0.03	1.5	**1.6**
Somnolence	0.4			0.7		1.1	0.8		5.9		1.4	0.2	0.6	**0.7**
Hypotension, postural	0.5	0.2	0.7		0.3	1.7	1.2			0.1	1.3		0.3	**0.6**
Flushing	1.8				0.3	0.03	0.3	5.9	0.4	0.1	0.03		0.6	**0.6**
Headache	0.1	2.9	0.3	8.6	1.4	0.2	0.7		5.3	0.1	0.3	0.1	0.4	**0.6**
Stomach upset		0.2					0.02			1.0	0.6	0.3	0.6	**0.6**
Constipation						0.03	0.02	1.3	1.9	0.3	0.1	0.2	0.4	**0.3**
Nausea and vomiting	3.2	3.1	0.3	5.0	1.4		0.9							**0.3**
Sedation			4.1	2.9			0.5							**0.2**
Circulatory failure	0.1						0.02			0.3		0.3	0.2	**0.2**
Sleep disorder								1.9		0.04	0.03		0.2	**0.1**
Pruritus	0.1			0.7			0.03		1.8	0.1	0.1	0.03	0.2	**0.1**
Abdominal pain	0.1	0.4					0.1		1.5	0.2		0.03	0.2	**0.1**
Diarrhoea								0.6	1.4	0.1			0.2	**0.1**
Tachycardia	1.3						0.2	0.5	0.1	0.1			0.1	**0.1**
Local irritation								1.6					0.1	**0.1**

Abbreviations: all = all dose formulations; IM = intramuscular; inj = injection; IV = intravenous; PCA = patient-controlled analgesia.

or observed by the physician were recorded. Tramadol administered at dosages of up to 400mg daily produced adverse effects in 15.3% of patients, and these mainly corresponded to adverse effects known to occur with opioids. Unspecified central nervous system irritation (dizziness and trembling) occurred in 6.54%. Nausea was reported in 4.54% of patients; however, the incidence of nausea in other studies has been greater.[35] Other adverse reactions were uncommon. Euphoria occurred extremely infrequently (0.09%).

No significant changes were noted in clinical laboratory values, electrocardiograms, ophthalmological examinations, blood pressure, pulse rate, or physical examinations. Seizures have been reported uncommonly in patients receiving tramadol, but a relationship to dose is not apparent.[37] Furthermore, the administration of tramadol may enhance the risk of seizure in patients taking MAO inhibitors, neuroleptics, and drugs that reduce the seizure threshold.

A more recent review by Cossmann and Kohnen[38] examines the tolerability of tramadol in more than 21 000 patients in all clinical trials involving tramadol (controlled and uncontrolled, short term and multiple dose). Table I summarises the overall incidence of adverse events and reactions associated with tramadol in clinical and postmarketing surveillance studies.

Dalgin[39] recently reported that, during the first 30 days of treatment with tramadol in 554 patients, the incidence of dizziness (6.8%), nausea (10.3%), constipation (6.8%) or somnolence (6.0%) was not appreciably different from that with paracetamol plus codeine or aspirin plus codeine; however, with all drug regimens there was a trend towards accu-

mulative adverse effects for up to 90 days.[39] 24% of patients receiving tramadol discontinued the drug because of an adverse event, whereas 9.6% of patients receiving paracetamol plus codeine as well as 18.5% of the patients taking aspirin plus codeine dropped out of the study. In 53% of tramadol-treated patients, drug withdrawal occurred within the first week.[39] The package insert for tramadol provides the following incidence of adverse reactions for up to 90 days (this 90-day period applies only to the US data sheet) of therapy: dizziness/ vertigo (33%), nausea (40%), constipation (40%), headache (22%), vomiting (17%), pruritus (11%), CNS stimulation (14%), asthenia (12%), sweating (9%), dyspepsia (12%), dry mouth (10%), and diarrhoea (10%).

9. Addiction, Tolerance, and Dependence

There has been little evidence of tramadol abuse in the European experience.[7] Tramadol produces effects similar to those of an opioid, yet the development of tolerance has been reported to be relatively mild, and symptoms of withdrawal, when present, are not considered to be as severe as those produced by other opioids. In several studies in animals, tolerance to the analgesic effect of tramadol after repeated administration was minimal and less than that produced by morphine.[39] In humans, there was no difference between tramadol and placebo with regard to abuse potential and euphoric or dysphoric effects.[6,41,42]

The data collected by the Substance Abuse Warning System in Germany indicate that over a 14-year period tramadol was abused less often than dihydrocodeine, codeine, or tilidine/naloxone, but more often than dextropropoxyphene.[7] However, when the number of abuse reports was compared with the amount of drug prescribed, there were 0.23 abuse reports per million single dose units for tramadol, 10 for dihydrocodeine, 7.9 for codeine phosphate, 0.59 for tilidine/naloxone, and 0.38 for dextropropoxyphene.

10. The Role of Tramadol in the Management of Osteoarthritis

Until now, there has been little research to support the use of alternatives to NSAIDs in the treatment of osteoarthritis.[43] These drugs have been the mainstay of most treatment regimens, despite the lack of a clear-cut role of inflammation in osteoarthritis. The federal Food and Drug Administration (FDA) has demanded that, before marketing of NSAIDs for osteoarthritis can be approved, these agents must first satisfy rigorous double-blind studies, always in comparison with aspirin. Little attention was paid to drugs of equal efficacy. Brandt[43] and others have been sceptical about the use of NSAIDs as first-line therapy in osteoarthritis for several reasons, including the following:

- There is no evidence that they are more effective than certain pure analgesics.[44] The most widely quoted study is that of Bradley et al.[3] This group randomised 184 patients with osteoarthritis of the knee into the 3 following treatment groups for 4 weeks: a) paracetamol 4000mg daily; b) ibuprofen 1200mg daily; c) ibuprofen 2400mg daily. There were no differences in pain relief or anti-inflammatory effect between the paracetamol and NSAID groups.
- NSAID groups are only partially effective. Todd and Clissold[45] report a 30% reduction in pain and a 15% improvement in function.
- The correlation between joint pain and synovitis is poor.[46]
- Adverse reactions are associated with the administration of NSAIDs for all conditions, but their use in the elderly population is particularly dangerous.[4,47]

Accordingly, there is a recent trend towards the use of pure analgesics as first-line treatment of painful osteoarthritis. The American College of Rheumatology recommends a multidisciplinary approach for the treatment of osteoarthritis of the hip and knee consisting of 'patient education, physical and occupational medicine, other non-pharmacological modalities, and drug therapy with a nonopioid oral analgesic'. 'Opioid analgesics, such as propoxyphene, codeine, or oxycodone

should be avoided for long term use...' because of their abuse potential.[48,49] Paracetamol is a reasonable first-line approach because of the excellent benefit/risk/cost ratio. If low dose intermittent ibuprofen, in over-the-counter dosages, can be used with good pain relief, then there is no good reason to use tramadol. However, if ibuprofen is not sufficiently efficacious, or produces adverse effects, or if the patient has a relative or absolute contraindication, then tramadol can be used, especially if the patient has failed to respond to paracetamol. In that most patients with osteoarthritis are older than 60 years, NSAIDs pose particular problems of increased gastrointestinal complications, aggravation of hypertension, and precipitation of congestive heart failure because of fluid retention. Tramadol is without these adverse effects. The low incidence of abuse potential in the elderly would further support the role of tramadol in osteoarthritis.

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Correspondence and reprints: Dr *W.A. Katz*, University of Pennsylvania Health Systems, 38th and Market Streets, Philadelphia, PA19104, USA.