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Tramadol/Paracetamol

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Contents

Abstract

▲ The orally administered fixed combination tablet of tramadol (centrally-acting opiate) plus paracetamol (acetaminophen; nonopiate, nonsalicylate analgesic) [37.5/325mg] provides effective analgesia in patients with moderate to severe acute pain and those with chronic painful conditions characterised by intermittent exacerbations of pain.

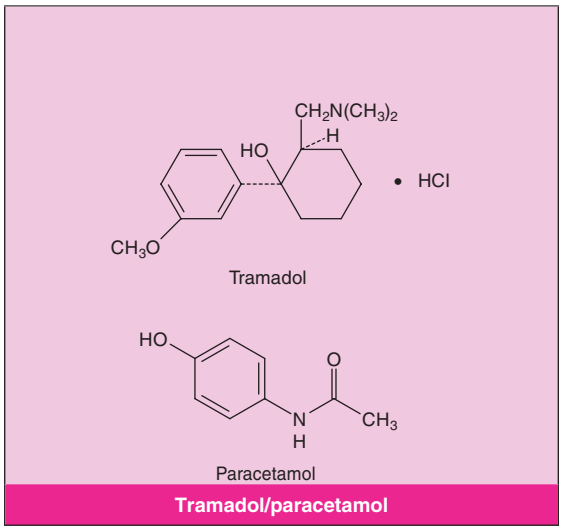
▲ Two tramadol/paracetamol 37.5/325mg tablets provided greater relief of dental pain over an 8-hour period than either agent alone, with a faster onset of action than tramadol alone and a longer duration of action than either agent as monotherapy.

▲ In patients with postoperative dental pain, two tramadol/paracetamol tablets (37.5/325mg) provided similar analgesia to hydrocodone/paracetamol 10/650mg over an 8-hour period.

▲ The addition of one or two tramadol/paracetamol 37.5/325mg tablets (up to four times daily) for 5 days to existing NSAID or cyclo-oxygenase-2 inhibitor analgesic therapy provided effective pain relief in patients with osteoarthritis flare pain.

▲ Tramadol/paracetamol 37.5/325mg provided similar efficacy to that of codeine/paracetamol 30/300mg in patients with chronic back pain in a 4-week, randomised, double-blind trial (a maximum of 10 tablets or capsules per day of the active drug).

Features and properties of tramadol/paracetamol (Ultracet™; Zaldiar®)	
Indications	
Symptomatic treatment of moderate to severe pain	
Mechanism of action	
Analgesic	Centrally acting opiate (tramadol) and non-opiate, non-salicylate analgesic (paracetamol)
Dosage and administration (Europe)	
Dosage	Initially two tablets of 37.5/325mg. Additional tablets as required
Route of administration	Oral
Frequency of administration	Dosage interval should not be <6 hours (maximum of 8 tablets/day)
Pharmacokinetic profile of tramadol and paracetamol after oral administration of tramadol 112.5mg plus paracetamol 975mg	
Peak plasma concentration	148 μg/L [(+)-tramadol]; 132 μg/L [(−)-tramadol]; 12.3 μg/mL (paracetamol)
Time to peak plasma concentration	2h (tramadol); 1h (paracetamol)
Plasma elimination half-life	5.8h [(+)-tramadol]; 5.2h [(−)-tramadol]; 2.8h (paracetamol)
Adverse events	
Most frequent (incidence ≥5%)	Somnolence, nausea, dizziness, constipation, headache, vomiting, diarrhoea, dry mouth, fatigue, dyspepsia



Management of acute and chronic pain is important, not only for the patient's well-being, but also to prevent long-term complications and morbidity.[1-4] Furthermore, acute pain may rapidly evolve into chronic pain if left untreated, with preclinical studies indicating that the expression of genes associated with neuronal remodelling and sensitisation to pain occurs within 20 minutes of injury.[1,2]

The response to nociceptor sensory input is a multifactorial process, with both central and peripheral mechanisms involved.[2] Several neurotransmitters and receptors participate in the transmission and modulation of this multifaceted process and thus, it is often difficult to achieve complete pain control using a single pharmacological agent without significant adverse events.[2] Hence, combining two analgesic agents with complementary mechanisms of action may enhance analgesia and at the same time reduce the risk of adverse events.[5] Furthermore, the ease of taking two analgesic agents as a fixed tablet may improve compliance.[5]

Tramadol and paracetamol (acetaminophen) are two analgesics that have shown efficacy in widespread clinical use.[6,7] A fixed-dose oral combination of tramadol 37.5mg and paracetamol 325mg (Ultracet™[1]; Zaldiar®), the focus of this review, is now available for the treatment of patients with acute pain and chronic painful conditions.

1. Pharmacodynamic Profile

The pharmacodynamic effects of tramadol and paracetamol monotherapy have been reported in depth previously,[6,7] but few studies have examined the pharmacodynamic effects of the two drugs when administered together. This section provides a brief overview of the mechanism of action of each drug, and a review of the findings of a pharmacodynamic study of the two drugs when coadministered.

- Tramadol is a synthetic, centrally-acting opioid analgesic that is a racemic mixture of two enantiomers that have two distinct, but complementary, mechanisms of action: the drug binds weakly to μ-opioid receptors and also inhibits reuptake of noradrenaline (norepinephrine) and serotonin within pain pathways of the CNS.[6,8] The affinity of tramadol for the μ-receptor is approximately 6000 times weaker than that of morphine and 10 times weaker than that of codeine.[6]
- The *O*-desmethyl metabolite (M1) of tramadol contributes to the opioid component of tramadol-induced analgesia, having an approximately 200-fold higher affinity for opioid receptors than the parent compound.[6] Individuals deficient in cytochrome P450 (CYP) 2D6 (the enzyme responsible for the *O*-desmethylation of tramadol), i.e. poor metabolisers, have shown reduced levels of analgesia after administration of the parent drug.[6]
- Paracetamol is a nonopiate, nonsalicylate analgesic.[7] Its mechanism of action is not clear but it appears to act centrally by inhibiting *N*-methyl-D-aspartate (NMDA)- or substance P-mediated nitric oxide synthesis.[9] It may also inhibit the release of prostaglandin E_2 in the CNS.[10]
- The addition of paracetamol to tramadol caused synergistic analgesia within a specified range of dose ratios in virus-free, CD-1® mice (18–24g; Charles River Laboratories).[11] For dose ratios similar to that in the fixed-dose combination (tramadol:paracetamol 1 : 8.67), the effects were

1 Use of tradenames is for identification purposes only and does not imply endorsement.

additive (dose ratio 1 : 5.7) or significantly synergistic (dose ratio 1 : 19; $p < 0.05$).

2. Pharmacokinetic Profile

The pharmacokinetic properties of tramadol and paracetamol monotherapies have been widely reported.[6,7] Therefore, this section only presents pharmacokinetic data regarding combination therapy; in particular, how the pharmacokinetic properties of each agent are affected by coadministration of the other.

- Coadministration of tramadol 112.5mg and paracetamol 975mg had no effects on the single-dose pharmacokinetics of the individual agents in a 3-way crossover study involving 24 healthy volunteers.[12] After oral administration of combination therapy, maximum plasma levels of (+)-tramadol, (−)-tramadol and paracetamol (148 μg/L, 132 μg/L and 12.3 μg/mL, respectively) were reached in approximately 2, 2 and 1 hour. Plasma elimination half-lives of the respective agents were 5.8, 5.2 and 2.8 hours. No significant differences in the pharmacokinetics of (+)- or (−)-tramadol, M1 or paracetamol were reported after combination therapy versus monotherapy.
- After repeated administration of oral tramadol/paracetamol 37.5/325mg to steady state in healthy volunteers, the bioavailabilities of tramadol and M1 were lower than those reported after monotherapy but the bioavailability of paracetamol was unchanged.[13] The area under the plasma concentration-time curve values for (+)-tramadol, (−)-tramadol, (+)-M1 and (−)-M1 were reduced by 14%, 10.4%, 11.9% and 24.2%, respectively, compared with those after tramadol monotherapy. The plasma elimination half-life of racemic tramadol increased to between 7 and 9 hours after multiple dose administration.[13]

Special Patient Populations

- Evaluation of four pharmacokinetic studies in 84 healthy volunteers showed that after coadministration of tramadol and paracetamol, bodyweight was the most important determinant of paracetamol clearance and volume of distribution.[14] Gender had no significant impact on paracetamol clearance, or on the pharmacokinetics of tramadol and M1. In poor CYP 2D6 metabolisers, tramadol clearance was slightly reduced and M1 formation was reduced by 70%.
- The pharmacokinetics of tramadol/paracetamol have not been studied in patients with renal or hepatic dysfunction or in children.[13] Based on the pharmacokinetics of tramadol and/or paracetamol, the fixed combination tablet is not recommended in patients with severe renal impairment (creatinine clearance < 0.6 L/h [<10 mL/min]) or those with severe hepatic impairment.[13,15] In those with moderate renal dysfunction (creatinine clearance 0.6–1.8 L/h [10–30 mL/min]), the dosage interval should be increased to 12 hours.[15]

3. Therapeutic Efficacy

Single-Dose Treatment of Dental Pain

Most of the therapeutic trials of tramadol/paracetamol conducted to date have used the dental pain model (pain after removal of impacted third molars), a useful clinical model[16] for the evaluation of oral analgesics in the treatment of acute pain. In studies of dental pain reported in this section, baseline pain was assessed using a visual analogue scale. Likert scales were used to assess pain relief (rated from 0 = no relief to 4 = complete relief) and pain intensity (rated from 0 = none to 3 = severe) during the study, starting 30 minutes after drug administration and repeated hourly for up to 8 hours.

- Two tablets of tramadol/paracetamol (total dose 75/650mg) provided faster analgesia than tramadol 75mg alone and longer lasting pain relief than monotherapy in a meta-analysis of three single-dose studies involving 1197 patients with moderate or severe postoperative dental pain.[17] The estimated times to onset of pain relief with tramadol/paracetamol, tramadol or paracetamol 650mg were 17 minutes (95% CI 15–20 minutes), 51 minutes (95% CI 40–70 minutes) and 18 minutes (95% CI 16–21 minutes), respectively; corresponding values for the duration of analgesia (time to remedication) were 5.03, 2.03 and 3.05 hours.

• In addition, total pain relief over 8 hours (TOTPAR8) with tramadol/paracetamol (mean score 12.1) was greater than that reported with tramadol (6.7), paracetamol (8.6) or placebo (3.3) [all $p \leq 0.0001$] and similar to that with ibuprofen 400mg (13.6) in this meta-analysis.[17] Tramadol/paracetamol recipients also showed significantly greater improvements in mean pain intensity score over 8 hours than those receiving tramadol or paracetamol monotherapy (mean score 4.7, 0.9 and 2.7, respectively; $p \leq 0.0004$ for both comparators vs tramadol/paracetamol).

• A second meta-analysis evaluating seven single-dose studies, five of which assessed dental pain, has also shown that tramadol/paracetamol 75/650mg provides more effective analgesia than either agent alone in patients with moderate to severe post-operative dental pain.[18] A total of 1376 patients were observed over an 8-hour period after drug administration. Using 'number-needed-to-treat' (NNT) calculations (i.e. the number of patients needed to be treated for one patient to obtain ≥50% pain relief compared with placebo), tramadol/paracetamol 75/650mg was shown to be more effective over an 8-hour period than either tramadol 75mg or paracetamol 650mg alone (NNT 2.9 vs 10 and 4.4, respectively). Similar between-group differences favouring the combination tablet were found for pain intensity (NNT 3.9 vs 8.0 and 6.3).

• Two tramadol/paracetamol 37.5/325mg tablets provided similar analgesia to that with one hydrocodone/paracetamol 10/650mg tablet for up to 8 hours after tooth extraction in a randomised, double-blind study in 200 patients.[19] Patients in both treatment groups reported significantly greater pain relief compared with placebo ($p < 0.05$) for all time intervals up to 8 hours post-dose (figure 1). The median time to onset of pain relief with two tramadol/paracetamol tablets was slower than that of hydrocodone/paracetamol (34 vs 25.4 minutes); there were no significant between-group differences with regard to duration or intensity of pain relief, or the need for supplemental analgesia.[19] Patients with moderate to severe pain after extraction of ≥2 impacted third molars received either one or two tramadol/paracetamol 37.5/325mg tablets, one hydrocodone/paracetamol 10/650mg tablet, or placebo (n = 50 patients per group).

Short-Term Treatment of Chronic Pain

• The addition of tramadol/paracetamol to existing NSAID or cyclo-oxygenase (COX)-2 inhibitor therapy was more effective than placebo in the treatment of osteoarthritis flare pain.[20] Add-on tramadol/paracetamol therapy resulted in significantly lower average daily pain intensity scores (1.4 vs 1.7; $p < 0.001$) and significantly higher average daily pain relief score (2.1 vs 1.7; $p < 0.001$) compared with add-on placebo. In this randomised, double-blind, multicentre study, patients who reported flare pain despite ongoing treatment with either an NSAID or a COX-2 inhibitor were randomised to receive additional tramadol/paracetamol 37.5/325mg or 75/650mg (n = 197) or placebo (n = 111) up to four times daily for 10 days. Primary efficacy endpoints were average daily pain intensity (assessed on a 4-point scale from 0 = none to 3 = severe) and

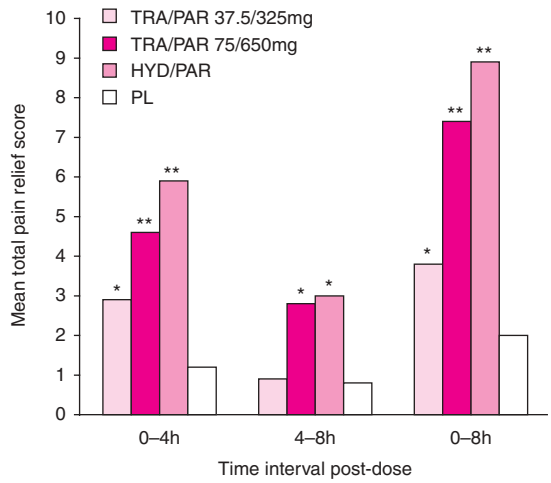


Fig. 1. Comparative analgesic efficacy of single-dose tramadol/paracetamol (TRA/PAR) and hydrocodone/paracetamol (HYD/PAR) in patients with moderate to severe dental pain. In a randomised, double-blind study, patients received one (n = 50) or two (n = 50) TRA/PAR 37.5/325mg tablets, one HYD/PAR 10/650mg tablet (n = 50) or placebo (PL; n = 50).[19] Pain relief, rated on a 5-point scale (0 = no relief to 4 = complete relief), was assessed 30 minutes after drug administration and then hourly for 8 hours so that, after 8 hours, the total score ranged from 0 (no relief) to 32 (complete relief). * $p < 0.05$, ** $p < 0.001$ vs placebo.

average daily pain relief (assessed on a 6-point scale from –1 = worse to 4 = complete), calculated for days 1 through 5.

● Furthermore, tramadol/paracetamol also provided better efficacy than placebo in elderly patients (≥65 years of age) in this double-blind study, according to a subgroup analysis.[21] Average pain intensity scores and average pain relief scores were significantly improved in the tramadol/paracetamol group (n = 69) relative to the placebo group (n = 44) at day 5 and 10 (no data reported in abstract; all $p < 0.05$). Health-related quality of life (HRQOL), as assessed using the self-administered, disease-specific Western Ontario and McMasters Universities Osteoarthritis (WOMAC) Index, also significantly improved in the overall, pain and physical functioning categories with tramadol/paracetamol versus placebo (no data reported in abstract; all $p < 0.05$).[21]

● Ten days' treatment with tramadol/paracetamol provided similar analgesia to tramadol monotherapy in patients with subacute back pain, according to the global assessment of patient satisfaction (no data reported in abstract).[22] In this 10-day, randomised, double-blind, multicentre trial patients received tramadol/paracetamol 37.5/325mg (n = 59) or tramadol 50mg (n = 60), with the dosage titrated as required up to a maximum of eight tablets/capsules per day.[15,22] There were no between-group differences in baseline demographics.[22]

Longer-Term Treatment of Chronic Pain

● Tramadol/paracetamol tablets provided similar analgesic efficacy to codeine/paracetamol capsules in patients with chronic nonmalignant lower back pain and/or osteoarthritis pain in a 4-week, randomised, double-blind, double-dummy, multicentre trial.[23] There were no differences between treatment groups in analgesic efficacy in terms of mean scores for TOTPAR6, the sum of pain intensity differences over the 6-hour study period and the sum of pain relief plus pain intensity differences over the 6-hour study period, with scores at study end illustrated in figure 2.

● In this double-blind trial, patients received tramadol/paracetamol 37.5/325mg (n = 309) or codeine/paracetamol 30/300mg (n = 153) for 4 weeks.[23] Patients took one or two tablets plus the same number of capsules every 4–6 hours as required, up to a maximum of 10 tablets and 10 capsules per day. Pain relief was rated on a 5-point scale (0 = no relief to 4 = complete relief) after 30 minutes and then hourly for 6 hours, with pain intensity assessed on a 4-point scale (0 = no pain to 3 = severe pain) for the same period. Mean overall efficacy scores, assessed using a 5-point scale (1 = poor to 5 = excellent), were also similar in both treatment groups at 4 weeks, as evaluated by patients (mean score 2.9 in both groups) and investigators (3 vs 2.9 in the codeine/paracetamol group).[23]

● A 23-month nonblind extension (n = 154) of this 4-week, double-blind trial indicated that overall efficacy was maintained for up to 2 years with tramadol/paracetamol, with 39% and 40% of patients and investigators rating efficacy as "very good" or "excellent" at 24 months' follow-up.[24] Mean maximum pain relief scores remained constant throughout the 2-year study period (range 2.2–2.7). The average daily dosage of tramadol/paracetamol re-

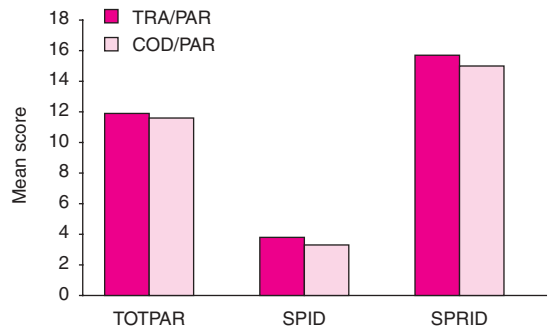


Fig. 2. Comparative analgesic efficacy of tramadol/paracetamol (TRA/PAR) versus codeine/paracetamol (COD/PAR) at 4 weeks. Adult patients with chronic nonmalignant lower back pain and/or osteoarthritis pain received tramadol/paracetamol 37.5/325mg (n = 309) or codeine/paracetamol 30/300mg (n = 153) for 4 weeks in a randomised, double-blind, double-dummy, multicentre trial.[23] Recipients took one or two tablets plus the same number of capsules every 4–6 hours as required, up to a maximum of 10 tablets and 10 capsules per day. Pain relief was rated on a 5-point scale (0 = no relief to 4 = complete relief) after 30 minutes and then hourly for 6 hours, with pain intensity assessed on a 4-point scale (0 = no pain to 3 = severe pain) for the same period. **SPID** = sum of pain intensity differences over 6 hours; **SPRID** = sum of pain relief plus pain intensity differences over 6 hours; **TOTPAR** = total pain relief over 6 hours.

mained constant from 13 weeks onward (between 4.9 and 5.2 tablets), with average daily dosages (251/2178 mg/day) markedly below the maximum dosages permitted.[24]

- As add-on therapy with a COX-2 inhibitor or NSAID, tramadol/paracetamol provided better pain relief than placebo in patients with osteoarthritis pain in a 91-day, randomised, double-blind, multicentre study [available as an abstract].[25] Mean visual analogue pain scores (primary endpoint) were significantly lower in the tramadol/paracetamol group than those in the placebo group (41.5 vs 48.3mm; $p = 0.025$) at study end.[25] Outpatients (mean age 61 years) with inadequately controlled pain of the knee or hip (pain score of ≥50mm on a visual analogue scale), despite treatment for at least 2 weeks with rofecoxib or celecoxib, received add-on therapy with tramadol/paracetamol 37.5/325mg (n = 153) or placebo (n = 153). The dosage was titrated every 3 days by one tablet per day up to a total of four tablets per day on day 10 (maximum of eight tablets/day).

- In two further 3-month, randomised, double-blind, placebo-controlled trials in patients with fibromyalgia[26] or chronic lower back pain,[27] tramadol/paracetamol provided better efficacy than placebo (available as abstracts). In this latter study, tramadol/paracetamol also provided greater improvements in HRQOL (secondary endpoint) than placebo.[27] HRQOL was assessed using the Roland Disability Questionnaire (RDQ), Short-form McGill Pain Questionnaire (SF-MPQ) and Short-form 36 Health Survey (SF36). Scores for the sensory component, present pain index and total score categories of the SF-MPQ, those for physical functioning, bodily pain, mental health and physical component summary of the SF36 and overall scores for the RDQ were all significantly ($p < 0.05$) lower in tramadol/paracetamol recipients than in placebo recipients (no data were reported in the abstract).[27] Furthermore, significantly fewer recipients of the fixed combination tablet discontinued treatment because of insufficient pain relief (22.9% vs 54.7% of placebo recipients; $p < 0.001$).[27]

4. Tolerability

This section provides an overview of treatment-emergent events (all events, regardless of relationship to treatment) reported by patients taking tramadol/paracetamol in clinical studies discussed in section 3.

Single-Dose Trials

- The tolerability profile of tramadol/paracetamol 75/650mg (n = 240) was similar to that of tramadol 75mg (n = 238) in a meta-analysis of three single-dose studies of patients with postoperative dental pain.[17] Treatment-emergent events were generally transient and of mild to moderate intensity, with the most common being nausea (23% of patients vs 24%), vomiting (21% vs 21%) and dizziness (5% vs 5%). Corresponding incidences reported with paracetamol 650mg (n = 240) were 9%, 7% and 4%; incidences with ibuprofen (n = 240) were 10%, 7% and 3%, and those with placebo were 16%, 10% and 4%.[17]

- Tramadol/paracetamol was better tolerated than hydrocodone/paracetamol in a study of 200 patients with postoperative dental pain.[19] Treatment-emergent adverse events were reported by up to 34% of patients taking either one or two tramadol/paracetamol 37.5/325mg tablets compared with 56% of hydrocodone/paracetamol 10/650mg and 48% of placebo recipients. Nausea (14% and 18% vs 36% of patients; $p < 0.05$) and vomiting (12% and 12% vs 30%; $p < 0.05$) were reported less often with either dosage of tramadol/paracetamol than with hydrocodone/paracetamol. In the placebo group, nausea and vomiting occurred in 12% and 8% of patients.

- Treatment-emergent adverse events were more common with tramadol/paracetamol 75/650mg (35.8% of patients) and tramadol 75mg (37.1%) than with paracetamol 650mg (15.9%) or ibuprofen 400mg (12.1%) in a meta-analysis of seven single-dose studies in >1300 patients with postoperative dental pain.[18] The most commonly reported events with combination therapy were vomiting (27% of

patients), nausea (26%), headache (6%), dizziness (4%) and somnolence (1.5%).

Multiple-Dose Trials

- The most common treatment-emergent adverse events were nausea (17.3%), dizziness (11.7%) and vomiting (9.1%) in 197 patients who received one or two tramadol/paracetamol 37.5/325mg tablets up to four times daily for 10 days as add-on therapy to a COX-2 inhibitor or NSAID for osteoarthritis flare pain.[20] Corresponding incidences in 111 placebo recipients were 3.6%, 4.5% and 1.8%. Treatment-related withdrawals were reported in 12.7% of tramadol/paracetamol recipients compared with 5.4% of placebo recipients. No serious adverse events were reported.

Furthermore, significantly fewer patients receiving tramadol/paracetamol 37.5/325mg (n = 30) experienced an adverse event compared with recipients of tramadol 50 mg (n = 44) [50.85 vs 73.33%; $p < 0.01$].[22] There was also a significantly lower incidence of dry mouth, constipation, nausea, vomiting, loss appetite and vertigo in the tramadol/paracetamol group ($p < 0.05$ for all comparisons; no data reported in abstract).[22]

- In patients with chronic pain, significantly ($p < 0.01$) fewer tramadol/paracetamol (37.5/325mg) than codeine/paracetamol (30/300mg) recipients experienced constipation in a 4-week double-blind multicentre trial, with a strong trend ($p = 0.05$) for a reduced incidence of somnolence in the tramadol/paracetamol group (figure 3; see section 3.3 for dosage details).[23] The most common treatment-emergent adverse events (incidence ≥5%) were somnolence, nausea, dizziness, constipation, headache, vomiting, diarrhoea, dry mouth, fatigue and dyspepsia (figure 3). A similar percentage of patients in both treatment groups experienced at least one treatment-emergent adverse event (71% vs 76% of codeine/paracetamol recipients), with no serious adverse events reported.

5. Dosage and Administration

In Europe, the fixed combination tramadol/paracetamol tablet is indicated in adolescents (>12 years of age) and adults for the symptomatic treatment of moderate to severe pain.[15] In the US[13] tramadol/paracetamol is recommended for the short-term management of acute pain in adults (>16 years of age). The initial recommended dosage is two tramadol/paracetamol 37.5/325mg tablets. Additional doses may taken as required for pain relief (maximum eight tablets per day); the interval between doses should be at least 6 hours.[15]

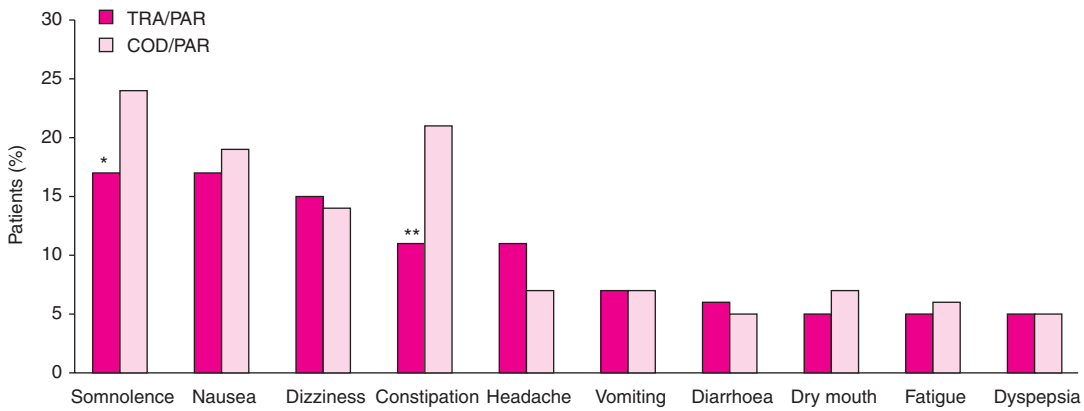


Fig. 3. Comparative tolerability profile of tramadol/paracetamol (TRA/PAR) versus codeine/paracetamol (COD/PAR). Treatment-emergent adverse events occurring in ≥5% of patients with chronic nonmalignant lower back pain and/or osteoarthritis in a randomised, double-blind, double-dummy, multicentre trial.[23] Patients received TRA/PAR 37.5/325mg (n = 309) or COD/PAR 30/300mg (n = 153) for 4 weeks. Recipients took one or two tablets plus the same number of capsules every 4–6 hours as required, up to a maximum of 10 tablets and 10 capsules per day. * $p = 0.05$, ** $p < 0.01$ vs COD/PAR.

6. Tramadol/Paracetamol: Current Status

Tramadol/paracetamol has proven to be an effective analgesic for the treatment of moderate to severe painful conditions. In clinical trials, tramadol/paracetamol provided effective analgesia in patients with postoperative dental pain, in those with osteoarthritis flare pain and in those with chronic lower back pain and/or osteoarthritis. Tramadol/paracetamol appears to be generally well tolerated.

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