

# The Place of the Fixed-Dose Tramadol/Paracetamol Combination in Pain Management

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**Received date:** 24/10/2017; **Accepted date:** 13/11/2017; **Published date:** 20/11/2017

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## Review Article

### ABSTRACT

The fixed-dose combination of tramadol and paracetamol has a central effect on the  $\mu$ -opioid receptor, the re-uptake of serotonin and norepinephrine, and acts on cyclo-oxygenase and the nitric oxide system in the central nervous system.

The combined analgesic provides multimodal analgesia and good pain control in many patients with acute or chronic pain. The combination has synergistic action so that lower doses of single substances are needed what improves its pharmacological profile.

The combination of tramadol and paracetamol is an analgesic with a low potential for abuse and dependence what makes possibility to be used without restrictive prescribing regimen, and makes it more accessible to patients for the relief of moderate to severe pain.

**Keywords:** Fixed-dose tramadol/paracetamol combination, Mode of action, Prescribing regimen, Pain management

### INTRODUCTION

Pain is an unpleasant sensory or and emotional experience caused by a known or hidden trigger. Different types of pain are classified based on its duration, pathophysiology, cause and site of occurrence. There is a general opinion that acute pain is easier manageable than chronic pain. However, acute pain is often the cause of chronic pain, if it is not properly managed. Effective treatment of acute pain prevents sensitisation and modifications of the pain perception system <sup>[1,2]</sup>.

Chronic pain occurs as a result of complicated pathophysiological events triggered by a specific response to pain stimuli and alterations in the conduction of pain in the nervous system. Chronic pain causes significant physical and psychological problems and reduces working capacity. All this significantly affects the quality of life of the affected. Chronic pain afflicts one in five Europeans and is so prevalent that it presents a social problem and a significant burden for the health-care system <sup>[3,4]</sup>. The economic burden of chronic pain consists of treatment costs and costs that result from lost productivity, sick leave and early retirement <sup>[5,6]</sup>.

We have gained a good understanding of pain and its management. Many mechanisms of the origination of pain and mechanisms of action of pain medication and other methods of pain therapy have been discovered. We have also reached a greater understanding of the bad side of pain medication and are trying to find ways to improve its clinical efficacy and tolerability. In the management of chronic pain we use a multidisciplinary approach. New treatment methods are being developed, with promising results. Chronic pain patients receiving different pharmacological and non-pharmacological therapies often complain of unsatisfactory pain relief. The use of pharmacological substances is often limited by adverse effects of medicines or their harmful effects on body organs, or regulatory requirements <sup>[7]</sup>.

Outcomes of pain treatment can be improved if several pain mechanisms are addressed simultaneously and a multimodal treatment approach is used <sup>[8]</sup>. This can be achieved by using a combination of medicines. Reasons to use a combination of medicines in pain relief are:

- A single substance does not provide effective pain relief,

- An effective substance causes unacceptable adverse reactions,
- The use of a combination is recommended in treatment guidelines,
- Lower doses of single substances and less serious adverse reactions,
- Additive and synergistic effect of the substances in the combination.

From the same reason medicines are being developed that act on different mechanisms and combinations of substances that act on different processes in the transmission of the pain signal. In addition to all the benefits provided by the properties of the combination components, pain therapy with combination medicines has been shown to facilitate prescribing and improve patient adherence to treatment. Among these medicines are tramadol and the combination of tramadol and paracetamol.

### **Fixed-Dose Combination of Tramadol and Paracetamol**

The fixed-dose combination of tramadol and paracetamol is an analgesic with several mechanisms of action. It has a central effect on the  $\mu$ -opioid receptor, the re-uptake of serotonin and norepinephrine, and acts on cyclo-oxygenase and the nitric oxide system in the central nervous system.

Tramadol has been used as a weak opioid in clinical practice since 1977. Its analgesic effect is brought about by the agonistic effect of its metabolite O-desmethyl tramadol at  $\mu$ -opioid receptors and its inhibitory effect on the re-uptake of serotonin and norepinephrine. The safety of tramadol, if compared to other opioids, is attributed to its ten times lower potency compared to morphine. The main adverse reactions to tramadol are nausea (6.1%), vomiting (1.7%) and dizziness (4.6%), which occur during the initiation of treatment and mostly disappear during its continuation. Tramadol does not cause respiratory depression in patients without reduced respiratory reserve. It causes less constipation than potent opioids. Interactions with other medicines can occur if tramadol is used concomitantly with CYP3A4 inducers and medicines inhibiting the re-uptake of serotonin. Its potential to produce epileptic seizures is increased if it is used concomitantly with tricyclic antidepressants, selective serotonin re-uptake inhibitors or other neuroleptics.

Tramadol is used all over the world and included in numerous guidelines for the treatment of pain conditions. It is mostly not mentioned in current guidelines for the use of opioids in the treatment of chronic pain. Interestingly, exceptional use of tramadol in fibromyalgia is mentioned in the latest German guidelines among contraindications for the use of opioid analgesics [9]. In the treatment of cancer pain, tramadol is a step II medicine on the WHO analgesic ladder. It has a lower potential for abuse and dependence than other opioids [10-13].

Paracetamol is a non-opioid analgesic approved in 1957. It is widely used for the relief of pain, as monotherapy and in combination with other substances, and for lowering elevated body temperature. It is presumed that it acts on cyclo-oxygenase in the central nervous system and that it is devoid of adverse effects known for the inhibitors of peripheral cyclo-oxygenases. In addition, it inhibits the synthesis of nitric oxide and supports the serotonergic system [14,15]. Its pharmacological profile allows paracetamol to be dispensed without medical prescription in pharmacies.

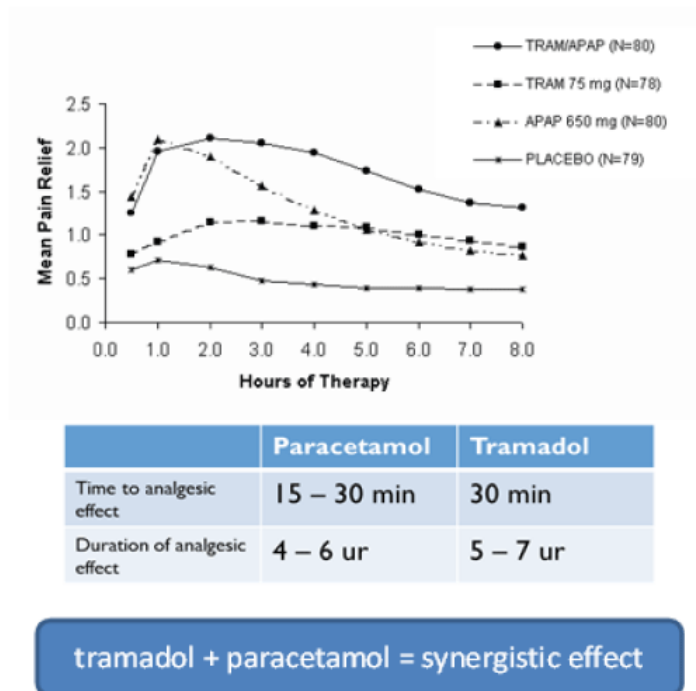
### **Rationale for Fixed Dose Combination of Tramadol and Paracetamol**

The main reasons for developing combination analgesics are to gain efficacy and to reduce toxicity. Combining analgesics that act at different locations along the pain pathway may do this. Other potential benefits of combining analgesics include increasing the duration of analgesia, widening the spectrum of efficacy, and improving patient compliance. Additionally, in the case of opioid analgesics the combination may reduce abuse potential.

Analgesic combinations can be considered to interact either pharmacokinetically and/or pharmacodynamically. A rationally developed analgesic combination should be without risk of the interactions which could increase the risk of the severity of side effects [8].

The multimodal and synergistic action of the fixed-dose combination of tramadol and paracetamol provides adequate analgesia for moderate to severe pain with lower doses of usually used doses of single substances (by 25% for tramadol and by 35% for paracetamol) [16,17]. The combination has a better pharmacological profile compared to monotherapy, manifested by improved analgesic action at onset and faster onset of action (**Figure 1**) [18]. Pharmacodynamic modelling combined with the isobolographic technique showed supra-additive effect of the combination of paracetamol and tramadol concerning analgesia and anti-hyperalgesia [19]. Adverse reactions associated with the combination do not differ from adverse reactions known for the single components, and no increase in their severity has been observed. The combination of tramadol and paracetamol had no additional tolerability issues relative to its components and, overall, the tolerability profile of the combination was generally similar to that of other active comparators (fixed-dose combination of single agents); however, incidence of some adverse events were lower in the combination than in active comparator recipients [20]. The fixed-dose combination has been demonstrated to be more effective than non-steroidal anti-inflammatory agents (NSAIDs) in older patients with osteoarthritis, without causing organ damage seen with NSAIDs, which is an important aspect in the treatment of elderly with age-related organ involution and organ dysfunction [21].

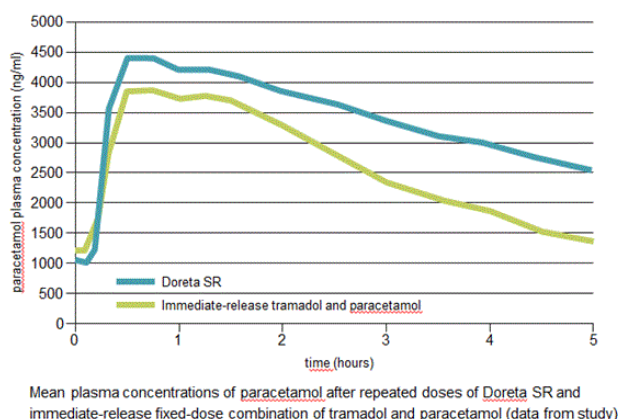
Acting on the central nervous system, the medicine is classified as having a potential for abuse and physical and psychological dependence.



**Figure 1.** The efficacy of tramadol and paracetamol in combination and used separately compared with placebo [14]. TRAM: Tramadol; APAP: Paracetamol.

The combination has been demonstrated to produce effective analgesia in patients with various etiologies of acute and chronic pain, including acute flare of osteoarthritis, chronic lower back pain, post-operative pain, fibromyalgia and neuropathic pain [19,22-26]. Owing to a rather short duration of effect, the recommended dose should be administered at intervals of 4 to 6 h.

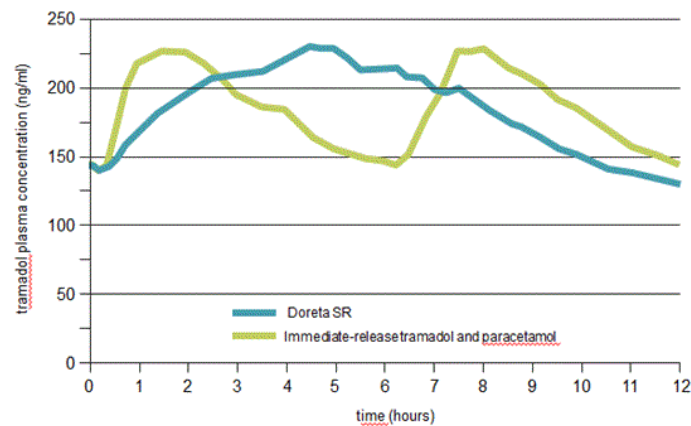
The prolonged-release formulation of the fixed-dose combination of tramadol and paracetamol (Doreta SR) contributes to the favourable profile of the medicine by providing a more even analgesia because of diminished oscillation of plasma concentrations of tramadol and paracetamol, a better tolerability and having a lower potential for abuse (Figures 2 and 3) [17,27].



**Figure 2.** The mean plasma concentrations of paracetamol after repeated fixed-doses of slow release combination of tramadol and paracetamol (Doreta SR: tramadol 75 mg and paracetamol 325 mg) and immediate - release combination (tramadol 75 mg and paracetamol 325 mg).

## Prescribing of Tramadol-Containing Medicines

Tramadol-containing medicines are classified into different legal categories in different countries. In the USA tramadol had been classified among non-controlled analgesics until 2014. In 2011 there was an increase in non-medical use of tramadol in the USA, which led in 2014 to its classification into the fourth group of controlled medicines as a medicine with a low potential for abuse and dependence. Physical dependence has been associated with long-term use of higher doses. In Europe tramadol is mostly prescribed in the same way as other medicines from the fourth group of controlled medicines (benzodiazepines), without limitations that must be observed when medicines from the second and third group of controlled medicines are prescribed (opioids, ketamine).



Mean plasma concentrations of tramadol after repeated doses of Doreta SR and immediate-release fixed-dose combination of tramadol and paracetamol (data from study)

**Figure 3.** The mean plasma concentrations of tramadol after repeated fixed-doses of slow release combination of tramadol and paracetamol (Doreta SR: tramadol 75 mg and paracetamol 325 mg) and immediate - release combination (tramadol 75 mg and paracetamol 325 mg).

Regulatory limitations on the use of medicines often result from poor understanding among the political leaders of what controlled substances are and what is their therapeutic value. Insufficient knowledge and fear of abuse are the main reasons for the reluctance among medical professionals to prescribe controlled substances. Too restrictive legislation and regulations do not prevent misuse of controlled medicines but do hinder their availability and accessibility [28].

Owing to its dual mechanism of action, the actual potential for abuse and dependence of tramadol is questionable. At the beginning of its use, tramadol was not classified into the group of controlled medicines by the World Health Organization Expert Committee for Drug Dependence (in 2003, 2006 and 2014) [29]. With the appearance of the fixed-dose combination of tramadol and paracetamol, the pharmacological profile of the medicine was further improved by an additive effect of the substances that allows lower doses of the single components. Tramadol and the combination of tramadol and paracetamol became exceptionally useful and, with increased use, individual reports on its abuse and dependence began to appear. In 2013, a monitoring in France assessed the abuse and dependence potential of the medicine as very low and staying at a stable level and not presenting a significant health hazard [30]. Data from Germany show that tramadol abuse occurs in 0.21 cases per one million daily defined doses (300 mg) and tramadol dependence in 0.12 cases per one million of daily defined doses [31].

Tramadol and the combination of tramadol and paracetamol are in Slovenia first medicines on the list of most commonly prescribed analgesics acting on the nervous system (class N02A) [32]. Their prescribing does not require the special prescribing regimen obligatory in potent opioids. As yet, there are no data showing an alarming abuse or dependence associated with the use of these substances. The results of several post-marketing and non-interventional studies have demonstrated their good efficacy and safety in patients with moderate to severe pain.

## CONCLUSION

The fixed-dose combination of tramadol and paracetamol provides good pain control in many patients with acute or chronic pain. Owing to its additive effect, the combination produces a better analgesic effect, which is reached with lower doses of the single substances, compared to that of equal doses used in monotherapy. The combination of tramadol and paracetamol is an analgesic with a low potential for abuse and dependence. In several European countries its use is not

limited by a restrictive prescribing regimen, which makes it more accessible to patients for the relief of moderate to severe pain.

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