

# Infectious Smiles

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## Tramadol/paracetamol fixed-dose combination in the treatment of moderate to severe pain

### Abstract

*Pain is the most common reason patients seek medical attention and pain relief has been put forward as an ethical obligation of clinicians and a fundamental human right.*

However, pain management is challenging because the pathophysiology of pain is complex and not completely understood. Widely used analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol (acetaminophen) have been associated with adverse events.

Adverse event rates are of concern, especially in long-term treatment or at high doses. Paracetamol and NSAIDs are available by prescription, over the counter, and in combination preparations. Patients may be unaware of the risk associated with high dosages or long-term use of paracetamol and NSAIDs. Clinicians should encourage patients to disclose all medications they take in a “do ask, do tell” approach that includes patient education about the risks and benefits of common pain relievers.

The ideal pain reliever would have few risks and enhanced analgesic efficacy. Fixed-dose combination analgesics with two or more agents may offer additive or synergistic benefits to treat the multiple mechanisms of pain. Therefore, pain may be effectively treated while toxicity is reduced due to lower doses. One fixed-dose combination analgesic product combines tramadol, a centrally acting weak opioid analgesic, with low-dose paracetamol. Evidence-based guidelines recognize the potential value of combination analgesics in specific situations.

### Pharmacological aspects: why combinations might be better than single agents

Rarely does a single known mechanism cause pain. Obviously, no single analgesic agent can fully address multiple mechanisms of pain. Combination analgesic products have been effective because they activate multiple pain-inhibitory pathways and offer a broader spectrum of relief. This may include multiple afferents and pathways as well as multiple processes.

Combination analgesics might reduce adverse events. A given analgesic provides pain relief at a specific dosage and is associated with dose-dependent adverse effects. Combining analgesics may allow for lower doses of the individual agents, with doses possibly low enough to significantly reduce potential adverse events. While the theory of combination analgesic products holds promise, combination products require rigorous scrutiny and testing since not all combinations are ideal.

“ Combination analgesics might reduce adverse events. ”

### Overview on experience with fixed-dose tramadol/paracetamol in the treatment of moderate to severe pain in nonacute conditions: differences to NSAIDs

The Table below summarizes the strengths and weaknesses of NSAIDs versus tramadol/paracetamol fixed-dose combination products. Recent guidelines for pain management and the position of paracetamol, NSAIDs, and fixed-dose combinations such as tramadol/paracetamol are shown in.

Table: Strengths and weakness of tramadol/paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs)

	NSAIDs	Tramadol/paracetamol
<b>Strengths</b>	<ul style="list-style-type: none"> <li>Frequently prescribed</li> <li>Ubiquitous</li> <li>Gold standard for many conditions: ibuprofen</li> <li>Well tolerated short term</li> <li>Over-the-counter availability</li> </ul>	<ul style="list-style-type: none"> <li>Recent combination of established analgesics with scientifically and clinically based rationale</li> <li>Good benefit–risk balance</li> <li>No specific warnings</li> </ul>
<b>Weaknesses</b>	<ul style="list-style-type: none"> <li>Recent warnings</li> <li>Safety profile (gastrointestinal, renal, and cardiovascular risks)</li> <li>Coadministration with other drugs</li> </ul>	<ul style="list-style-type: none"> <li>Combination therapy not well established</li> <li>Difficult to differentiate from tramadol immediate release, tramadol extended release</li> <li>Not well tolerated short term</li> </ul>

Potential advantages of a fixed-dose tramadol/paracetamol analgesic product include a broader analgesic spectrum, a complementary pharmacokinetic profile, potentially synergistic analgesic effect, greater convenience (possibly resulting in better compliance, thus, improved therapy), and an improved ratio of efficacy to adverse effects.

### Conclusion

Pain management is a global challenge to clinicians and, despite the plethora of evidence-based guidelines, all analgesic options must be individually assessed and weighed for specific risks and benefits in a given patient. Many effective analgesics exist but are associated with adverse events. NSAIDs and paracetamol are effective pain relievers, but recent studies have raised safety concerns, particularly when these agents are used at high doses, long-term, or in special patient populations. Opioid analgesics are effective but are associated with adverse events as well as concerns over tolerance and addiction. Finding an analgesic product that offers both effective pain relief and a good safety profile has led to increasing interest in combination products.

Combination agents may offer analgesic synergy that allows them to provide effective analgesia at reduced doses. However, careful study of combination agents is warranted, as such combination products might also exacerbate side effects. New fixed-dose combination products may offer an improved method of treating the newly recognized multi-mechanistic nature of pain.

### Reference

Pergolizzi, J., van de Laar, Langford, Mellinghoff, Morón Merchante, & Nalamachu, S. et al. (2012). Tramadol/paracetamol fixed-dose combination in the treatment of moderate to severe pain. *Journal Of Pain Research*, 327. doi:10.2147/jpr.s33112

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