



REVIEW

# Tramadol/Diclofenac Fixed-Dose Combination: A Review of Its Use in Severe Acute Pain

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## ABSTRACT

Pain is a health issue affecting all populations, regardless of age, gender, economic status, race, or geography. Acute pain is the most common type of pain, with a complex aetiology. Inadequately managed acute pain adversely affects quality of life and imposes significant economic burden. The majority of the available pain-relieving drugs have monomodal mechanisms of analgesia, which necessitates combining drugs with non-redundant mechanisms of action in order to provide adequate pain relief and reduce the side effects from higher doses of individual drugs. In this regard, combining an oral opioid (such as codeine or tramadol) and a non-opioid (such as paracetamol or non-steroidal anti-inflammatory drug) offers a plausible option.

Tramadol/diclofenac fixed-dose combination (FDC) is one such analgesic combination which has demonstrated promising clinical activity via its multimodal mechanisms of action. This review seeks to provide an up-to-date narrative on the current scientific literature regarding the pharmacological properties, clinical efficacy, and tolerability of tramadol/diclofenac FDC in the treatment of acute severe pain. A comprehensive, qualitative review of the literature was conducted using a structured search strategy in Medline/PubMed and additional Internet-based sources to identify relevant studies. Based on the available scientific literature, evidence of the efficacy and safety of tramadol/diclofenac FDC for treatment of patients with acute severe pain, including musculoskeletal pain, postoperative pain, and acute flare-up of osteoarthritis or rheumatoid arthritis, appears to be substantial. Although additional comparative studies would be required to definitively position tramadol/diclofenac FDC with respect to other analgesic combinations, the available data suggest that tramadol/diclofenac FDC is a valuable treatment option for patients with acute severe pain.

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## Key Summary Points

### Why carry out this study?

Acute pain is the most common type of pain, with a complex aetiology which may adversely affect quality of life and impose an economic burden.

The majority of the available pain-relieving drugs have monomodal mechanisms of analgesia. However, tramadol/diclofenac fixed-dose combination (FDC) is an analgesic combination which has demonstrated promising clinical activity via its multimodal mechanisms of action.

This comprehensive, qualitative review seeks to provide an up-to-date narrative on the current scientific literature regarding the pharmacological properties, clinical efficacy, and tolerability of tramadol/diclofenac FDC in the treatment of acute severe pain.

### What was learned from the study?

Based on the available scientific literature, there appears to be substantial evidence of the efficacy and safety of tramadol/diclofenac FDC for treatment of patients with acute severe pain, including musculoskeletal pain, postoperative pain, and acute flare-up of osteoarthritis or rheumatoid arthritis.

Although additional comparative studies would be required to definitively position tramadol/diclofenac FDC with respect to other analgesic combinations, available data suggest that tramadol/diclofenac FDC is a valuable treatment option for patients with acute severe pain.

emotional experience associated with actual or potential tissue damage or described in terms of such damage" [1]. Pain is a public health issue worldwide and remains the most common cause for physician consultation and hospital admission [2]. Pain affects all populations, regardless of age, gender, economic status, race, or geography [2]. Acute pain is the most common type of pain, and can occur due to injury, acute illness, surgery, or arthritis, making its aetiology a complex and transdisciplinary affair [2, 3]. The global prevalence of postoperative pain varies from 14 to 70%, and the scenario is even more serious in India, where > 80% of patients experience postoperative pain [4–8]. Pain due to musculoskeletal disorders is another common form of acute pain, and occupation-specific prevalence is reported to be ~ 90% in India [9]. Acute flare-ups of rheumatoid arthritis and osteoarthritis are significant contributors to the burden of acute pain in India. Inadequately managed acute pain adversely affects quality of life, physical function, and functional recovery [10, 11]. Moreover, inadequately managed pain leads to significant economic burden in terms of healthcare utilisation and labour force participation [12, 13].

### Current Challenges in, and the Available Options for, the Effective Management of Acute Pain

Despite recent advances in the understanding of the cellular mechanisms underlying pain initiation, including the discovery of novel molecular targets, the management of acute pain remains suboptimal in the majority of patients [14–18]. Consequently, there is an unmet need to identify and address the barriers to appropriate management of acute pain [18]. This could be addressed in part with increased appreciation of the complex interplay between the peripheral and central nervous systems in pain transmission, facilitation, and inhibition [18].

The current armamentarium for pain management comprises multiple options, the majority based on monomodal mechanisms of analgesia [19, 20]. However, acute pain is

## INTRODUCTION

The International Association for the Study of Pain defines pain as “an unpleasant sensory and

multidimensional in nature, involving sensory, affective, cognitive, and behavioural aspects. Therefore, achieving adequate pain control with a single drug may not be beneficial [19, 20]. Moreover, most analgesics exhibit a ceiling of efficacy and have significant safety concerns [21]. An optimal approach to multimodal pain management might be to combine drugs with non-redundant mechanisms of action that would provide adequate pain relief and also reduce side effects. Emerging evidence shows additive or synergistic actions of multimodal analgesia in various combinations of analgesic agents [22]. Combining analgesics has several advantages, such as a broader spectrum of action, improved efficacy and compliance, and a better efficacy/safety ratio [23]. A line of evidence shows that the combination of opioids and non-steroidal anti-inflammatory drugs (NSAIDs) improves efficacy and reduces the dose of individual drugs when compared with monotherapy [22, 24–26]. Given the clinical significance of these benefits and the current global concerns regarding the opioid epidemic, the American Pain Society (APS), World Health Organization (WHO), and American College of Rheumatology (ACR) now recommend analgesic combinations.

### Fixed-Dose Analgesic Combinations

Decreased pill burden, greater ease of administration, and the need for lower dosages of individual drug components are key benefits offered by fixed-dose combination (FDC) analgesics. Combining oral opioids (such as codeine or tramadol) and non-opioids (such as paracetamol or NSAIDs) offers a more suitable option [27]. Among the currently available FDCs, paracetamol is the most commonly used non-opioid agent. In addition to the known hepatotoxic potential of paracetamol, its cardiovascular and gastrointestinal (GI) risk has been a recent cause for concern [28, 29]. Paracetamol also lacks the anti-inflammatory effect that is observed predominantly with NSAIDs [30]. Moreover, NSAIDs relieve pain more effectively than paracetamol or a paracetamol/codeine combination [31–33]. Combining NSAIDs with

opioids, therefore, seems to be a preferable alternative. Due to the opioid-sparing action of NSAIDs, the combination of these two drugs significantly reduces opioid dose and mitigates the incidence of adverse events (AEs) such as nausea, vomiting, and respiratory depression. For an effective analgesic combination, the selection of the right NSAID and opioid agent at optimal doses is essential.

A combination of sustained-release diclofenac and immediate-release tramadol has recently been developed and widely used in clinical practice. This FDC provides multimodal analgesia at lower and better-tolerated doses than monotherapy with either drug [34, 35]. The selected doses are diclofenac 75 mg and tramadol 50 mg. This FDC is available under the brand names DURAPAIN<sup>®</sup>, RESYNC<sup>®</sup>, DIBOL<sup>®</sup>, and DIBOLS<sup>®</sup> in India. This review outlines the pharmacological properties, clinical efficacy, and tolerability of this FDC combination in adults with acute severe pain.

## METHODS

### Source

Medical literature published since 1986 on tramadol and/or diclofenac was identified using Medline/PubMed. Additional literature was identified from the reference lists of published articles. Other bibliographic information was also requested from the company manufacturing the drugs.

### Search Strategy

Search terms used for PubMed were ‘diclofenac plus tramadol’ or ‘tramadol and diclofenac combination’ or ‘tramadol’ or ‘diclofenac’ or ‘diclofenac plus tramadol bilayer tablet’ or ‘diclofenac/tramadol’ or ‘tramadol/diclofenac’. Searches were last updated on 6 December 2018.

### Selection

Studies were selected based on the methods in which patients received tramadol/diclofenac.

## Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

## PHARMACODYNAMIC PROPERTIES

The pharmacodynamic properties of tramadol and diclofenac have been reviewed extensively elsewhere [36–45]. The key pharmacodynamic properties of both of these analgesic agents are described below.

### Tramadol

Tramadol is an atypical opioid with a dual mode of action: it acts as a  $\mu$ -opioid receptor agonist and an inhibitor of monoamine neurotransmitter re-uptake, which together causes a reduction in afferent pain signalling and amplification of efferent inhibitory signalling [36–39, 46]. Unlike other opioids, tramadol acts primarily on the descending-inhibitory pathway of the central nervous system and inhibits the transmission and perception of pain [36, 38]. The synergistic activity associated with the analgesic and anti-nociceptive effects of tramadol is due to the racemic nature of this molecule [37, 38]. Amongst two enantiomers, serotonin re-uptake inhibitor is (+) tramadol, which has a higher affinity for  $\mu$ -opioid receptors, while (–) tramadol is a potent inhibitor of norepinephrine, and triggers auto-receptor activation [37, 38, 47]. Besides analgesia, other pharmacological actions of tramadol are similar to opioids, namely constipation, dizziness, sweating, nausea, somnolence, and pruritus. Unlike other opioid agents, treatment with tramadol is not associated with respiratory and cardiac depression. Further, drug dependence potential is low in patients who are treated with tramadol [37, 38]. Unlike morphine, tramadol does not cause histamine release [39, 48]. Tramadol is metabolised via cytochrome P450 enzyme sparteine-oxygenase (CYP2D6), to *O*-desmethyltramadol (M1) in the liver [38, 48].

M1 has an approximately 200-fold higher affinity for  $\mu$ -receptor, which produces potent analgesic effects compared with ( $\pm$ ) tramadol [38, 40].

### Diclofenac

Diclofenac is an NSAID exhibiting analgesic, anti-inflammatory, and antipyretic activity. Its mode of action is not well characterised. Although diclofenac is classified as a non-specific COX inhibitor, it is a specific COX-2 isoform inhibitor which effectively inhibits prostaglandin-E2 and thromboxane-A2 synthesis and possesses pro-nociceptive action at peripheral and spinal sites [49, 50]. Additionally, diclofenac acts as an eicosanoid oxidoreductase inhibitor and inhibits eicosanoids and lipoxins [51, 52]. It also increases plasma-endorphin levels and attenuates *N*-methyl-D-aspartate (NMDA)-mediated nociceptive discharge via the L-arginine–nitric oxide–cGMP (cyclic guanosine monophosphate) pathway [49, 51, 53]. Diclofenac has been shown to reduce prostaglandin and interleukin-6 levels in plasma and synovial fluid in patients with rheumatoid arthritis and osteoarthritis [51, 54, 55]. Compared with other NSAIDs, irrespective of COX-specificity, diclofenac shows greater inhibition of platelet aggregation and acts as a competitive antagonist of thromboxane-prostanoid receptor, signifying potential cardiovascular safety [51, 56].

## PHARMACOKINETIC PROPERTIES

The data for the pharmacokinetics of tramadol/diclofenac FDC are obtained largely from the product characteristics of tramadol and diclofenac combinations [57]. Investigating the pharmacokinetics of this FDC will be of future interest.

### Tramadol

After oral administration, tramadol is quickly and completely absorbed. Its absorption is delayed by approximately 30 min, and

absorption half-life is  $23 \pm 11$  min. Plasma concentration and area under the concentration–time curve (AUC) increase linearly over a dose range of 50–400 mg [58]. Mean peak plasma concentration ( $C_{max}$ ) is 280 ng/mL [57]. The mean absolute bioavailability of tramadol is 68–72%, corresponding to 20–30% first-pass metabolism [57, 58]. Tramadol is rapidly distributed in the body, with a volume of distribution of 2–3 L/kg in young adults, which reduces by about 25% in elderly patients ( $\geq 75$  years). It effectively crosses the placental and blood–brain barriers, and small amounts (0.1%) are excreted in breast milk [37, 57, 58]. Tramadol achieves peak brain concentration 10 min after oral administration; the corresponding value for active metabolite M1 is 20–60 min [58]. It shows 20% protein binding [57].

Following oral administration, tramadol is extensively metabolised in the liver, largely via *O*- and *N*-demethylation and conjugation reactions forming glucuronides and sulphates [58]. CYP2D6 catalyses *O*-demethylation of tramadol to the pharmacologically active metabolite, M1, whereas CYP3A4 and CYP2B6 catalyse *N*-demethylation of tramadol to the metabolite *N*-desmethyltramadol (M2) [37, 58]. Owing to genetic polymorphisms in the gene encoding CYP2D6, tramadol metabolism varies in different phenotypes [59]. In a study of 104 healthy adult volunteers, those who were poor metabolisers of sparteine, an *in vivo* probe for CYP2D6 enzyme activity, exhibited significantly higher mean metabolic ratios of tramadol to M1 than extensive metabolisers (4.4 vs. 0.8,  $p < 0.0001$ ) [60]. After a 2 mg/kg dose of tramadol, poor metabolisers had inferior analgesia and 3- to 33-fold lower concentrations of (+) M1 than extensive metabolisers, influencing the overall therapeutic response and tolerability [61]. Tramadol and its metabolites are excreted predominantly by the kidneys, with a cumulative renal excretion rate of approximately 95%; about 15–19% of tramadol is excreted in the urine as unchanged drug, with a total clearance range of 430–610 mL/min. In young adults, the half-life of tramadol is 5–7 h and the half-life of M1 is 6–8 h [57].

## Diclofenac

Diclofenac is well absorbed orally and has a calculated apparent volume of distribution of 0.12–0.17 L/kg [57]. The AUC of diclofenac is proportional to the orally administered dose between 25 and 150 mg. Peak concentration in synovial fluid, which is the site of action of NSAIDs, is achieved 2–4 h after attaining peak plasma levels [57]. Diclofenac binds extensively to plasma proteins (99.7%), mainly albumin [57, 62].

Following oral administration, biotransformation of diclofenac is ensured mainly by single and multiple hydroxylation, methoxylation, and partial glucuronidation, resulting in phenolic metabolites which are then converted to glucuronide conjugates. Total systemic clearance of diclofenac is 263.56 mL/min [57]. After glucuronidation and sulfation, the metabolites of diclofenac are excreted in the urine (65%) and bile (35%) [30]. Elimination from synovial fluid takes around 3–6 h [57]. The terminal half-life in plasma is 1–2 h [30, 43, 57].

## Drug Interactions and Pharmacokinetics in Special Populations

The tramadol/diclofenac FDC is not recommended for patients with severe renal impairment [57, 63]. Approximately 25% of medications, such as antiarrhythmic, antiemetics, antidepressants, antipsychotics, analgesics, and tamoxifen, are metabolised by the CYP2D6 enzymes, many of which are commonly administered to ambulatory patients receiving tramadol and are likely to cause drug–drug interactions [64]. Concurrent use of tramadol and serotonergic medications results in a hyperserotonergic state soon after treatment initiation or changes in the doses of serotonergic medications. The underlying reason for this effect is the inhibition of metabolic enzymes [42]. The combination of tramadol with partial opiate agonists/antagonists and abrupt cessation of tramadol is not advisable due to risk of withdrawal symptoms [42]. Concomitant use of coumarin derivatives and tramadol may lead to an increased international

normalised ratio which may lead to major bleeding and ecchymosis in some patients [37, 57]. Co-administration with carbamazepine causes significant increase in tramadol metabolism, presumably through metabolic induction which raises the recommended dose of tramadol [58].

In vitro studies indicate that diclofenac has no significant effect on the serum protein binding of acenocoumarol, prednisolone, salicylic acid, tolbutamide, or warfarin [45]. Concomitant administration of antiplatelet medication and anticoagulants with diclofenac could increase the risk of bleeding [45, 57]. If used concurrently, diclofenac may raise plasma concentrations of lithium by 26%, with a potential risk of intoxication [43]. In hypertensive and/or elderly patients, simultaneous use of diclofenac with antihypertensives (beta-blockers and angiotensin-converting enzyme inhibitors) and potassium-sparing diuretics should be avoided, as it reduces the antihypertensive effects and increases serum potassium levels [57]. Diclofenac raises digoxin and methotrexate concentrations, resulting in increased toxicity of these drugs. It also exhibits nephrotoxic and neurological effects when co-administered with cyclosporine and quinolones, respectively [57]. Like other NSAIDs, diclofenac should be used at the lowest effective dose for the shortest duration to reduce the risk of severe hepatic reactions [50].

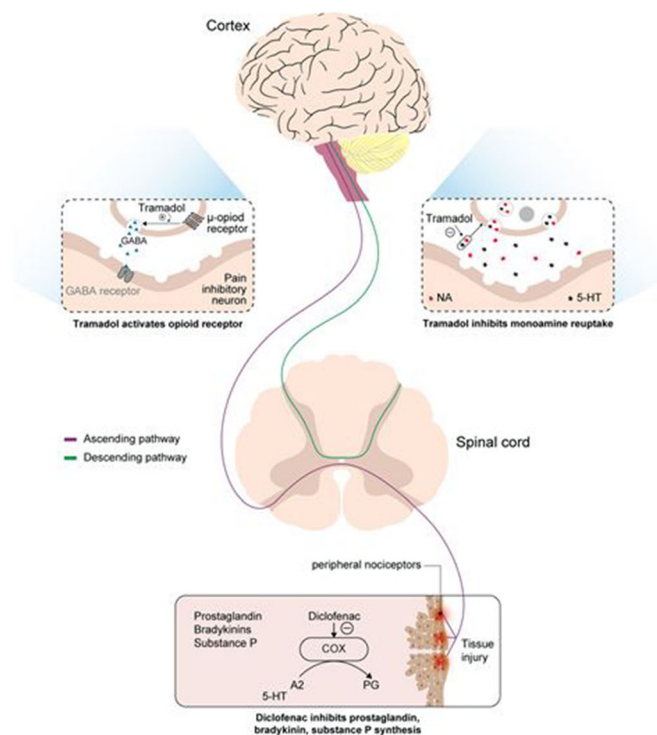
## DOSAGE AND ADMINISTRATION

The recommended dose of tramadol/diclofenac FDC is one tablet twice daily after meals, for a period not exceeding 5 days [57]. This combination is indicated for symptomatic treatment of severe pain in adults with severe acute pain of trauma, postoperative pain, low back pain, and musculoskeletal pain. Tramadol is recommended as an important WHO step 2 analgesic and is widely prescribed in clinical practice for the treatment of acute pain, labour pain, and chronic cancer and non-cancer pain [65, 66]. Tramadol is prescribed when paracetamol and/or NSAIDs and COX-2 inhibitors alone are inadequate and strong opioids are not

warranted or available. The use of tramadol in pain management has increased because of the serious safety issues associated with NSAIDs (GI bleeding) and COX-2 inhibitors (cardiovascular risks, nephrotoxicity), which limit their use in elderly patients and special populations [66]. Tramadol should be avoided in pregnant women and nursing mothers [37, 57]. The safety and effectiveness of tramadol/diclofenac FDC is not well studied in paediatric and elderly populations. Caution is warranted when using tramadol in patients with head injury, increased intracranial pressure, and severe impairment of hepatic or renal function, and in patients prone to respiratory depression, addiction, or convulsive disorders [57]. Diclofenac monotherapy is recommended at the lowest effective dose for the shortest duration of action, and is not recommended in patients with cardiovascular events, myocardial infarction, or stroke [57]. NSAIDs reportedly cause an increased risk of serious GI adverse events of bleeding, ulceration, and perforation of the stomach or intestine. Geriatric patients and those with a history of peptic ulcer disease and/or GI bleeding are at greater risk [57]. Local prescribing information should be consulted for information on dosage and administration, contraindications, drug interactions, precautions, and warnings.

## THERAPEUTIC EFFICACY

The tramadol/diclofenac combination demonstrated synergistic interactions in experimental nociceptive models, which provide the rationale for its use in acute severe pain [67]. This combination has complementary modes of action and targets multiple sites, as shown in Fig. 1. Limited evidence is available to support the efficacy of tramadol/diclofenac combinations. This section summarises data from a phase III trial of the tramadol/diclofenac FDC (CTRI/2011/091/000150 registered on: 01/02/2011) and a post-marketing observational study. Studies using different dosages and routes of administration for tramadol and diclofenac are also included to illustrate the additive effects of the combination.



GABA:  $\gamma$ -aminobutyric acid; COX: Cyclooxygenase; 5-HT: 5-hydroxytryptamine; MOR:  $\mu$ -opioid receptor; NA: Noradrenaline; PG: Prostaglandin; A2: Thromboxane-A2

**Fig. 1** Complementary modes of action of a tramadol/diclofenac combination [36, 38, 49–51]

The phase III trial included treatment-naïve male and female patients aged > 18 to < 60 years with acute pain, characterised by Visual Analog Scale (VAS) score > 50 mm [68]. Eligible patients were diagnosed with either acute musculoskeletal pain (AMSP; tendinitis, bursitis, synovitis), postoperative pain (POP), or acute flare-up of osteoarthritis (AFOA) or rheumatoid arthritis (AFRA). This 5-day randomised, open-label, comparative, parallel-group multicentre trial conducted at three centres in India included 204 patients: AMSP ( $n = 51$ ), AFOA ( $n = 52$ ), AFRA ( $n = 50$ ), and POP ( $n = 50$ ). The analgesic efficacy of short-term therapy with tramadol/diclofenac FDC was compared with tramadol/paracetamol FDC [68]. The key efficacy measures defined here are given in Table 1.

The efficacy results are summarised in Fig. 2a. Both FDC treatments significantly

reduced overall pain scores on day 3 and day 5; however, the reduction in the VAS scores was greater in patients treated with tramadol/diclofenac FDC than tramadol/paracetamol FDC at day 3 ( $-42.19\%$  vs.  $-29.65\%$ ,  $p = 0.001$ ) and day 5 ( $-67.83\%$  vs.  $-42.87\%$ ,  $p = 0.0001$ ). Similarly, pain relief was significantly better with tramadol/diclofenac when compared with tramadol/paracetamol for pain at rest and pain on movement. Approximately 80% of patients rated the efficacy of the tramadol/diclofenac FDC as very good or excellent, compared with 19% of patients treated with tramadol/paracetamol FDC ( $p = 0.0001$ ) [68].

Subgroup analysis showed that the tramadol/diclofenac FDC achieved significantly greater reduction in pain scores with 3 days of treatment in AFRA and POP patients, while it required 5 days of treatment in AMSP and AFOA patients (Fig. 2b). The analysis of disease-

**Table 1** Key efficacy measures with definitions used in clinical studies

Outcome measures	Definition
WOMAC [69]	Assessment of pain, stiffness, and physical function and the overall score on a 5-point scale in patients with acute flare-up of osteoarthritis
HAQ scale [70]	Assessment contains 8 items rated on a 4-point scale in patients with acute flare-up of rheumatoid arthritis
NRS [71]	On a 6-point rating scale (0 = no pain and 5 = the worst pain, the higher the score, the worse the pain) in patients with postoperative pain
Pain intensity, pain [71]	Pain intensity and pain was measured with a 0–100 mm VAS scale (for overall pain, pain at rest, and pain on movement)
Global assessment of effectiveness [72]	Assessed on a scale of 1–5 (1, poor; 2, satisfactory; 3, good; 4, very good; 5, excellent)

*WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index, *HAQ* Health Assessment Questionnaire, *NRS* Numerical Rating Scale

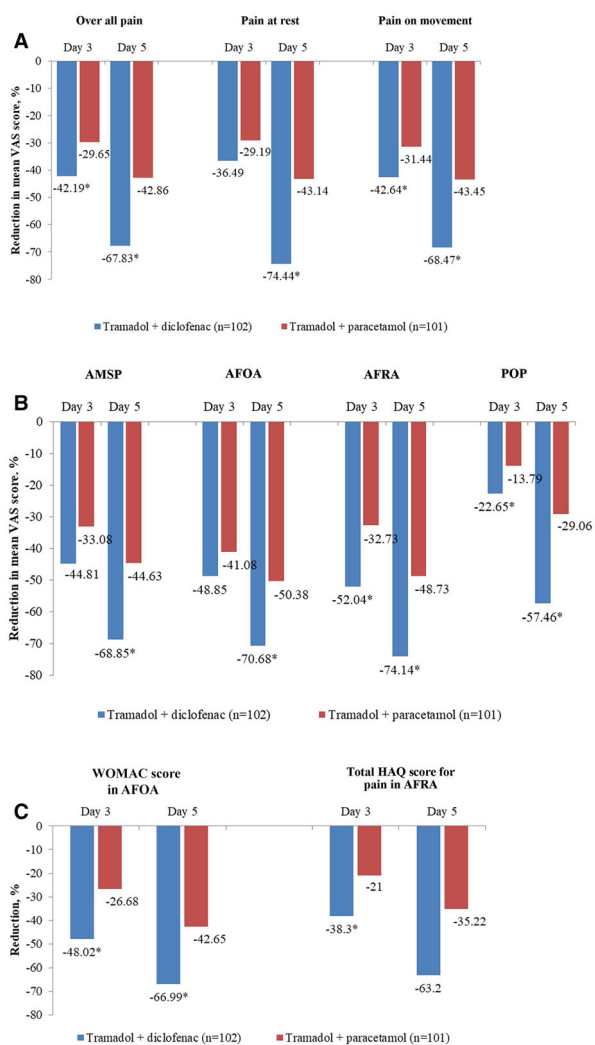
specific pain scores revealed a similar pattern of pain relief (Fig. 2c). Overall, the findings from this phase III trial demonstrated that tramadol/diclofenac FDC relieves acute pain in AMSP, AFOA, AFRA, and POP patients more effectively than tramadol/paracetamol FDC [68, 72].

The PRIME study—a prospective, multicentre, observational, non-randomised, non-controlled, single-arm post-marketing study—evaluated the real-world efficacy of tramadol/diclofenac FDC [73]. The study enrolled 351 patients (mean age 44.2 years, from 19 centres in India) who experienced musculoskeletal pain (41.9%), joint pain (43.9%), pain due to trauma (12%), postoperative pain (2.85%), and other types of pain (1.14%) [73]. The mean pain score was  $9.2 \pm 1.09$  at baseline, which was reduced to  $5.6 \pm 1.27$  at day 2 (mean reduction  $-3.7 \pm 1.41$ ) and  $2.8 \pm 1.73$  at day 5 ( $-6.4 \pm 2.18$  from baseline). The percentage of patients with severe pain was reduced from 100% at baseline to 18.3% at day 2 and 6.96% at day 5. More than 60% of patients rated the effectiveness of treatment as “very good to good” [73]. These results substantiated the findings of the phase III trial. In both studies, on tramadol/diclofenac FDC tablet was administered twice daily, whereas tramadol/paracetamol FDC was prescribed at a dosage of two tablets every 4–6 h, up to a maximum of eight tablets daily [68, 72]. Tramadol/diclofenac FDC

offered effective treatment at low doses of individual drugs and reduced the overall pill burden. Severity of pain is an important factor in the selection of analgesic agents by health-care professionals. Joint pain, traumatic pain, and musculoskeletal conditions are highly prevalent and the most common cause of severe acute pain and physical disability. These two studies support the use of a tramadol/diclofenac FDC, which targets multiple pain pathways and pain transmitter substances, in the management of patients with acute severe inflammatory and traumatic pain [68, 72].

In addition to the tramadol/diclofenac FDC studies mentioned above, several other studies have shown adequate pain control with the tramadol/diclofenac combination compared with either of the individual drugs or with paracetamol [35, 74]. In a randomised trial, pain intensity ratings at rest were significantly lower with the tramadol/diclofenac combination than with tramadol/placebo (at 30 min, 6 h, and 7 h post-injection,  $p < 0.04$ ) and double placebo (at 30 and 60 min and 6 and 7 h,  $p < 0.05$ ) when administered intramuscularly in women undergoing Caesarean section [34]. Pain ratings during movement were lower with the tramadol/diclofenac combination than with double placebo at 60 min and 6 h post-injection ( $p < 0.04$  and  $p < 0.0008$ , respectively) [34]. Post-Caesarean section intramuscular





**Fig. 2** a Reduction in mean VAS score (pooled data) [68]. b Reduction in mean VAS score in subgroup [68]. c Reduction in WOMAC score in AFOA and total HAQ score for pain in AFRA [68]. \*All  $p < 0.05$  for tramadol + diclofenac vs. tramadol + paracetamol. VAS Visual Analog Scale, WOMAC Western Ontario and McMaster Universities Osteoarthritis Index, AFOA Acute Flare-up of Osteoarthritis, HAQ Health Assessment Questionnaire, AFRA Acute Flare-up of Rheumatoid Arthritis, AMSP Acute Musculoskeletal Pain, POP Post-operative Pain

administration of tramadol/diclofenac combination reduced both primary and secondary hyperalgesia compared with their monotherapy, which reduced only primary hyperalgesia. This has significant clinical relevance, as surgery

causes hyperalgesia and allodynia at both local and distal sites [34].

In another randomised, double-blind, parallel-group study, Mitra et al. compared diclofenac/tramadol with diclofenac/paracetamol for pain relief after Caesarean section, which showed that overall pain scores for the entire observational period, measured as AUC, were significantly lower in the diclofenac/tramadol group [74]. In another randomised trial, tramadol/diclofenac had shorter onset and longer duration of analgesia and reduced AE incidence compared with the individual drugs [35].

### TOLERABILITY

This section focuses on tolerability data from the clinical trials discussed above. Chandanwale et al. assessed the safety of tramadol/diclofenac FDC versus tramadol/paracetamol FDC in patients with acute severe pain with respect to changes in swelling score, inflammation score, and number of rescue medications needed (Table 2) [68]. The tramadol/diclofenac FDC was associated with fewer AEs. The proportion of patients who experienced AEs on day 5 was significantly lower in the tramadol/diclofenac FDC group compared with the tramadol/paracetamol FDC group ([8.82%] vs. 21.78%,  $p = 0.019$ ). Most frequently observed AEs were nausea and vomiting, and their incidence was numerically greater in patients receiving tramadol/paracetamol FDC (Table 2). The swelling and inflammation scores and the need for rescue medication were low on both day 3 and day 5 in patients receiving tramadol/diclofenac FDC (Table 2). Global tolerability assessment was good in 77% of patients treated with tramadol/diclofenac FDC, compared with 42% for tramadol/paracetamol FDC ( $p < 0.0001$ ). Differences in the incidence of AEs were attributable to different doses of FDCs. Nausea and vomiting are important dose-dependent GI AEs which are associated with tramadol and can be prevented prophylactically by treatment with antiemetic and gastro-protective agents. Shah et al. observed similar results: global tolerability was rated as very good to good in 68.36% of patients treated with tramadol/

**Table 2** Safety and tolerability parameters for tramadol/diclofenac FDC and tramadol/paracetamol FDC (pooled data) [68]

Safety parameter	Tramadol + diclofenac ( <i>n</i> = 102)	Tramadol + paracetamol ( <i>n</i> = 101)	<i>p</i> value
Mean swelling score <sup>a</sup>			
Baseline mean (SEM)	1.88 (0.91)	1.84 (0.90)	0.805
Day 3	−0.94 (−50.00)	−0.41 (−22.32)	0.0001
Day 5	−1.44 (−76.69)	−0.93 (−50.57)	0.0001
Total inflammation score <sup>a</sup>			
Baseline mean (SEM)	3.44 (1.64)	3.22 (1.58)	0.373
Day3	−1.83 (−53.05)	−0.90 (−28.05)	0.0001
Day 5	−2.82 (−81.99)	−1.75 (−54.21)	0.0001
Rescue medication <sup>b</sup>			
Baseline	1 (4)	2 (10)	
Day 3	2 (3)	2 (7)	
Day 5	1 (2)	2 (5)	
Total no. of tablets, (%)	8 (7.92)	44 (43.56)	< 0.0001
Total no. of patients, (%)	9 (8.91)	22 (21.78)	0.0193
Adverse events, <i>n</i> (%)			
Day 3			
Drowsiness	0 (0)	1 (0.98)	
Epigastric pain	1 (0.98)	1 (0.98)	
Gastritis	3 (2.94)	5 (4.90)	
Nausea	6 (5.88)	23 (22.55)	
Vomiting	6 (5.88)	16 (15.69)	
Total events	16 (15.68)	46 (45.10)	< 0.0001
Day 5			
Drowsiness	0 (0)	0 (0)	
Epigastric pain	1 (0.98)	2 (1.96)	
Gastritis	2 (1.96)	0 (0)	
Nausea	4 (3.92)	14 (13.73)	
Vomiting	2 (1.96)	6 (5.88)	
Total events	9 (8.82)	22 (21.57)	0.019

FDC fixed-dose combination, SEM standard error of the mean

<sup>a</sup> All data points are mean change (% change) unless otherwise indicated

<sup>b</sup> All data points are number of tablets (number of patients unless mentioned)

diclofenac FDC [73]. In this study, five (1.42%) patients developed nine GI-related AEs; however, these AEs resolved after drug discontinuation [73]. In a study by Mitra et al. the incidence of side effects and the use of rescue analgesics were similar ( $p = 0.872$ ) in patients treated with intravenous tramadol/diclofenac combination compared with tramadol/paracetamol combination [74]. A low incidence of vomiting, drowsiness, and dizziness was reported in patients undergoing elective Caesarean section under spinal anaesthesia who were treated with diclofenac/tramadol FDC compared with monotherapy with either drug [35]. The incidence of nausea and vomiting in this study was comparable to those reported by Smith et al. [34].

## CURRENT PLACE OF TRAMADOL/DICLOFENAC IN MANAGEMENT OF SEVERE ACUTE PAIN

According to the WHO ladder, the combination of paracetamol or NSAIDs (diclofenac) with weak opioids (tramadol, codeine) is considered as the second step in the treatment of pain, based on an increase in the severity of pain [23, 68]. Similarly, an expert panel consensus for pharmacological treatment of acute pain in the Middle East recommends NSAIDs or selective COX inhibitors: diclofenac as step 2 treatment for severe pain and as step 1 for patients for whom paracetamol provides inadequate analgesia. Tramadol is also recommended as a widely prescribed step 2 analgesic in clinical practice for acute pain [75]. Given the multimodal origin of pain pathways, the concept of a platform, rather than a ladder, for appropriate selection of analgesic agents has recently gained popularity [23]. A clinician may choose an appropriate platform to explore treatment options based on a patient's clinical characteristics [23]. Recent pain management guidelines have recognised the importance of multimodal analgesia for the treatment of acute pain [23, 76–79]. The objective of multimodal analgesia is to enhance analgesia and reduce potential AEs by combining analgesics from different drug classes with different modes of

action [23, 80]. This can be attained by freely combining analgesics or with FDCs, the latter being simpler and more convenient to use [23, 80]. Tramadol/diclofenac FDC provides multimodal analgesic pain relief due to complementary and synergistic mechanisms of action, with a lower risk of AEs and dependency. Clinical studies evaluating tramadol/diclofenac FDC have so far demonstrated a safe, effective, and well-tolerated profile. We believe that this multimodal analgesic FDC may be used in routine clinical practice based on individualised patient needs.

## LIMITATIONS

Currently, data supporting the efficacy and safety of tramadol/diclofenac combinations are scarce. This review provides interesting insights into the efficacy and safety of tramadol/diclofenac FDC for management of acute severe pain in randomised and real-life settings. However, the effects of this combination are yet to be evaluated in special populations such as older patients or those with cancer, and hence should be the subject of future research.

## CONCLUSIONS

Current clinical evidence supports the efficacy of tramadol/diclofenac FDC versus tramadol/paracetamol FDC for the treatment of acute severe pain. Further, the low-dose regimen of tramadol/diclofenac FDC reduces the incidence of AEs and improves patient compliance. Therefore, tramadol/diclofenac FDC could be an effective alternative to tramadol/paracetamol FDC for the treatment of acute pain. However, studies evaluating the benefits in special populations are needed. In our opinion, tramadol/diclofenac FDC appears to be an effective and well-tolerated multimodal analgesic FDC for short-term treatment of acute severe pain and could be recommended in routine clinical practice.

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