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REVIEW ARTICLE

Revisiting Tramadol: A Multi-Modal Agent for Pain Management

Ahmed Barakat[1]

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Abstract
Tramadol—an atypical opioid analgesic—has a unique pharmacokinetic and pharmacodynamic profile, with opioidergic, noradrenergic, and serotonergic actions. Tramadol has long been used as a well-tolerated alternative to other drugs in moderate pain because of its opioidergic and monoaminergic activities. However, cumulative evidence has been gathered over the last few years that supports other likely mechanisms and uses of tramadol in pain management. Tramadol has modulatory effects on several mediators involved in pain signaling, such as voltage-gated sodium ion channels, transient receptor potential V1 channels, glutamate receptors, α_2-adrenoceptors, adenosine receptors, and mechanisms involving substance P, calcitonin gene-related peptide, prostaglandin E_2, and proinflammatory cytokines. Tramadol also modifies the crosstalk between neuronal and non-neuronal cells in peripheral and central sites. Through these molecular effects, tramadol could modulate peripheral and central neuronal hyperexcitability. Given the broad spectrum of molecular targets, tramadol as a unimodal analgesic relieves a broad range of pain types, such as postoperative, low back, and neuropathic pain and that associated with labor, osteoarthritis, fibromyalgia, and cancer. Moreover, tramadol has anxiolytic, antidepressant, and anti-shivering activities that could improve pain management outcomes. The aim of this review was to address these issues in the context of maladaptive physiological and psychological processes that are associated with different pain types.

Key Points

Tramadol attenuates the hyperexcitability of nociceptive neurons in incisional, inflammatory, and neuropathic pain by interfering with peripheral and central sensitizing mediators.

Tramadol has wide applicability in different pain conditions, including postoperative, labor, neuropathic, and low back pain.

Tramadol has other applications in pain management aside from the analgesic and anti-hyperalgesic modalities, including antidepressant, anxiolytic and anti-shivering roles.

1 Pain

1.1 Pain Burden

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [1]. Pain, in its physiologic form as acute pain, acts as a warning sign against potential tissue damage and as such has an adaptive defensive role to maintain the integrity of tissues and organs. However, pain encountered in clinical settings, especially persisting and chronic pain, is pathophysiological and deviates from this paradigm and contributes to patient morbidity and mortality [2, 3]. A great deal of attention has been paid to effective control of pain due to increased awareness of its consequences. The World Health Organization (WHO) global burden of disease report in 2015 indicated that the leading cause of disability worldwide is pain, and this has been the case since 1990 [4].

Unrelieved pain has adverse effects on different biological systems, such as endocrine, immunological, cardiovascular, gastrointestinal, urinary, and musculoskeletal systems. These effects collectively constitute the classic stress response [2]. Although stress response has an adaptive function to

✉ Ahmed Barakat
ahmedbarakat@aun.edu.eg

[1] Department of Medical Pharmacology, Faculty of Medicine, Assiut University, Assiut 71515, Egypt

promote survival in case of tissue injury, its persistence increases patient morbidity and might lead to shock [2]. Pain also has a significant impact on quality of life, especially in patients with chronic pain. One of the most important consequences of unrelieved pain is the development of anxiety and depression as common comorbidities [5, 6]. This has resulted in the use of anxiolytics and antidepressants as adjuvants during pain management [7]. The economic costs of untreated pain, either as direct or indirect expenses, have also risen dramatically [8].

Despite the increased awareness of its consequences, pain is undertreated, and this includes acute pain [9], cancer pain [10], low back pain [11], neuropathic pain [12], and osteoarthritis pain [13]. It has been proposed that further understanding of pain signaling mechanisms and mediators, together with improved knowledge about the pharmacology of different analgesic agents would substantially enhance pain control in different patient populations [3].

1.2 Pain Neuroplasticity

Significant advances in understanding the pathophysiologic basis of different pain types have been realized over the past few decades. Perhaps the most significant of these is that pain, though signaled through neurons, is not a hard-wired process but rather a dynamic one with changes in activity and strength depending on many factors, such as genetic [14], epigenetic [15], and environmental features [16]. Among the most important pain-modulating factors are the stimulus intensity and duration, whereby intense long-term stimulus induces biochemical, transcriptional, and structural changes in different pain-processing stages i.e., activity-dependent plasticity [17]. Another important discovery suggests that pain is not mediated solely via neuronal cells but also via non-neuronal cells, i.e., macrophages and glial cells actively precipitate pathological pain [18]. These non-neuronal cells act peripherally and centrally in a synergistic way to modulate pain [19]. Thus, pain could be viewed as neuronal/neuronal cell interactions and non-neuronal/neuronal cell interactions.

Understanding the dynamic nature of pain helps to highlight the analgesic and anti-hyperalgesic mechanisms of tramadol. This is important given that pain management is moving from empirical symptom control to mechanism-based pharmacological approaches [3, 20].

1.3 Peripheral and Central Sensitization

The increased sensitivity to stimuli that occurs in the periphery after tissue injury is termed peripheral sensitization and manifests as primary hyperalgesia. This process involves the action of a group of chemical mediators, for example, protons, bradykinin, substance P (SP), prostaglandin E_2 (PGE_2), histamine, serotonin (5-HT), adenosine triphosphate (ATP), proinflammatory cytokines, neuropeptides, and nerve growth factor [21], that are known collectively as "peripheral sensitizing soup" [2]. These mediators can cause direct stimulation of nociceptors, generating nerve impulses, or can sensitize nociceptors, increasing their excitability by lowering their activation threshold. Primary targets of these mediators are ion channels, and these are affected either directly via ligand-gated ion channels or indirectly via changes in the level of secondary messengers and transcriptional and post-transcriptional changes [21]. For example, protons directly activate acid-sensitive ion channels and heat-sensitive transient receptor potential V1 (TRPV1) channels, ATP activates P2X receptors, and 5-HT activates 5-HT_3 receptors. On the other hand, mediators such as PGE_2, cytokines, SP, and nerve growth factor indirectly activate nociceptors via phosphorylation or increased ion channel expression. The intermediary molecules of this process are cyclic adenosine monophosphate (cAMP), calcium, protein kinase A, and protein kinase C [22].

Continued exposure to intense impulse activity from peripheral C fibers initiates a state termed central sensitization, manifesting as spinal neuron hyperexcitability [23]. This then persists beyond the initiating stimulus via transcriptional and structural changes in the spinal cord [24]. In central sensitization, dorsal horn neurons are spontaneously active, with increased discharge, expanded receptive field, and decreased descending inhibitory pathway [25]. Manifestations of central sensitization are secondary hyperalgesia (exaggerated response to suprathreshold stimuli of uninjured tissue produced by Aδ fibers), allodynia (response to subthreshold stimuli produced by Aβ fibers), referred pain (response from uninjured tissue), and persistent pain (prolonged response after transient stimulus) [25]. Although central sensitization needs peripheral sensitization to develop, once it is established, peripheral input plays little or no role in maintaining it. This development in understanding followed the finding that local anesthetics have little effect on central sensitization when administered peripherally [26]. Hence, the attenuation of peripheral nociceptive input would have only a limited impact on effective pain management [17].

Central sensitization depends on various neurotransmitters, pro-inflammatory mediators, and secondary messengers. These factors collectively constitute what could be characterized as "central sensitizing soup". One of the key mediators of central sensitization is the action of glutamate on N-methyl-D-aspartate (NMDA) receptors [2]. Cyclooxygenase (COX)-2 and its product PGE_2 also contribute to central sensitization [27]. Other important mediators include glial cell activation—with the subsequent release of nitric oxide (NO)—ATP, reactive oxygen species, and proinflammatory cytokines [28]. SP, dynorphin, and neurokinin A

participate in central sensitization. These different mediators form positive feedback loops, i.e., every member stimulates the release of other mediators and consequently increases synaptic transmission strength. Attenuation of these molecular targets via NMDA antagonists, COX inhibitors, and glial inhibitors has proven efficacious in alleviating central sensitization [3, 17, 29].

All those changes culminate in the development of long-term potentiation (LTP) at central synapses, which represents a convergence point for different hyperalgesia-associated conditions [30, 31]. An interesting observation regarding central sensitization is its role in diverse pain states. Central sensitization plays an active role in post-injury hypersensitivity, various chronic pain conditions (rheumatoid arthritis, osteoarthritis, fibromyalgia, neuropathic pain, and headache), transition from acute to chronic pain, and opioid-induced hyperalgesia [17, 29, 32–34]. Central sensitization is suggested to be a common etiology of these different syndromes, which in turn indicates that targeting neuronal hyperexcitability would have efficacy in different pain types [17].

Collectively, these data demonstrate that peripheral and central sensitization could be represented as a gymnastic barbell, with peripheral and central components representing the ends of the barbell. Hence, effective alleviation of pain requires dual modulation at both sites (Fig. 1a).

2 Tramadol

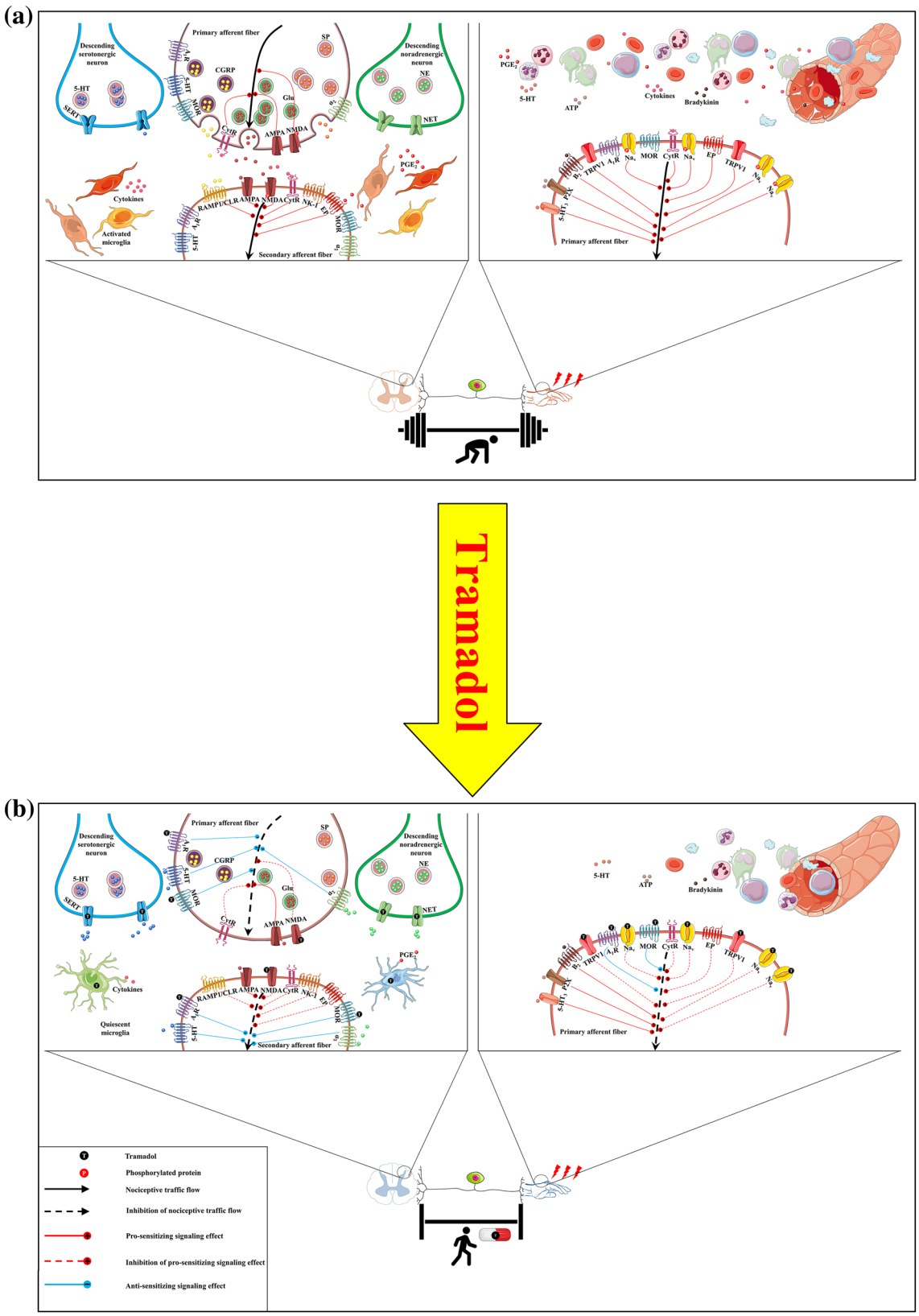
2.1 Tramadol Pharmacology

Tramadol is a synthetic analog of morphine and codeine with a unique mechanism of action and pharmacological effects that differ from those of other opioid drugs. Table 1 summarizes pharmacokinetic data for tramadol following oral and parenteral administration [35–38]. The main pharmacological effect of tramadol is alleviation of pain. Traditionally, tramadol analgesia has been attributed to opioidergic and monoaminergic effects [35–37], but other potential mechanisms and mediators that contribute to tramadol analgesia have been identified over the past few years as discussed in Sects. 2.2 and 2.3. Tramadol also affects muscarinic (M1 and M3) [39, 40], nicotinic (α_7) [41], and serotonergic (5-HT_{2C}) receptors [42] and K^+ (delayed rectifier) ion channels [43]. However, the contribution of these effects to tramadol analgesia remains unclear. Tramadol has demonstrated efficacy in different pain types, including incisional and neuropathic pain, both acute and chronic pain, and pain of moderate to severe intensity [35–37]. Tramadol is recommended as a suitable drug for step 2 of the WHO Analgesic Ladder [44]. This wide spectrum of tramadol efficacy was reflected in the 2016 US drug spending report, as tramadol was among the top 20 prescribed medications [45]. Despite this, tramadol is not listed in the WHO essential medicines report [46], albeit it is included in other national reports of essential medicines [38].

Tramadol has a favorable adverse effect profile and is well-tolerated, with the most frequent adverse effects being nausea (6.1%), dizziness (4.6%), drowsiness (2.4%), fatigue (2.3%), sweating (1.9%), vomiting (1.7%), and dry mouth (1.6%) [37]. Other less common adverse effects include diarrhea and cardiovascular complications (tachycardia and postural hypotension; 0.1–1%) [38]. Respiratory depression, convulsions, tremors, bradycardia, hallucinations, and anxiety are rare (0.01–0.1%) [38]. Tramadol was reported as having a minimal effect on respiration at the recommended dosage in different clinical settings, even childbirth. The respiratory-depressant effect of tramadol is less than that of morphine, nalbuphine, buprenorphine, oxycodone, and pethidine. Cases of tramadol-precipitated respiratory depression showed parenteral administration of supra-therapeutic doses of tramadol 1000 mg in respiratory-compromised patients. This advantage is likely to benefit patients with respiratory disease, children, those in labor, and day-surgery patients [35–37]. Similarly, tramadol exerts few hemodynamic effects [35–37]. Another advantage of tramadol is the qualitative and quantitative similarity of the adverse effect profile with short- and long-term administration. Hence, unlike morphine, tramadol has no cumulative adverse effects that manifest with repeated administration [35–37]. Tramadol is described as having a pro-convulsant effect, with an estimated seizure frequency of $< 1\%$ [47]. However, this incidence is no different from that associated with other analgesics.

Overdose of tramadol is associated with lethargy (30%), nausea (14%), tachycardia (13%), agitation (10%), seizures (8%), coma (5%), hypertension (5%), respiratory depression (2%), and serotonin syndrome [35–37]. Tramadol toxicity is not considered lethal [35–37] and is relatively safe compared with other classic opioid analgesics [38]. Tramadol intoxication frequently includes co-ingestion of other drugs or alcohol [38]. Treatment of tramadol overdose involves respiratory support, administration of an opioid antagonist, naloxone or nalmefene, and anticonvulsant drugs, e.g., benzodiazepines in case of seizures [48].

Regarding the potential for tramadol dependence, animal studies showed that tramadol might produce physical dependence with mild withdrawal symptoms, but this was not reported in all studies [49, 50]. Human studies reported the dependence potential was low compared with that of morphine [50]. This was attributed to the lower affinity of tramadol and its metabolite to the μ-opioid receptor (MOR).


(a)
Descending serotonergic neuron
5-HT
SERT
Primary afferent fiber
CGRP
5-HT
MOR
CytR
Glu
AMPA
NMDA
SP
Descending noradrenergic neuron
NE
NET
PGE2
5-HT
ATP
Cytokines
Bradykinin
Na+
MOR
CytR
Ep
TRPV1
Primary afferent fiber
Cytokines
Activated microglia
RAMP1/CLR
NK-1
Secondary afferent fiber
Tramadol
(b)
Quiescent microglia
Tramadol
Phosphorylated protein
Nociceptive traffic flow
Inhibition of nociceptive traffic flow
Pro-sensitizing signaling effect
Inhibition of pro-sensitizing signaling effect
Anti-sensitizing signaling effect

◂**Fig. 1** **a** Tissue injury initiates peripheral and central sensitization through activating a plethora of mediators. Peripheral mediators include Na_v, TRPV1 channels, cytokines, PGE_2, bradykinin, adenosine, and serotonin. Central mediators comprise Glu, SP, cytokines, PGE_2, CGRP, macrophage polarization, and glial activation. This sensitization places a heavy burden on patient life quality. **b** Tramadol administration results in inhibiting neuronal sensitization via interfering with several key mediators. Molecular targets of tramadol include Na_v, TRPV1 channels, MOR, NET, SERT, NK-1, AMPA, NMDA, A_1 receptors, PGE_2, cytokines, CGRP release, and inhibiting macrophage polarization and activated glial cells. This in turn could alleviate pain burden. *5-HT* serotonin, *5-HT*$_3$ ionotropic serotonin receptor 3, *A*$_1$*R* adenosine receptor 1, *AMPA* amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, *ATP* adenosine triphosphate, *B*$_2$ bradykinin receptor 2, *CGRP* calcitonin gene-related peptide, *CLR* calcitonin-like receptor, *CytR* cytokine receptor, *EP* prostaglandin E_2 receptor, *Glu* glutamate, *MOR* μ-opioid receptor, *Na*$_v$ voltage-gated sodium ion channel, *NE* norepinephrine, *NET* norepinephrine transporter, *NK-1* neurokinin-1 receptor, *NMDA* N-methyl-D-aspartate receptor, *P2X* adenosine triphosphate ionotropic receptor, *PGE*$_2$ prostaglandin E_2, *RAMP1* receptor activity modifying protein 1, *SERT* serotonin transporter, *SP* substance P, *TRPV1* transient receptor potential V1

Tramadol abuse potential increases with chronic administration. Tramadol withdrawal symptoms are similar to those in classic opioid abstinence syndrome and include restlessness, agitation, anxiety, sweating, insomnia, hyperkinesia, tremor, paresthesias, and gastrointestinal symptoms [38].

Self-administration studies in animals showed low abuse potential compared with morphine [38, 50, 51]. Clinical studies reported reinforcing effects of tramadol, but these were mild with less abuse potential than morphine [38, 50, 52]. This was confirmed by an epidemiologic study that extended over 14 years in Germany [53], and a post-marketing surveillance study in the US reached a similar conclusion [54]. Tramadol abuse is greater in individuals with a history of substance abuse, with an increasing incidence in African and West Asian countries. A WHO expert committee on drug dependence noted that tramadol's status as a controlled drug differed internationally [38]. A risk-benefit assessment report of tramadol use in acute and chronic pain endorsed tramadol use in those conditions except for severe cancer pain and during general anesthesia [55]. The WHO expert committee also stated that tramadol is a relatively safe drug with a dependence and abuse potential lower than that of morphine [38].

2.2 Tramadol: Old and New Molecular Targets

Interestingly, molecular targets of tramadol are integral parts of the development of peripheral and central sensitization. Hence, through these molecular effects, tramadol could modulate peripheral and central neuronal hyperexcitability (Fig. 1b). Table 2 lists all the receptors and sites of tramadol action.

2.2.1 Effects of Tramadol on Neuronal/Neuronal Cell Interactions

Tramadol binds with low affinity (6000-fold less than that of morphine) to MOR and weakly to κ- and δ-opioid receptors. Tramadol's active metabolite (M1) contributes significantly to its analgesic effects. MOR produces analgesia at three levels: supraspinal, spinal, and peripheral. Supraspinal analgesia is mediated at the thalamus, midbrain periaqueductal gray (PAG), and the rostral ventromedial medulla (RVM) [56]. Spinal action occurs through inhibition of the ascending pain pathway via closure of presynaptic Ca_v channels and activation of postsynaptic K_v channels, resulting in decreasing nociceptive transmitter release and postsynaptic neuronal inhibition, respectively, and activation of the descending modulatory pain pathway via neuronal disinhibition. Opioid receptors on sensory nerve endings mediate a peripheral analgesic role via decreased peripheral firing of nociceptive stimuli [35–37, 57, 58].

Tramadol inhibits the reuptake of norepinephrine (NE) and 5-HT [35–37]. This transporter-blocking activity was achieved at concentrations that activate opioid receptors [$K_i = 2.1$ μM; $K_i = 0.78$ μM for the norepinephrine transporter (NET) and $K_i = 0.9$ μM for the serotonin transporter (SERT)] [35, 36]. NE and 5-HT are involved in the modulation of pain via activation of descending pain inhibitory pathways from the PAG and pons to secondary neurons of the spinal cord [59]. Much evidence has accumulated in both animal and human studies that supports the dual synergistic nature of tramadol analgesia [35–37]. Administration of the opioid antagonist naloxone resulted in partial antagonism of tramadol analgesia. Similar results were obtained with the α_2-adrenoceptor (α_2AR) blocker yohimbine and the 5-HT_2 antagonist ritanserin [35–37].

Voltage-gated sodium ion channels have a well-recognized effect in the transduction and transmission of pain impulses and generation of ectopic impulses. Tramadol blocked $Na_{V1.2}$ ion channels in vitro [60]. In vitro, tramadol's blocking activity had similar kinetics to those of lidocaine with a higher affinity to fast inactivated sodium ion channels than to resting channels, and exhibited use-dependent blockade [60]. Hence, tramadol would not only suppress nerve conduction but also inhibits ectopic activities in sensitized neurons. This was confirmed in rat sciatic nerve preparations where tramadol and lidocaine produced the same conduction block with frequency dependence [61]. The membrane-stabilizing effect of tramadol was achieved at a higher concentration (half maximal inhibition (IC_{50}) = 21 μM) than the typical plasma concentration of tramadol (1 μM) after a dose of 50 mg [60]. However, other in vivo studies reported that the local anesthetic concentration of tramadol did not significantly differ from that of established local anesthetics [62–64]. Other clinical

Table 1 Pharmacokinetic properties of tramadol and its active metabolite, M1, after oral (single and repeated) and intravenous administration

Pharmacokinetic process	Parameter/route	Single oral		Multiple oral		Intravenous
		Parent compound	M1 metabolite	Parent compound	M1 metabolite	
Absorption	Bioavailability (%)	67.9		> 90		100
	Peak plasma conc. (μg/L)	308	55	592	110	347.4
	Time to peak plasma conc. (h)	1.6	2.97	2.25	2.43	
Distribution	Distribution half-life (h)					0.1 then 1.7
	Volume of distribution (L)	306				203
	Plasma protein binding (%)	20				
	Placental distribution[a]	80				
Elimination	Elimination half-life (h)	5.64	6.69	6.71	6.98	5.5
	Renal clearance (L/h)	6.6	11.3	4.38	8.04	
	Total clearance (L/h)	43				28
	Renal excretion (%)	90				
	Unchanged excretion (%)	10–30	15			16
	Milk excretion (%)	0.1	0.1			
Area under curve (μg/L·h)		2649	722	3679	835	1556
Effective plasma concentration (μg/L)	100–300					
Pharmacokinetic model	Linear over the dose range 50–400 mg					
Duration (h)	Normal-release tablets: 4–6; extended-release tablets: 24					
Dosage range (mg)	50–400 due to increased risk of adverse effects such as seizures					

The Pharmacokinetic of oral and intravenous tramadol do not differ significantly between adults and children [38]

[a]% of maternal plasma concentration

Table 2 Summary of tramadol's pharmacological targets that could contribute to its analgesic and anti-hyperalgesic activities

Pharmacological target	Location	Pro-/anti-nociceptive effect	Effect of tramadol	Documented contribution to tramadol analgesia	References
Neuronal/neuronal cell targets					
μ-Opioid receptor	Peripheral + Central	Anti	Stimulate	Yes	[35–37]
Norepinephrine and serotonin transporters	Central	Pro	Inhibit	Yes	[35–37]
Voltage-gated sodium ion channels	Peripheral + Central	Pro	Inhibit	Yes	[62–64]
Transient receptorpotential V1, Transient receptor-potential ankyrin 1	Peripheral + Central	Pro	Initially stimulate then inhibit	No	[70, 71]
N-methyl- D-aspartatereceptors	Central	Pro	Inhibit + dephosphorylate	Yes	[72, 122]
Neurokinin 1 receptor	Central	Pro	Inhibit	No	[76]
Calcitonin gene-related peptide	Central	Pro	Inhibit release	No	[82]
Adenosine A_1 receptors	Peripheral + Central	Anti	Stimulate	Yes	[83]
α_2-Adrenoceptors	Central	Anti	Stimulate	Yes	[87, 90]
Non-neuronal/neuronal cell targets					
Cytokines	Peripheral + Central	Pro	Inhibit release	Yes	[92–95]
Prostaglandin E_2	Peripheral + Central	Pro	Inhibit release	Yes	[100, 101]
Nuclear factor-κB	Peripheral + Central	Pro	Inhibit activation and expression	Yes	[102]
Nitric oxide	Peripheral + Central	Controversial	Controversial	Controversial	[109, 110]
M1 macrophages	Peripheral	Pro	Change polarization state	No	[111]
Activated glial cells	Central	Pro	Inhibit	Yes	[94, 113, 114]

studies that employed regional applications of tramadol supported its local anesthetic activity, for example, intradermal injection of tramadol produced loss of pain, touch, and temperature sensations [65]. Similar studies found that tramadol, like lidocaine and other local anesthetics, inhibited incisional pain and propofol injection pain [63, 66]. A possible explanation for this discrepancy is the sodium channel type involved. Peripheral sensory nerves harbor different types of sodium ion channels, such as $Na_{v1.1}$, $Na_{v1.7}$, $Na_{v1.8}$, and $Na_{v1.9}$. Tramadol could affect these types within its therapeutic range, but this remains to be investigated. Interestingly, the local anesthetic activity of tramadol was demonstrated in central synapses, where it produced central neural blockade after intrathecal injection in rats [67]. The local anesthetic activity of tramadol is not related to binding to MOR or inhibition of NET and SERT [68]. Tramadol analgesia was higher when administered locally rather than systematically, which might be attributed to higher local concentrations [69].

Tramadol also has actions at TRPV1 channels. In an in vitro study, tramadol activated the TRPV1 channel similarly to capsaicin, and its action was antagonized by capsazepine (TRPV1 receptor antagonist) [70]. This agonist activity was followed by tachyphylaxis. The action of tramadol on this channel could participate in its analgesic activity via desensitization of neurons in a similar manner to capsaicin. The half maximal effective concentration (EC_{50}) of this effect was 0.08 ± 0.03 μM, which is within the systemic therapeutic range. In support of this notion, local administration of tramadol caused an initial burning sensation, pain, and erythema before the local anesthetic effect developed. Another in vitro study reported that tramadol did not affect this ion channel but rather blocked transient receptor potential ankyrin 1 (TRPA1) at concentrations of 0.1–10 μM. This ion channel is also expressed in sensory neurons with TRPV1 and is involved similarly in pain transmission and cold hyperalgesia [71]. This discrepancy was attributed to a difference in cell culture lines.

Tramadol and its active metabolite non-competitively blocked NMDA receptors in a dose-dependent manner in vitro [72]. Moreover, in vivo, tramadol blocked nociception induced by glutamate injection in the periphery [62]. Similarly, tramadol administered via intraperitoneal and intrathecal routes inhibited glutamate and amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-induced biting behavior in experimental mice [73]. Another line of evidence comes from studies of tramadol as an antidepressant. Tramadol exerted antidepressant activity in the forced swimming test, which was attributed to NMDA-blocking activity [74]. Given the critical role of glutamate in nociception and neuroplastic changes in nociceptive transmission, it could be anticipated that tramadol might have a robust modulatory effect on this neuroplasticity.

Another potential mechanism of tramadol analgesia is blocking of the SP receptor, neurokinin-1 (NK1). The tramadol parent compound had little effect on NK1 expressed on *Xenopus* oocytes in vitro [75], but its active metabolite, *O*-demethyl tramadol, suppressed the receptor at clinically relevant concentrations [76]. In an in vivo study, tramadol blocked SP-induced biting behavior in mice [73]. SP is a primary neurotransmitter of afferent neurons of the ascending pain pathway; it is also involved in pain sensitization and cytokine release after tissue injury [77]. Several clinical trials have demonstrated the efficacy of tramadol in relieving osteoarthritis pain [78], activity that was attributed in one study to a significant reduction of synovial fluid concentrations of SP [79].

The role of calcitonin gene-related peptide (CGRP) is well-delineated in incisional, inflammatory, and neuropathic pain [80]. It has a dynamic role in the development and maintenance of peripheral and central sensitization to nociceptive stimuli [81]. In vitro, tramadol and tapentadol inhibited CGRP release centrally via serotonergic mechanisms mediated via $5\text{-}HT_3$ receptors [82]. This effect was achieved at clinically relevant tramadol concentrations (0.001–100 μM) [82].

Recently, tramadol's antinociceptive action was shown to be mediated via adenosine A_1 receptors in vivo [83]. Adenosine A_1 receptors are located along the ascending pain pathway from peripheral to spinal to supraspinal sites and exert analgesic activity along this pathway [84]. Tramadol demonstrated analgesic activity in a formalin pain model when administered systemically and peripherally. This activity was reversed by administration of caffeine (non-selective adenosine receptor antagonist) and DPCPX (selective A_1 receptor antagonist). Peripheral and spinal A_1 receptors contributed to this analgesic activity [83]. Peripheral A_1 receptors produce a decrease in the signaling of cAMP, protein kinase A, and NO/cyclic guanosine monophosphate (cGMP)/protein kinase G. Spinal actions of A_1 receptors include pre- and post-synaptic inhibition of spinal neurons, decreased glutamate and neuropeptide release from primary afferent neurons, increased NE release from descending neurons, and decreased microglial activation. Supraspinal mechanisms are increased K_v channel conductance with hyperpolarization and decreased γ-amino-hydroxy butyric acid (GABA) transmission in the PAG. The wide array of adenosine actions explains its efficacy in inflammatory and neuropathic pain [84].

α_2ARs located mainly in the spinal cord mediate the analgesic action of clonidine and other α_2-agonists [85]. Spinal α_2ARs regulate several mechanisms to inhibit nociceptive transmission, such as decreasing neurotransmitter release from first-order neurons through closing of Ca_v ion channels, hyperpolarizing dorsal horn neurons through opening K_v ion channels, inhibiting adenylate cyclase and thereby cAMP

formation, and decreasing sympathetic outflow at the spinal cord level and the adrenal gland, given that NE plays an active role in sympathetically maintained pain [86]. Tramadol binding to α_2AR was confirmed via radioligand-binding assay in vivo [87]. Similar findings were reported from studies of locus coeruleus (LC) activity, where in vitro and in vivo studies showed that tramadol attenuated LC activity indirectly through α_2AR [88, 89]. This attenuation was not related to tramadol opioid activity but rather to increased extracellular NE concentrations secondary to inhibition of NET, similar to antidepressants [88, 89]. Tramadol's effect on these receptors was achieved at clinically relevant concentrations (0.1–100 μM) [89]. Yohimbine (α_2AR blocker) blocked the analgesic effects of tramadol [90].

2.2.2 Effects of Tramadol on Non-Neuronal/Neuronal Cell Interactions

In addition to effects on signaling between neurons, tramadol also has multiple effects on inflammatory mediators, signaling molecules, and cells. Various types of pain are associated with elevation of pro-inflammatory cytokine levels, and tramadol analgesia is associated with a decrease in these levels. For example, incisional pain in experimental rodents increased serum interleukin (IL)-6 and IL-2. Tramadol analgesia in these animals was associated with attenuation of the elevated cytokine levels [91]. Similarly, in osteoarthritis, tramadol decreased both the intensity of the joint pain and the rise in IL-6 levels [79]. In different preclinical pain models and clinical neuropathic pain (chronic constriction injury, spinal nerve ligation, herniated intervertebral disks, and carpal tunnel syndrome), tramadol diminished the elevations of pro-inflammatory cytokines IL-1β and tumor necrosis factor (TNF)-α and increased levels of the anti-inflammatory cytokines IL-10 [92–95].

PGE_2 is a well-known mediator of peripheral and central hyperalgesia [96, 97]. Analgesia by COX inhibitors is attributed in part to inhibition of the formation of this key mediator [98, 99]. Tramadol anti-inflammatory effects in the carrageenan inflammation model were associated with a decrease in PGE_2 levels in the inflammatory exudate [100]. Another study of inflammatory hyperalgesia using complete Freund's adjuvant found that tramadol not only attenuated mechanical hyperalgesia but also decreased the elevation of PGE_2 and TNF-α levels in the cerebrospinal fluid [101].

Another mediator of the tramadol anti-inflammatory effect is nuclear factor (NF)-κB. Evidence of the effects of tramadol on this crucial signaling mediator comes from a study of tramadol in a rodent model of myocardial infarction. In that study, tramadol not only attenuated the expression of NF-κB but also inhibited its activation [102]. Although this study was not focused on tramadol's effect on pain, it does appear that inflammation plays a prominent role in both conditions. Similar results were reported in the formalin-inflammatory pain model [103]. NF-κB contributes to inflammatory hyperalgesia through upregulation of the COX-2 enzyme [104] and plays a significant role in glial activation following nerve injury [105]. This observation has been exploited by targeting this transcription factor to alleviate pathological pain [106]. Further studies are required to clarify the contribution of NF-κB to the actions of tramadol.

NO plays peripheral and central bi-modal roles in modulating pain transmission [107, 108]. NO has pro- and antinociceptive effects depending on a host of factors, including NO concentration, location, and the pathophysiological process [107]. Inflammatory pain includes induction of NO synthase (NOS) in the periphery, and a positive feedback loop between NO and cytokines has been observed. The central actions of this gaseous transmitter enhance pain signaling via different mechanisms—for example, glutamate signaling is mediated in large part via release of NO, whereas glutamate-induced secondary hyperalgesia is mediated via NO. NO also enhances the release of SP and CGRP via retrograde transmission [107]. Stimulation of the COX enzyme and production of hyperalgesic prostaglandins is driven by the release of NO. NOS inhibitors have proven efficacy in the alleviation of neuropathy-associated hyperalgesia. On the other hand, NO precursors such as sodium nitroprusside and nitrates induced peripheral analgesia in nociceptive tests [107]. Additionally, NO was reported to mediate the peripheral and central antinociceptive effects of different analgesics, including opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and acetylcholine [107]. This uncertainty extends to detecting the role of NO signaling in mediating tramadol analgesia. Thus, some studies found that tramadol produced its effect via activation of the NO–cGMP pathway, whereas NOS inhibitors reduced tramadol analgesia [109]. On the other hand, tramadol analgesia was increased by NOS inhibitors and reduced by NO precursors [110]. Given these contradictory observations, the contribution of NO signaling to tramadol analgesia remains to be determined.

Tramadol also modulates the activity of non-neuronal immune cells that operate in peripheral and central synapses. In one in vitro study, tramadol regulated the polarization of M1 and M2 macrophages by inhibiting cytokines secreted from M1 cells and enhancing the expression of Arg1, Mrc1, Ym1, and Fizz1 from M2 cells, which are known to combat inflammation [111]. Macrophage polarization is a well-known contributor to the development of peripheral inflammation and sensitization in different pain conditions, and shifting the polarization towards an M2 state could relieve neuropathic pain [112]. However, more studies are required to determine whether this effect indeed contributes to tramadol analgesia in vivo.

Regarding the effects of tramadol on central glial cells, several preclinical studies showed that tramadol inhibits the activation of these cells [94, 113, 114]. It could be assumed that tramadol's inhibitory effect on glial cells could occur secondary to neuronal inhibition via MOR given the crosstalk between neuronal and glial cells. However, this assumption is erroneous since morphine, which is more potent than tramadol, has no reported inhibitory effect on glial cells. This confirms that tramadol inhibits glial activation directly and not by dampening neuronal activity [113].

2.3 Tramadol, Other Opioids, and Hyperalgesia

As discussed, peripheral and central sensitization are now widely accepted to be an integral part of every pain condition, from mild headache and fibromyalgia to the transition from acute to chronic pain [17, 34]. The search for drugs that can modify these processes and hence improve pain control is ongoing, but there is still a significant way to go to achieve this goal. For example, between 10 and 30% of surgical patients develop chronic postsurgical pain after one year postoperatively [115]. Moreover, some analgesic drugs such as morphine potentiate this neuronal sensitization rather than dampen it. Morphine, fentanyl, and other opioids are known to produce opioid-induced hyperalgesia during acute or chronic administration [116]. The manifestations and molecular mechanisms of opioid-induced hyperalgesia is similar to hyperalgesia encountered in different pain settings [117]. One important interaction exists between tissue injury and opioid administration: the so-called "two hit hypothesis", where hyperalgesia develops after two hits occurring in any order, opioid administration and tissue injury [118]. Inflammation has been held responsible for this interaction, where both tissue injury and opioid administration have pro-inflammatory effects that cooperate to produce the observable effect [118]. For this reason, opioids such as morphine facilitate the transition from acute to chronic pain and can worsen some forms of chronic pain [118–120].

Studies that have tested the effects of tramadol on peripheral and central sensitization in terms of nerve electrical activity and synaptic potentiation are currently lacking. However, the anti-sensitizing effects of tramadol have been demonstrated in the three types of pain: incisional, inflammatory, and neuropathic. Remarkably, the efficacy of tramadol in those models has been associated with modulation of integral components in peripheral and central sensitization, such as glial activation, glutamatergic transmission, and cytokine and prostaglandin release. In a preclinical study of incisional pain, latent pain sensitization developed 21 days after incision (latent pain sensitization is responsible for chronic postsurgical pain), and a single administration of tramadol before the surgical insult inhibited this sensitization [121]. In that study, tramadol efficacy was attributed to inhibition of microglial activation. In a parallel study, tramadol reversed mechanical hyperalgesia that developed after incisional pain, with simultaneous reduction in elevated levels of IL-6 [91].

The development of central sensitization in a preclinical animal model of rheumatoid arthritis was linked to phosphorylation and increased expression of NMDA receptors [122]. In this study, a NMDA receptor antagonist reduced hyperalgesia. Interestingly, intrathecal administration of tramadol attenuated hyperalgesia and the expression and phosphorylation of NMDA receptors. In another study, complete Freund's adjuvant-induced mechanical hyperalgesia was associated with elevations in PGE_2 and TNF-α. Tramadol administration reversed this hyperalgesia with concurrent reduction in PGE_2 level. Similarly, tramadol activity in animal behavioral tests could be used to infer its effects on sensitization phenomenon. Thermal and mechanical hyperalgesia to paw inflammation was suggested to be a valid model of sensitization [24, 123]. This model confirmed the activity of different anti-hyperalgesic agents, including NMDA receptor antagonists, COX inhibitors, and the antiepileptics [124–126]. Hence, tramadol efficacy in this model could be used as a predictor of its anti-hyperalgesic properties [127]. Systemic and local (in the hind paw of rats) administration of tramadol alleviated inflammation-associated hyperalgesia even at doses that did not affect basal nociceptive thresholds [127, 128].

Additional evidence for efficacy comes from the effects of tramadol on neuropathic pain. Neuropathic pain involves neuronal sensitization in its pathophysiology [129]. Several studies that established the efficacy of tramadol in neuropathic pain have related the efficacy to depressing glial activation and cytokine release [93, 95, 113, 114]. In one of those reports, efficacy was still demonstrable even after tramadol cessation for about 1 week. That study suggested that repeated tramadol administration induces long-term plastic changes in pain signaling pathways that persist after its withdrawal [113]. Glial cells have a critical time window for activation after encountering a painful stimulus, and the absence of glial cells via depletion has a long-term effect on pain hypersensitivity, even after glial repopulation [19]. Tramadol could similarly attenuate glial activation, and this effect would persist for extended periods. This extended analgesia was still demonstrable when tramadol analgesia blockers were used. It was suggested that pharmacological efficacy in neuropathic pain could be used as a likely predictor of neuronal sensitization modulation [130]. Given the efficacy of tramadol in attenuating neuropathic pain [131], this could be attributed in part to the ability of tramadol to alter sensitization.

Further evidence for tramadol's anti-hyperalgesic efficacy comes from its local anesthetic activity. Tramadol

exerts a membrane-stabilizing effect that is independent of its receptor profile [62–64, 68], and local anesthetic activity has been shown in peripheral and central synapses [67]. Intriguingly, peripheral and central administration of local anesthetics could normalize both arms of neuronal sensitization [132, 133]. Through neuronal blockade, lidocaine inhibited the development of chronic postsurgical pain [134]. Hence, by extrapolation, it could be anticipated that tramadol could exert a similar effect to local anesthetics. In support of this hypothesis, tramadol, when combined with an NSAID, inhibited transition from acute to chronic back pain when compared with NSAID alone [135]. Another study found that tramadol combined with diclofenac inhibited postoperative secondary hyperalgesia, which indicates attenuation of central sensitization [136]. For those reasons, the evidence for the anti-sensitizing effect of tramadol is strong and carries high translational value.

Two studies have reported conflicting findings, suggesting that tramadol exerts a hyperalgesic effect. One clinical report found that tramadol administration for 1 and 4 years in chronic pain produced hyperalgesia [137], whereas a preclinical study found that a single administration of tramadol in Wistar rats decreased the mechanical threshold in an absence-of-pain model [138]. The authors argued that tramadol's affinity to the MOR with subsequent activation of counter-regulatory pathways (e.g., glutamate activation, pro-inflammatory cytokine release, and glial activation) was responsible for tramadol-induced hyperalgesia [139]. However, this assumption and those studies contain some limitations. The contribution of MOR to hyperalgesia is controversial and not yet established [139]. Tramadol use is not associated with the counter-regulatory pathways mentioned—in fact the opposite is true, and this has been confirmed in several studies. The Toll-like receptor (TLR) is an important mediator of opioid-induced hyperalgesia, and tramadol has no reported affinity with this receptor. The first record was a case report of two subjects and is subject to the limitations of this source of information. For those reasons, the current evidence for the pro-sensitizing effect of tramadol is weak.

Tramadol is recommended as an anti-sensitizing agent that could be used to combat central sensitization in chronic pain states [33, 140]. The authors based their argument on the dual opioidergic and monoaminergic activities of tramadol to produce this effect. However, this does not rule out other mechanisms that may operate in tramadol-induced desensitization. Given the involvement of neuronal sensitization in most forms of pain, tramadol anti-sensitizing effects could explain its broad spectrum of efficacy in different pain conditions.

2.4 Tramadol Broad-Spectrum Analgesia

Tramadol use as a unimodal agent in different pain conditions has been investigated in several preclinical and clinical studies. Systematic reviews and meta-analyses have shown fair evidence of tramadol efficacy in different pain conditions, such as postoperative [141], procedural [142], dental [141], migraine headache [143], abdominal [144–147], cancer [148, 149], neuropathic [131], fibromyalgia [150], arthritis [78], and back pain [151]. A systematic review has reported similar evidence of tramadol efficacy in chronic non-cancer pain [152]. Preclinical studies likewise support the broad efficacy of tramadol [153]. Table 3 provides representative examples of clinical pain conditions that explored tramadol analgesia. Given space constraints, the author confined tramadol studies in each pain category to three trials, with clinical studies preferred over preclinical when available. Table 3 shows that tramadol is a broad-spectrum analgesic agent despite the variance in dosage, power of each study, subjects, reference drug, and primary and secondary outcomes. Similar findings about tramadol's spectrum of activity have been reported in other comprehensive reviews [35–37, 154, 155]. This broad-spectrum activity could be attributed in part to a tramadol synergistic interaction between opioidergic and monoaminergic activities. However, other mechanisms could also contribute.

An important fact about pain that should not be overlooked is that significant comorbidity exists, and patients can have multiple pain diagnoses [156]. For example, headache has been reported to be associated with other pain types [157]. Similar comorbidity has been found in pain related to cancer and multiple sclerosis [156] and in neuropathic and low back pain [158]. The occurrence of one pain type predisposes the affected individual to developing another pain type. This has been explained based on neuronal sensitization, whereby sensitized neurons have lower excitability thresholds, which prompt them to develop another pain [26]. This is reflected in prescription of more than one analgesic agent for each patient [156]. Multiple pain comorbidity is a huge clinical and economic challenge [156]. Theoretically, the broad-spectrum analgesia provided by tramadol could help in these conditions by replacing polypharmacy with a single agent with subsequent reduction in economic costs, patient noncompliance, and risk of drug interactions.

2.5 Other Applications of Tramadol in Pain Management

2.5.1 Combined Analgesia

One of the most widely employed strategies in the management of both acute and chronic pain is multimodal analgesia. The concept of multimodal analgesia implies the use of more

Table 3 Effects of tramadol as a unimodal analgesic in different pain types

Study type	Study subjects, primary outcome	Dosage regimen	Reference drug, dosage regimen	Result	References
Postoperative pain					
Randomized blind clinical	Gynecologic surgery, 18–65 y, moderate to severe pain; Categorical pain score	Intravenous 50 mg up to three times	Intravenous Morphine 5 mg up to three times	Tramadol = Morphine in moderate pain; Tramadol < Morphine in severe pain	[159]
Randomized clinical	Spinal fusion surgery, > 20 y; Visual pain score	Oral 150, 200, 250, or 300 mg once daily	Transdermal Buprenorphine 5, 10, 15, or 20 µg/h every 7 d	Tramadol = Buprenorphine	[160]
Randomized open clinical	Orthopedic surgery, ♂♀, 18–95 y; Visual pain score	Intramuscular 100 mg up to four times daily for 3 d	Intramuscular Ketorolac 30 mg up to threetimes daily for 3 d	Tramadol > Ketorolac	[161]
Procedural pain					
Randomized blind clinical	Hysteroscopy, 18–65 y; Visual pain score	Oral 100 mg	Oral Celecoxib 200 mg	Tramadol = Celecoxib	[162]
Randomized blind clinical	Colonoscopy, 19–68 y, ♂♀; Visual pain score	Intravenous 100 mg	Placebo	Tramadol > Placebo	[163]
Randomized blind clinical	Bone marrow aspiration, 17–93 y, ♂♀; Visual pain score	Oral drops 50 mg	Placebo	Tramadol > Placebo	[164]
Obstetrical pain					
Randomized blind clinical	Active labor pain, 15–38 y; Categorial pain score	Intramuscular 50, 100 mg	Intramuscular Pethidine 75 mg	Tramadol = Pethidine	[165]
Randomized blind clinical	Active labor pain; Visual pain score	Intramuscular 1 mg/kg	Intravenous Paracetamol 1 g	Tramadol = Paracetamol	[166]
Randomized blind clinical	Post-caesarean section, 18–55 y; Categorical pain score	Oral 75, 150 mg	Placebo; Oral Ketorolac + Propoxyphene 650 + 10 mg	Tramadol > Placebo; Tramadol 150 mg > Acetaminophen + Propoxyphene	[167]
Dental pain					
Randomized blind clinical	Third molar surgery, 18–70 y, ♂♀; Categorial pain score	Oral 50, 100 mg	Placebo; Oral Aspirin + Codeine 650 + 60 mg	Tramadol > Placebo; Tramadol = Aspirin + Codeine	[168]
Randomized blind clinical	Third molar surgery, ≥ 16 y, < 100 kg, ♂♀; Categorial pain score	Oral 37.5 mg	Placebo; Ibuprofen 200 mg; Paracetamol 325 mg	Tramadol > Placebo; Tramadol < Ibuprofen; Tramadol < Paracetamol	[169]
Randomized blind clinical	Dento-alveolar operations, > 18 y, ♂♀; Categorial pain score	50 mg twice daily, 50 or 100 mg four times daily	Placebo	Tramadol > Placebo	[170]
Headache					
Retrospective analysis	Tension headache, Self reporting of pain relief	–	–	55% of pts improved	[171]
Randomized blind clinical	Acute migraine, 18–65 y, ♂♀; Categorial pain score	Intramuscular 100 mg	Intramuscular Diclofenac 75 mg	Tramadol = Diclofenac	[172]
Randomized blind clinical	Acute migraine, 24–64 y, ♂♀; Visual pain score and Categorial pain score	Intravenous 100 mg	Placebo	Tramadol > Placebo	[173]
Abdominal pain					
Clinical	Biliary colic, 18–50 y, ♂♀; Visual pain score	Oral 50, 100 mg	Codeine; Diclofenac 50, 75 mg; Ibuprofen 400 mg; Paracetamol 1 g; Buscopan 20 mg	Tramadol > Codeine; Tramadol > Diclofenac; Tramadol > Ibuprofen; Tramadol > Paracetamol; Tramadol > Buscopan	[174]
Randomized clinical	Renal colic, Categorical pain score	Subcutaneous 1 mg	Intramuscular Ketorolac 30 mg	Tramadol = Ketorolac	[175]
Randomized blind clinical	Acute pancreatitis, 53 ± 13.3 y, ♂♀; Visual pain score	Intravenous 1 mg/kg	Intravenous Paracetamol 1 g; Intravenous Dexketoprofen 50 mg	Tramadol = Paracetamol; Tramadol = Dexketoprofen	[176]

Table 3 (continued)

Study type	Study subjects, primary outcome	Dosage regimen	Reference drug, dosage regimen	Result	References
Post-traumatic pain					
Randomized blind clinical	Musculoskeletal, > 18 y, < 100 kg; Categorial pain score	Intravenous 100, 150, or 200 mg	Intravenous Morphine 5, 10, 15, or 20 mg	Tramadol = Morphine	[177]
Randomized open clinical	Musculoskeletal (joint/ligament) adults, ♂♀; Visual pain score	Oral 100 mg twice daily 5–7 d	Oral Diclofenac 100 mg twice daily 5–7 d	Tramadol > Diclofenac	[178]
Randomized blind clinical	Pain: bone fracture or dislocation, 4–17 y, 27–58.5 kg, ♂♀; Visual pain score	Sublingual 2 mg/kg up to 100 mg	Sublingual Ketorolac 0.5 mg/kg up to 20 mg	Tramadol = Ketorolac	[179]
Burns pain					
Preclinical	Full-thickness thermal injury, Sprague-Dawley rats, 250–400 g, ♂; Paw withdrawal from thermal and mechanical stimuli	Intraperitoneal 10, 20, or 30 mg/kg	Intraperitoneal Morphine 5 mg/kg	Tramadol = Morphine	[180]
Randomized blind clinical	Dressing of second-degree burns; Visual pain score	50 mg	Lornoxicam 8 mg	Tramadol = Lornoxicam	[181]
Cancer pain					
Randomized blind clinical	Average age 57.1 and 62 y, ♂♀; Visual pain score	Oral 200 or 400 mg once daily 23 d	Oral Hydrocodone + Paracetamol 25 + 2500 or 50 + 5000 mg once daily for 23 d	Tramadol = Hydrocodone + Paracetamol	[182]
Randomized crossover clinical	Average age 61.4 y, ♂♀; Categorial pain score	Oral 300 mg once daily 7 d	Sublingual Buprenorphine 0.6 mg once daily 7 d	Tramadol > Buprenorphine	[183]
Randomized crossover blind clinical	26–75 y, ♂♀; Categorial pain score	Oral 50 mg six times daily 4 d	Oral Morphine 16 mg six times daily 4 d	Tramadol = Morphine	[184]
Neuropathic pain					
Randomized open clinical	Post-herpetic neuralgia, ≥ 65 y; Categorial pain score	Oral mean 250–290 mg; maximum 600 mg/d 6 wk	Oral Clomipramine mean 59.1–63.6 mg; maximum 100 mg/d 6 wk	Tramadol > Clomipramine	[185]
Randomized blind (placebo) open (amitriptyline) clinical	Post-amputation, 31–44 y, 56–69 kg, ♂♀; Visual pain score	Oral average 448 mg once daily 30 d	Placebo; Oral Amitriptyline mean 50 mg 30 d	Tramadol > Placebo; Tramadol = Amitriptyline	[186]
Randomized blind clinical	Diabetic neuropathy, 32–85 y, ♂♀; Categorial pain score	Oral average 210 mg once daily 42 d	Placebo	Tramadol > Placebo	[187]
Fibromyalgia					
Preclinical	Reserpine-induced myalgia, Sprague-Dawley rats, 9 wk, ♂; Von Frey hair test	Oral 3, 10, 30 mg/kg	Vehicle	Tramadol > Vehicle	[188]
Randomized blind clinical	Fibromyalgia, 18–75 y, ♂♀; time to discontinuation for inadequate pain relief	Oral 50–400 mg once daily for 42 d	Placebo	Tramadol > Placebo	[189]
Randomized crossover blind clinical	Fibromyalgia, ♂♀; Visual pain score, pressure dolorimetry	Intravenous 100 mg once	Placebo	Tramadol > Placebo	[190]
Low back pain					
Randomized blind clinical	Chronic low back, 21–79 y, ♂♀; time to discontinuation for inadequate pain relief; Visual pain score	Oral 200–400 mg once daily for 28 d	Placebo	Tramadol > Placebo	[191]
Randomized blind clinical	Chronic low back, adults; Visual pain score	Oral 200–300 mg ER once daily 84 d	Placebo	Tramadol > Placebo	[192]
Randomized blind clinical	Chronic low back, average age 58.5 y, ♂♀; Categorial pain score	Oral 200 mg ER once daily 42 d	Placebo	Tramadol > Placebo	[193]

Table 3 (continued)

Study type	Study subjects, primary outcome	Dosage regimen	Reference drug, dosage regimen	Result	References
Arthritis pain					
Randomized blind clinical	Osteoarthritis, 35–75 y, ♂♀; Categorial pain score	Oral 50 mg to 200–400 once daily 91 d	Placebo	Tramadol > Placebo	[194]
Randomized blind clinical	Osteoarthritis, ≥ 38 y, ♂♀; Visual pain score	Oral 50 mg threetimes daily 7 d	Oral Paracetamol 500 mg threetimes daily 7 d	Tramadol = Paracetamol	[79]
Randomized blind clinical	Osteoarthritis, 35–75 y, ♂♀; Visual pain score	Oral 200, 300, 400 mg once daily 56 d	Oral Diclofenac 75, 100, 150 mg once daily 56 d	Tramadol = Diclofenac	[195]

Systematic reviews and meta-analyses have shown the efficacy of tramadol in postoperative, procedural, dental, migraine headache, abdominal, cancer, neuropathic, fibromyalgia, arthritis, and back pain

than one method or modality to control pain with the target of enhancing the beneficial effects and reducing the adverse effects of the pain management. For example, combining NSAIDs or adjuvant analgesics with opioid drugs reduces opioid requirements, adverse effects, and the development of tolerance and dependence. Moreover, enhanced analgesia may be obtained through agents acting via different mechanisms [196–198]. Another reported advantage of multimodal analgesia is the possible reduction of acute pain transition to chronic pain [9].

In preclinical studies, tramadol potentiated the analgesic activities of several agents, such as acetaminophen [199], NSAIDs [200], morphine [201, 202], antidepressants [203], antiepileptics [204], local anesthetics [205], NMDA antagonists [206], α_2AR agonists [207], and corticosteroids [208]. Systematic reviews and meta-analyses of clinical studies have shown similar results relating to tramadol's synergistic interaction with other analgesics, such as acetaminophen [209] and morphine [210]. Fixed-dose combinations of tramadol have also reached the market in the form of tramadol + acetaminophen and tramadol + dexketoprofen [211, 212]. Other combinations are also in development, such as tramadol + celecoxib [213]. The analgesic spectrum of these combinations is wide, encompassing acute and chronic, incisional, inflammatory, and neuropathic pain states. This could be explained based on the wide variety of tramadol's molecular actions, which boost the efficacy of other analgesics. For example, (1) tramadol combined with gabapentin showed synergistic suppression of elevated IL-1β [214], and (2) tramadol prolonged lidocaine's duration in intravenous regional anesthesia, an effect that was mediated via the nerve-blocking activity of tramadol [215].

Despite the established value of multimodal analgesia, this does not imply that combining more than one analgesic in any pain category would result in superior efficacy and reduced adverse effects. Several clinical trials denied this notion, for example, the combination of a cholecystokinin antagonist and an opioid [216]. Furthermore, combined analgesics could have increased toxicity, such as serotonin syndrome with a tramadol + serotonergic antidepressant combination [216]. In view of such concerns, tramadol combination regimens should be carefully designed and should be properly justified based on three factors: (1) specific mechanism of each combined drug, (2) adverse effects of combined drugs, and (3) pain category-specific targets [216]. Knowledge of the analgesic mechanism, uses, and adverse effects of different analgesic drugs would help to unveil and optimize the value of combining tramadol with these agents in different pain conditions.

2.5.2 Local Analgesia

Incisional, inflammatory, and neuropathic pain involves activation of primary afferent neurons, resulting in hyperexcitability. Targeting peripheral neuronal facilitation via topical administration has been shown to be effective in combating these three pain types. Furthermore, this route of administration has other merits, including achieving a high concentration of the drug at the injury site, reducing systemic toxicity, and reducing drug interaction risk [22]. Topical agents that have shown efficacy in the clinical setting include NSAIDs, local anesthetics, corticosteroids, and capsaicin [22].

Topical tramadol application improved tonsillectomy pain (swabs soaked with tramadol were applied to tonsillar fossa) [217, 218]. Similar findings were reported in dental pain (tramadol was applied to extraction sockets and on the submucosa) [219, 220] and postoperative sore throat (tramadol was applied using gargle) [221]. Intra-articular injection of tramadol provided adequate analgesia in arthroscopic knee surgery and an animal model of joint inflammation [222–224]. This efficacy could be attributed to two factors, local anesthetic action and attenuation of peripheral inflammatory reactions. Given the involvement of multiple mediators in the activation of peripheral nerves, simultaneous targeting of those mediators would be advantageous. Topical tramadol could effectively control different pain types through effects on a wide variety of mediators, such as neuronal conduction, inflammatory mediators, and macrophage polarization.

2.5.3 Comorbid Diseases with Pain

It is now widely accepted that pain, especially when pain is chronic, is associated with other diseases that also increase the pain burden on both individuals and society. These pain-associated comorbidities include depression, anxiety, sleep disturbances, and fatigue. The most important of them are depression and anxiety, where 60% of patients with chronic pain also have depression, and 33% have severe depression [225]. In another study, 70% of patients with chronic pain had anxiety [226]. Interestingly, the severity of anxiety and depression was correlated with pain intensity. For those reasons, anxiolytics and antidepressants have a role in pain management [227, 228].

Tramadol use in pain is associated with anxiolytic and antidepressant activities. For example, in a preclinical model of neuropathic pain with anxiety and depression, tramadol's anti-hyperalgesic effect was associated with anxiolytic and antidepressant actions in elevated plus maze and forced swimming test [229]. In a clinical study of low back pain with depression, tramadol in combination with acetaminophen significantly improved pain and depression outcomes [230]. It has been suggested that the anxiolytic and antidepressant activities of tramadol occur secondary to alleviation of pain. However, preclinical studies in an animal model of depression with no pain have shown that tramadol indeed exerted antidepressant and anxiolytic actions independent of the presence or absence of pain stimuli [74, 231, 232]. Similarly, tramadol-independent effects on depression and anxiety have been reported in clinical settings [233, 234].

An emerging hypothesis of major depression has linked alterations in glutamate signaling and neuroplastic changes to the development of symptoms [235]. Ketamine, a NMDA receptor antagonist, has shown antidepressant activity in different preclinical and clinical studies [236]. Some studies have linked the antidepressant effect of tramadol to NMDA receptor antagonism [74, 231]. Another possible explanation for tramadol's antidepressant activity comes from microdialysis studies, in which tramadol was found to affect monoaminergic transmission in the ventral hippocampus of freely moving rats in a similar way to duloxetine, venlafaxine, and clomipramine [237], and changes in monoamine levels initiate neuroplastic changes associated with antidepressant activity [238].

2.5.4 Postoperative Shivering

Shivering is a common postanesthetic complication that increases patient discomfort and pain intensity, besides having other metabolic effects. The pathophysiology of this process is poorly understood, but perioperative hypothermia remains the main culprit [239]. Treatment of postanesthetic shivering consists of pharmacological and non-pharmacological approaches. Clinical pharmacological treatment is mostly empirical. To date, meperidine has been the most validated approach [239]. Tramadol's anti-shivering effects have been demonstrated in several clinical trials, and the efficacy of tramadol was comparable to that of meperidine [240, 241]. The mechanism behind tramadol's efficacy is unclear but was attributed to blocking of NMDA receptors [242]. Moreover, the high safety profile and weak sedative effect of tramadol add more weight to its potential therapeutic value [243].

3 New Drugs in Development

Although tramadol and other approved analgesics have shown good results in different pain conditions, they have limited efficacy in different clinical conditions. Hence, considerable research effort is ongoing to develop novel analgesic drugs despite obstacles imposed by the complexity of pain pathways, clinical pain heterogeneity, and poor translational value of preclinical models [244]. Drug development of novel analgesics is moving towards a more targeted-therapy approach, which offers promising prospects regarding better control of pain [20, 245].

Current drug discovery approaches are directed towards three targets: opioid and non-opioid G-protein-coupled receptors (GPCRs), ion channels, and enzymes [244]. Drug classes targeting opioid GPCRs include abuse-deterrent opioids, peripherally restricted receptor ligands, bivalent ligands, and biased ligands. Non-opioid GPCRs include cannabinoid, angiotensin type 2, α2ARs, and chemokine receptors. Ion channel targets are TRPV1, $Na_{v1.7}$, $Na_{v1.8}$ sodium channels, $Ca_{v2.2}$, $Ca_{v3.2}$ channels, and K_{v7} and K2P channels. Sepiapterin reductase, microsomal PGE_2 synthase 1, soluble epoxide hydrolase, and proteases are of interest for clinical development [244].

4 Conclusion and Future Directions

Current evidence proposes that different components of nociceptive signaling, such as primary afferent neuronal activity, glutamate signaling, macrophages, glial cells, cytokines, and chemokine release, are polarized by tissue/nerve injury in such a way that these components support hyperalgesia and that tramadol could interrupt this polarization. Therefore, tramadol as a uni- or multimodal agent could enhance the outcome of patients with different pain conditions. Despite the body of information summarized in this review, much work remains to establish the anti-sensitizing effect of tramadol. For example, tramadol's effect on other molecular mediators of pain and hyperalgesia, such as $Na_{v1.7}$, $Na_{v1.8}$, brain-derived neurotrophic factor, LTP development at central synapses, TLR signaling, and macrophage polarization, etc., should be thoroughly examined. Additionally, tramadol's utility in multiple pain comorbidity should be investigated and compared with other polymodal regimens, with pain intensity, patient compliance, and overall cost as primary and secondary outcomes.

Compliance with Ethical Standards

Conflict of interest Ahmed Barakat has no conflicts of interest that are directly relevant to the content of this article.

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