

Summary Report

Tramadol hydrochloride

Prepared for:

Food and Drug Administration

Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List

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Frequently Used Abbreviations

API	Active Pharmaceutical Ingredient
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
HCl	Hydrochloride
IRB	Institutional Review Board
OTC	Over-the-counter
ROA	Route of administration
SME	Subject matter expert
UK	United Kingdom
US	United States

INTRODUCTION

This report was created to assist the Food and Drug Administration (FDA) in their evaluation of the use of tramadol hydrochloride (tramadol HCl; UNII code: 9N7R477WCK), which was nominated for use as a bulk drug substance in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act.

The aim of this report was to describe how tramadol HCl is used in clinical research and practice to diagnose, prevent, or treat disease. Due to the broad, exploratory nature of this aim, scoping review methodology was used. Following the scoping review framework, a systematic literature review was conducted and healthcare practitioners were consulted to identify how tramadol HCl has been used historically and currently.¹⁻³ Assessment of study quality and risk of bias were not performed because the aim of this report was not to make specific recommendations on the use of this substance in clinical practice.^{1,4,5} Rather, the aim was to summarize the available evidence on the use of tramadol HCl and thereby assist the FDA to determine whether there is a need for the inclusion of this substance on the 503B Bulks List.

REVIEW OF NOMINATION

Tramadol HCl was nominated for inclusion on the 503B Bulks List by Fagron for moderate to moderately severe pain via a 50 mg/mL injection.

The nominator provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of tramadol HCl.⁶⁻⁸

The reason provided for nomination to the 503B Bulks List included reducing the necessary dose for pain relief by changing the dosage form from oral to injection and thereby reducing the potential for abuse and addiction.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of tramadol HCl products in the United States (US) and around the world. The World Health Organization, the European Medicines Agency (EMA), and globalEDGE were used to identify regulatory agencies in non-US countries. The medicine registers of non-US regulatory agencies were selected for inclusion if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information, specifically, product trade name, active ingredient, strength, form, route of administration (ROA), and approval status, provided in a useable format. Based on these criteria, the medicine registers of 13 countries/regions were searched: US, Canada, European Union (EU), United Kingdom (UK), Ireland, Belgium, Latvia, Australia, New Zealand, Saudi Arabia, Abu Dhabi, Hong Kong, and Namibia. Both the EMA and the national registers of select EU countries (Ireland, UK, Belgium, and Latvia) were searched because some medicines were authorized for use in the EU and not available in a member country and vice versa.

Each medicine register was searched for tramadol HCl; name variations of tramadol HCl were entered if the initial search retrieved no results. The following information from the search results of each register was recorded in a spreadsheet: product trade name; active ingredient; strength; form; ROA; status and/or schedule; approval date. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations.

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.5) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing tramadol HCl. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

Search strategy

A medical librarian constructed comprehensive search strategies for Ovid MEDLINE and Embase. The search strategies used a combination of controlled vocabulary terms and keywords to describe three concepts: tramadol HCl, injectable administration, and therapeutic use for pain (refer to Appendix 1 for full search strategies). Keywords for brand or proprietary products were not included in the search strategy because studies that utilized such products were excluded. Results were limited to human studies in English language. Searches were conducted on March 8, 2020. The reference lists of relevant systematic reviews and meta-analyses, retrieved in a separate search of Ovid MEDLINE, were reviewed to identify additional studies. In addition, the ECRI Guidelines Trust[®] repository was searched on March 8, 2020 for clinical practice guidelines that recommended the use of tramadol HCl and provided sufficient dosing and administration instructions.

Results were exported to EndNote for Windows version X9.2 (Clarivate Analytics), and duplicates were removed. The de-duplicated results were uploaded to Covidence (Veritas Health Innovation) for screening.

Study selection

Studies in which tramadol HCl was used in the nominated dosage form, ROA, and/or combination product to diagnose, prevent or treat the nominated disease or condition, or other conditions not specified in the nomination, were included. Studies were excluded if they were: written in a language other than English; reviews or meta-analyses; surveys or questionnaires (cross-sectional design); designed to evaluate cost-effectiveness, mechanism of action, pre-clinical use, safety, or toxicity; or any study design other than a randomized controlled trial conducted in a non-US country. Studies were also excluded if tramadol HCl was used as: a brand or proprietary product; an FDA-approved product in the nominated dosage form, ROA, or combination; a dosage form, ROA, or combination that was not nominated; or as a rescue medication in a trial not designed to evaluate the effect of tramadol. Studies in which tramadol HCl was used to diagnose, prevent, or treat autism were excluded due to a separate project examining the use of compounded substances in individuals with autism. Studies that did not meet the inclusion criteria but provided valuable information about the pharmacological or current or historical use of the substance were noted and put in a separate group in the EndNote library. Two reviewers independently screened titles and abstracts and reviewed full-text articles. A third reviewer reconciled all disagreements.

Data extraction

The following information was recorded in a standard data extraction form: author names; article title; journal; year of publication; country; study type; historical use of tramadol HCl; setting; total number of patients; number of patients who received tramadol HCl; patient population; indication for use of tramadol HCl; dosage form and strength; dose; ROA; frequency and duration of therapy; use of tramadol HCl in a combination product; use and formulation of tramadol HCl in a compounded product; use of tramadol HCl compared to FDA-approved drugs or other treatments; outcome

measures; authors' conclusions. One reviewer extracted data from the included studies; a second reviewer checked the data extraction.

Interviews

Semi-structured interviews with subject matter experts (SME) were conducted to understand how and in what circumstances tramadol HCl was used in a clinical setting. The systematic literature review and indication from the nomination were reviewed to identify the following medical specialties that would potentially use tramadol HCl: anesthesiology, dentistry, pain management, and surgery. Potential SMEs within the relevant medical specialties were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. In addition, the American Society of Health-System Pharmacists (ASHP) and select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided oral informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were entered into NVivo 12 (QSR International) for qualitative data analysis. Several members of the research team independently coded the transcriptions of two representative interviews for themes. The team members discussed the codes that emerged from their independent analysis, as well as those codes that were determined a priori. The code book was developed out of the integration of these coding schemes.

Survey

A survey was distributed to the members of professional medical associations to determine the use of tramadol HCl in clinical practice. The online survey was created using Qualtrics® software (refer to Appendix 2 for complete survey). A Google™ search was conducted to identify the professional associations in the US for the relevant medical specialties. An association's website was searched to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used. An email describing the project and requesting distribution of the survey to the association's members was sent to the identified person(s). Associations that declined, did not respond, or did not provide significant data in project Year 1, were not contacted to distribute the project Year 2 surveys.

The survey was posted on the project website and the survey link was distributed to the associations that agreed to participate (refer to Appendix 3 for associations that participated and those that did not).

Participation was anonymous and voluntary. The estimated time for completion was 15 minutes with a target of 50 responses per survey.

The University of Maryland, Baltimore Institutional Review Board (IRB) and the FDA IRB reviewed the interview and survey methods and found both to be exempt. The Office of Management and Budget approved this project.

CURRENT AND HISTORIC USE

Results of background information

- Tramadol HCl is not available as an FDA-approved product in the nominated dosage form and ROA.
- Tramadol HCl is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for tramadol HCl.
- Tramadol HCl is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, the EU, Hong Kong, Ireland, Namibia, New Zealand, and the UK.

Table 1. Currently approved products – US

No approved products in the US

Table 2. Currently approved products – select non-US countries and regions^a

Active Ingredient	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date ^b
Tramadol HCl	50 mg/mL	–	Injection	EU	Authorized	–
				Namibia	–	02/08/2006
		Solution	Infusion, injection, intramuscular, intravenous, subcutaneous	Abu Dhabi	Active	12/24/2016
				Australia	Prescription-only medication	05/18/1998
				Belgium	Medical prescription	02/02/2003
				Hong Kong	Prescription only medicine	01/14/1997
				Ireland	Prescription-only non-renewable	06/25/1999
				New Zealand	Prescription	09/25/1997
				Saudi Arabia	Prescription	–
				UK	Prescription-only medication	05/26/2005

Abbreviation: “–”, not mentioned.

^aMedicine registers of national regulatory agencies were searched if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information (product trade name, active ingredient, strength, form, ROA, and approval status) provided in a useable format. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations. See Methodology for full explanation.

^bIf multiple approval dates and/or multiple strengths, then earliest date provided.

Results of literature review

Study selection

Database searches yielded 2393 references; 7 additional references were identified from searching ECRI Guidelines Trust® and the literature reviews of other substances. After duplicates were removed, 1657 titles and abstracts were screened. After screening, the full text of 744 articles was reviewed. Three hundred twenty-nine studies were included; after multiple reports of the same study were merged, there were 316 included studies. Four hundred fifteen studies were excluded for the following reasons: tramadol HCl only mentioned briefly (172 studies); wrong study design (147); tramadol HCl used as brand or proprietary product (61); dosage form or ROA not nominated (13); unable to obtain full text (5); language other than English (4); duplicate study (3); tramadol HCl not used clinically (3); used in FDA-approved dosage form or ROA (3); wrong indication (2); wrong substance (2).

Refer to Figure 1 for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Characteristics of included studies

The 316 included studies were published between 1986 and 2020. There were 315 experimental studies, 1 observational study, 0 descriptive studies, and 0 clinical practice guidelines. The 316 studies were conducted in the following countries: Australia, Austria, Bangladesh, Belgium, Brazil, China, Croatia, Czech Republic, Denmark, Egypt, Finland, France, Germany, Greece, Hong Kong, India, Iran, Italy, Korea, Kosovo, Lebanon, Malaysia, Mexico, New Zealand, Nigeria, Pakistan, Philippines, Poland, Portugal, Russia, Saudi Arabia, Serbia, Singapore, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, the Netherlands, Tunisia, Turkey, United Arab Emirates, UK, US, and Uzbekistan.

A total of 26,496 patients participated in the 316 included studies. The number of patients in each study ranged from 17 to 430.

Outcome measures differed among the included studies and included: pain scores; duration of analgesia; rescue medication requirements; hemodynamic variables; side effects.

Refer to Table 5 for summary of study country, design, patient population, intervention and comparator, and outcome measures.

Use of tramadol HCl

Thirteen thousand four hundred thirty-seven patients received tramadol HCl for analgesia, administered via buccal, caudal, caudal epidural, caudal extradural, epidural, infiltration, intraarticular, intracutaneous, intradermal, intraincisional, intramuscular, intraperitoneal, intrathecal, intravenous, perineural, peritonsillar, subcutaneous, subdural, and submucosal injections in doses ranging from 0.1 mg/kg to 12 mg/kg. Duration of treatment ranged from once to 14 days.

Refer to Tables 6 and 7 for summaries of dosage by indication.

Tramadol HCl was used as a compounded product (refer to Table 9).

In 145 studies, the authors' concluding statement recommended the use of tramadol HCl for analgesia via caudal, caudal epidural, epidural, infiltration, intraarticular, intracutaneous, intramuscular, intraperitoneal, intrathecal, intravenous, perineural, peritonsillar, subcutaneous, subdural, and submucosal injections.⁹⁻¹⁵⁴ In 81 studies, the authors concluded that the use of tramadol HCl was not

recommended for analgesia via caudal, combined spinal-epidural, epidural, intraarticular, intradermal, intramuscular, and intravenous injections.¹⁵⁵⁻²³⁶ In 32 studies, the authors concluded that further studies were necessary on the use of tramadol HCl for analgesia via buccal, caudal extradural, intravenous, perineural, subcutaneous, and submucosal injections.²³⁷⁻²⁶⁷ In 28 studies, the authors did not provide a definitive conclusion for the recommendation of tramadol HCl.²⁶⁸⁻²⁹⁵ In 27 studies, the authors' conclusions did not address the use of tramadol HCl.²⁹⁶⁻³²² In 1 study, the authors found no difference in either the quality of analgesia or incidence of nausea in vomiting between intravenous and subcutaneous tramadol.³²³ In 1 study, there was no conclusion for the use of tramadol HCl since the trial is still ongoing.³²⁴ Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

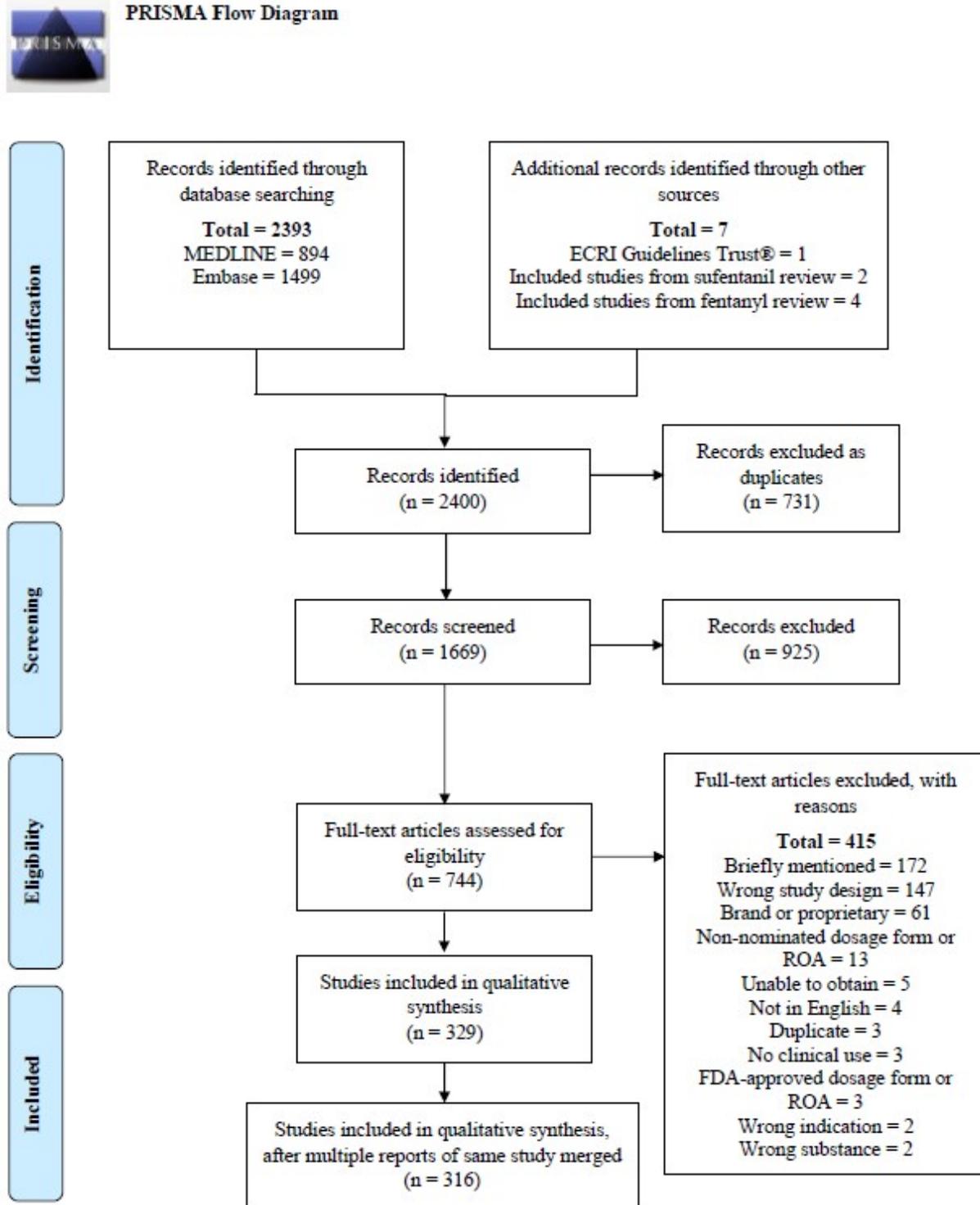
In addition to the 316 included studies, 1 study was identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of tramadol HCl.

Tramadol HCl was first developed in Germany during the late 1970s and approved by the FDA in 1995.³²⁵ At the time of approval, tramadol HCl was the only nonscheduled opioid available; however, it became a Schedule IV substance in 2014.³²⁵ While tramadol HCl is only available as an oral preparation in the US, other countries have suppository and parenteral preparations.³²⁵ The oldest study that was included in the literature review, published in 1986, compared tramadol HCl (a new analgesic at the time) to morphine and pethidine in Thailand.¹¹³

Tramadol HCl is a dual action synthetic analgesic, with activity as an opioid agonist and as a serotonin and norepinephrine reuptake inhibitor (SNRI).³²⁵ Additionally, tramadol HCl is a prodrug, converted by hepatic CYP450 enzymes 3A4 and 2D6 into active and inactive metabolites; approximately 80% is metabolized by CYP2D6.³²⁵ As a result, a patient's analgesic effect depends on if they are a poor metabolizer, intermediate metabolizer, extensive metabolizer, or an ultra-metabolizer of CYP2D6.³²⁵ With tramadol HCl, ultra-metabolizers of CYP2D6 have increased pain tolerance, as well as greater miosis and nausea when compared to extensive metabolizers.³²⁵ Furthermore, tramadol HCl's reliance on CYP2D6 as well as its serotonergic activities puts it at an increased risk of interactions with drug classes such as antiarrhythmics, antiemetics, antidepressants, antipsychotics, analgesics, and tamoxifen; when administered with other serotonergic medications, the patient is at increased risk of serotonin syndrome.³²⁵ Tramadol HCl is also associated with increasing a patient's risk of seizures through the lowering of the seizure threshold at both therapeutic and supratherapeutic doses in patients with and without a history of seizure disorder.³²⁵

While tramadol HCl's dual action has benefits regarding analgesic activity, abrupt cessation of therapy is also associated with withdrawal symptoms typical of both opioids and SNRIs.³²⁵ While there is no literature regarding a tapering schedule for tramadol HCl, lorazepam and clonidine have been suggested for symptomatic relief of withdrawal symptoms.³²⁵

Figure 1. PRISMA flow diagram showing literature screening and selection.



Adapted from:

Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006-1012. Available from: <http://www.prisma-statement.org/>.

Table 3. Types of studies

Types of Studies	Number of Studies
Descriptive	0
Observational ²⁵³	1
Experimental ^{19-252,254-324,326}	315

Table 4. Number of studies by country

Country	Number of Studies
Australia ²¹¹	1
Austria ^{78,187,285}	3
Bangladesh ²¹	1
Belgium ^{37,39,101,111,281}	5
Brazil ^{30,52,86,107,170,274,323}	7
China ^{32,55,76,125,131,144-146,186,192,199,200,223,232,235,254,324}	17
Croatia ^{54,56,92,193,298}	5
Czech Republic ¹⁶⁶	1
Denmark ²²¹	1
Egypt ^{43,44,63,142,150,155,160,161,175,179,255,316}	12
Finland ^{133,292,293}	3
France ²²⁹	1
Germany ^{34,49,64,130,147,217,220,305,306,318}	10
Greece ^{17,77,287}	3
Hong Kong ^{87,104,310}	3
India ^{16,25,27,31,33,38,41,51,53,65,66,69,73,75,83-85,93,94,102,103,114,122,124,126,129,141,158,162,171,180,182,183,196-198,201,202,207,208,212,218,225,226,236,248,250,262,283,288,309,322}	52
Iran ^{61,62,71,72,74,80,97,117,119,120,128,140,157,194,234,238,247,251,263,284,291}	21
Italy ^{13,29,35,50,88,90,91,96,110,115,159,172,181,227,243,271,273,277,278,300,303,317}	22
Korea ^{213,252,307,308}	4
Kosovo ¹⁰⁰	1
Lebanon ^{23,151,269}	3
Malaysia ^{280,301,302}	3
Mexico ^{112,188,189}	3
New Zealand ^{127,270}	2

Nigeria ^{9,42,152,239}	4
Pakistan ^{15,18,68,121,123,143,219,289,290,297}	10
Philippines ^{60,206}	2
Poland ⁴⁸	1
Portugal ³¹⁵	1
Russia ⁷⁰	1
Saudi Arabia ^{14,209,266,268}	4
Serbia ^{95,153}	2
Singapore ^{132,267}	2
South Africa ^{28,36,249,282}	4
Spain ^{116,214,286,294}	4
Sweden ^{177,222}	2
Switzerland ^{230,295}	2
Taiwan ^{47,89,167,272,314}	5
Thailand ^{113,210}	2
The Netherlands ⁶⁷	1
Tunisia ²⁷⁹	1
Turkey ^{10-12,19,20,26,40,46,57-59,79,81,82,98,99,105,106,108,109,118,134-139,148,149,154,156,163,164,168,169,173,174,176,178,184,185,195,203-205,215,216,228,233,237,240,242,244-246,256,257,260,261,264,265,275,276,299,304,311-313,319-321}	71
United Arab Emirates ²⁴	1
UK ^{22,45,165,190,191,224,231,241,258,259}	10
US ²⁵³	1
Uzbekistan ²⁹⁶	1
Total US: 1	
Total Non-US Countries: 315	

Table 5. Summary of included studies

Refer to Appendix 2

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Analgesia ²⁵³	468 mg	–	–	Intravenous	2.2 hours

Abbreviation: “–”, not mentioned.

Table 7. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment	
Analgesia ^{9-14,17,18,20,21,23-31,33-54,56-66,68,69,71-80,82-85,87,89-99,103,105-108,110-114,117-122,124-129,133-138,140-142,146-148,150,151,155-158,160,162-172,174-192,194,195,197-199,201-208,210,212-217,219-223,225-230,232-235,237-247,249-252,255,258,259,262-267,269,271,273,274,276-279,281,283-285,288-291,296-301,304-307,309,317,322-324,326}	0.1-3 mg/kg; 10-100 mg	1-2 mg/kg/2-20 mL; 0.25-200 mg/mL	Solution	Buccal, Caudal, Caudal epidural, Caudal extradural, Epidural, Infiltration, Intraarticular, Intracutaneous, Intradermal, Intraincisional, Intramuscular, Intraperitoneal, Intrathecal, Perineural, Peritonsillar, Subcutaneous, Subdural, Submucosal	1-3 doses	
	Loading 100 mg Infusion 0.1-0.2 mg/kg/hour; 5 mg/hour	1-2 mg/kg/40 mL	–		–	–
	1-12 mg/kg/day; 50-825 mg/day	10 mg/mL	–		–	1-3 days
		0.16-10 mg/kg; 37.5-400 mg	1-3 mg/kg/3-100 mL; 0.2-50 mg/mL	Solution	Intravenous	1-3 doses Until VAS ≤ 1
		2 mL/hour	–	–		48 hours
	Loading 0.5-2 mg/kg; 50-20 mg Infusion 0.1-1.2 mg/kg/hour; 5-16.67 mg/hour	1.2-15 mg/kg/100-500 mL; 0.5-2.5 mg/mL	Solution	24-72 hours Duration of operation		
		2-12 mg/kg/day; 50-600 mg/day	2 mg/kg/10 mL; 0.05-100 mg/mL	Solution		12 hours – 7 days Average of 14 days

Patient-controlled analgesia ^{15,19,32,40,55,70,88,104,109,116,118,123,130,131,139,149,173,200,209,224,254,256,257,260,261,272,275,280,282,286,292-294,308,310-314,316,318-321}	Loading 0.3-2.5 mg/kg; 25-100 mg Infusion 0.1-0.9 mg/kg/hour; 0.6-25 mg/hour Demand 0.125-0.45 mg/kg; 1-20 mg, 5-30-minute lockout	0.05-50 mg/mL	Solution	Epidural, Intravenous, Subcutaneous	18-72hours Average of 14 days Duration of operation Until complete cervical dilation
	Loading 1.3 mg/kg, 50 mg 0.065-0.7 mg/kg/hour Demand 0.091-10 mg/kg/hour, 6-20-minute lockout	13 mg/kg/100 mL	Solution		72 hours

Abbreviations: “–”, not mentioned; VAS, visual analogue score.

Table 8. Number of studies by combination

No combination products were nominated

Table 9. Compounded products – US

Indication	Publication Year	Compounding Method	Dosage Form	Final Strength
Analgesia ²⁵³	2011	“Tramadol is indicated for pain but is not available in the US in an IV form. We prepared a sterile injectable form of tramadol”	–	–

Abbreviations: “–”, not mentioned; IV, intravenous.

Table 10. Compounded products – non-US countries

No compounded products from reported studies

Results of interviews

Two hundred eighty-five SMEs were contacted for interviews; 96 agreed to be interviewed, and 189 declined or failed to respond to the interview request. Twelve SMEs discussed tramadol HCl. Amongst these 12 SMEs, there were 6 dentists, 3 medical doctors, 2 pharmacists, and 1 registered nurse practitioner. The SMEs specialized and/or were board-certified in anesthesiology, dentistry, maxillofacial surgery, oncology/hematology, pain medicine, primary care and family medicine, and rheumatology, working in academic medical practice, private practice/clinic, and retired. The SMEs had been in practice for 5 to 39 years.

The SMEs who specialized in dentistry said that they use nonsteroidal anti-inflammatory drugs (NSAIDs) and oral opioids for postoperative pain management. Typically, they use a combination that includes Tylenol®, such as Tylenol #2 or Tylenol #3 (acetaminophen and codeine), Norco® (acetaminophen and hydrocodone), or Percocet® (acetaminophen and oxycodone). They may also use acetaminophen or NSAIDs such as etodolac or ibuprofen. A couple of SMEs said that the injectable NSAID Toradol® (ketorolac) is a popular option amongst oral surgeons as an adjunct analgesic during sedation or for postoperative pain control. Several SMEs who specialized in dentistry were familiar with using Ultracet® (tramadol HCl) as an oral product postoperatively. One SME said that they occasionally use tramadol if a patient is unable to take another opioid due to allergy; sometimes they also use morphine. Another SME said that although it was not their main pain medication, they used it if their patient needed something stronger over a weekend since they could call it into the pharmacy instead of needing a written prescription. Another SME said that they used to prescribe tramadol tablets for severe pain or if they suspected a patient might experience more pain after a tooth extraction, but they do not use it as much anymore.

Several SMEs who specialized in dentistry said that they could see the injectable tramadol HCl being useful in situations such as intravenous sedation but have never used it as such themselves. One SME said that they use midazolam for sedation and a long acting local anesthetic such as Marcaine® (bupivacaine) for anesthesia when they do procedures. Additionally, they said that the oral surgeons who require a deeper sedation already have an opioid that controls pain for a while and were not sure why they would need another injectable analgesic, especially since there are increased regulations with stocking narcotics in the dental office. One dentist said that some of their patients need to be asleep for dental procedures and the primary narcotic that they use is intravenous fentanyl; they also might use alfentanil or remifentanil if they want something with a faster metabolism.

One SME who specialized in oncology said that they do not think tramadol HCl works at all; they use it in patients who want something stronger than acetaminophen but are not willing to take oxycodone or morphine. However, they have never had a patient tell them that it works, and they always end up using an opioid. While oxycodone and morphine are similar drugs, they usually start with oxycodone unless insurance agencies will only pay for morphine first. They typically prescribe patients a long-acting pain medication for maintenance therapy and a short-acting drug for breakthrough pain; the SME said that they try to keep with the same long-acting drug that they used for the short-acting drug. They use fentanyl patches frequently, especially with patients who have head and neck cancer and cannot take things by mouth. They also said that they are using more methadone.

One SME who specialized in pain medicine said that they use oral tramadol but think an intravenous formulation would be great in an acute pain setting. Another SME who specialized in primary care said that when tramadol came out practitioners thought it was “like the greatest thing ever” because people were convinced that it was not going to be addicting. As it turns out, it was, just like any other opioid.

Furthermore, differences in patient metabolism of tramadol HCl can result in patients having unpredictable responses to standardized doses. For these reasons, tramadol HCl has been taken out of their standard order sets. The opioids they prescribe most often are oxycodone, hydrocodone, methadone, and morphine. In their practice, they typically use a combination of long- and short-acting pain medications.

Several SMEs who specialized in palliative care were not fans of tramadol HCl, with one SME describing it as the “world’s dumbest drug” and “trama-don’t.” Tramadol HCl is a very weak opioid-like drug and the mu opioid receptor is hit by its metabolite, which is 1/6000 the potency of morphine. Furthermore, it lowers the seizure threshold, increases the fall risk in elderly patients, and causes hypoglycemia and serotonin syndrome; “it causes all the side effects of more potent drugs without the good stuff of the big-dog opioids.” Tramadol HCl is also a prodrug; therefore, it must be metabolized by one of the liver enzymes to be activated and if the enzyme works faster (either due to other drugs or genetics), it can increase the risk of overdose. One SME said that “Tramadol makes the prescriber feel better. I would not have it injectable in this country. I think it is a misleading drug.”

One SME who specialized in rheumatology said that they mainly use Percocet® for pain management in their patients and occasionally use acetaminophen and codeine or oxycodone. They use tramadol HCl as well, “but that is not really an opioid.”

One SME who specialized in dentistry said that compounded drugs for dentistry typically are topical local anesthetics. One SME who specialized in palliative care said that they try to minimize the use of compounded drugs due to limited data. Furthermore, they said that “A lot of hospice nurses suffer under a misperception about compounds. Hospice nurses tend to think you can take any tablet or capsule and put it into the rectum and everything is great, which is not true. They think anything you put into a base, you can slab it onto intact skin and it’s going to be absorbed and do well. It is not true. I am not a fan.”

Results of survey

One person responded to the survey distributed via professional medical associations and available on the project website; refer to Table 11 for respondent characteristics.

The one survey respondent reported using tramadol HCl, but not as an injectable product.

A separate survey was distributed by the Ambulatory Surgery Center Association (ASCA); 230 people responded to this survey (refer to Appendix 2.2 for survey instrument).

Amongst respondents to the ASCA survey, 97 (42% of 230 total respondents) were very familiar with the term ‘503B outsourcing facility’, 86 (37%) were somewhat familiar with this term, and 47 (20%) were not familiar with this term (refer to Table 15).

One hundred ten survey respondents (54% of 203 people who responded to this question) utilized a 503B outsourcing facility to acquire compounded drugs; 93 survey respondents (46%) did not utilize a 503B outsourcing facility. Two respondents (0.7% of 290 responses, where respondents were allowed to select multiple drug products) obtained tramadol HCl from a 503B outsourcing facility (refer to Table 16).

The most common types of procedures performed at the facilities where the ASCA survey respondents worked were: ophthalmology (115, 17% of responses, where respondents were allowed to select multiple procedure types); orthopedics (89, 13%); pain (80, 12%); podiatry (74, 11%); and plastics (72, 10%) (refer to Table 17).

Table 11. Characteristics of survey respondents

Terminal Clinical Degree	Responses, n (N=1)
Doctor of Medicine (MD)	0
Doctor of Osteopathic Medicine (DO)	0
Doctor of Medicine in Dentistry (DMD/DDS)	0
Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)	1
Naturopathic Doctor (ND)	0
Nurse Practitioner (NP)	0
Physician Assistant (PA)	0
Practice Setting	Respondents, n (N=1)
Physician office or private practice	0
Outpatient clinic	0
Hospital or health system	0
Academic medical center	1
Emergency room	0
Operating room	0

Table 12. Conditions for which tramadol HCl prescribed or administered

No survey respondents used injectable tramadol HCl

Table 13. Reasons for using compounded tramadol HCl

No survey respondents used injectable tramadol HCl

Table 14. Use of non-patient-specific compounded tramadol HCl

No survey respondents used injectable tramadol HCl

Table 15. Ambulatory Surgery Center Association respondents' familiarity with compounding terms

Compounded drugs (medications prepared to meet a patient-specific need)	Responses, n (N=230)
Very familiar	153
Somewhat familiar	70
Not familiar	7
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed to meet a patient-specific need)	Responses, n (N=230)
Very familiar	118
Somewhat familiar	91
Not familiar	21
503B Outsourcing facility (a facility that compounds larger quantities without a patient-specific prescription)	Responses, n (N=230)
Very familiar	97
Somewhat familiar	86
Not familiar	47

Table 16. Products obtained from a 503B outsourcing facility

Product	Responses, n (N=290)^a
Amitriptyline / Ketoprofen / Oxymetazoline	1
Budesonide	2
Calcium gluconate	2
Droperidol	2
Epinephrine	11
Epinephrine for ophthalmic administration	16
Epinephrine / Lidocaine for ophthalmic administration	31

Epinephrine / Bupivacaine / Fentanyl	3
Fentanyl	10
Flurbiprofen	3
Flurbiprofen for ophthalmic administration	6
Hydromorphone	5
Ipamorelin	1
Ketoprofen / Nifedipine	3
Lidocaine / Epinephrine / Tetracaine	13
Meperidine	3
Morphine	5
Naloxone	5
Neomycin	5
Phentolamine	1
Promethazine	5
Remifentanyl	4
Sufentanyl	2
Tramadol	2
None of the above	75
Do not obtain any compounded drugs from 503B outsourcing facility	74

^aSurvey respondents allowed to select multiple products.

Table 17. Type of specialty procedures performed at ambulatory surgery facility

Procedure Type	Responses, n (N=686)^a
Dental	23
Dermatology	9
Endoscopy	65
Neurosurgery	22
Obstetrics/gynecology	39
Ophthalmology	115
Otolaryngology	58
Orthopedics	89
Pain	80
Plastics	72
Podiatry	74
Other ^b	40

^aSurvey respondents were allowed to select multiple procedure types.

^bNo respondents provided description for 'Other' procedure type.

CONCLUSION

Tramadol HCl was nominated for inclusion on the 503B Bulks List as an injectable product to treat moderate to moderately severe pain. Tramadol HCl is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, the EU, Hong Kong, Ireland, Namibia, New Zealand, and the UK.

From the literature review and interviews conducted, tramadol HCl is used as a parenteral preparation in many countries. However, it is only available in the US as an oral product. Tramadol HCl has dual mechanisms of action and is dependent upon hepatic metabolism to be converted into the active metabolites. It is also associated with numerous drug-drug interactions, increases patient risk of seizures through the lowering of the seizure threshold, and increases the risk of serotonin syndrome when administered with other serotonergic medications. Through the literature review, tramadol HCl is administered via a wide variety of injectable routes. None of the SMEs were familiar with using tramadol HCl as an injectable product, though a couple of SMEs who specialized in dentistry and pain medicine thought there might be a use for an injectable preparation for intravenous sedation or for an acute pain setting. While all the SMEs were familiar with administration of oral tramadol HCl, practitioners who specialized in oncology, primary care, and palliative care expressed doubt about the effectiveness of the drug, in addition to concern about its side effects. One SME specifically said that they would not want it available as an injectable drug in the US.

From the survey responses, 1 out of 1 respondent used tramadol HCl, but not as an injectable product. Two hundred thirty people responded to the survey distributed via the ASCA. Two respondents reported obtaining tramadol HCl from a 503B outsourcing facility.

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APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process and other non-indexed citations and daily 1946 to March 6, 2020
- Date last searched: March 8, 2020
- Limits: Humans (search hedge); English language
- Number of results: 894

1	tramadol/	3067
2	tramadol\$.tw.	5008
3	or/1-2	5363
4	drug administration routes/	5638
5	exp administration, intravenous/	141866
6	infusions, parenteral/	26196
7	infusions, subcutaneous/	1049
8	injections, intramuscular/	30794
9	injections, subcutaneous/	32433
10	injections, intra-articular/	7727
11	inject\$.tw.	728574
12	(parenteral\$ adj2 (administ\$ or therap\$ or treat\$ or deliver\$)).tw.	12013
13	subcutaneous\$.tw.	162832
14	intravenous\$.tw.	335064
15	intra venous\$.tw.	568
16	intravascular\$.tw.	46962
17	intra vascular\$.tw.	296
18	intramuscular\$.tw.	51528
19	intra muscular\$.tw.	709
20	intraarticular\$.tw.	5397

21	intra articular\$.tw.	15342
22	or/4-21	1270419
23	exp pain/	388990
24	pain management/	32811
25	analgesia/	19720
26	analgesia, patient-controlled/	4520
27	drug therapy/	30357
28	dt.fs.	2184738
29	ad.fs.	1393722
30	tu.fs.	2191668
31	pain\$.tw.	673880
32	analgesi\$.tw.	120483
33	or/23-32	4334555
34	and/3,22,33	1279
35	exp animals/ not humans/	4675662
36	34 not 35	1029
37	limit 36 to english language	894

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: March 8, 2020
- Limits: Humans (search hedge); English language
- Number of results: 1499

1	tramadol'/mj	4352
2	tramadol*':ti,ab,tn	8439
3	#1 OR #2	8952
4	parenteral drug administration'/de	2103
5	intramuscular drug administration'/de	71558
6	intravascular drug administration'/exp	417229
7	subcutaneous drug administration'/de	100774
8	intraarticular drug administration'/de	7328
9	inject*':ti,ab	1082000
10	(parenteral* NEAR/2 (administ* OR therap* OR treat* OR deliver*)):ti,ab	18105
11	subcutaneous*':ti,ab	245757
12	intravenous*':ti,ab	482508
13	intra venous*':ti,ab	1434
14	intravascular*':ti,ab	67454
15	intra vascular*':ti,ab	675
16	intramuscular*':ti,ab	74342
17	intra muscular*':ti,ab	1269
18	intraarticular*':ti,ab	27033
19	intra articular*':ti,ab	20468
20	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	2054010
21	pain'/exp	1359950
22	analgesia'/de	125966

23	postoperative analgesia'/de	16788
24	patient controlled analgesia'/de	9487
25	drug therapy'/de	711199
26	add on therapy'/de	18515
27	drug dose':lnk	621819
28	drug administration':lnk	1718631
29	drug therapy':lnk	3843836
30	pain*':ti,ab	1035488
31	analgesi*':ti,ab	177680
32	#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31	6355158
33	#3 AND #20 AND #32	2197
34	[animals]/lim NOT [humans]/lim	6001338
35	#33 NOT #34	1818
36	#33 NOT #34 AND [english]/lim	1499

Appendix 2. Summary of included studies

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication: Pain					
Abdallah <i>et al.</i> , 2003, Egypt ¹⁵⁵	Controlled, randomized, double-blind study	60 In-patients undergoing elective subumbilical surgery (gender not specified; range 3-7 y)	Caudal bupivacaine plus: <ul style="list-style-type: none"> • Intravenous (IV) placebo (20) • Caudal tramadol (20) • IV tramadol (20) 	Pain scores	"Co-administration of tramadol with caudal bupivacaine, whether caudally or intravenously, to improve the quality of analgesia was not satisfactory considering both the efficacy and duration provided."
Abdurakhmonov, 2013, Uzbekistan ²⁹⁶	–	120 In-patients undergoing shockwave lithotripsy (SWL; gender and age not specified)	<ul style="list-style-type: none"> • IV Fentanyl • Intramuscular (IM) Diclofenac sodium • IM Tramadol • EMLA cream containing lidocaine and prilocaine 	Pain intensity; sedation; side effects	"Application of EMLA cream was as safe and effective as fentanyl, diclofenac, and tramadol, and reduction of the fentanyl dose during SWL was possible."
Adeniji and Atanda, 2013, Nigeria ⁹	Randomized comparison of effectiveness	120 In-patients with uncomplicated cesarean deliveries Pentazocine (0%, mean 29.20 y ± 3.61) Tramadol (0%, mean 30.12 y ± 3.43) Pentazocine and piroxicam (0%, mean 29.64 y ± 2.82) Tramadol and piroxicam (0%, mean 29.23 y ± 3.10)	<ul style="list-style-type: none"> • Pentazocine (30) • Tramadol (30) • Pentazocine and piroxicam group (30) • Tramadol and piroxicam group (30) 	Control of postoperative pain	"In conclusion, in a resource-poor setting like Nigeria, where more potent opioids are not readily available and affordable, our study has shown that a multimodal approach combining pentazocine or tramadol with an NSAID [nonsteroidal anti-inflammatory drug], such as piroxicam, would achieve better pain relief and maternal satisfaction following cesarean section."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Afolayan <i>et al.</i> , 2014, Nigeria ¹⁵²	Prospective, randomized, placebo-controlled clinical study	186 In-patients scheduled for emergency appendectomy Fentanyl (37.1%, mean 28.58 y ± 1.37) Normal saline (40.3%, mean 28.79 y ± 1.34) Tramadol (35.5%, mean 28.55 y ± 1.23)	Hyperbaric bupivacaine plus: <ul style="list-style-type: none"> • Fentanyl (62) • Normal saline (62) • Tramadol (62) 	Pain scores, frequency of subjective symptoms, duration of analgesia	"This study showed that intrathecal tramadol (25 mg) can safely replace intrathecal fentanyl (25 mcg) in the management of visceral pain and discomfort during subarachnoid block for appendectomy."
Ahmad <i>et al.</i> , 2006, Pakistan ²⁹⁷	Experimental comparative study	60 In-patients undergoing laparoscopic cholecystectomy (gender and age not specified)	<ul style="list-style-type: none"> • IM ketorolac (30) • IM ketorolac, IM tramadol, plus local infiltration with 0.5% bupivacaine injection (30) 	Pain relief	"Multimodal analgesia has much more advantage over single analgesia in patients undergoing Laparoscopic Cholecystectomy."
Akinci <i>et al.</i> , 2008, Turkey ¹⁰	Randomized, Double-blind	61 In-patients scheduled for laparoscopic cholecystectomy Control (35%, mean 47 y ± 11) Intravenous tramadol (33%, mean 43 y ± 10) Intraperitoneal (IP) tramadol (40%, mean 52 y ± 13)	<ul style="list-style-type: none"> • IV tramadol (21) • IP tramadol (20) • Control (20) 	Parietal pain; visceral pain	"Intravenous tramadol provides superior postoperative analgesia in the early postoperative period after laparoscopic cholecystectomy compared with an equivalent dose of tramadol administered intraperitoneally and with normal saline in patients undergoing laparoscopic cholecystectomy."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Akinci <i>et al.</i> , 2003, Turkey ³²⁷ Akinci <i>et al.</i> , 2005, Turkey ¹¹	Prospective double-blind randomized trial	75 Out-patients scheduled to undergo elective arthroscopic surgery Control (60%, mean 41 y ± 17) Morphine (64%, mean 34 y ± 15) Tramadol (68%, mean 34 y ± 17)	<ul style="list-style-type: none"> • Tramadol (25) • Morphine (25) • Control (25) 	Verbal pain rating (VRS)	"We conclude that these 2 drugs at these doses provide similar analgesia when given intra-articularly. Further studies, with a larger number of patients are needed to compare the side effects of IA [intraarticular] administration of morphine and those of tramadol."
Akkaya <i>et al.</i> , 2009, Turkey ¹²	Randomized, prospective, double-blind clinical study.	66 In-patients scheduled for adenotonsillectomy IV Tramadol (45%, mean 6.09 y ± 1.70) Peritonsillar tramadol (52%, mean 6.12 y ± 1.56)	<ul style="list-style-type: none"> • IV tramadol (33) • Peritonsillar tramadol (33) 	Pain scores	"Besides, peritonsillar tramadol infiltration significantly lowers the incidence of nausea and vomiting at the early postoperative period. So, we think that peritonsillar tramadol infiltration is a better choice than classical methods for adenotonsillectomy in children."
Aksoy and Ege, 2020, Turkey ²³⁷	Randomized controlled, double-blind clinical trial	90 In-patients scheduled for root canal treatment Control (43.3%, mean 38.83 y ± 10.37) Tramadol (60.0%, mean 38.10 y ± 13.23) Dexamethasone (46.7%, mean 36.30 y ± 13.50)	<ul style="list-style-type: none"> • Control (30) • Tramadol (30) • Dexamethasone (30) 	Pain levels	"The preoperative submucosal administration of dexamethasone and tramadol resulted in decreased post-endodontic pain in the first 48 h. Dexamethasone was more effective than tramadol within the first 12 h. Further comprehensive and detailed clinical studies investigating the effect of various administration methods are of great interest to better understand the potential of these drugs in endodontic procedures"

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Alemanno <i>et al.</i> , 2012, Italy ¹³	Prospective, randomized, double-blinded study	120 In-patients undergoing shoulder arthroplasty (gender not specified) Placebo (mean 58 y ± 12) Perineural tramadol (mean 54 y ± 13) IM tramadol (mean 55 y ± 16)	Perineural levobupivacaine plus: <ul style="list-style-type: none"> • Placebo (40) • Perineural tramadol (40) • IM tramadol (40) 	Duration of analgesia	"In conclusion, when added to single-shot middle interscalene block performed with 0.5% levobupivacaine, tramadol extends the duration of postoperative analgesia without significant side effects."
Ali <i>et al.</i> , 2006, Saudi Arabia ¹⁴	Single dose, double blind, randomized clinical trial	60 Patients undergoing laparoscopic dye test (gender and age not specified)	<ul style="list-style-type: none"> • IV tramadol • IV ketorolac 	Pain, nausea and vomiting	"Study showed that tramadol is a better analgesic compared to ketorolac for patients undergoing day care gynaecological laparoscopic procedure."
Ali and Khan, 2009, Pakistan ¹⁵	Prospective randomized double-blind clinical	60 In-patients presenting for laparoscopy and dye test Tramadol (0%, mean 30.8 y ± 5.2) Tramadol and Paracetamol (0%, mean 28.7 y ± 3.3)	<ul style="list-style-type: none"> • IV Tramadol (30) • IV Tramadol plus oral Paracetamol (30) 	Pain	"We conclude that reducing the dose of tramadol to 1 mg/kg and combining it with paracetamol 1 g orally decreased the incidence of side effects of tramadol without reducing analgesic efficacy."
Ali <i>et al.</i> , 2008, Iran ²³⁸	Randomized, prospective, double-blind and placebo-controlled study design	90 In-patients scheduled for adenotonsillectomy (gender not specified) Placebo (mean 7.61 y ± 1.93) Dextromethorphan (mean 7.46 y ± 1.85) Tramadol (mean 7.53 y ± 1.88)	<ul style="list-style-type: none"> • Placebo (30) • Oral dextromethorphan (30) • Tramadol (30) 	Pain (VAS ratings)	" However, future studies in pediatric anesthesia assessing these potentials are required before these drugs can be recommended for their use. In conclusion, we found that tramadol is more suitable than dextromethorphan in reducing postop pain in children undergoing adenotonsillectomy"

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Ali <i>et al.</i> , 2017, India ¹⁶	Prospective, randomized, double-blind study	124 In-patients undergoing major abdominal surgery (gender not specified, range 1-8 y)	<ul style="list-style-type: none"> • IV tramadol (62) • IV tramadol plus rectal paracetamol (62) 	Postoperative pain scores	"We recommend use of an infusion of tramadol in a dose of 0.25 mg/kg/h in the first 24 h after surgery, in combination with a regular per rectal paracetamol in a daily dose of 90 mg/kg/day in four divided doses for children after major abdominal surgery if facilities for continuous infusion of epidural analgesia are not available. However, a close nursing supervision is essential to increase the safety profile"
Ali <i>et al.</i> , 2009, Saudi Arabia ²⁶⁸	Double-blinded randomized controlled study	108 In-patients scheduled for sleeve gastrectomy or gastric bypass surgeries (gender and age not specified)	Patient-controlled analgesia (PCA) with: <ul style="list-style-type: none"> • Morphine • Fentanyl • Tramadol 	Cumulative opioid dose; highest pain score; mean oxygen saturation during hypoxemic episodes	"There was significant increase in fentanyl and Tramadol consumption over morphine to control postoperative pain in obese patients undergoing laparoscopic bariatric surgery with fewer side effects. Patients in Tramadol group presented in the second day with less consumption and better pain scores than the first day. The use of Opioids to control pain in this group of patients is associated with hypoxemia."
Andreotti <i>et al.</i> , 2012, Greece ¹⁷	–	45 In-patients scheduled to undergo elective orthopedic surgery (gender and age not specified)	Levobupivacaine plus: <ul style="list-style-type: none"> • Fentanyl (15) • Tramadol (15) • Tramadol and clonidine (15) 	Motor blockage; analgesia duration	"Tramadol and clonidine added to levobupivacaine for SA [spinal anesthesia] significantly prolong the pain free period when compared to fentanyl or tramadol alone."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Arici <i>et al.</i> , 2003, Turkey ¹⁵⁶	–	26 Out-patients undergoing ambulatory colonoscopy (gender not specified, range 18-65 y)	Midazolam plus: <ul style="list-style-type: none"> • Remifentanil (18) • Tramadol (18) 	Hemodynamic variables; respiratory depression; level of sedation; postoperative recovery; patient and gastroenterologist satisfaction	"Our results suggests that, sedoanalgesia with midazolam/remifentanil may be an alternative to sedoanalgesia with midazolam/tramadol for colonoscopy."
Arti and Mehdiinasab, 2011, Iran ¹⁵⁷	Controlled double blind randomized clinical trial	150 In-patients undergoing arthroscopic anterior cruciate ligament (ACL) reconstruction surgery Morphine (76.7%, mean 31.5 y ± 5.9) Methadone (73.3%, mean 28.9 y ± 7.63) Pethidine (76.7%, mean 26.8 y ± 7.8) Tramadol (73.3%, mean 27.5 y ± 7.4)	Bupivacaine and epinephrine plus: <ul style="list-style-type: none"> • Methadone (30) • Morphine (30) • Pethidine (30) • Tramadol (30) • Control (30) 	Postoperative pain scores; responses to analgesics	"Considering the results, unlike methadone, pethidine and tramadol did not have significant long-term efficacy on pain relief after knee surgery. 5 mg intra-articular morphine was preferable, safe and useful and its use with bupivacaine is recommended for pain relief after knee surgery."
Asad, 2016, Pakistan ¹⁸	Double blind comparison	60 In-patients undergoing upper limb surgery (gender not specified, range 25-60 y)	Perineural ropivacaine plus: <ul style="list-style-type: none"> • Saline (30) • Tramadol (30) 	Sensory and motor block were assessed at 5, 10, 15, 20 and 25 minutes	"Tramadol when used as an additive with ropivacaine provides better anesthesia and analgesia in peripheral nerve block."
Ashwani and Dhanpal, 2009, India ¹⁵⁸	Randomized, prospective, double blind, clinical trial	90 In-patients undergoing emergency and elective surgery (gender not specified, range 20-60 y)	<ul style="list-style-type: none"> • Lignocaine (30) • Thiopentone (30) • Tramadol (30) 	Heart rate, blood pressure, discomfort, pain tolerability, and postoperative recall	"40 mg lignocaine pretreatment with a venous tourniquet for 1 min is the most effective means of relieving the pain on intravenous injection of propofol."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Aurilio <i>et al.</i> , 2009, Italy ¹⁵⁹	–	60 In-patients undergoing surgery (gender and age not specified)	<ul style="list-style-type: none"> • Oral tramadol plus acetaminophen (30) • IV tramadol plus ketorolac and ranitidine (30) 	Pain scores; side effects	"The oral association of tramadol 37,5 mg plus acetaminophen 325 mg is effective in the management of postoperative pain with safety profile better than continuous intravenous infusion of tramadol plus ketorolac."
Aygun <i>et al.</i> , 2004, Turkey ¹⁹	–	80 In-patients undergoing lower abdominal surgery Group 1 (30%, mean 40.2 y ± 11.7) Group 2 (30%, mean 39.8 y ± 11.5) Group 3 (20%, mean 38.1 y ± 9.9) Group 4 (25%, mean 38.5 y ± 10.4)	PCA analgesia with: <ul style="list-style-type: none"> • Group 1 - IV tramadol (20) • Group 2 - IV fentanyl (20) • Group 3 - epidural tramadol (20) • Group 4 - epidural ropivacaine, fentanyl (20) 	Adequate analgesia over time; level of sedation	"In conclusion, intravenous tramadol, intravenous fentanyl, epidural tramadol, and an epidural ropivacaine and fentanyl combination can all provide adequate pain relief in patient-controlled analgesia after surgery. Although the intravenous use of tramadol or fentanyl avoids the necessity of placing an epidural catheter, both drugs are associated with a disturbingly high incidence of nausea and vomiting."
Ayoglu <i>et al.</i> , 2010, Turkey ²⁰	Prospective randomized study	80 In-patients undergoing elective arthroscopic knee surgery for meniscal tears Tramadol (40%, mean 41.5 y ± 2.9) Tramadol and ketamine (60%, mean 40.9 y ± 2.9) Ropivacaine (55%, mean 40.1 y ± 2.9) Ropivacaine and ketamine (55%, mean 40.2 y ± 2.3)	<ul style="list-style-type: none"> • Tramadol (20) • Tramadol plus ketamine (20) • Ropivacaine (20) • Ropivacaine plus ketamine (20) 	Postoperative pain scores; total morphine consumption; side effects	"We concluded that the combination of IA tramadol and ketamine administered postoperatively provided a significant analgesic benefit and decreased the opioid requirements after arthroscopic knee surgery, when compared to tramadol or ropivacaine alone or in combination. The addition of ketamine to IA study drugs improved postoperative analgesia. IA tramadol–ketamine combination may be a viable alternative for pain control after knee arthroscopy."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Aziz <i>et al.</i> , 2003, Bangladesh ²¹	Double blind study	100 Patients receiving treatment for postoperative pain (gender and age not specified)	<ul style="list-style-type: none"> • Tramadol (25) • Ketorolac (25) • Diclofenac (25) • Pethidine (25) 	Pain scales; pulse rate; blood pressure; incidence of nausea; vomiting; sedation and recovery score	"Tramadol, ketorolac and diclofenac infusion appears to be an effective and well-tolerated analgesic in post-operative pain."
Bahram <i>et al.</i> , 2016, Egypt ¹⁶⁰	Double-blind, prospective controlled study	400 In-patients undergoing laparoscopic cholecystectomy (33.75%, range 18-65 y)	<ul style="list-style-type: none"> • Ropivacaine (200) • Tramadol (200) 	The intensity of postoperative pain using visual analogue scale (VAS) and shoulder pain was evaluated	"Intraperitoneal installation of ropivacaine hydrochloride reduces the intensity of visceral, parietal, and shoulder pain in comparison with IM tramadol injection."
Bakr <i>et al.</i> , 2016, Egypt ¹⁶¹	Prospective clinical trial	60 In-patients scheduled for modified radical mastectomy Morphine (0%, mean 50.90 y ± 12.32) Tramadol (0%, mean 45.25 y ± 13.95) Ketorolac (0%, mean 46.25 y ± 10.42)	<ul style="list-style-type: none"> • Morphine (20) • Tramadol (20) • Ketorolac (20) 	Observation of heart rate, systolic, and diastolic blood pressure, respiratory rate, oxygen saturation, and VAS (at rest) were recorded	"In conclusion, IV morphine, tramadol, and ketorolac suppressed stress and immune responses, but ketorolac was the least immunosuppressive among the 3 drugs in patients who underwent modified radical mastectomy."
Bamigbade <i>et al.</i> , 1998, UK ²²	Prospective, randomized, double-blind study	228 Patients scheduled to undergo groin surgery (gender and age not specified)	<ul style="list-style-type: none"> • IV or oral tramadol (not reported) • IV fentanyl or oral Co-codamol (codeine / paracetamol; not reported) 	Pain intensity and relief	"This study has demonstrated that when the analgesic requirement is highest, on the day of discharge, tramadol is statistically superior to Co-codamol in analgesic efficacy, with an acceptably low incidence of side effects."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Bandey and Singh, 2016, India ¹⁶²	Prospective, randomized controlled trial	60 In-patients who were scheduled for elective laparoscopic cholecystectomy Paracetamol (53.3%, mean 43.17 y ± 9.13) Tramadol (53.3%, mean 42.90 y ± 10.45)	<ul style="list-style-type: none"> • IV paracetamol (30) • IV tramadol (30) 	Pain intensity (VAS scores)	"Thus intravenous infusion of Paracetamol can safely and effectively be recommended for postoperative pain relief in patients undergoing laparoscopic cholecystectomy."
Baraka <i>et al.</i> , 1993, Lebanon ²³	–	20 In-patients undergoing elective major abdominal surgery Tramadol (90%, mean 59.8 y ± 12.3) Morphine (60%, mean 58.4 y ± 8.8)	Epidural lidocaine plus: <ul style="list-style-type: none"> • Tramadol (10) • Morphine (10) 	Pain score	"In conclusion, our report shows that epidural tramadol can provide adequate and prolonged postoperative analgesia, without early or delayed clinical respiratory depression."
Baraka <i>et al.</i> , 1998, Lebanon ²⁶⁹	Randomized double-blinded study	40 In-patients undergoing elective Caesarean section (0%, mean 30 y ± 5)	<ul style="list-style-type: none"> • Tramadol (20) • Fentanyl (20) 	Umbilical vein blood gases and Apgar scores	"Tramadol is associated with a high incidence of intraoperative maternal recall and can result in lower umbilical vein PO ₂ and higher PCO ₂ than in the fentanyl group."
Barsoum, 1995, United Arab Emirates ²⁴	Open Randomized Study	75 In-patients with moderate or severe pain after mainly lower abdominal surgery Tramadol (80%, mean 6.3 y ± 2.9) Pethidine (76%, mean 6.2 y ± 2.8) Nalbuphine (88%, mean 5.4 y ± 2.6)	<ul style="list-style-type: none"> • Tramadol (25) • Pethidine (25) • Nalbuphine (25) 	Percentage of patients with no or only slight pain 60 minutes after initial administration of the study drug	"All 3 drugs produced a similar and minimal amount of respiratory and cardiovascular depression. Thus, tramadol 2 mg/kg by intramuscular injection appears to be an effective and well-tolerated analgesic, suitable for use in children with moderate or severe postoperative pain."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Basar <i>et al.</i> , 2003, Turkey ¹⁶³	–	100 Patients scheduled for elective shockwave lithotripsy Fentanyl (60%, mean 44 y ± 2) Diclofenac (64%, mean 39 y ± 2) Tramadol (56%, mean 41 y ± 3.52) EMLA cream (64%, mean 46 y ± 2.55)	<ul style="list-style-type: none"> • Fentanyl (25) • Diclofenac (25) • Tramadol (25) • EMLA cream (25) 	Pain score (VAS); sedation (Observer's Assessment of Alertness/Sedation; OAS/S)	"Therefore, we recommend EMLA cream with a very small doses of fentanyl for any SWL treatment"
Bashir <i>et al.</i> , 2011, India ²⁵	Prospective randomized study	120 In-patients admitted for different elective general surgical procedures (gender and age not specified)	<ul style="list-style-type: none"> • Propofol only (30) • Lignocaine followed by propofol (30) • Tramadol followed by propofol (30) • Normal saline followed by propofol (30) 	Incidence and severity of pain	"Lignocaine and tramadol are equally effective in reducing both incidence and severity of pain due to propofol injection. Tramadol being as effective as lignocaine in prevention of propofol induced pain, may replace lignocaine, thereby minimizing risk to the population, as lignocaine is well known to have cardiorespiratory depressant property."
Bedirli <i>et al.</i> , 2011, Turkey ³²⁸ Bedirli <i>et al.</i> , 2017, Turkey ²⁶	Prospective, randomized, double blinded clinical study	77 In-patients undergoing adenotonsillectomy Tramadol (67.5%, mean 8.4 y ± 2.1) Dexmedetomidine (52.5%, mean 6.7 y ± 3.1)	<ul style="list-style-type: none"> • Tramadol (39) • Dexmedetomidine (38) 	Postoperative recovery including pain; sedation; emerge reactions; and hemodynamics	"In this study, we have demonstrated that in pediatric patients undergoing ambulatory adenotonsillectomy both dexmedetomidine and tramadol were effective on controlling postoperative pain and emergency agitation but in comparison to tramadol dexmedetomidine administration resulted in higher incidence of, intraoperative bradycardia, hypotension, postoperative prolonged sedation, and prolonged PACU [postoperative care unit] stay."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Beigh <i>et al.</i> , 2013, India ²⁷	Prospective randomized study	46 Patients undergoing tonsillectomy Tramadol (57%, mean 17 y ± 4) Saline (61%, mean 16 y ± 5)	<ul style="list-style-type: none"> • Tramadol and adrenaline (23) • Saline (23) 	Time to hemostasis; postoperative pain; side effects/complications	"Therefore the use of Tramadol plus adrenaline infiltration should be further promoted and implemented as routine use in tonsillectomy surgeries."
Bekavac Misak <i>et al.</i> , 2015, Croatia ²⁹⁸	Prospective, randomized, controlled open-label study	63 In-patients undergoing open renal surgery (gender and age not specified)	<ul style="list-style-type: none"> • IV sufentanil plus ketamine (22) • Epidural levobupivacaine plus sufentanil (20) • IV tramadol, metamizole, and non-steroid anti-rheumatic drug (21) 	Serum hormone levels; pain	"All three postoperative pain management modalities resulted in satisfactory pain reduction. However, the endocrine response to trauma and pain cannot be completely blocked by any type of analgesia."
Bello <i>et al.</i> , 2008, Nigeria ²³⁹	Prospective randomized study	84 Patients undergoing hysterosalpingography (HSG) Tramadol (0%, mean 32.3 y) Control (0%, mean 30.75 y)	IV hyoscine N butyl bromide plus: <ul style="list-style-type: none"> • IV tramadol (40) • Control (44) 	Pain scores	"In conclusion, this study does not show a statistically significant decrease in pain perception in patients premedicated with Tramadol; we believe more studies should be done in our environment to know the technical innovation and analgesic agent that will result in significant reduction of pain experienced during HSG."
Beyzadeoglu <i>et al.</i> , 2007, Turkey ²⁹⁹	Prospective, randomized, double-blind study	74 Out-patients undergoing arthroscopic partial meniscectomy Tramadol-bupivacaine (68%, mean 40 y ± 15) Bupivacaine-bupivacaine (57.5%, mean 39 y ± 16)	Periarticular incisional bupivacaine plus: <ul style="list-style-type: none"> • IA tramadol (41) • IA bupivacaine (33) 	Pain scores; time to analgesic requirement	"Intraarticular tramadol plus periarticular bupivacaine provides better pain relief and less analgesic requirement following arthroscopic outpatient partial meniscectomy surgery."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Borazan <i>et al.</i> , 2012, Turkey ²⁴⁰	–	119 In-patients undergoing orthopedic and otolaryngologic surgery Control (68%, mean 8.76 y ± 2.38) Tramadol (60%, mean 8.37 y ± 2.22) Lidocaine (72.5%, mean 8.46 y ± 1.9)	<ul style="list-style-type: none"> • Control (39) • Tramadol (40) • Lidocaine (40) 	Pain scores; postoperative analgesic requirement	"In conclusion, it was shown in this study that pretreatment with iv tramadol to be equally effective in relieving propofol injection pain compared to lidocaine mixed with propofol and it is also useful for intraoperative and postoperative analgesia when relatively such these minor operations are undertaken. Further studies comparing tramadol with other opioids that have been shown to reduce propofol injection pain are needed in pediatric population, especially dose ranging studies."
Bösenberg and Ratcliffe, 1998, South Africa ²⁸	Randomized double-blind, placebo-controlled study	88 In-patients presenting for inguinal surgery Tramadol 1 mg/kg (100%, mean 6 y ± 3) Tramadol 2 mg/kg (100%, mean 5 y ± 2) Pethidine (95.65%, mean 5 y ± 2) Placebo (100%, mean 5 y ± 2)	<ul style="list-style-type: none"> • Tramadol 1 mg/kg (22) • Tramadol 2 mg/kg (22) • Pethidine 1 mg/kg (22) • Placebo (22) 	The rate of recovery from anesthesia was assessed using the Aldrete postanesthetic recovery score	"This study suggests that tramadol 2 mg/kg is more effective without significant increase in detrimental side-effects and that tramadol appears safe for use in children for postoperative analgesia following minor surgical procedures."
Bozlu <i>et al.</i> , 2004, Turkey ¹⁶⁴	Prospective, randomized, double-blind, placebo-controlled study	54 Patients undergoing transrectal ultrasound-guided 12-core prostate biopsy (100%, mean 63.1 y ± 8.1)	Placebo nerve blockade plus: <ul style="list-style-type: none"> • IV placebo (9) • IV meperidine (9) • IV tramadol (9) Lidocaine nerve blockade plus: <ul style="list-style-type: none"> • IV placebo (9) • IV meperidine (9) • IV tramadol (9) 	Pain scores	"Periprostatic lidocaine infiltration and/or intravenous synthetic opioid analgesics are not beneficial in significantly reducing pain during biopsy. We think that most of the patients do have pain during biopsy, however the intensity of pain is tolerable and does not require analgesics."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Broome <i>et al.</i> , 1999, UK ¹⁶⁵	Randomized, double-blinded comparative study	109 Out-patients undergoing elective multiple third molar extractions Fentanyl-metoclopramide (14%, mean 28.2 y ± 8.4) Tramadol-metoclopramide (28%, mean 28.1 y ± 9.6) Fentanyl-ondansetron (27%, mean 26 y ± 5.1) Tramadol-ondansetron (27%, mean 27.1 y ± 6.3)	<ul style="list-style-type: none"> • Fentanyl and metoclopramide (28) • Tramadol and metoclopramide (25) • Fentanyl and ondansetron (30) • Tramadol and ondansetron (26) 	Pain scores; nausea	"Because all our patients received a NSAID, our results cannot give clear information as to whether tramadol has a place as an alternative to NSAIDs in oral surgery when the latter are contraindicated. However, we have shown that the addition of tramadol to a NSAID results in no useful improvement in analgesic efficacy, and that the use of ondansetron does not result in any reduction in the nausea associated with tramadol."
Byrne <i>et al.</i> , 2017, New Zealand ²⁷⁰	–	83 In-patients with postoperative analgesic failure Morphine (49%, mean 42.7 y ± 15.1) Tramadol (42.5%, mean 43.7 y ± 14.3)	<ul style="list-style-type: none"> • Morphine (43) • Tramadol (40) 	Time to readiness for discharge; pain scores; side effects	"It shows that there is no clear benefit or detriment to treating difficult-to-control pain with tramadol over morphine, when the patient has already received 10 mg morphine in the recovery room...Further research needs to be done to fully elucidate the reasons for inadequate analgesic response to opioids and to investigate alternative methods for treatment of refractory pain in the recovery room."
Cagney <i>et al.</i> , 1999, UK ²⁴¹	Double-blind, randomized, controlled study	65 Patients undergoing outpatient arthroscopic surgery of the knee joint (91.8%, range 15-55 y)	<ul style="list-style-type: none"> • Fentanyl (30) • Tramadol (31) 	Pain scores; supplemental analgesic requirements; incidence of side-effects	"We conclude that tramadol offers little benefit clinically compared with fentanyl when used at induction of anesthesia for day case arthroscopic knee surgery. Further studies are indicated in patients with more severe pain to determine the role of tramadol in post-operative analgesia."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Cander <i>et al.</i> , 2005, Turkey ²⁴²	–	100 patients with isolated traumatic injuries of the extremities (42%, mean 32 y ± 14)	<ul style="list-style-type: none"> • IV metamizole (36) • IM diclofenac (40) • IV tramadol (24) • 	Pain intensity using a visual analog scale	"In conclusion, tramadol was found to be the most effective analgesic, perhaps because metamizole and diclofenac do not affect the CNS [central nervous system]. Because these results were collected from a relatively small sample, additional investigations are warranted."
Canepa <i>et al.</i> , 1993, Italy ²⁹	Controlled study	60 In-patients undergoing surgical operations on the abdomen involving opening of the peritoneum (51.67%, range 20-70 y)	<ul style="list-style-type: none"> • IM tramadol (30) • IM Nisdin(30) 	Analgesic action using a visual analogue scale (VAS)	"In conclusion, given its analgesic action combined with its good safety at the level of the cardiorespiratory system and the low incidence of side-effects, tramadol, on the basis of the results documented in the literature and confirmed in the present work, is indicated in the treatment of post-operative pain."
Cattabriga <i>et al.</i> , 2007, Italy ³⁰⁰	Double-blind, randomized, controlled trial	113 In-patients undergoing non-emergency cardiac operation (71.7%, range 20-84 y)	Tramadol plus: <ul style="list-style-type: none"> • Paracetamol (56) • Placebo (57) 	Postoperative pain, morphine (rescue) use	"In conclusion, our data suggest that the i.v. paracetamol as adjunctive treatment to tramadol-based background analgesia supplies good analgesic cover after cardiac interventions carried out with a medial sternotomy. The complications that arose and that led to the interruption of treatment do not seem correlated with the use of either of the drugs."
Cecchetti <i>et al.</i> , 2014, Brazil ³⁰	Double-blind, split-mouth, placebo-controlled, single-dose, crossover investigation	52 Patients undergoing mandibular third molar surgery (30.8%, mean 22.10 y ± 3.84)	<ul style="list-style-type: none"> • Tramadol (52) • Normal saline (52) 	Anesthetic blockade duration; time of intake and amount of analgesic rescue drug; postoperative pain intensity	"Nevertheless no beneficial effect of tramadol in lengthening the sensory blockade produced with mepivacaine was observed. Additional studies comparing the effects of tramadol with those of other local anesthetics or systemic analgesic drugs are desirable."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Cermak <i>et al.</i> , 2009, Czech Republic ¹⁶⁶	–	349 Patients undergoing prostate biopsy guided by transrectal ultrasonography (TRUS; 100%, age not specified)	<ul style="list-style-type: none"> • No anesthesia (72) • IM tramadol (76) • Trimecaine nerve block (55) • Trimecaine 1% infiltration (79) • Tetracaine suppository (67) 	Pain scores with the 10-degree visual analogue scale	"We proved a significant pain reduction during prostate biopsy using local anesthetic injection (peri-prostatic nerve block or intraprostatic infiltration) but not by suppository, or tramadol premedication. There was no significant difference in efficacy between the two kinds of injection anesthesia. According to our results, using local injection anesthesia should become a routine part of TRUS-guided prostate biopsy and should not be replaced by non-sufficient anesthetic suppository."
Chakraborty <i>et al.</i> , 2008, India ³¹	Randomized double blind placebo-controlled protocol	50 In-patients scheduled for major gynecological surgery (0%, range 45-60 y)	Hyperbaric bupivacaine and: <ul style="list-style-type: none"> • Normal saline (25) • Tramadol (25) 	Assessment of pain with the VAS	"In conclusion, this study has demonstrated that tramadol (0.25mg/kg body weight) when used with 0.5% hyperbaric bupivacaine intrathecally, significantly prolongs postoperative analgesia after major gynecological surgeries."
Chatrath <i>et al.</i> , 2015, India ²³⁶	Prospective, randomized, double-blind study	60 In-patients receiving combined spinal-epidural analgesia for labor Fentanyl (0%, mean 23.73 ± 2.97) Tramadol (0%, 24.37 y ± 3.42)	Intrathecal (IT) levobupivacaine plus intervention, followed by epidural top-ups of the same combination <ul style="list-style-type: none"> • Fentanyl (30) • Tramadol (30) 	Duration of analgesia of intrathecal drugs	"Labor analgesia in both the groups, that is, fentanyl and tramadol group was effective and patients were hemodynamically stable throughout the labor. Although both drugs could be used to provide pain relief during labor, intrathecal tramadol was better with respect to prolonged analgesia and lesser side-effects."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Chew and Shaharudin, 2017, Malaysia ³⁰¹	Open-label randomized controlled trial	20 patients with moderate to severe pain due to acute musculoskeletal injuries (80%, range 18-65 y)	<ul style="list-style-type: none"> Intranasal fentanyl plus IV tramadol (10) IV tramadol (10) 	Pain severity assessed using VAS	"In conclusion, although intranasal fentanyl is possibly an effective analgesic alternative, we cannot be certain whether it is a safe option due to its side effects of hypotension and dizziness...Thus, larger randomized double-blind studies on the efficacy and safety of intranasal fentanyl as an alternative analgesic are warranted."
Chi <i>et al.</i> , 2017, China ³²	Prospective, randomized, double-blind, controlled study	146 In-patients scheduled for cesarean section Sufentanil (0%, mean 30.78 y ± 4.92) Tramadol (0%, mean 30.12 y ± 4.82)	<ul style="list-style-type: none"> Sufentanil (73) Tramadol (73) 	Movement-evoked pain intensity using	"PCIA [patient-controlled intravenous analgesia] with tramadol may be preferred due to lower movement-evoked pain scores, higher quality of recovery, and earlier commencement of lactation for patients after cesarean section under general anesthesia."
Chia and Liu, 1998, Taiwan ¹⁶⁷	Prospective and randomized trial	120 Out-patients undergoing extracorporeal shockwave lithotripsy (ESWL; 69.2%) Fentanyl (mean 63.7 y ± 1.8) Tramadol (mean 67.8 y ± 2.1) Tenoxicam (mean 67.3 y ± 1.7)	<ul style="list-style-type: none"> Fentanyl (40) Tramadol (40) Tenoxicam (40) 	Pain score; mean dose of supplementary fentanyl; side effects	"In summary, this study demonstrates that administering intravenous fentanyl, tramadol hydrochloride or tenoxicam, combined with supplementary small dose of fentanyl under adequate monitoring can successfully achieve a pain-free condition for ESWL [extracorporeal shock wave lithotripsy]. Tenoxicam, due to its extended half life and fewer side effect, appears to be a safer and more suitable analgesic for outpatient ESWL."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Chiaretti <i>et al.</i> , 2000, Italy ²⁷¹	Randomized, prospective trial	42 Patients undergoing neurosurgery (52.4%, mean 68 months \pm 53.9)	<ul style="list-style-type: none"> • IV tramadol 1 mg/kg (14) • IV tramadol 0.5 mg/kg followed by continuous infusion at the rate of 150 mcg/kg/hour (14) • Fentanyl (14) 	Changes in behavior (AFS scale and CHEOPS score) and hemodynamic (heart rate, respiratory rate, systolic and diastolic arterial pressure, oxygen saturation, O ₂ and CO ₂ partial pressure) parameters.	"Tramadol efficacy seems to be better when it is administered in continuous infusion; this treatment modality also leads to fewer adverse effects. Fentanyl, in contrast, proved to be superior to tramadol in the treatment of postoperative pain. In conclusion, preemptive analgesia is a valid technique for the treatment of acute pain in children undergoing major neurosurgical operations."
Choo <i>et al.</i> , 2019, Malaysia ³⁰²	Randomized, double-blinded, placebo-controlled trial	191 Patients presenting with traumatic injuries of extremities requiring tramadol for pain relief (75.9%, range 18-89 y)	<ul style="list-style-type: none"> • Metoclopramide (96) • Placebo (95) <p>All patients were given IV tramadol 50 mg to see if metoclopramide helped with nausea/vomiting</p>	Mean change in severity rating on the VAS	"However, the incidence of tramadol-induced vomiting is low, only one patient vomited in this trial. Therefore, evaluation of prophylactic metoclopramide in larger trials of patients seems warranted. Further study may include patients who present with other illnesses besides trauma and also include different routes of tramadol administration."
Chowdhary <i>et al.</i> , 2018, India ³³	Randomized prospective study	50 Patients who underwent laparoscopic cholecystectomy (gender not specified, range 18-70 y)	<ul style="list-style-type: none"> • Diclofenac (25) • Tramadol (25) 	VAS; Time until pain relief; Side effects	"In this study, we concluded that the patients receiving injectable tramadol had smooth postoperative period after elective laparoscopic cholecystectomy as compared with diclofenac with minimal side effects."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Chrubasik <i>et al.</i> , 1992, Germany ³⁴	–	35 Patients undergoing major abdominal gynecological surgery Tramadol (0%, mean 46 y ± 13) Saline (0%, mean 50 y ± 19)	<ul style="list-style-type: none"> • Tramadol (16) • Saline (15) 	Total tramadol consumption; Pain score; Sedation scores; Side effects	"In conclusion, post-operative pain treatment offering a maintenance tramadol i.v infusion following an initial loading dose and additional i.v tramadol on demand does not increase the risk of tramadol overdosage. The earlier onset of analgesia as well as the good quality of analgesia offered by this form of therapy suggest a safe and recommended mode of intravenous analgesia in patients after pelvic operations."
Chu <i>et al.</i> , 2006, Taiwan ²⁷²	Controlled, randomized, double-blind study	40 In-patients scheduled for atrial or ventricular septal defect repair and tracheal extubation in the pediatric intensive care unit Morphine (75%, mean 42 months ± 26) Tramadol (65%, mean 37 months ± 35)	<ul style="list-style-type: none"> • Morphine (20) • Tramadol (20) 	Daily Consumption and Number of Nurse-Controlled Analgesic Boluses; Postoperative Sedation Scores; Adverse effects; Postoperative CHEOPS scores; Intensive Care Unit Course and Outcome	"In summary, we have demonstrated tramadol, with an initial loading dose given intraoperatively and then NCA [nurse-controlled analgesia] boluses with background infusions, caused earlier awakening from general anesthesia, less sedation, and earlier tracheal extubation in the immediate post-operative period. It has equivalent analgesic efficacy and a comparable incidence of postoperative emesis as morphine in children 6 years of age after cardiac surgery."
Clemente <i>et al.</i> , 2002, Italy ³⁵	Prospective randomized double-blind study	30 Patients undergoing abdominal surgery (gender and age not specified)	<ul style="list-style-type: none"> • Tramadol plus ketorolac • Tramadol 	Pain score by VAS; Brief Pain Inventory score; adverse effects	"The PCA is an effective technique for the treatment of postoperative pain. The combination of PCA and continuous infusion of tramadol or tramadol + ketorolac reduces a morphine consumption and its side effects. Patients liked to control pain themselves with PCA delivery system."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Cocelli <i>et al.</i> , 2012, Turkey ¹⁶⁸	Randomized placebo-controlled study	90 In-patients who underwent tonsillectomy Saline (46.7%, mean 6.30 y ± 0.002) Ropivacaine (46.7%, mean 6.17 y ± 1.599) Tramadol (46.7%, mean 6.10 y ± 1.517)	<ul style="list-style-type: none"> • Saline (30) • Ropivacaine (30) • Tramadol (30) 	Maunuksela pain scores; hemodynamic parameters; nausea-vomiting	"Peritonsillar ropivacaine infiltration may be preferred as a favorable alternative because of minimizing effects on postoperative pain and nausea-vomiting. Prospective randomized large-scale further studies are needed to address this administration in standard clinical practice."
Coetzee and Van Loggerenberg, 1998, South Africa ³⁶	Comparative, double-blind, randomized study	40 Patients who underwent abdominal hysterectomy Tramadol (0%, mean 38.2 y ± 8) Morphine (0%, mean 41.9 y ± 10.9)	<ul style="list-style-type: none"> • Morphine (20) • Tramadol (20) 	Arterial pressure and heart rate; Times to spontaneous respiration; awakening and orientation; incidence of nausea; pain scores; supplementary analgesia; P-deletion counts	"We suggest that tramadol has a useful role in anesthetic practice, particularly for day-surgery where rapid return to normal activities is desired"
Colletti <i>et al.</i> , 1998, Italy ²⁴³	Multicenter, open-label, randomized, controlled trial	77 In-patients who had undergone surgery of the nose or paranasal sinuses (66.2%, mean 31.0 y ± 10.5)	<ul style="list-style-type: none"> • Tramadol (39) • Ketorolac tromethamine (38) 	Pain relief and quality of sleep; adverse events; Analgesic effect (five-point semiquantitative rating scale)	"For the anesthetist and surgeon, tramadol is an interesting drug that is easy to handle in the available formulations (ampules, capsules, enteric-coated tablets, and drops) and can be administered by different routes (IM, intravenously, by infusion, and orally). Although these results are encouraging, additional randomized, controlled clinical trials should be performed in a larger study population."

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Colonna <i>et al.</i> , 2001, Italy ²⁷³	–	45 In-patients undergoing abdominal surgery (gender and age not specified)	<ul style="list-style-type: none"> • Tramadol plus ketorolac (20) • Ropivacaine plus morphine (25) 	Perfusion velocities; pain intensity; side effects	"The frequency of low pain intensity in the first day of the postoperative period was higher in the group of patients treated with ropivacaine+morphine. The side-effects of the two treatments were practically nil with a slight prevalence of PONV [postoperative nausea and vomiting] in the patients treated with tramadol and ketorolac. In the latter group a tendency to decreasing cardiac frequency was observed in the second postoperative day compared to patients treated with ropivacaine and morphine but this observation was difficult to interpret."
Cuneyitoglu <i>et al.</i> , 2015, Turkey ¹⁶⁹	Prospective and randomized study	<p>75 In-patients scheduled for a gynecological surgery with Pfannenstiel incision</p> <p>Ultrasound-guided rectus sheath block (0%, mean 45.2 y ± 12.1)</p> <p>Surgical rectus sheath block (0%, mean 44.0 y ± 7.3)</p> <p>Tramadol (0%, mean 44.2 y ± 9.6)</p>	<ul style="list-style-type: none"> • Ultrasound-guided rectus sheath block (25) • Surgical rectus sheath block (25) • Tramadol (25) 	Pain scores; total tramadol consumption; supplemental analgesic requirement and side effects	"Ultrasound-guided rectus sheath block helps to provide effective and reliable postoperative analgesia without serious side effects, reduces anesthetic and analgesic agent consumption in patients undergoing gynecological surgery with Pfannenstiel incision."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
da Silva <i>et al.</i> , 2011, Brazil ¹⁷⁰	–	24 In-patients with the indication of sympathectomy for treatment of palmar hyperhidrosis (gender not specified) Tramadol (mean 27.5 y ± 3.3) Ropivacaine 0.33% (mean 23.0 y ± 1.8) Ropivacaine 0.5% (mean 25.5 y ± 2.1)	IV dipyrene plus: <ul style="list-style-type: none"> • IV tramadol and intrapleural saline (8) • Intrapleural ropivacaine 0.33% (8) • Intrapleural ropivacaine 0.5% (8) 	inspiratory capacity; respiratory rate and pain score (VAS)	"Intrapleural analgesia by ropivacaine, in relation to conventional analgesia, reduces pain in the late postoperative period of patients submitted to thoracic sympathectomy, and when used in its higher concentration, it determines better global analgesic results and less alteration in ventilatory mechanics, thus producing a better respiratory outcome."
Dahiya and Malik, 2015, India ³²⁹ Dahiya, 2017, India ¹⁷¹	Randomized prospective study	200 In-patients in active labor Paracetamol (0%, mean 25.55 y ± 3.849) Tramadol (0%, mean 25.60 y ± 3.655)	<ul style="list-style-type: none"> • Tramadol (100) • Paracetamol (100) 	Adequate analgesia as measured by a change in the VAS	"In the present study both paracetamol and tramadol were equally effective for labor analgesia but paracetamol has emerged as safe alternative as compared to tramadol due to low incidence of side effects."
Dauri <i>et al.</i> , 2003, Italy ¹⁷²	Prospective randomized study	25 Patients undergoing cadaveric kidney transplantation (56%, mean 43.3 y ± 9.21)	<ul style="list-style-type: none"> • Epidural ropivacaine and fentanyl with general anesthesia of propofol and atracurium (13) • General anesthesia with fentanyl, propofol, and atracurium followed by postoperative intravenous tramadol (12) 	Hemodynamics; renal function; arterial blood gases	"Combined epidural-general anesthesia is as valid a technique as any for renal transplantation; however postoperative epidural ropivacaine analgesia resulted more effective than intravenous tramadol. Respiratory function appeared less affected, facilitating a fast and uncomplicated postoperative recovery."

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De Alencar <i>et al.</i> , 2012, Brazil ²⁷⁴	Controlled, blind, randomized clinical trial	160 In-patients receiving postoperative analgesia (gender not specified, mean 199 hours \pm 63)	<ul style="list-style-type: none"> • Fentanyl (80) • Tramadol (80) 	Time in hours from the end of surgical procedure until extubation	"Tramadol was as effective as fentanyl for postoperative pain relief, but did not appear to offer advantages over fentanyl regarding the duration of mechanical ventilation and the time to reach full enteral feeding. There is a strong need to study the efficacy and safety profiles of analgesics in age-compatible populations in order to find alternatives to treat pain for critically ill newborn infants."
De Franceschi <i>et al.</i> , 2013, Italy ³⁰³	Open double-dummy active clinical trial	<p>Patients with sickle cell disease (SCD) suffering from painful vaso-occlusive crisis (VOC; gender not specified, range 18-45 y)</p> <p>Number of patients not provided</p>	<ul style="list-style-type: none"> • TK group: continuous IV infusion of ketorolac, tramadol, and metoclopramide • TKF group: TK group plus fentanyl buccal tablet (FBT) 	Time-weighted sum of pain intensity differences from 3 to 24 hours after the administration of study drugs	"These data suggest FBT [<i>sic</i>] as an interesting new tool in management of pain of VOCs in adult SCD patients."
De Witte <i>et al.</i> , 1998, Belgium ³⁷	Prospective, randomized and double-blind study	<p>40 In-patients who underwent laparoscopic surgery</p> <p>Saline (75%, mean 47 y \pm 13)</p> <p>Tramadol (75%, mean 47 y \pm 13)</p>	<p>Droperidol plus:</p> <ul style="list-style-type: none"> • Tramadol (20) • Saline (20) 	Pain scores; Adverse effects; supplemental medication; discharge ready-time; extubation and sedation	"In conclusion, this study demonstrates that tramadol 3 mg/kg i.v. administered at wound closure prevents shivering without prolongation of extubation time nor increasing the sedation score. Fewer patients needed supplemental medication in the PACU, and the discharge-ready time was significantly shortened."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Degala and Nehal, 2018, India ³⁸	–	46 Patients scheduled for oral and maxillofacial surgical procedure (85%, 39 patients ≤ 40 y and 7 patients >40 y)	<ul style="list-style-type: none"> • Tramadol (23) • Ketorolac (23) 	Pain scores (VAS); vital signs; side effects	"Apart from first 2 h where the changes are insignificant may be due to faster onset of action of intravenous ketorolac in comparison to tramadol, intravenous tramadol always resulted as a better analgesic regimen in every scheduled postoperative hour and was statistically significant. The side effects of both the drugs were insignificant and did not have any effect on the result."
Dejonckheere <i>et al.</i> , 2001, Belgium ³⁹	–	80 In-patients undergoing thyroidectomy Propacetamol (15%, mean 46.9 y ± 2.1) Tramadol (10%, mean 44.1 y ± 1.8)	<ul style="list-style-type: none"> • Propacetamol (40) • Tramadol (40) 	Morphine consumption; VAS pain score; nausea and vomiting	"In conclusion, the administration of a single IV dose of tramadol 1.5mg/kg seems to provide better analgesia than a single dose of propacetamol 2gr, without any increase in side-effects, but fails to obtain optimal analgesia within the first six hours after thyroidectomy. A maintenance analgesia regimen using tramadol and a combination of drugs might be more appropriate."
Demirel and Guzeldemir, 2009, Turkey ¹⁷³	–	60 In-patients undergoing major abdominal surgery (gender and age not specified)	<ul style="list-style-type: none"> • PCA tramadol (20) • PCA lornoxicam (20) • PCA morphine (20) 	VAS; Ramsey sedation scores; incidence of nausea/vomiting; return of bowel sounds; supplemental analgesic requirements	"Conclusions: We concluded that lornoxicam alone or in combination with other drugs provides an effective and safe alternative to morphine or tramadol for the treatment of postoperative pain."
Demirel <i>et al.</i> , 2014, Turkey ⁴⁰	–	40 In-patients scheduled for elective cesarean section Continuous tramadol (0%, mean 31.85 y ± 5.18) PCA tramadol (0%, mean 28.40 y ± 6.48)	Tramadol via: <ul style="list-style-type: none"> • Continuous IV (20) • PCIA (20) 	VAS; mean arterial pressure (MAP); heart rate; total tramadol consumption; sedation scores; side-effects (nausea/vomiting) and patient satisfaction	"While tramadol administration by either of the methods used may ensure efficient early postoperative anesthesia in cesarean section patients, i.v. PCA may be preferred because of the lower drug consumption and higher patient satisfaction associated with it."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Dikmen <i>et al.</i> , 2009, Turkey ²⁴⁴	–	40 In-patients scheduled for arteriovenous fistula surgery Ropivacaine (25%, mean 55.1 y ± 14.5) Ropivacaine plus tramadol (30%, mean 61.5 y ± 10.9)	<ul style="list-style-type: none"> • Ropivacaine (20) • Ropivacaine plus tramadol (20) 	The onset and duration of sensory and motor block in the distribution of the radial, median, and ulnar nerves; the duration of analgesia; the time to first requirement of analgesic; hemodynamics; and side effects	"In conclusion, a sufficient-quality axillary brachial plexus block was achieved in both groups (3.75 mg/mL ropivacaine and 100 mg tramadol added 3.75 mg/mL in 40 mL) for creation of arteriovenous fistula in patients with chronic renal failure. Further studies with lower ropivacaine concentrations may offer further clarification on the influence of tramadol on axillary brachial plexus block characteristics."
Dogra <i>et al.</i> , 2018, India ⁴¹	Randomized, double-blinded interventional study	78 In-patients undergoing inguinal hernia surgeries Levobupivacaine (gender not specified; mean 3.88 y ± 3.21) Tramadol (gender not specified; mean 4.08 y ± 2.13) Levobupivacaine and tramadol (gender not specified; mean 3.58 y ± 1.88)	<ul style="list-style-type: none"> • Levobupivacaine (26) • Tramadol (26) • Levobupivacaine and tramadol (26) 	Duration of analgesia	"A combination of 1.5 mg/kg of tramadol and 0.125% levobupivacaine-administered caudally provided long-lasting analgesia without any adverse effects following inguinal hernia surgery."
Dos Santos <i>et al.</i> , 2010, Brazil ³²³	Prospective study	30 In-patients undergoing inguinal herniorrhaphy IV tramadol (100%, mean 40.2 y ± 12.8) Subcutaneous tramadol (100%, mean 44.2 y ± 12.9)	Tramadol via: <ul style="list-style-type: none"> • IV (15) • Subcutaneous (15) 	Anthropometric data; quality of analgesia; and the development of postoperative nausea and vomiting in the first eight hours	"This study concluded that a difference between intravenous and subcutaneous tramadol regarding the incidence of nausea and vomiting and the quality of analgesia was not observed during the 8 hours following its administration."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Edomwonyi <i>et al.</i> , 2017, Nigeria ⁴²	Randomized, double-blind, comparative study	120 In-patients scheduled for cesarean section under spinal surgery Bupivacaine plus dexamethasone (0%, mean 30.62 y ± 5.93) Bupivacaine plus tramadol (0%, mean 30.90 y ± 5.17)	Bupivacaine wound infiltration plus: <ul style="list-style-type: none"> • IV dexamethasone (60) • IV tramadol (60) 	Time to first analgesic request	"Combination of bupivacaine wound infiltration and IV tramadol provided better quality pain relief."
Ege <i>et al.</i> , 2018, Turkey ²⁴⁵	Randomized double-blinded study	50 Healthy volunteers receiving maxillary infiltration anesthesia (62%, mean 22.68 y ± 1.3)	<ul style="list-style-type: none"> • Tramadol (50) • Lidocaine (50) Each participant received both, one on each buccal side	Total duration of anesthesia; start and finish times of anesthesia; soft tissue (sensory) innervation; depth of anesthetic; possible side effects; and satisfaction levels	"Tramadol hydrochloride can be a good alternative to local anesthetic agents and beneficial to support anesthesia during long operations."
Ekmekçi <i>et al.</i> , 2017, Turkey ¹⁷⁴	Randomized, controlled double-blinded study	60 In-patients undergoing cesarean section Levobupivacaine plus tramadol 1 mg/kg (0%, mean 29.9 y ± 5.1) Levobupivacaine plus tramadol 2 mg/kg (0%, mean 27.4 y ± 5.5) Levobupivacaine (0%, mean 28.2 y ± 4.4)	<ul style="list-style-type: none"> • Levobupivacaine 0.25% plus tramadol 1 mg/kg (21) • levobupivacaine 0.25% plus tramadol 2 mg/kg (21) • Levobupivacaine alone (21) 	VAS at rest and with 20 degrees leg lift; time to first additional analgesic; total additional analgesic consumption; side effects; and sedation scores	"Different doses of tramadol as adjunct to local anesthetics in continuous wound infiltration following cesarean section do not seem to provide superior analgesia."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
El Deeb and El-Morsy, 2011, Egypt ⁴³	Randomized double blind study	80 In-patients undergoing inguinal herniotomy (100%, range 2-12 y)	<ul style="list-style-type: none"> • Tramadol (40) • Ketorolac (40) 	Postoperative pain score; Postoperative rescue analgesic; Time to first analgesia; requirement for additional analgesics; sedation level; bleeding time and side effects	"In conclusion, preemptive tramadol 1 mg/kg provided longer duration of postoperative analgesia and reduced requirement for rescue analgesic compared with intravenous ketorolac 1 mg/kg in children undergoing inguinal herniotomy. Further studies are needed to compare effects of ketorolac before and after surgery or combination with other non steroidal anti inflammatory drugs."
Elhakim <i>et al.</i> , 2005, Egypt ⁴⁴	Randomized double-blind study	60 In-patients undergoing elective Caesarean section (0%, range 22-39 y)	<ul style="list-style-type: none"> • Tramadol (30) • Famotidine (30) 	Apgar score; cord blood gas analysis; and neurobehavioural assessment; pain score; sedations core; Nalbuphine consumption in the first 24 h after operation; side effects	"In summary, our study shows that single dose i.m. tramadol 1 h before elective Caesarean delivery is effective in lowering the risk of acid aspiration during operation and improving pain relief during 24 h after surgery. We could not attribute any problem to tramadol in our patients, although no conclusion can be drawn about safety from the number of patients used in this study."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Elkassem, 2008, Egypt ¹⁷⁵	Prospective randomized double blinded study	60 In-patients undergoing cruciate ligament reconstruction surgery (gender and age not specified)	Patient controlled epidural analgesia (PCEA) with bupivacaine plus: <ul style="list-style-type: none"> • Control (20) • IV Ketamine (20) • IV Tramadol (20) 	Number of PCEA bupivacaine boluses in 24 h; number of patients requiring rescue analgesia and total dose of meperidine in 24 h; the severity of postoperative pain using VAS; side effects; postoperative heart rate & noninvasive mean blood pressure	"Both postoperative low dose intravenous ketamine 0.1 mg/kg/h and low dose intravenous tramadol 0.1 mg/kg/h reduce postoperative pain and significantly decrease the postoperative patient controlled epidural analgesia with bupivacaine 0.125% requirements than postoperative patient controlled epidural analgesia with bupivacaine 0.125% alone with less incidence of side effects with ketamine after cruciate ligament reconstruction surgery."
Engelhardt <i>et al.</i> , 2003, UK ⁴⁵	Prospective, double-blind, randomized controlled trial	60 Patients scheduled for elective tonsillectomy or adenotonsillectomy (gender not specified) Morphine (mean 8.1 y ± 4.2) Tramadol 1 mg/kg (mean 7.1 y ± 3.6) Tramadol 2 mg/kg (mean 7 y ± 4.2)	<ul style="list-style-type: none"> • Morphine (20) • Tramadol 1 mg/kg (20) • Tramadol 2 mg/kg (20) 	Postoperative pain scores; analgesic requirements; sedation scores; signs of respiratory depression and nausea and vomiting	"In conclusion, we found that tramadol has similar analgesic properties when compared with morphine, and is a suitable alternative to morphine for intra- and immediate postoperative pain relief. Its pharmaceutical presentation, as well as its current classification as a noncontrolled drug, could lead to an increased use in pediatric anesthesia once licensed for children in the UK."
Engindeniz <i>et al.</i> , 2005, Turkey ⁴⁶	Prospective, randomized, double-blind study	40 Patients admitted to the emergency department with acute migraine attack Diclofenac (30%, mean 37.9 y ± 13.3) Tramadol (15%, mean 37.0 y ± 11.06)	<ul style="list-style-type: none"> • Diclofenac (20) • Tramadol (20) 	2-h pain response after the injection of the study drug	"In conclusion, in selected patients, tramadol 100 mg IM may be an effective and reliable alternative treatment choice in acute migraine attacks."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Eray <i>et al.</i> , 2002, Turkey ¹⁷⁶	Double-blind, randomized clinical trial	47 Patients with suspected renal colic Tramadol (69.6%, mean 39 y ± 14) Meperidine (75%, mean 41 y ± 13)	<ul style="list-style-type: none"> • Tramadol (23) • Meperidine (24) 	Pain relief at 15 and 30 min after the analgesics	"Meperidine 50 mg was superior to tramadol 50 mg for acute pain relief in patients with suspected renal colic when given intravenously. Because many patients in both groups received supplemental meperidine and the response to tramadol alone cannot be predicted, clinicians may want to choose higher doses of meperidine alone or other alternative combinations."
Erdivanli <i>et al.</i> , 2018, Turkey ²⁴⁶	Double-blind randomized controlled trial	88 In-patients scheduled for functional endoscopic sinus surgery Metoprolol plus tramadol (72.7%, mean 39.3 y ± 10.6) Remifentanil (63.6%, mean 37.8 y ± 10.1)	<ul style="list-style-type: none"> • Metoprolol plus tramadol (44) • Remifentanil (44) 	Quality of surgical field and incidence of adverse hemodynamic effects	"The present study indicates that providing sufficient analgesia with tramadol and eliminating the stress response with metoprolol can provide a stable heart rate and a good surgical field with no need for additional hypotension...Future studies investigating the advantages of this technique for patients with stenotic arteries or ischemic organ diseases are needed."
Eriksson <i>et al.</i> , 2017, Sweden ¹⁷⁷	Randomized, placebo controlled, single blinded clinical trial	Patients undergoing third molar surgery with dental fear (gender and age not specified) Number of patients not specified	<ul style="list-style-type: none"> • Tramadol with IV midazolam • Placebo 	Pain score by VAS	"Tramadol gave no reduction in postoperative pain but an increased frequency of desaturation and side effects. Other drugs or other doses ought to be tried for this kind of postoperative pain management."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Erolçay and Yüceyar, 2003, Turkey ²⁷⁵	Randomized and double-blind study	40 In-patients scheduled for thoracotomy Tramadol (84.2%, mean 57.66 y ± 15.2) Morphine (85.7%, mean 51.76 y ± 11.43)	<ul style="list-style-type: none"> • Tramadol (19) • Morphine (21) 	Arterial pressure; heart rate; respiratory rate; nausea; vomiting; mean tramadol and morphine consumption	"In this clinical setting, which includes intrapleural morphine pre-emptively, postoperative analgesia provided by tramadol was similar to that of morphine at rest and during deep inspiration. Side-effects were slight and comparable between the patients receiving morphine and tramadol."
Ertugrul <i>et al.</i> , 2006, Turkey ²⁷⁶	–	45 Patients undergoing adenotonsillectomy Ketamine (46.7%, mean 4.26 y ± 1.57) Tramadol (40%, mean 3.93 y ± 1.66) Meperidine (33.3%, mean 4.07 y ± 1.54)	<ul style="list-style-type: none"> • IM ketamine (15) • IM meperidine (15) • IM tramadol (15) 	Pain score; agitation score; extubation; side effects	"We conclude that ketamine, meperidine and tramadol had very similar effects on post-operative pain after adenotonsillectomy in children. They provided adequate post-operative analgesia in pediatric patients undergoing day-case adenotonsillectomy."
Esme <i>et al.</i> , 2010, Turkey ³³⁰ Esme <i>et al.</i> , 2012, Turkey ¹⁷⁸	Prospective double-blind randomized trial	45 In-patients undergoing elective lobectomy Bupivacaine (53.3%, mean 49.13 y ± 13.37) Morphine (66.7%, mean 54.4 y ± 12.64) Tramadol (60%, mean 51.86 y ± 11.5)	<ul style="list-style-type: none"> • Paravertebral Bupivacaine (15) • Paravertebral Morphine (15) • IV Tramadol plus metamizole (15) 	Visual analog pain scores; need for supplementary intravenous analgesia; pulmonary function tests; and postoperative pulmonary complications	"Because of its associated safety and efficacy, paravertebral subpleural morphine administration may be a suitable alternative to intermittent systemic opioids for analgesia after thoracotomy."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Esme <i>et al.</i> , 2011, Turkey ³⁰⁴	Double-blind, randomized study	40 In-patients undergoing posterolateral thoracotomy Tramadol (60%, median 50.4 y) Tramadol and flurbiprofen (65%, median 55.3 y)	<ul style="list-style-type: none"> • Tramadol (20) • Tramadol plus flurbiprofen (20) 	VAS; Spirometric measurement of forced expiratory volume; serum C-reactive protein (CRP); interleukin-6 (IL-6); and tumor necrosis factor- α (TNF- α .)	"In conclusion, we observed that patients undergoing thoracotomy showed reduced postoperative pain, mean additional analgesic consumption, and serum IL-6 and CRP levels, when flurbiprofen added to the systemic analgesic therapy. Analgesia with antiinflammatory drug may contribute to the attenuation of the postoperative inflammatory response and prevent postoperative pain in patients undergoing thoracotomy."
Fahim <i>et al.</i> , 2005, Egypt ¹⁷⁹	–	60 Out-patients undergoing ambulatory hand surgery (gender and age not specified)	<ul style="list-style-type: none"> • Lidocaine (15) • Lidocaine plus sufentanil (15) • Lidocaine plus tramadol (15) • Lidocaine plus dexmedetomidine (15) 	Onset and duration of sensory and motor block; the quality of the anesthesia; intraoperative and postoperative hemodynamics; intraoperative and postoperative pain and sedation	"The addition of sufentanil, tramadol or dexmedetomidine shortened the onset of the sensory block, delayed the onset time of tourniquet pain and reduced the intraoperative consumption of opioid with the dexmedetomidine being the best of the three study drugs."
Fan <i>et al.</i> , 2000, Taiwan ⁴⁷	–	40 In-patients scheduled for inguinal surgery Tramadol (85%, mean 3.1 y \pm 1.7) Control (85%, mean 2.9 y \pm 1.6)	<ul style="list-style-type: none"> • Tramadol (20) • Control (20) 	VAS pain score and agitation score; length of recovery stages; complications	"In conclusion, intraoperative IV tramadol (1mg/kg) is effective in decreasing the emergence of agitation and postoperative pain after sevoflurane anesthesia for children undergoing ambulatory inguinal surgery."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Ferber <i>et al.</i> , 2000, Poland ⁴⁸	–	35 Patients after craniotomy (gender not specified, mean 46 y)	<ul style="list-style-type: none"> • Tramadol 0.75 mg/kg (11) • Tramadol 1 mg/kg over 5 minutes (13) • Tramadol 1 mg/kg over 10 minutes (11) 	PaCO ₂ ; heart rate; mean arterial blood pressure; respiratory frequency; pain intensity; intracranial pressure (ICP) and cerebral perfusion pressure (CPP)	"We conclude that tramadol in doses of 0.75 mg/kg and 1.0 mg/kg i.v. does not affect ICP and CPP in adult postcraniotomy patients and seems to be a safe and effective analgesic at a dose of 1.0 mg/kg for postcraniotomy pain control."
Filitz <i>et al.</i> , 2008, Germany ⁴⁹	Double-blind and placebo-controlled study in cross-over design	17 Healthy volunteers (58.8%, mean 26.1 y ± 6.6)	<ul style="list-style-type: none"> • Acetaminophen • Tramadol • Combination of acetaminophen and tramadol • Saline 0.9% 	Pain intensities; extent of areas of hyperalgesia	"Although the specific interactions of tramadol and acetaminophen still remain unclear, the supra-additive reduction of pain and hyperalgesia of the combination could result in more effective treatment strategies for different pain states containing both, acute nociceptor pain and hyperalgesia."
Fodale <i>et al.</i> , 2005, Italy ²⁷⁷	Prospective, randomized study	46 Patients scheduled for minor surgical procedures (58.7%, range 33-71 y)	<ul style="list-style-type: none"> • Control (23) • Tramadol and ketorolac (23) 	BIS (Bispectral index) values; mean arterial pressure; heart rate; end-tidal carbon dioxide	"In conclusion, administration of tramadol, together with ketorolac, to prevent postoperative pain does not further modify the values of BIS during anesthesia with sevoflurane and remifentanyl when the BIS is kept between 40 and 50."
Fodale <i>et al.</i> , 2006, Italy ²⁷⁸	Prospective observational randomized study	44 Patients scheduled for minor surgical procedures Control (54.5%, mean 58 y ± 8) Tramadol (50%, mean 56 y ± 11)	<ul style="list-style-type: none"> • Control (22) • Tramadol (22) 	BIS values; heart rate; mean arterial pressure	"The clinical relevance of this study is that tramadol can be administered as pre-emptive or preventive analgesia during intravenous propofol-remifentanyl anesthesia without affecting the depth of anesthesia, as evaluated by BIS monitoring. This suggests that clinical doses of tramadol do not increase the risk of awareness."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Forst <i>et al.</i> , 1999, Germany ³⁰⁵	Prospective randomized trial	38 Patients undergoing elective total hip or knee arthroplasty PCA (36.8%, mean 61.9 y ± 13.1) Conventional pain therapy (42.1%, mean 67.5 y ± 6.3)	<ul style="list-style-type: none"> • PCA piritramid (19) • Conventional pain therapy: IM or oral tramadol, or IV piritramid (19) 	Pain scores (VAS); patient satisfaction	"From these results we draw the conclusion that even if the patients feel satisfied by the pain therapy administered, the majority are objectively treated below their individual subjective pain threshold."
Frikha <i>et al.</i> , 2007, Tunisia ²⁷⁹	Prospective study	40 In-patients undergoing labor receiving combined spinal-epidural analgesia Sufentanil (0%, mean 29 y ± 3) Tramadol (0%, mean 29 y ± 5)	Bupivacaine with: <ul style="list-style-type: none"> • IT sufentanil (20) • IT tramadol (20) 	Duration of analgesia; frequency of adverse maternal and fetal side effects	"2.5 micrograms of intrathecal sufentanil combined with 2.5 mg bupivacaine provides rapid-onset and profound analgesia during the first stage of labor without adverse maternal or fetal effects. 25 mg intrathecal tramadol with 2.5 mg bupivacaine had longer-lasting analgesia. The major side effect was vomiting."
Galante <i>et al.</i> , 2018, Italy ⁵⁰	–	66 In-patients undergoing inguinal hernia repair (gender not specified, range 1-5 y)	Caudal epidural: <ul style="list-style-type: none"> • Levobupivacaine alone • Levobupivacaine plus tramadol 	Mean time to 1st rescue dose; number of rescue doses administered; sedation scores	"This study demonstrated that caudal levobupivacaine and tramadol injection provided longer duration of analgesia in children undergoing inguinal hernia repair procedures compared to levobupivacaine alone with satisfactory recovery profile."
Gandhe <i>et al.</i> , 1998, India ⁵¹	Prospective study	50 Patients with postoperative pain following coronary artery bypass graft (CABG) surgery through sternotomy (gender and age not specified)	<ul style="list-style-type: none"> • Tramadol through PCA pump • Tramadol boluses intravenously as needed 	Pain score; sedation score; hemodynamic parameters; respiratory rate; oxygen saturation	"Using PCA device, tramadol hydrochloride was found to provide better pain relief in these patients with less incidence of adverse events, less drug requirement and better patient acceptability and satisfaction about post operative pain control."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Giraldes <i>et al.</i> , 2016, Brazil ⁵²	Prospective double-blind randomized clinical trial	40 In-patients undergoing unilateral inguinal hernia repair Group I (41%, mean 57.15 months \pm 30.28) Group II (39%, mean 70.66 months \pm 28.72)	<ul style="list-style-type: none"> • IV tramadol (20) • Tramadol wound infiltration (20) 	Pain intensity; nausea and vomiting; time to first rescue medication; total rescue morphine and dipyrone consumption	"We concluded that tramadol was effective in reducing postoperative pain in children, and there was no difference in pain intensity, nausea and vomiting, or somnolence regarding IV route or wound infiltration."
Goel <i>et al.</i> , 2005, India ⁵³	Randomized double blind comparative observational study	100 Patients undergoing elective surgery under general anesthesia Lignocaine (45%, mean 31.1 y \pm 7.25) Tramadol (50%, mean 34.1 y \pm 12.22) Ketorolac (50%, mean 32.35 y \pm 9.07) Ketoprofen (55%, mean 35.45 y \pm 7.91) Control (60%, mean 35.1 y \pm 9.00)	<ul style="list-style-type: none"> • Lignocaine (20) • Tramadol (20) • Ketorolac (20) • Ketoprofen (20) • Control (20) Administered before propofol injection	VAS scores	"In conclusion, intravenous lignocaine, tramadol, ketorolac and ketoprofen pretreatment significantly reduce the incidence and intensity of pain on injection of propofol. However, lignocaine appears to be more acceptable in view of the negligible side effects and better efficacy in reducing pain. We recommend the use of these agents as pretreatment to increase patient's acceptability of this ideal intravenous anesthetic agent."
Golubović, <i>et al.</i> , 2007, Croatia ⁵⁴	Randomized double-blinded study	63 In-patients who had undergone laparoscopic cholecystectomy (gender and age not specified)	<ul style="list-style-type: none"> • IP tramadol (33) • IV tramadol (30) 	VAS pain score; postoperative nausea and vomiting	"Intraperitoneal administration of tramadol is effective and therefore recommended in patients undergoing laparoscopic cholecystectomy."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Gong <i>et al.</i> , 2003, China ⁵⁵	–	59 In-patients scheduled for elective abdominal hysterectomy or hysteromyomectomy (gender not specified) Tramadol (mean 42 y ± 6) Morphine (mean 44 y ± 7)	<ul style="list-style-type: none"> • Tramadol (29) • Morphine (30) 	Total pain relief; pain intensity	"In conclusion, analgesic efficacy of tramadol in postoperative PCA was comparable to that of morphine, and tramadol can cause slighter gastrointestinal adverse effects. Tramadol can be an alternative drug for morphine in postoperative PCA."
Gopalraju <i>et al.</i> , 2014, India ¹⁸⁰	Comparative, prospective, randomized, controlled study	40 Patients requiring surgical extraction of unilateral impacted mandibular third molars Tramadol (65%, mean 25.4 y) Ketorolac (60%, mean 25.95 y)	<ul style="list-style-type: none"> • Tramadol (20) • Ketorolac (20) 	Pain intensity (VAS scores); median time to rescue analgesics; number of analgesics consumed; patient's overall 5-point global assessment scale	"The current study shows that pre-emptive use of Inj. Ketorolac 30 mg intravenously can reduce the severity of the postoperative sequelae of asymptomatic impacted mandibular third molar surgery."
Grizelj Stojcic <i>et al.</i> , 2010, Croatia ⁵⁶	–	40 In-patients undergoing major abdominal surgery (gender not specified, >70 y)	<ul style="list-style-type: none"> • Patient controlled epidural analgesia morphine • IV tramadol and metamizole 	VAS scores; patients' satisfaction; arterial oxygen saturation; respiratory rate; episodes of nausea; vomiting; pruritus and dizziness	"We conclude that combination of tramadol and metamizole provided postoperative analgesia equivalent to that provided by epidural morphine in early postoperative period. The both analgesic regimens were safe and suitable for the management of postoperative pain in elderly patients."
Grossi <i>et al.</i> , 2004, Italy ¹⁸¹	Double-blind randomized placebo-controlled study	50 Patients undergoing total colonoscopy (54%, range 19-68 y)	<ul style="list-style-type: none"> • Tramadol (28) • Placebo (22) 	VAS scores	"In conclusion tramadol, at least as a monotherapy, seems scarcely effective for the preparation of patients undergoing to colonoscopy. It remains to be elucidated whether a combination of tramadol with a benzodiazepine would be more effective, equally safe, and able to eliminate the need for narcotics during endoscopic procedures."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Güneş <i>et al.</i> , 2011, Turkey ⁵⁸	Double-blind, randomized study	50 In-patients undergoing supratentorial craniotomy for space-occupying lesion Paracetamol (52%, mean 44.07 y ± 11.29) Diclofenac sodium (44%, mean 42.27 y ± 11.43)	Tramadol plus: <ul style="list-style-type: none"> • Paracetamol (25) • Diclofenac sodium (25) 	VAS scores; discomfort; sedation; side effects	“In conclusion, our study demonstrates that paracetamol (1 g, intravenously) and diclofenac sodium (intramuscular) plus tramadol (1.5 mg/kg intravenously) for patients undergoing craniotomy provided effective post-operative analgesia, without causing any side effects. In addition, diclofenac sodium-tramadol combination obtained better postoperative pain relief and less analgesic requirements than paracetamol-tramadol combination.”
Güneş <i>et al.</i> , 2004, Turkey ⁵⁷	–	134 In-patients scheduled for hypospadias repair (100%) Group I (mean 1.96 y ± 0.91) Group II (mean 1.69 y ± 0.88) Group III (mean 1.97 y ± 0.90) Group IV (mean 1.76 y ± 0.88)	<ul style="list-style-type: none"> • Group 1: Caudal tramadol after surgery before reversing of neuromuscular blockade (33) • Caudal tramadol 15 min before incision (33) • IV tramadol after surgery before reversal of neuromuscular blockade (34) • IV tramadol 15 min before incision (34) 	Recovery rate; heart rate; arterial pressure; peripheral oxygen saturation; respiratory rate; pain and sedation scores; side effects	“We concluded that caudal tramadol provide better and long-lasting postoperative analgesia than i.v. tramadol. These results also suggest that preoperative caudal tramadol did not offer any clinically perceptible benefits compared with postoperative caudal tramadol.”
Gupta <i>et al.</i> , 2008, India ¹⁸²	Randomized study	50 In-patients planned for elective surgery under general anesthesia Group I (56%, mean 52.4 y) Group II (52%, mean 51.6 y) The intervention administered in each group was not specified	<ul style="list-style-type: none"> • Butorphanol (25) • Tramadol (25) 	Heart rate; blood pressure; side effects; sedation score; pain; time to first rescue analgesic	"Butorphanol is very effective and contributes to balanced anesthesia."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Gürses <i>et al.</i> , 2003, Turkey ⁵⁹	Prospective, randomized and double-blind study	90 In-patients scheduled for undergoing lower abdominal surgery Tramadol (47%, mean 53.8 y ± 9.4) Droperidol (40%, mean 51.3 y ± 9.1) Clonidine (50%, mean 52.3 y ± 8.9)	<ul style="list-style-type: none"> • Tramadol (30) • Tramadol plus droperidol (30) • Tramadol plus clonidine (30) 	Onset time of analgesia; duration of analgesia; visual analogue pain scores; sedation; nausea scores; vital signs; side effects	"In conclusion, our results suggest that the addition of droperidol or clonidine to epidural tramadol provides a shorter onset time and a longer duration of analgesia. Droperidol seems to be a more suitable adjunct when its adverse effects and antiemetic properties are taken into consideration."
Guzman <i>et al.</i> , 2015, Philippines ⁶⁰	Double blind randomized controlled trial	Patients with acute onset of right lower quadrant abdominal pain (72.9%, mean 37.5 y ± 5.05) Number of patients not specified	<ul style="list-style-type: none"> • Tramadol (not reported) • Placebo (not reported) 	Mean abdominal pain VAS score; abdominal tenderness VAS score	"Patients suspected with appendicitis can be given tramadol because it can provide significant reduction in abdominal pain and tenderness without altering the diagnostic confidence of the surgeon."
Hadi <i>et al.</i> , 2006, Malaysia ²⁸⁰	Randomized, double-blind, prospective study	160 In-patients who underwent major operations (21.9%) Morphine (mean 35.6 y ± 10.8) Tramadol (mean 36.7 y ± 9.6)	<ul style="list-style-type: none"> • Morphine (80) • Tramadol (80) 	Pain; sedation; side effects	"Patient-controlled analgesia tramadol is as equally effective as PCA morphine in controlling post operative pain."
Hashimi, 2012, Serbia ¹⁵³	–	50 In-patients scheduled for orthopedic surgery under caudal block (gender not specified, range 2-8 y)	Bupivacaine plus: <ul style="list-style-type: none"> • Fentanyl (25) • Tramadol (25) 	Analgesia; side effects	" Adding fentanyl or tramadol to bupivacaine for caudal block increases and improves quality of analgesia during and after the surgery."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Hassan <i>et al.</i> , 2012, India ¹⁸³	Comparative study	40 Out-patients with impacted asymptomatic mandibular third molars Butorphanol (50%, mean 23.15 y \pm 4.18) Tramadol (60%, mean 20.75 y \pm 6.71)	<ul style="list-style-type: none"> • Butorphanol (20) • Tramadol (20) 	Time of injection; amount of anesthetic injected; duration of surgery; efficacy; adverse events; need of rescue medication	“Butorphanol 1 mg was more effective than tramadol 50 mg in respect to postoperative analgesia.”
Hatami <i>et al.</i> , 2018, Iran ⁶¹	Double-blinded clinical trial study	60 Patients who underwent tonsillectomy (gender not specified, 18-35 y)	<ul style="list-style-type: none"> • Tramadol • Saline plus honey 	Pain scores; waking up times during night due to pain; nausea and vomiting	“The current investigation confirmed the positive impact of tramadol on post-tonsillectomy pain relief in adults especially in the first 24 hours after the surgery. The authors also found that honey can be used as a complementary treatment for reducing post-tonsillectomy pain. Considering honey impact on wound healing and its anti-inflammatory effect, and as the side effects of honey appear to be negligible, it is suggested as an adjunctive regimen after surgery for better pain control.”
Hatipoglu <i>et al.</i> , 2018, Turkey ¹⁸⁴	Prospective randomized study	53 In-patients scheduled for percutaneous nephrolithotomy (PCNL) Paravertebral block (PVB; 61.5%, mean 41.8 y \pm 12.3) Tramadol (62.96%, mean 44.5 y \pm 14.0)	<ul style="list-style-type: none"> • Ultrasound-guided PVB (26) • Tramadol (27) 	Hemodynamic parameters; VAS scores; side effects; complications; tramadol consumption; additional analgesic requirements	“Ultrasound-guided PVB was found to be an effective analgesia compared to tramadol, and no additional complications were encountered.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Hazhir <i>et al.</i> , 2010, Iran ⁶²	–	90 Patients with renal colic (54%, mean 35.20 y ± 13.26)	<ul style="list-style-type: none"> • IM Tramadol (30) • Intranasal Desmopressin (30) • IM Tramadol plus intranasal desmopressin (30) 	VAS scores	"Intranasal desmopressin relieved pain in about one third of the patients; thus, it is not as effective as narcotics. In addition, tramadol was more effective than desmopressin."
Hegazy and Ghoneim, 2013, Egypt ⁶³	Prospective randomized controlled trial	40 In-patients scheduled for abdominal surgery in cancer Group T (70%, range 1-3.1 y) Group B (50%, range 1-4 y)	<ul style="list-style-type: none"> • Bupivacaine (20) • Bupivacaine plus tramadol (20) 	Hemodynamic parameters; duration of analgesia; pain score	"We recommend the routine use of caudal bupivacaine tramadol combination for infraumbilical surgery in pediatric patients provided that there is no contraindication."
Heid <i>et al.</i> , 2008, Germany ⁶⁴	Randomized, placebo-controlled, double-blind study	60 In-patients scheduled for lumbar disc surgery with remifentanil-isoflurane general anesthesia Tramadol (50%, mean 48.2 y ± 13.5) Control (70%, mean 50.05 y ± 13.5)	<ul style="list-style-type: none"> • Tramadol (30) • Saline (30) 	Incidence of shivering during the first 2 postoperative hours	"In conclusion, the incidence and intensity of post-anesthetic shivering was significantly reduced after intraoperative administration of 2 mg/kg-1 tramadol compared with placebo after remifentanil-based anesthesia. However, we could not demonstrate pain-modulating effects."
Hemanth <i>et al.</i> , 2013, India ⁶⁵	Prospective, randomized, single blind, parallel group clinical study	60 In-patients who had undergone minor surgeries (gender and age not specified)	<ul style="list-style-type: none"> • Lignocaine (30) • Tramadol (30) 	Mean pain scores (VAS)	"It can be concluded that there is no significant difference between the two groups in terms of mean pain scores and adverse effect profile. But need for additional analgesic was less and statistically significant in T group when compared to L group. Hence Tramadol can be a good choice in minor surgeries less than 5 cms"

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Hom Choudhuri <i>et al.</i> , 2008, India ⁶⁶	Randomized and double-blind	75 In-patients scheduled for unilateral inguinal herniotomy (gender not specified) Group B (mean 5.1 y ± 0.4) Group BK (mean 5.9 y ± 0.6) Group BT (mean 5.2 y ± 0.7)	<ul style="list-style-type: none"> • Bupivacaine plus ketamine (25) • Bupivacaine plus tramadol (25) • Bupivacaine (25) 	Mean arterial pressure; heart rate; pulse oximetry; respiratory rate; sedation and pain scores	"In conclusion, our study demonstrates that the addition of 0.5 mg/kg ketamine or 1 mg/kg tramadol to 0.25% bupivacaine 0.5 ml/kg significantly prolongs the duration of effective caudal analgesia without any increase in the adverse effects in children having surgery for inguinal hernia."
Honca <i>et al.</i> , 2013, Turkey ¹⁸⁵	Prospective randomized double-blind study	200 Patients who underwent elective gynecologic surgery (0%) Tramadol (mean 42.3 y ± 11.5) Sufentanil (mean 40.1 y ± 11.8) Meperidine (mean 38 y ± 11.4) Lidocaine (mean 40.1 y ± 11.4)	<ul style="list-style-type: none"> • Tramadol (50) • Sufentanil (50) • Meperidine (50) • Lidocaine (50) 	Incidence of pain; side effects	"In conclusion, the analgesic effect of meperidine was not significantly superior to that of the other analgesic agents. Our results showed that lidocaine was the most effective drug, whereas sufentanil was the least effective for alleviating the pain resulting from injection of rocuronium."
Hoogewijs <i>et al.</i> , 2000, Belgium ²⁸¹	Prospective, open, single blind, randomized study	160 Patients presenting to the emergency department (ED) with single peripheral trauma Propacetamol (72%, mean 46.3 y ± 22.6) Piritramide (89%, mean 41.4 y ± 17.1) Tramadol (76%, mean 47.2 y ± 22.8) Diclofenac (62%, mean 45.1 y ± 22.5)	<ul style="list-style-type: none"> • Propacetamol (40) • Piritramide (40) • Tramadol (40) • Diclofenac (40) 	Pain scores (VAS); cardiorespiratory variables; side effects	"We found only small differences concerning analgesic efficacy of the studied analgesics when treating patients with a single peripheral injury in an ED setting. When compared with the intravenously administered drugs the intramuscular administration of the strong opioid piritramide resulted in a delayed decrease of pain scores and an increased incidence of side effects. On the other hand, piritramide i.m. has a low cost compared with the other studied substances."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Hopkins <i>et al.</i> , 1998, South Africa ²⁸²	Double-blind randomized controlled study	40 In-patients scheduled for elective major orthopedic surgery Tramadol (65%, mean 49 y ± 3) Morphine (30%, mean 49 y ± 3)	<ul style="list-style-type: none"> • Tramadol (20) • Morphine (20) 	Pain scores (VAS); drug consumption and total PCA demands; vital signs (blood pressure and heart rate); oxygen saturation and respiratory rate; side effects	“Tramadol is an effective analgesic agent for the relief of acute postoperative pain when administered by PCA via the subcutaneous route. Under these conditions tramadol behaves much like morphine with a similar side-effect profile.”
Hou <i>et al.</i> , 2016, China ¹⁸⁶	Double-blinded and randomized study	90 Patients scheduled for thyroid surgery Sufentanil (16.7%, mean 50.3 y ± 8.1) Tramadol (6.7%, mean 47.5 y ± 9.2) Dezoxine (6.7%, mean 47.9 y ± 7.9)	<ul style="list-style-type: none"> • Sufentanil (30) • Tramadol (30) • Dezocine (30) 	VAS; overall pain performance scores; Bruggemann comfort scale; Observer's assessment of alertness/sedation; Ramsay sedation scale	“In conclusion, the administration of sufentanil induced more effective analgesia than tramadol and dezocine for postoperative pain management after thyroidectomy. Sufentanil transiently depressed respiratory and delayed the extubation compared with dezocine. No differences on consciousness recovery and other side effects were observed between the three groups.”
Houmes <i>et al.</i> , 1992, The Netherlands ⁶⁷	Comparative double-blind randomized study	150 Patients experiencing moderate or severe pain requiring an IV centrally acting analgesic after gynecologic surgery (0%) Tramadol (mean 35.6 y ± 7.5) Morphine (mean 36.4 y ± 7.8)	<ul style="list-style-type: none"> • Tramadol (100) • Morphine (50) 	Pain intensity; pain relief; oxygen saturation	“Our results indicate that the 50-mg treatment dose of tramadol fulfills the requirements of an analgesic for treatment of moderate postoperative pain, whereas for severe pain a higher dose is recommended. In demonstrating the absence of clinically relevant respiratory depression with tramadol, we underline one of the potential dangers of morphine and therefore suggest first-line use of another analgesic (e.g., tramadol) for postoperative pain.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Hussain <i>et al.</i> , 2014, Pakistan ⁶⁸	Randomized double blind study	60 Patients undergoing elective cesarean section (0%) Tramadol (mean 27.07 y ± 3.6) Ranitidine (mean 28.57 y ± 3.2)	<ul style="list-style-type: none"> • Tramadol (30) • Ranitidine (30) 	Gastric fluid volume and pH	"In comparison with Ranitidine, the administration of Tramadol in patients undergoing elective Caesarean Sections under GA [general anesthesia] resulted in significantly greater volume and acidity of the gastric contents, lower Neonatal APGAR 1 minute, reduced post operative opioid consumption, no change in the frequency of PONV."
Ilias and Jansen, 1996, Austria ¹⁸⁷	Randomized, double-blind, placebo-controlled study	78 In-patients with moderate to intolerable postoperative pain following hysterectomy (0%, range 20-65 y)	<ul style="list-style-type: none"> • Lornoxicam 4 mg (18) • Lornoxicam 8 mg (20) • Tramadol (20) • Placebo (20) 	Pain intensity; time to first remedication; safety profile	"In conclusion, this study's results suggest that lornoxicam 8 mg iv is at least, if not slightly more, effective in controlling moderate to severe post-hysterectomy pain than tramadol 50 mg iv. Lornoxicam was also well tolerated and associated with a lower incidence of adverse events than tramadol."
Iqbal and Shetty, 2019, India ⁶⁹	Prospective, double-blind, randomized controlled trial	60 Out-patients undergoing surgical extraction of impacted mandibular third molars (53%, range 19-45 y)	<ul style="list-style-type: none"> • Tramadol (30) • Control (30) 	Visual analogue pain scale (VAPS); rescue analgesics taken; total number of analgesics taken	"The overall outcomes of our study show that submucosal injection of tramadol has a significant effect on postoperative pain control after surgical extraction of impacted third molars even though its exact mechanism of action remains unknown."
Isiordia-Espinoza <i>et al.</i> , 2016, Mexico ¹⁸⁸	Parallel, double-blind, randomized, placebo-controlled clinical trial	30 Patients undergoing mandibular third molar surgery (36.7%, range 18-27 y)	<ul style="list-style-type: none"> • Oral ketorolac plus IM placebo (15) • Oral placebo plus IM tramadol (15) 	First analgesic rescue medication; pain intensity; total analgesic consumption; adverse effects	"According to the VAS and AUC [area under the curve] results, this study suggest that 10 mg of oral ketorolac had better analgesic effect than 50 mg of tramadol when administered before a mandibular third molar surgery. Further studies employing a larger sample size are necessary to confirm these finding."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Isiordia-Espinoza <i>et al.</i> , 2012, Mexico ¹⁸⁹	Double-blind, randomized, parallel-group clinical trial	30 Patients undergoing mandibular third molar surgery Meloxicam (33.3%, mean 21.86 y ± 2.13) Tramadol (66.7%, mean 21.13 y ± 2.03)	<ul style="list-style-type: none"> • Meloxicam (15) • Tramadol (15) 	Pain intensity; analgesic consumption; swelling; trismus	“The patients receiving 15 mg of preoperative meloxicam had less pain intensity and total analgesic consumption than those receiving 50 mg of preoperative tramadol.”
Ivanova <i>et al.</i> , 2015, Russia ⁷⁰	–	68 Patients with stage 2-3 oral mucositis after hematopoietic stem cell transplant (gender not specified, range 5-18 y)	<ul style="list-style-type: none"> • Continuous IV tramadol (36) • PCA tramadol (32) 	VAS scores; number of night awakenings; average duration of tramadol course; average tramadol dosage; adverse events	“Tramadol is effective and safe analgesic for children and teenagers with OM [oral mucositis] stage 2-3 after PCT [polychemotherapy] and hematopoietic stem cell transplantation. PCA with tramadol has several advantages such as customized dosage optimization, sleep improvement, anxiety relief, that improves quality of life.”
Jabalameh, 2010, Iran ⁷¹	–	120 In-patients scheduled for cesarean section (0%, age not specified)	<ul style="list-style-type: none"> • Pethidine (not reported) • Tramadol (not reported) • Bupivacaine (not reported) • Saline (not reported) 	Pain intensity; frequency of nausea and vomiting; opioid consumption	“The administration of subcutaneous pethidine or tramadol after cesarean delivery improves analgesia and has a significant morphine sparing effect compared with bupivacaine and control groups. So, we conclude that pethidine or tramadol may be good choices for postcesarean pain relief.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Jabalameli <i>et al.</i> , 2013, Iran ²⁴⁷	Randomized double blinded placebo-controlled study	90 Patients scheduled for elective lower abdomen surgeries Tramadol (57.8%, mean 46.9 y ± 13.99) Placebo (48.9%, mean 45.1 y ± 16.3)	<ul style="list-style-type: none"> • Tramadol (45) • Placebo (45) 	VAS scores; opium total dose consumption	"In conclusion considering the mentioned studies, preemptive subcutaneous infiltration of T [tramadol], is not only an appropriate pain relieving method for post-operative pain treatment and reduces the need for more opioid considerably but also increases patient's satisfaction following the surgery. Yet, further studies should be planned in this regard."
Jabalameli <i>et al.</i> , 2012, Iran ⁷²	–	120 Patients scheduled for elective cesarean section (0%) Bupivacaine (mean 27.1 y ± 4.9) Pethidine (mean 26.5 y ± 3.9) Tramadol (mean 26.3 y ± 4.7) Control (mean 26.6 y ± 4.5)	<ul style="list-style-type: none"> • Bupivacaine (30) • Pethidine (30) • Tramadol (30) • Control (30) 	VAS scores; opioid consumption	"The administration of subcutaneous pethidine or tramadol after cesarean section improves analgesia and has a significant morphine-sparing effect compared with bupivacaine and control groups."
Jackson <i>et al.</i> , 2004, UK ¹⁹⁰	–	110 Patients scheduled for day-case arthroscopy Treatment (71.4%, mean 38.9 y ± 11.2) Control (72.2%, mean 37.6 y ± 13.9)	<ul style="list-style-type: none"> • Tramadol (56) • Placebo (54) 	Pain scores; nausea scores; perioperative complications; analgesic requirements	"In conclusion this study has shown that the use of tramadol as pre-emptive analgesia in day-case arthroscopy patients does not significantly reduce postoperative pain scores or requirements for analgesia. In addition, the higher incidence of perioperative bradycardia together with PONV suggests that its use in this group of patients is of questionable benefit. It is conceivable that using a larger study population would identify an improvement in pain scores."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Jain <i>et al.</i> , 2017, India ²⁴⁸	Prospective study	<p>40 Patients with mandibular trauma scheduled for open reduction and internal fixation (ORIF) under general anesthesia</p> <p>Group T (85%, mean 30.1 y ± 7.8)</p> <p>Group L (90%, mean 29.9 y ± 8.4)</p>	<ul style="list-style-type: none"> • Tramadol (20) • Lornoxicam (20) 	Pain intensity (VAS); adverse effects	<p>“Although both tramadol and lornoxicam were effective in controlling postoperative pain in patients with mandibular trauma undergoing ORIF under general anesthesia, the comparative results clearly demonstrate that pain control by intravenous administration of lornoxicam is significantly better than intravenous administration of tramadol at 24th postoperative hour. However, the side effects produced by both the study drugs were minor and had no apparent effect on the study results. More conclusive investigation needs to be performed to attest to these aforementioned facts.”</p>
Jain <i>et al.</i> , 2003, India ²⁸³	–	<p>128 In-patients in active labor (0%)</p> <p>Epidural (mean 25.7 y ± 3.1)</p> <p>Meperidine (mean 24.8 y ± 2.6)</p> <p>Tramadol (mean 24.1 y ± 2.8)</p>	<ul style="list-style-type: none"> • Epidural bupivacaine and fentanyl (43) • Meperidine (39) • Tramadol (44) 	VAS scores; analgesic efficacy; effect on labor; other maternal side effects; perinatal outcome; maternal satisfaction	<p>“In conclusion, this prospective study has shown that although epidural analgesia provide better labor analgesia, opioids can be a good alternative when epidural is not feasible as they also provide maternal satisfaction in a significant number of cases. Tramadol may be preferred over meperidine as it is associated with less maternal sedation. However, its efficacy in the second stage of labor was not found to be as good as meperidine.”</p>

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Jaitley <i>et al.</i> , 2011, India ⁷³	–	90 In-patients in established active stage of labor (0%) IV (mean 24.67 y) Epidural (mean 25 y) Control (mean 24.76 y)	<ul style="list-style-type: none"> • IV tramadol (30) • Epidural tramadol plus bupivacaine (30) • Control (30) 	Pain relief; time to onset of analgesia; maternal and neonatal parameters	“Epidural tramadol is a simple and effective method for painless and safe delivery. Analgesia produced is significantly more effective than intravenous tramadol. Maternal side effects are minor without any fetal or neonatal respiratory depression.”
James <i>et al.</i> , 1996, South Africa ²⁴⁹	Randomized, double-blind study	39 In-patients undergoing thoracotomy Tramadol (65%, mean 36.0 y ± 15.1) Morphine (37%, mean 56.0 y ± 14.0)	<ul style="list-style-type: none"> • Tramadol (20) • Morphine (19) 	Pain scores; morphine consumption; arterial blood gases; vital capacity values	“We conclude that a single dose of 150 mg tramadol given at the end of surgery provided postoperative analgesia equivalent to that provided by this dosage regimen of epidural morphine for the initial postoperative period.”
Jandial <i>et al.</i> , 2018, India ²⁵⁰	Prospective randomized study	105 In-patients scheduled for routine elective surgical procedure Group I (48.6%, mean 39.51 y ± 11.18) Group II (42.85%, mean 42.6 y ± 9.57) Group III (45.7%, mean 42.42 y ± 10.17)	<ul style="list-style-type: none"> • Dexmedetomidine (35) • Lignocaine (35) • Tramadol (35) 	Incidence of pain	“In conclusion, injection dexmedetomidine is equally effective and can be used as an alternative to time tested injection lignocaine for relief of pain due to propofol injection without any significant effects. Also, injection tramadol can be used alternatively to injection lidocaine as seen in the present study. Further studies are needed to justify use of dexmedetomidine as an alternative to lignocaine and tramadol for prevention of propofol injection pain.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Jazayeri <i>et al.</i> , 2012, Iran ⁷⁴	Randomized double blinded clinical trial	132 In-patients undergoing minor arthroscopic knee surgery Morphine (70.7%, mean 41.0 y ± 11.6) Tramadol (68.4%, mean 40.5 y ± 10.9)	<ul style="list-style-type: none"> • Morphine (75) • Tramadol (57) 	Pain scores; time of first analgesic request; need for supplemental analgesic	“We have found a postoperative analgesic effect of intra-articularly administered morphine and tramadol following minor arthroscopic knee surgery with a maximum effect 6 hours post injection.”
Jeffrey <i>et al.</i> , 1999, UK ¹⁹¹	Prospective, double-blind study	65 In-patients undergoing elective intracranial surgery Codeine (44.4%, mean 51.0 y) Tramadol 50 mg (50%, mean 54.1 y) Tramadol 75 mg (28%, mean 52.2 y)	<ul style="list-style-type: none"> • Codeine (18) • Tramadol 50 mg (22) • Tramadol 75 mg (25) 	Pain scores; VAS scores; number of analgesic injections required; use of additional ‘escape’ analgesia; side effects	“In summary, although it may have been expected that tramadol would have potential benefits for postoperative analgesia after intracranial surgery, we have demonstrated that it conferred no benefit over codeine phosphate in such patients. Codeine provided significantly better postoperative pain relief than tramadol. The higher dose of tramadol caused more sedation and nausea and vomiting, and cannot be recommended after this type of surgery.”
Jendi and Talathi, 2019, India ⁷⁵	Randomized, split-mouth, double-blinded study design	50 Patients not undergoing intraoral treatment (60%, mean 27.52 y ± 4.1)	<ul style="list-style-type: none"> • Tramadol in the soft tissues over maxillary canine tooth as local infiltration on one side and lignocaine on the contralateral side (50) 	Allergic reaction; pain on injection; onset and duration of anesthesia; side effect and response of participants	“Tramadol has a local anesthetic effect similar to lignocaine when injected as infiltration in oral soft tissues.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Jia <i>et al.</i> , 2010, China ⁷⁶	–	80 In-patients undergoing cervical spine surgery Group 1 (55.6%, mean 53.6 y ± 2.4) Group 2 (55.0%, mean 54.2 y ± 2.9) Group 3 (55.0%, mean 51.7 y ± 3.3) Group 4 (60.0%, mean 53.2 y ± 3.1)	All patients received tramadol 30 minutes before the end of surgery, followed by a continuous infusion of tramadol plus: <ul style="list-style-type: none"> • Group 1: control (20) • Group 2: 0.05 mcg/kg/h naloxone (20) • Group 3: 0.10 mcg/kg/h naloxone (20) • Group 4: 0.20 mcg/kg/h naloxone (20) 	Pain during rest and cough; nausea; sedation	"Based on these results, we suggest that a small-dose naloxone should be added once initiate the tramadol intravenous administration for moderate to severe postoperative pain control."
Jiang <i>et al.</i> , 2015, China ¹⁹²	–	120 In-patients scheduled for elective colorectal cancer surgery (gender not specified) Flurbiprofen (mean 47.1 y ± 5.9) Morphine (mean 48.4 y ± 8.9) Tramadol (mean 49.5 y ± 9.2)	<ul style="list-style-type: none"> • Flurbiprofen axetil (40) • Morphine (40) • Tramadol (40) 	Cellular immune function and response; trauma/stress response	"In conclusion, flurbiprofen axetil, a new non-steroidal analgesic drug, can attenuate the stress response during the perioperative period. Similar to morphine and tramadol, this drug showed good analgesic action and showed few postoperative adverse effects. Thus, flurbiprofen may be useful for clinical application."
Kakagia <i>et al.</i> , 2012, Greece ⁷⁷	Double-blind, randomized study	88 Patients undergoing excision of cutaneous lesions Tramadol (60.9%, mean 56 y ± 19) Lidocaine (59.5%, mean 54 y ± 16)	Adrenaline plus: <ul style="list-style-type: none"> • Tramadol (46) • Lidocaine (42) 	Pain at the injection site; sensory block; patient-rated analgesia	"Tramadol may be used as a reliable, safe, and effective agent for local infiltrative anesthesia in patients undergoing excision of cutaneous lesions requiring minor reconstruction."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Kalagac Fabris <i>et al.</i> , 2015, Croatia ¹⁹³	–	Patients undergoing laparoscopic dermoido-cystecto-ovariectomy (0%, age not specified)	<ul style="list-style-type: none"> Intraperitoneal instillation of levobupivacaine, dexamethasone, and tramadol IV tramadol and ketoprofen 	Cough-evoked pain	"Intraperitoneal instillation of triple analgesic therapy, as a part of a multimodal approach, at the end of the laparoscopic surgery resulted in significant reduction in postoperative VAS scores at rest and movement as well as tramadol consumption compared with intravenous analgesia during the first postoperative day. Lower incidence of nausea and vomiting was an additional advantage."
Kapral <i>et al.</i> , 1999, Austria ⁷⁸	Prospective, controlled, double-blinded study	<p>60 In-patients scheduled for forearm and hand surgery after trauma</p> <p>Group A (55.0%, mean 44 y ± 21)</p> <p>Group B (55.0%, mean 48 y ± 18)</p> <p>Group C (50.0%, mean 46 y ± 19)</p>	<p>Mepivacaine plus:</p> <ul style="list-style-type: none"> Group A: isotonic sodium chloride solution (20) Group B: tramadol (20) Group C: isotonic sodium chloride solution and IV tramadol (20) 	Sensory and motor blockade	"This study demonstrates that the admixture of 100 mg of tramadol with mepivacaine 1% for brachial plexus block provides a pronounced prolongation of blockade without side effects. Our data support a specific analgesic effect of tramadol on peripheral nerves."
Kaufmann <i>et al.</i> , 2004, Germany ³⁰⁶	Randomized, double-blinded study	<p>35 In-patients scheduled for elective retinal surgery (scleral buckle, macular translocation)</p> <p>Controlled-release oxycodone (56.3%, mean 68 y ± 13)</p> <p>Tramadol and metamizole (68.4%, mean 67 y ± 10)</p>	<ul style="list-style-type: none"> Controlled-released oxycodone (CRO) and IV isotonic saline solution (16) Placebo tablet and IV tramadol and metamizole (19) 	Wound pain at rest; area under the curve	"In conclusion, CRO administered twice in the first 24h postoperatively is superior to intravenous tramadol/metamizole combination for postoperative analgesia after retinal surgery, with fewer adverse events and greater patient satisfaction."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Kesriklioğlu <i>et al.</i> , 2002, Turkey ¹⁵⁴	–	63 Patients undergoing transurethral prostate resection under epidural anesthesia (100%, age not specified)	<ul style="list-style-type: none"> • Epidural bupivacaine plus tramadol (22) • Epidural bupivacaine plus fentanyl (21) • Epidural bupivacaine (20) 	Heart rate, mean arterial pressure, breath rate, oxygen saturation, levels of sensorial block, maximum sensorial block level and motor block level, time to analgesic supplement	"In conclusion, tramadol-bupivacaine combination increases postoperative analgesia time significantly compared with fentanyl-bupivacaine combination and plain bupivacaine while providing stable hemodynamic responses and similar side effects."
Kayacan <i>et al.</i> , 2002, Turkey ⁷⁹	–	40 Out-patients scheduled for arthroscopic knee surgery Neostigmine (40.0%, mean 43.5 y ± 12) Tramadol (50.0%, mean 39.5 y ± 14.9) Tenoxicam (30.0%, mean 41.9 y ± 11.1) Bupivacaine (20.0%, mean 43.0 y ± 12.4)	<ul style="list-style-type: none"> • Neostigmine (10) • Tramadol (10) • Tenoxicam (10) • Bupivacaine (10) <p>The study solutions were injected into the knee joint at the end of the surgery in 20 ml normal saline 10 min before tourniquet release</p>	Postoperative analgesia; time at which patient first requested pain medication	"We conclude that the intra-articular administration of neostigmine, tramadol, tenoxicam and bupivacaine after day case arthroscopic knee procedures is a simple, effective, safe and well-tolerated analgesic technique, offering superior postoperative pain control."
Khajavi <i>et al.</i> , 2009, Iran ²⁵¹	Double-blind, randomized clinical trial	60 In-patients awaiting pyelolithotomy IV tramadol (43.3%, mean 33.8 y ± 4.1) Subcutaneous wound infiltration tramadol (56.7%, mean 35 y ± 2.4)	<ul style="list-style-type: none"> • IV tramadol (30) • Subcutaneous wound infiltration with tramadol (30) 	Hemodynamic changes; pain intensity; level of consciousness; meperidine consumption	"In conclusion, following subcutaneous wound infiltration with tramadol, postoperative analgesia was prolonged and the need for more opioid was reduced considerably. However, administration of tramadol at the operation site requires further studies."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Khajavi <i>et al.</i> , 2016, Iran ¹⁹⁴	Randomized, double-blinded, clinical trial	60 In-patients undergoing various types of kidney surgeries (gender not specified) Tramadol (mean 42.2 y ± 16.1) Ketamine (mean 46.9 y ± 14.6)	IV paracetamol plus: • Tramadol (30) • Ketamine (30)	Pain intensity; level of consciousness and agitation	"The combination of intravenous paracetamol 1 gr and ketamine 0.5 mg/kg resulted in an overall reduction in pain scores, decreased postoperative analgesic requirements, and lower agitation score compared with intravenous paracetamol 1 gr and tramadol 0.7 mg/kg for patients undergoing renal surgery."
Khooshideh and Shahriari, 2009, Iran ²⁸⁴	Randomized, prospective study	160 In-patients undergoing labor (0%) Pethidine (mean 26.7 y ± 3.2) Tramadol (mean 25.8 y ± 2.8)	• Pethidine (80) • Tramadol (80)	Labor duration	"But the analgesic efficacy of tramadol was not found to be as good as pethidine especially in the second stage of labor. Further randomized investigations are needed to achieve an excellent pain relief by higher dosage of pethidine."
Khosravi <i>et al.</i> , 2006, Iran ⁸⁰	Double-blind, prospective, randomized study	60 In-patients undergoing herniorrhaphy (97%) Intravenous tramadol (mean 4.2 y ± 1.5) Ilio-inguinal and iliohypogastric nerve block (mean 4.0 y ± 1.4)	• IV tramadol (30) • Ilioinguinal and iliohypogastric nerve block (30)	Child's pain status; complications; rescue analgesia use	"We concluded that tramadol can have at least the same analgesic effect as that of ilioinguinal and iliohypogastric nerve blocks for postherniorrhaphy pain in children, with even a superior effect at the time of maximal analgesia. We also highlight the troublesome side-effect of nausea and vomiting which brings into question the benefits of using this opioid that seems to lack respiratory depression."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Kim <i>et al.</i> , 2009, Korea ³³¹ Kim <i>et al.</i> , 2009, Korea ²⁵²	–	150 In-patients scheduled for elective surgical procedures Control (42%, mean 49.5 y ± 9.41) Tramadol (52%, mean 50.5 y ± 12.87)	<ul style="list-style-type: none"> • Tramadol 1.5 mg/kg (50) • Tramadol 3.0 mg/kg (50) • Normal saline (50) 	Intraoperative awareness (Bispectral Index, modified Brice interview) and hemodynamic changes	“The results indicate that the administration of tramadol while maintaining anesthesia with desflurane, adjusted to keep the BIS between 50 and 60, does not modified BIS values. So we propose that tramadol can be safely administered as an immediate postoperative analgesia without concern about intra-operative awareness.”
Kim <i>et al.</i> , 2011, Korea ³⁰⁷	Prospective, randomized, single-blinded study	430 Out-patients who underwent transrectal ultrasound-guided prostate biopsy (100%) Group 1 (mean 65.9 y ± 8.5) Group 2 (mean 67.4 y ± 10.3) Group 3 (mean 65.3 y ± 10.0)	<ul style="list-style-type: none"> • Group 1: periprostatic nerve block with 1% lidocaine injection (125) • Group 2: oral acetaminophen 650 mg (158) • Group 3: EMLA cream: 2.5% lidocaine, 2.5% prilocaine (147) <p>All patients received tramadol before the procedure</p>	Pain (visual analog scale score); patient willingness to undergo procedure in future if required	"According to the results of our study, oral administration of 650 mg acetaminophen and topical application of EMLA cream, in addition of intravenous tramadol, reduce pain and are both technically easy, noninvasive, and safe. Moreover, these methods were more effective for pain relief than was the conventional periprostatic nerve block method. Therefore, they are thought to be useful methods of relieving pain during prostate biopsy."
Kim and Kang, 2019, Korea ³⁰⁸	Randomized, noninferiority study	100 In-patients undergoing laparoscopic gynecologic surgery (0%, range 23-64 y)	Tramadol plus: <ul style="list-style-type: none"> • Ramosetron (49) • Saline (51) 	Cumulative postoperative tramadol dose	"In conclusion, continuous administration of ramosetron did not decrease the analgesic action of tramadol. Therefore, we concluded that ramosetron will not affect dose of tramadol."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Kirdemir <i>et al.</i> , 2006, Turkey ¹⁹⁵	Randomized study	68 In-patients undergoing knee arthroscopy Neostigmine (75.0%, mean 38.8 y ± 3.7) Tramadol (50.0%, mean 39.2 y ± 4.7) Tenoxicam (40.0%, mean 34.2 y ± 3.2) Placebo (55.6%, mean 36.1 y ± 2.1)	<ul style="list-style-type: none"> • Neostigmine (16) • Tramadol (14) • Tenoxicam (20) • Placebo (18) 	Postoperative pain; heart rate; mean arterial pressure	"All drugs provided acceptable post-operative analgesia with excellent satisfaction in Group III. According to these results i.a. tenoxicam may be a good choice for post-operative analgesia"
Kocabas <i>et al.</i> , 2005, Turkey ⁸¹	–	60 In-patients undergoing abdominal hysterectomy (gender and age not specified)	<ul style="list-style-type: none"> • Tramadol (30) • Control (30) 	Analgesic efficacy	"The addition of a tramadol infusion to morphine PCA resulted in improved analgesic efficacy and reduced morphine requirements compared with morphine PCA alone after abdominal hysterectomy."
Köroğlu <i>et al.</i> , 2016, Turkey ⁸²	Randomized prospective double-blind study	90 In-patients receiving surgery under general anesthesia (gender and age not specified)	<ul style="list-style-type: none"> • Meperidine (30) • Ketamine (30) • Tramadol (30) 	Tympanic membrane temperature; shivering; modified observer's assessment of alertness/sedation scale and VAS pain score	"Therefore, tramadol can be chosen as an alternative agent for the prophylactic treatment of PAS [post-anesthesia shivering] and pain."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Krishna <i>et al.</i> , 2019, India ¹⁹⁶	Prospective, randomized, controlled, single-blinded study	110 In-patients undergoing elective cardiac surgery with cardiopulmonary bypass Group 1 (58.5%, mean 48.3 y ± 1.7) Group 2 (56.6%, mean 49.6 y ± 1.5)	<ul style="list-style-type: none"> Group 1: ultrasound-guided bilateral erector spinae plane (ESP) block with 3 mg/kg of 0.375% ropivacaine before anesthesia induction (55) Group 2: paracetamol and tramadol in the postoperative period (55) 	Pain at rest using an 11-point numeric rating scale (NRS)	"The authors conclude that ESP block provided superior analgesia for a longer duration compared with an intravenous paracetamol plus tramadol regimen."
Krishnadas <i>et al.</i> , 2016, India ⁸³	Prospective, randomized, double-blinded comparative study	60 In-patients undergoing subumbilical surgeries Group R (75.0%, mean 3.5 y ± 1.4) Group RT (95.0%, mean 3.2 y ± 1.4) Group RM (80.0%, mean 2.8 y ± 0.8)	<ul style="list-style-type: none"> Group R: ropivacaine (20) Group RT: ropivacaine plus tramadol (20) Group RM: ropivacaine plus midazolam (20) 	Time interval from the caudal block to the administration of rescue analgesic	"Addition of tramadol or midazolam to caudal epidural block with ropivacaine showed significant prolongation of post-operative analgesia compared to ropivacaine alone. The mean duration of analgesia in tramadol group was more than the midazolam group through this difference was statistically not significant."
Cagle and Krusz, 2011, US ³³² Krusz <i>et al.</i> , 2011, US ²⁵³	–	34 Out-patients with either chronic daily headaches (CDH) or new daily persistent headaches (NDPH) (38.2%, age not specified)	<ul style="list-style-type: none"> IV tramadol (34) 	Pain severity	"We conclude that tramadol, given IV, can rapidly and safely reduce typical daily headache severity in CDH and NDPH. There is virtually no toxicity acutely with this medication. This can be the starting point of treatment with oral tramadol for these difficult headache subtypes. The rapidity with which tramadol acts when given IV is far faster in time course and degree of effect than when used orally...Double-blind studies are warranted to follow up on this new potential treatment for pervasive and severe headache patterns."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Kumar <i>et al.</i> , 2016, India ¹⁹⁷	Prospective, randomized, comparative study	60 In-patients scheduled for surgery under general anesthesia Tramadol (46.7%, mean 41.5 y ± 15.1) Diclofenac (50.0%, mean 38.7 y ± 12.9)	When patients started complaining of pain, they were allocated randomly into two groups: <ul style="list-style-type: none"> • Tramadol (30) • Diclofenac (30) 	Time to onset of analgesia; duration of analgesia; mean pain score	"In terms of quicker onset in postoperative analgesia diclofenac appears to be a better choice."
Kumar <i>et al.</i> , 2018, India ⁸⁴	Prospective, randomized trial	41 In-patients with acute pancreatitis pain (68.3%, mean 44.3 y ± 13.8)	<ul style="list-style-type: none"> • Diclofenac (20) • Tramadol (21) 	Pain; patient satisfaction	"Both diclofenac and tramadol are potent and equally effective in controlling pain in AP [acute pancreatitis] with similar adverse reaction profile."
Kushtagi and Surpaneni, 2012, India ⁸⁵	–	213 In-patients in active labor (0%, mean 25.1 y ± 2.5)	<ul style="list-style-type: none"> • Tramadol 50 mg (54) • Tramadol 100 mg (55) • Meperidine (54) • Control (50) 	Pain relief	"Tramadol 100 mg is an equally effective labor analgesic as meperidine with less maternal and perinatal side effects."
Lallar <i>et al.</i> , 2015, India ¹⁹⁸	Single-blinded, prospective-randomized study	200 In-patients in active labor Paracetamol (0%, mean 26.0 y ± 2.8) Tramadol (0%, mean 26.1 y ± 2.6)	<ul style="list-style-type: none"> • Paracetamol (100) • Tramadol (100) 	Pain	"So from our study, we can conclude that intravenous paracetamol is simple, cost-effective, feasible option as labor analgesic."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Lauretti <i>et al.</i> , 1997, Brazil ⁸⁶	–	48 Patients scheduled for minor abdominal procedures Control (66.7%, mean 48.5 y ± 15.4) Beta-cyclodextrin piroxicam (BCP; 50.0%, mean 37.8 y ± 19.7) Tramadol (58.3%, mean 41.3 y ± 20.1) BCP plus tramadol (83.3%, mean 38.3 y ± 21.3)	Oral premedication and intravenous maintenance: • Control: Placebo tablet, IV saline and propofol (12) • BCP tablet, IV saline and propofol (12) • Placebo tablet, IV propofol and tramadol (12) • BCP tablet, IV propofol and tramadol (12)	Pain; blood pressure; heart rate	"In conclusion, the combination of tramadol and beta-cyclodextrin piroxicam provided adequate perioperative analgesia for minor surgical procedures."
Lee <i>et al.</i> , 2008, Hong Kong ⁸⁷	Prospective, randomized, double-blinded, control study	78 In-patients with moderate to severe acute musculoskeletal pain and acute arthritis (including gout) presenting to the emergency department within 72 hours of onset (55.1%, range 18-65 y)	Oral paracetamol plus: • IM tramadol (39) • IM ketorolac (39)	Pain control	"The analgesic effect of the tramadol and paracetamol combination is as effective as the ketorolac and paracetamol combination. Tramadol is well tolerated and relatively safe. It is also cheaper than ketorolac. Hence, we recommend tramadol and paracetamol combination for acute moderate to severe musculoskeletal pain in the emergency setting."
Lepri <i>et al.</i> , 2006, Italy ⁸⁸	Double-blinded, randomized controlled trial	60 In-patients scheduled for elective intra-abdominal surgery under general anesthesia Tramadol (60.0%, mean 62.8 y ± 15.4) Tramadol plus ketorolac (53.3%, mean 58.9 y ± 17.6)	• Tramadol (30) • Tramadol plus ketorolac (30)	Pain; sedation	"We concluded that the combination of ketorolac plus tramadol in the same PCA device was an effective and safe treatment for postoperative analgesia in abdominal surgery."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Li and Liao, 2016, China ³²⁴	Prospective, randomized controlled trial	94 In-patients undergoing elective prostate surgery with urinary catheterization (100%, age not specified)	<ul style="list-style-type: none"> • Pudendal nerve block with ropivacaine (47) • Tramadol (47) 	Incidence of catheter-related bladder discomfort	<i>According to NCT, this trial is still in the recruitment stage, with no progress made there (NCT02683070)</i>
Li <i>et al.</i> , 2019, China ¹⁹⁹	Prospective, randomized controlled trial	44 In-patients scheduled for elective radical thyroidectomy Group M (20.0%, mean 42.4 y ± 8.7) Group C (30.0%, mean 39.5 y ± 8.4)	<ul style="list-style-type: none"> • Group M: subcuticular wound infiltration with ropivacaine, then flurbiprofen axetil 20 min before end of surgery (22) • Group C: no wound infiltration, then IV tramadol 20 min before end of surgery (22) 	Analgesic effect	“Multimodal analgesia with ropivacaine wound infiltration and intravenous flurbiprofen axetil provided better analgesia than tramadol after radical thyroidectomy.”
Likar <i>et al.</i> , 1995, Austria ²⁸⁵	Randomized, double-blind, comparative study	93 In-patients undergoing arthroscopic surgery at 2 independent centers Center 1 <ul style="list-style-type: none"> • Morphine (75.0%, mean 30.5 y ± 13.6) • Tramadol (85.0%, mean 29.8 y ± 9.5) Center 2 <ul style="list-style-type: none"> • Morphine (81.0%, mean 37.3 y ± 14.7) • Tramadol (56.0%, mean 40.6 y ± 12.5) 	<ul style="list-style-type: none"> • Morphine (41) • Tramadol (45) 	Pain; sedation	“It appears that intra-articular administration of morphine or tramadol is a simple, safe and effective means of controlling pain after arthroscopic surgery. Morphine may have an advantage over tramadol in this indication, but further studies are necessary to confirm this finding.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Lin <i>et al.</i> , 2012, Taiwan ⁸⁹	Prospective, randomized, double-blind, placebo-controlled study	110 In-patients undergoing elective lumbar microdiscectomy with intubated total intravenous anesthesia (54.5%, range 18-83 y)	<ul style="list-style-type: none"> • Fentanyl (55) • Tramadol (55) 	Incidence of cough; quality of extubation; heart rate; blood pressure; postoperative pain score; fentanyl consumption; side effects	"In conclusion, our study demonstrated that 1 mg/kg of IV administered tramadol 30 minutes before extubation decreases the incidence of cough, improves the quality of tracheal extubation, and diminishes the fluctuation of emergence hemodynamics compared with fentanyl."
Liu <i>et al.</i> , 2015, China ²⁰⁰	Randomized controlled clinical study	120 In-patients in first stage active labor (0%) HANS (mean 27.5 y ± 3.8) PCIA (mean 28.3 y ± 4.0) PCEA (mean 28.0 y ± 4.1) Control (mean 26.6 y ± 3.8)	<ul style="list-style-type: none"> • HANS: Han's Acupoint Nerve Stimulator (30) • PCIA tramadol plus ondansetron (30) • PCEA ropivacaine plus sufentanil (30) • Control (30) 	Pain (VAS); vital signs; analgesic effect; length of labor stages; Apgar score; rate of cesarean section; use of rescue analgesia; postpartum hemorrhage; side effects	"In conclusion, HANS can be a non-pharmacological analgesic therapy for labor pain with fewer side effects"
Long and Yue, 2003, China ²⁵⁴	–	80 In-patients in active labor Control (0%, mean 27.1 y ± 1.9) Ropivacaine and fentanyl (0%, mean 27.2 y ± 2.2) Tramadol (0%, mean 26.8 y ± 1.7)	<ul style="list-style-type: none"> • Control (30) • Spinal ropivacaine plus fentanyl, then with PCEA (30) • PCIA tramadol (20) 	Pain intensity (VAS); analgesia onset time; Apgar scores; length of labor; cesarean delivery rate; side effects	"The most common misgivings for PCIA with tramadol is newborn depression. We found from our study that Apgar scores of the PCIA group were lower than the control group and the CSEA [combined spinal-epidural analgesia] combined PCEA group, however, there is insufficient data to draw strong conclusions. Further evaluation needs to be forthcoming."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Madan <i>et al.</i> , 2016, India ²⁰¹	Prospective, randomized double blinded single center study	100 In-patients scheduled for elective surgery under general anesthesia with propofol Lignocaine (40%, mean 37.52 y ± 9.68) Tramadol (40%, mean 38.40 y ± 7.94) Ketorolac (44%, mean 38.36 y ± 11.24) Normal saline (44%, mean 38.44 y ± 9.19)	<ul style="list-style-type: none"> • Lignocaine (25) • Tramadol (25) • Ketorolac (25) • Normal saline (25) 	Pain score; incidence of pain; side effects	"Thus, pre-treatment with any of these 3 drugs significantly reduce propofol injection pain. However, lignocaine was more acceptable because of less pain and fewer side effects than tramadol and ketorolac. We recommend the use of these agents as pre-treatment to propofol to increase the patient acceptability of this agent ideal anesthetic agent."
Magrini <i>et al.</i> , 1998, Italy ⁹⁰	Controlled, completely randomized trial	50 In-patients undergoing hemorrhoidectomy or traumatological or abdominal surgery Tramadol (56%, mean 48.8 y ± 12.5) Pentazocine (68%, mean 48.4 y ± 15.0)	<ul style="list-style-type: none"> • Tramadol (25) • Pentazocine (25) 	Severity of pain; quality of sleep; local reactions; systemic reactions	"To conclude, therefore, tramadol at an intramuscular dose of 300 mg/day appears to be particularly indicated for postoperative pain relief on account of its prompt, lasting action, ease of handling and safety in use."
Mais <i>et al.</i> , 1997, Italy ⁹¹	Multicenter trial	66 In-patients undergoing laparotomic or vaginal hysterectomy, with postoperative pain classified as strong/unbearable (0%, mean 49 y ± 6.9)	<ul style="list-style-type: none"> • Tramadol • Ketorolac 	Severity of pain; analgesic consumption; sleep quality	"The analgesic effect of intramuscular tramadol in hysterectomy pain is confirmed, and its pharmacodynamic features make it a drug of first choice for postoperative pain."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Maldini <i>et al.</i> , 1997, Croatia ⁹²	–	42 In-patients recovering from major surgery (gender not specified, mean 9.2 y)	<ul style="list-style-type: none"> • Intermittent tramadol (18) • Continuous tramadol (24) 	Analgesic efficacy; side effects	<p>Intermittent: "In many cases, it was found inadequate, i.e. the dose was too small and usually given too late. There were no significant changes in pulse rate and blood pressure."</p> <p>Continuous: "In all children, satisfactory pain control was achieved regardless of the pain etiology. The dose required for complete pain control ranged from 0.2 to 0.6 mg/kg/h of tramadol."</p>
Mandal and Pawar, 1997, India ⁹³	–	150 In-patients undergoing operation (gender and age not specified)	<ul style="list-style-type: none"> • Tramadol (100) • Morphine (50) 	Heart rate; blood pressure; quality of analgesia; requirement for muscle relaxants; postoperative complications	"Hence it is concluded that both tramadol and morphine are effective intraoperative analgesics, but tramadol is devoid of postoperative respiratory complications."
Manne and Gondi, 2017, India ⁹⁴	Randomized study	<p>100 In-patients that were prospective kidney donors undergoing nephrectomy</p> <p>Tramadol (30%, mean 45.0 y ± 5.80)</p> <p>Paracetamol (30%, mean 46.16 y ± 4.86)</p>	<ul style="list-style-type: none"> • Paracetamol (50) • Tramadol (50) 	Postoperative pain relief (VAS); variations in vital parameters	"Postoperative analgesia is the key factor of successful recovery from any surgery. From the different parameters compared in our study, both tramadol and paracetamol offer adequate postoperative analgesia. Tramadol due to its quick onset of action and fewer side effects is better than intravenous paracetamol for postoperative analgesia."
Marinkovic <i>et al.</i> , 2014, Serbia ⁹⁵	Randomized, prospective study	45 In-patients undergoing arthroscopic knee surgery (gender and age not specified)	<ul style="list-style-type: none"> • Tramadol (15) • Tramadol plus levobupivacaine (20) • Sodium chloride (10) 	Time to first pain; severity of postop pain; need for supplemental analgesia; vital parameters; side effects	"Low doses of intraarticular opioid analgesics can significantly reduce pain after arthroscopic knee surgery. Maximum effect was obtained 6-8 hours after the injections of the drug. In combination with a low dose of the local anesthetic analgesic effect can be extended up to 24 hours."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Marino <i>et al.</i> , 2013, Italy ⁹⁶	Prospective randomized trial	50 In-patients who underwent conventional Milligan-Morgah hemorrhoidectomy (gender and age not specified)	<ul style="list-style-type: none"> • Paracetamol (25) • Tramadol plus ketorolac (25) 	Pain; bleeding; length of hospital stay	"Pain after hemorrhoidectomy is more likely to be controlled by a constant-infusion pump of tramadol plus ketorolac than by interspersed infusion of paracetamol. There is no increased risk of hemorrhage using a nonsteroidal anti-inflammatory drugs for pain control. A better pain control is associated with a shorter hospital stay."
Maryam <i>et al.</i> , 2017, Iran ⁹⁷	Double-blinded clinical trial study	80 In-patients undergoing tonsillectomy (gender not specified, range 5-12 y)	<ul style="list-style-type: none"> • Before surgery tramadol administration (40) • After surgery tramadol administration (40) 	Pain; sedation; nausea and vomiting	"We concluded from our study that peritonsillar infiltration of tramadol before surgery controlled postoperative pain better from 8 h after the surgery to hospital discharge (late effect), but that local infiltration of tramadol after surgery controlled postoperative pain better up to 2 h after the operation (early effect)."
Mathew <i>et al.</i> , 2019, India ²⁰²	Randomized controlled trial	80 In-patients undergoing total abdominal hysterectomy (0%) Epidural (0%, mean 50.2 y ± 6.7) Parenteral (0%, mean 46.7 y ± 5.4) Transversus abdominis plane (TAP) block (0%, mean 45.5 y ± 6.7)	<ul style="list-style-type: none"> • Epidural bupivacaine (20) • Parenteral diclofenac plus tramadol (20) • TAP block bupivacaine (20) 	Quality of postoperative recovery (QoR); postoperative pain; time to first rescue analgesia; postoperative morphine consumption; sedation	"The QoR after abdominal hysterectomy is similar with either intravenous analgesics or epidural analgesia or TAP block when used with rescue analgesia to manage postoperative pain. TAP block provides superior analgesia and reduces 24-h morphine consumption when compared with parenteral and epidural analgesia."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Matkap <i>et al.</i> , 2011, Turkey ²⁰³	Prospective, randomized	70 In-patients undergoing laparoscopic cholecystectomy IV (20%, mean 48.6 y ± 12.5) Infiltration (20%, mean 53.3 y ± 12.1)	<ul style="list-style-type: none"> • IV tramadol (35) • Infiltration tramadol (35) 	Pain; nausea and vomiting	"In conclusion, trocar site infiltration with tramadol in patients undergoing laparoscopic cholecystectomy provided effective analgesia. Trocar site infiltration significantly lowered the frequency of PONV as compared with its IV administration."
Memi <i>et al.</i> , 2002, Turkey ²⁰⁴	Randomized, double blind	250 In-patients undergoing elective operations Placebo (36%, mean 37.3 y ± 15.1) Ondansetron (38%, mean 40.5 y ± 15.4) Lidocaine (54%, mean 38.6 y ± 17.3) Tramadol (44%, mean 42.2 y ± 14.2) Fentanyl (48%, mean 41.6 y ± 8.82)	<ul style="list-style-type: none"> • Placebo (50) • Ondansetron (50) • Lidocaine (50) • Tramadol (50) • Fentanyl (50) 	Pain	"We conclude that ondansetron, lidocaine, tramadol, and fentanyl were effective in decreasing the level of rocuronium injection pain. According to our study, lidocaine was the most effective drug, whereas fentanyl was the least effective, in reducing injection pain."
Memis <i>et al.</i> , 2005, Turkey ⁹⁸	–	100 In-patients undergoing total abdominal hysterectomy (0%, age not specified)	<ul style="list-style-type: none"> • IP placebo (25) • IP bupivacaine (25) • IP bupivacaine plus tramadol (25) • IV tramadol (25) 	Pain; mean arterial pressure; heart rate; peripheral oxygen saturation; need for rescue analgesia	"In our study, we found that tramadol when added to intraperitoneal bupivacaine was as effective in the early postoperative period as i.v. tramadol."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Memis <i>et al.</i> , 2002, Turkey ²⁰⁵	–	100 In-patients undergoing elective operations Tramadol (44%, mean 38.2 y ± 15.1) Ondansetron (58%, mean 41.7 y ± 16.4)	<ul style="list-style-type: none"> • Tramadol (50) • Ondansetron (50) 	Pain; nausea and vomiting; degree of sedation	"There was no difference between the effectiveness of ondansetron and tramadol in preventing the pain of injection of propofol. Ondansetron had the added benefit of a lower incidence of PONV and this could be an argument for choosing this drug. In addition, if the use of ondansetron is anticipated its administration could be timed to exploit its local anesthetic properties"
Mentes and Bagci, 2009, Turkey ⁹⁹	Double blind, randomized study	160 In-patients undergoing inguinal hernia repair (gender not specified) Lornoxicam (mean 23.92 y ± 9.08) Tramadol (mean 25.60 y ± 11.20)	<ul style="list-style-type: none"> • Lornoxicam (80) • Tramadol (80) 	Pain (VAS); side effects	"Lornoxicam 8 mg i.v. and b.i.d. [twice daily], tramadol 1 mg/kg at the end of the surgery and every 6 h up to 24 h after inguinal hernia repair provided rapid and effective analgesia and was well tolerated."
Metry <i>et al.</i> , 2019, Egypt ²⁵⁵	Prospective comparative study	220 In-patients undergoing knee arthroscopy Preoperative levobupivacaine (61.8%, mean 31.4 y ± 8.9) Preoperative levobupivacaine and tramadol (65.5%, mean 30.9 y ± 8.1) Postoperative levobupivacaine and tramadol (56.4%, mean 30 y ± 7.1) Preoperative and postoperative levobupivacaine and tramadol (60%, mean 28.6 y ± 8.8)	<ul style="list-style-type: none"> • Preoperative levobupivacaine (55) • Preoperative levobupivacaine and tramadol (55) • Postoperative levobupivacaine and tramadol (55) • Preoperative and postoperative levobupivacaine and tramadol (55) 	Pain; time to first rescue analgesia; number of requests for rescue analgesia	"It could be concluded that PE [preemptive] levobupivacaine and tramadol IAI [intraarticular injection] provided satisfactory level of PO [postoperative] analgesia after therapeutic arthroscopy comparable to PO administration. However, combined PE and PO levobupivacaine and tramadol IAI of half-doses provided PO analgesia superior to that provided by either PE or PO full-dose IAI. Wider scale studies are mandatory to establish outcome of combined-reduced dose of levobupivacaine and tramadol IAI."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Miranda <i>et al.</i> , 2014, Philippines ²⁰⁶	Double-blind study	30 In-patients scheduled for elective surgery (gender not specified, range 18-70 y)	<ul style="list-style-type: none"> • IV tramadol • Infiltration tramadol 	Postoperative pain; sedation; side effects	"Local wound infiltration of Tramadol seems to be superior to intravenous Tramadol with regards to its analgesic effect producing better and longer pain relief but with decreased side effects."
Mitra <i>et al.</i> , 2011, India ²⁰⁷	Prospective, randomized, double-blind study	60 In-patients undergoing arthroscopic knee surgery Bupivacaine (60%, mean 28.05 y ± 10.76) Bupivacaine plus fentanyl (60%, mean 26.55 y ± 8.02) Bupivacaine plus tramadol (60%, mean 31.65 y ± 12.86)	Bupivacaine plus: <ul style="list-style-type: none"> • Normal saline (20) • Fentanyl (20) • Tramadol (20) 	VAS pain score; use of rescue analgesia; adverse events	"Thus IA bupivacaine-fentanyl appears to be the best combination for relief of postoperative pain in patients undergoing arthroscopic knee surgery, followed by IA bupivacaine-tramadol."
Mitra <i>et al.</i> , 2012, India ²⁰⁸	Randomized, double-blind, parallel-group controlled trial	204 In-patients undergoing cesarean section (0%) Diclofenac and tramadol (mean 26.04 y ± 3.65) Diclofenac and acetaminophen (mean 25.95 y ± 3.09)	<ul style="list-style-type: none"> • Rectal diclofenac plus IV tramadol (103) • Rectal diclofenac plus IV acetaminophen (101) 	Overall pain scores	"Overall, it may be concluded that both diclofenac–acetaminophen and diclofenac–tramadol combinations effectively control pain in women undergoing caesarean section. The diclofenac–tramadol combination was overall more efficacious for pain control, but it was also associated with higher incidence of post-operative nausea."
Montes <i>et al.</i> , 2000, Spain ²⁸⁶	–	101 In-patients undergoing hysterectomy (0%, range 34-70 y)	<ul style="list-style-type: none"> • Tramadol 100 mg (21) • Metamizole 1.2 g (21) • Tramadol 5 mg plus metamizole 60 mg (20) • Tramadol 7.5 mg plus metamizole 30 mg (19) • Tramadol 2.5 mg plus metamizole 90 mg (20) 	Pain scores; adverse effects	"Thus, the results show that when beneficial and pooled adverse effects were evaluated, tramadol and metamizole interact synergistically when combined in a 1:1 ratio."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Morina <i>et al.</i> , 2015, Kosovo ¹⁰⁰	–	120 In-patients undergoing laparoscopic cholecystectomy (LC; gender and age not specified)	<ul style="list-style-type: none"> • Intraperitoneal bupivacaine only (40) • IP bupivacaine plus IV tramadol (40) • IV tramadol only (40) 	Analgesia; postoperative nausea and vomiting	"Pain management following elective LC is best achieved with combination intraperitoneal bupivacaine and intravenous tramadol, achieving the least incidence of postoperative vomiting."
Mortelmans <i>et al.</i> , 2006, Belgium ¹⁰¹	Prospective study	300 In-patients referred for, or presenting with renal colic-like symptoms (70%, mean 44.5 y)	<ul style="list-style-type: none"> • Butylhiscinebromide (75) • Butylhiscinebromide plus tramadol drip (75) • Glucose (75) • Glucose plus tramadol drip (75) 	Pain scores; need for rescue medication; side effects	"Therefore, we consider the continuous IV administration of tramadol a safe, efficient, and elegant measure for the management of renal colic."
Muktesh <i>et al.</i> , 2018, India ¹⁰²	Randomized controlled trial	41 In-patients with acute pancreatitis (68.3%, mean 44.34 y ± 13.77)	<ul style="list-style-type: none"> • Diclofenac (20) • Tramadol (21) 	Mean pain scores; use of rescue drug; side effects	"Both diclofenac and tramadol are potent and equally effective in controlling pain in AP [acute pancreatitis] with similar adverse reaction profile."
Murmu <i>et al.</i> , 2015, India ³⁰⁹	Prospective, randomized, placebo-controlled, double-blind parallel group study	126 In-patients undergoing hemithyroidectomy Ondansetron (30%, mean 41.3 y ± 8.9) Saline (21%, mean 42.4 y ± 9.78)	Tramadol plus: <ul style="list-style-type: none"> • Ondansetron (63) • Saline (63) 	Duration of analgesia; postoperative pain score; sedation score	"Ondansetron reduces the duration and quality of analgesia of tramadol administered conventionally without a PCA device."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Nagpal <i>et al.</i> , 2015, India ¹⁰³	Prospective, randomized, controlled, double-blind study	90 In-patients scheduled for upper limb surgeries (gender not specified) IV saline (mean 40.4 y ± 14.63) IV tramadol (mean 40.93 y ± 12.77) Tramadol block (mean 35.53 y ± 12.16)	Bupivacaine block plus: <ul style="list-style-type: none"> • Saline IV (30) • Tramadol IV (30) • Tramadol block (30) 	Onset and duration of sensory and motor block; demand for rescue analgesia	"The use of tramadol as an adjunct to bupivacaine in supraclavicular brachial plexus block hastens the onset of block, increases the duration of motor blockade. It also delays the requirement of the first dose of analgesic postoperatively without causing any side effects in comparison to systemically administered tramadol group and control group."
Naguib <i>et al.</i> , 1998, Saudi Arabia ²⁰⁹	Prospective, randomized, double-blind study	100 In-patients undergoing elective laparoscopic cholecystectomy (16%, mean 33 y ± 7.6)	<ul style="list-style-type: none"> • Tramadol (50) • Morphine (50) 	Intraoperative consumption; blood pressure; pain scores	In conclusion, this study demonstrated that there was no difference between the use of tramadol and morphine to treat pain after laparoscopic cholecystectomy from 90 min after the end of surgery. Morphine was more effective than tramadol as an intraoperative analgesic."
Ng <i>et al.</i> , 1998, Hong Kong ¹⁰⁴	Randomized, double-blind	38 In-patients undergoing lower abdominal operations Morphine (53%, mean 59.26 y ± 18.02) Tramadol (37%, mean 57.68 y ± 13.9)	<ul style="list-style-type: none"> • Morphine (19) • Tramadol (19) 	Dizziness; nausea; overall satisfaction	"We conclude from our study that tramadol is comparable with morphine when used in post-operative PCA in terms of safety and efficacy following lower abdominal operations. However, the concomitant use of intravenous morphine intraoperatively is associated with a more frequent incidence of nausea and dizziness. Further investigations are required to overcome this problem."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Ng <i>et al.</i> , 1997, Hong Kong ³¹⁰	Randomized, double-blind study	34 In-patients undergoing elective colorectal or head and neck surgery Tramadol (50%, mean 61.8 y ± 8.7) Tramadol plus droperidol (50%, mean 57.9 y ± 14.6)	<ul style="list-style-type: none"> • Tramadol only (18) • Tramadol plus droperidol (16) 	Nausea; vomiting; need for rescue anti-emetic; pain score; sedation; satisfaction	"In conclusion, our study demonstrated that a mixture of tramadol and droperidol is associated with a reduced incidence and severity of nausea and vomiting compared with tramadol alone when used in PCA after colorectal or head and neck surgery procedures. This was not associated with any differences in the degree of sedation or quality of analgesia."
Nimmaanrat <i>et al.</i> , 2007, Thailand ²¹⁰	Double-blind randomized, controlled trial	149 Out-patients undergoing ambulatory gynecologic laparoscopic procedures Tramadol (0%, mean 34.2 y ± 5.5) Placebo (0%, mean 35 y ± 5.3)	<ul style="list-style-type: none"> • Tramadol (75) • Placebo (74) 	Pain; fentanyl requirement; time to first fentanyl dose; side effects	"Intravenous tramadol 50 mg given before anesthetic induction did not reduce pain intensity but was well tolerated. Although tramadol statistically reduced the paracetamol requirement in the first 24 h postoperatively, it did not seem to provide a significant clinical advantage."
Ntritsou <i>et al.</i> , 2013, Greece ²⁸⁷	–	277 In-patients undergoing major urologic surgery (gender and age not specified)	<ul style="list-style-type: none"> • Nalbuphine (94) • Tramadol (78) • Morphine (105) 	Analgesia; need for additional analgesics; side effects; sedation	"Intravenous administration of nalbuphine, morphine and tramadol in combination with ketamine after major urologic surgery were effective concerning postoperative analgesia. Tramadol plus Ketamine group was associated with greater incidence of pain, additional analgesics and lower incidence of PONV. Nalbuphine, Morphine plus Ketamine groups presented significant higher incidence of PONV."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Oguzturk <i>et al.</i> , 2012, Turkey ¹⁰⁵	Prospective, randomized, placebo controlled double blind study	210 In-patients with non-traumatic acute abdominal pain lasting less than 72 hours Tramadol (44.3%, mean 30.8 y ± 10.8) Paracetamol (34.3%, mean 33.6 y ± 12.2) Placebo (54.3%, mean 34.2 y ± 13)	<ul style="list-style-type: none"> • Tramadol (70) • Paracetamol (70) • Placebo (70) 	Pain scores; side effects; diagnostic accuracy	"Tramadol and paracetamol lead to decrease in the level of abdominal pain. The appropriate use of analgesics in patients with acute abdominal pain effectively decreased pain and did not interfere with diagnosis or treatment."
Ökmen and Metin Ökmen, 2018, Turkey ³¹¹	Randomized, single blind study	40 In-patients undergoing video-assisted thoracoscopic surgery (VATS; 50%, mean 54.20 y)	<ul style="list-style-type: none"> • Tramadol (20) • Tramadol plus Serratus Anterior Plane Block (SAPB; 20) 	Postoperative pain	"Our study results show that SAPB can be an effective treatment option for postoperative VATS analgesia. Current analgesic approaches are designed as multimodal applications; however, treatment schemes may be in use in the coming years for postoperative VATS analgesia. Although SAPB is advantageous due to its relative ease of application, further RCTs [randomized controlled trials] are required to investigate the efficacy and indications for SAPB."
Ökmen and Metin Ökmen, 2018, Turkey ³¹²	Prospective, randomized, single blind study	50 In-patients undergoing tympanomastoid surgery SCP block (20%, mean 33.80 y ± 8.25) GAN block (28%, mean 34.40 y ± 9.20)	Tramadol plus: <ul style="list-style-type: none"> • Superficial cervical plexus block (SCP; 25) • Greater auricular nerve block (GAN; 25) 	Postoperative pain; tramadol use	"The results of this study show that SCP and GAN blocks are similar in pain control after tympanomastoid surgery."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Oksar <i>et al.</i> , 2016, Turkey ³¹³	Prospective, randomized, double-blinded clinical study	60 In-patients undergoing laparoscopic cholecystectomy (28.3%, range 18-74 y)	Tramadol PCA plus: <ul style="list-style-type: none"> • TAP block (20) • Oblique subcostal TAP (OSTAP) block (20) • Control (20) 	Intraoperative remifentanyl use; postoperative pain scores; PCA demand; total analgesic consumption	"TAP and OSTAP blocks improved postoperative analgesia in patients receiving laparoscopic cholecystectomy, which resulted in lower VAS scores and reduction in total analgesic consumption."
Olischar <i>et al.</i> , 2014, Australia ²¹¹	Randomized placebo-controlled trial	71 In-patients requiring major thoraco-abdominal surgery likely to require postoperative ventilation (49.3%, newborns)	<ul style="list-style-type: none"> • Tramadol (36) • Placebo (35) 	Time to extubation; morphine and midazolam exposure; pain score; cranial ultrasound; seizures	"Tramadol's addition to standard analgesia in this small group of postsurgical neonates did not appear to have any positive effect on time to extubation, morphine or midazolam exposure, or pain scores. This questions the benefit of tramadol for postsurgical neonates who may potentially be at greater risk of tramadol toxicity compared with adults."
Olmez <i>et al.</i> , 2008, Turkey ¹⁰⁶	Randomized prospective study	62 Patients undergoing transrectal ultrasound-guided biopsy of the prostate (TRUSP) Lornoxicam (100%, mean 64.33 y ± 6.46) Tramadol (100%, mean 62.71 y ± 7.26) Control (100%, mean 67.5 y ± 9.58)	<ul style="list-style-type: none"> • Lornoxicam (21) • Tramadol (21) • Control (20) 	Pain scores; comfort; willingness to consent to future TRUSP	"TRUSP is a painful procedure. Lornoxicam or tramadol use for pain relief for this procedure is a practical, effective and comfortable method compared to the experience of the control group. In addition, tramadol was found to be more effective than lornoxicam."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Omero and Ortega, 2012, Brazil ¹⁰⁷	Randomized, prospective, descriptive and inferential simple blind person study	100 Patients undergoing surgery for intertrochanteric fracture of hip (gender and age not specified)	Bupivacaine and hyperbaric lidocaine plus: <ul style="list-style-type: none"> • Tramadol (50) • Morphine (50) 	Duration of analgesia; hemodynamics; adverse events	"Tramadol is an excellent alternative analgesic by subdural route and must be catalogued as a new anesthetic technique in combination with anesthetic premises in elderly patients with intertrochanteric fracture of the hip since besides offering duration of an acceptably lasting post operating analgesia of up to twelve hours, with a good hemodynamic stability has less adverse reactions than morphine."
Özalevli <i>et al.</i> , 2005, Turkey ²⁵⁶	Prospective, randomized, double-blind study	60 In-patients undergoing tonsillectomy (61.7%, range 6-12 y)	<ul style="list-style-type: none"> • Tramadol (30) • Morphine (30) 	Pain; sedation; nausea; bolus and total PCA doses; hemodynamic parameters; side effects	"We conclude that i.v. patient-controlled tramadol is a suitable alternative to PCA morphine for postoperative pain relief in children after tonsillectomy. Morphine offers better postoperative pain relief than tramadol, but at the cost of a greater incidence of nausea. Further studies are required to clarify the analgesic efficacy and relative safety of PCA tramadol compared with opioids and to explore the possible additive or synergistic effects of combination therapy with acetaminophen, paracetamol or nonsteroidal anti-inflammatory drugs."
Ozcan <i>et al.</i> , 2002, Turkey ¹⁰⁸	–	60 Out-patients undergoing elective ESWL Fentanyl (55%, mean 41 y ± 9) Diclofenac (40%, mean 37 y ± 13) Tramadol (45%, mean 39 y ± 18)	<ul style="list-style-type: none"> • Fentanyl (20) • Diclofenac (20) • Tramadol (20) 	Hemodynamics; pain intensity; sedation; side effects	"In conclusion, IM tramadol HCl and diclofenac sodium provided safe and adequate analgesia and patient comfort in the outpatient ESWL procedure."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Ozkan <i>et al.</i> , 2012, Turkey ¹⁰⁹	Prospective controlled study	95 Patients undergoing SWL (76.8%, mean 42 y ± 14.2)	<ul style="list-style-type: none"> • Lornoxicam plus Tramadol (32) • Paracetamol plus Tramadol (31) • Tramadol only (32) 	Pain scores; analgesic consumption; hemodynamics; side effects	<p>"As a result, the combination of lornoxicam and tramadol, which is one of the analgesic drug combinations known as multimodal analgesic, showed much more efficacy against acute pain due to SWL treatment in comparison other groups in this study. On the other hand, although there was no difference with respect to side effects and hemodynamic parameters among all the three groups, it may be speculated that the combination of lornoxicam and tramadol may be preferred instead of other combinations in pain control during SWL according to the results of this study. It should also be stated that there is a need for more comprehensive studies to evaluate the efficacy of multimodal analgesics in the future."</p>

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Oztekin <i>et al.</i> , 2006, Turkey ²⁵⁷	Prospective randomized trial	50 In-patients undergoing open-heart surgery Morphine (80%, mean 58.8 y ± 7.96) Fentanyl (60%, mean 55.1 y ± 6.98) Meperidine (80%, mean 49 y ± 15.18) Remifentanyl (70%, mean 57.12 y ± 11.99) Tramadol (70%, mean 55.33 y ± 12.75)	<ul style="list-style-type: none"> • Morphine (10) • Fentanyl (10) • Meperidine (10) • Remifentanyl (10) • Tramadol (10) 	Pain scores; hemodynamics; side effects	"It is concluded that, there were no significant differences among the groups for pain management except the highest VAS value on tramadol. The side effects such as nausea, vomiting, headache, stomachache and respiratory depression of the narcotic analgesics were observed in this study. Remifentanyl and meperidine in the study had shown less side effects than other three drugs. All these side effects need to be checked frequently and form the basis for the nursing interventions in the postoperative period. Further studies with higher number of patients are needed to establish statistically more reliable results, especially for side effects."
Pandit <i>et al.</i> , 2011, India ²¹²	Randomized and double blind	44 Out-patients with impacted mandibular third molars Diclofenac (61%, mean 26.57 y ± 5.6) Tramadol (86%, mean 25.76 y ± 4.1)	<ul style="list-style-type: none"> • Diclofenac (23) • Tramadol (21) 	Pain intensity; time to rescue analgesic; postoperative acetaminophen consumption; global assessment	"This study shows that intravenous diclofenac provides better preventive analgesic efficacy than tramadol when given preoperatively for third molar surgery. The reduction of postoperative pain is significantly long to control the peak postoperative pain at 6–8 h for impacted third molar surgery."
Pang <i>et al.</i> , 2000, Taiwan ³¹⁴	Prospective, randomized, and double-blinded study	50 In-patients undergoing major orthopedic surgery Tramadol (48%, mean 74.4 y ± 8.3) Tramadol plus LAS (44%, mean 72.8 y ± 9.6)	<ul style="list-style-type: none"> • Tramadol (25) • Tramadol plus lysine acetyl salicylate (25) 	Pain control; patient satisfaction; adverse effects	"We conclude that aspirin can be used as an effective and safe adjuvant to tramadol for PCA after orthopedic surgery."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Park, 2013, Korea ²¹³	Randomized, single-center study	59 Out-patients with lumbar radicular pain Morphine (62.5%, mean 53.9 y ± 13.6) Tramadol (48%, mean 61 y ± 15.3)	Transforaminal epidural injection (TFEI) with ropivacaine plus: <ul style="list-style-type: none"> • Morphine (32) • Tramadol (27) 	Pain scores	"TFEI of an opioid plus local anesthetic proved effective in treating radicular pain. Although morphine surpassed tramadol in pain relief scores, the difference was not statistically significant."
Passavanti <i>et al.</i> , 2009, Italy ¹¹⁰	–	20 Out-patients undergoing middle-large excisions of basal cell epitheliomas on face with local flaps in day surgery (gender not specified, range 30-60 y)	<ul style="list-style-type: none"> • Tramadol (10) • Ropivacaine (10) 	Pain scores; time to discharge; analgesic request; side effects; vital signs; local cutaneous reactions	"As the anesthetic and the analgesic effects are both present without adverse reactions, the use of tramadol may be considered a good choice during these procedures."
Pato and Pedro, 2019, Portugal ³¹⁵	Randomized and controlled study	38 In-patients undergoing knee arthroplasty (gender not specified, range 53-87 y)	Spinal anesthesia with hyperbaric bupivacaine, sufentanil, and morphine with postoperative: <ul style="list-style-type: none"> • Epidural ropivacaine (not reported) • IV tramadol plus droperidol (not reported) 	Pain scores; side effects; patient satisfaction	"There seems to be no significant difference between epidural and intravenous analgesia; however, there are not enough registers... Spinal analgesia combined with ITM [IT morphine] (0,2 mg) provides an effective pain relief for knee arthroplasty, especially if coupled with epidural perfusion of local anesthetic. ITM 0,2 mg is still associated with a high prevalence of side effects."
Pendeville <i>et al.</i> , 2000, Belgium ¹¹¹	Double-blind randomized prospective study	50 Out-patients undergoing tonsillectomy Tramadol (gender not specified, mean 4.8 y ± 1.8) Paracetamol (gender not specified, mean 4.4 y ± 1.8)	<ul style="list-style-type: none"> • Tramadol (25) • Paracetamol (25) 	Pain scores; rescue analgesic use; serious adverse effects	"Hence, in this study of limited size, tramadol appeared safe and effective for use in children for postoperative analgesia following tonsillectomy."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Penide <i>et al.</i> , 2012, Spain ²¹⁴	Prospective clinical trial	40 Patients undergoing mastectomy (gender and age not specified)	<ul style="list-style-type: none"> • IV tramadol (not reported) • Continuous paravertebral block (CPB; not reported) 	Peak pain; hemodynamics; satisfaction; circadian cycle	"The use of the CPB may reduce the risk of PMPS [post mastectomy pain syndrome] in reconstructive breast surgery (in a second time)."
Polat <i>et al.</i> , 2013, Turkey ²¹⁵ Tuncel <i>et al.</i> , 2012, Turkey ³³³	–	70 Out-patients undergoing circumcision (100%, range 7-12 y)	<ul style="list-style-type: none"> • Lidocaine plus epinephrine with Ali's clamp (26) • Lidocaine plus epinephrine with conventional circumcision (35) • Tramadol with conventional circumcision (12) 	Anxiety scores; pain scores	"Tramadol may not provide effective local anesthesia in male circumcision. The child's anxiety before the circumcision seems to have a negative effect on pain level."
Pozos <i>et al.</i> , 2007, Mexico ¹¹²	Double-blind, randomized, placebo-controlled clinical trial	48 Out-patients with impacted mandibular third molars (43.75%, range 19-26 y)	<ul style="list-style-type: none"> • Systemic tramadol (12) • Local tramadol (12) • Combination systemic and local tramadol (12) • Control (12) 	Pain score; time to first analgesic; plasma tramadol concentration	"Finally, although the local anesthetic action of tramadol remains unclear, our study provides evidence of benefit in dental surgical procedures in which tramadol is administered to the surgical site. We conclude that tramadol extends the duration of anesthetic effect and, when used in combination of routes (local and systemic), improves the quality of postoperative analgesia."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Prasertsawat <i>et al.</i> , 1986, Thailand ¹¹³	Prospective blind, randomized study	135 In-patients in active labor Tramadol (0%, mean 27.4 y ± 4.63) Morphine (0%, mean 28.9 y ± 4.81) Pethidine (0%, mean 27.7 y ± 4.31)	<ul style="list-style-type: none"> • Tramadol (45) • Morphine (45) • Pethidine (45) 	Analgesia; side effects; neonatal effects	"We conclude that tramadol, as well as morphine and pethidine, caused no complication, either fetal or maternal, with the study regime. Labor pain was adequately relieved, side effects were minimal, and there was no respiratory depression in the neonates. Hence, tramadol has no significant advantage over morphine or pethidine except that it is available with no legal restriction."
Prosser <i>et al.</i> , 1997, UK ²⁵⁸	–	90 In-patients undergoing repair of hypospadias (100%, range 13-53 months)	<ul style="list-style-type: none"> • Bupivacaine (30) • Tramadol (30) • Bupivacaine plus tramadol (30) 	Postoperative pain; additional analgesia requirement; time to additional analgesia; sedation; side effects	"In conclusion, we have shown that when a single caudal injection of tramadol was used in young children it provided analgesia for up to 12 h without a significant incidence of side effects...Further dose-ranging and pharmacokinetic studies in young children are required before the optimum route of administration of tramadol can be determined."
Putland and McCluskey, 1999, UK ²⁵⁹	Prospective, randomized, double-blind study	60 Out-patients undergoing laparoscopic sterilization Tramadol (0%, mean 34.1 y ± 6) Ketorolac (0%, mean 33 y ± 6.7)	<ul style="list-style-type: none"> • Tramadol (30) • Ketorolac (30) 	Duration of anesthesia; time to recovery; time to hospital discharge; side effects	"In conclusion, the results of the present study suggest tramadol is an effective and well-tolerated analgesic for day-case laparoscopic sterilization. Further work is required to determine the optimal dose of tramadol and its efficacy when used in combination with nonsteroidal anti-inflammatory drugs and local anesthetic techniques."
Rajkumar <i>et al.</i> , 2004, India ¹¹⁴	–	40 Patients undergoing routine operations (gender not specified, range 20-65 y)	<ul style="list-style-type: none"> • Tramadol (20) • Normal saline (20) 	Pain intensity of injection	"It may be concluded that pre-treatment with tramadol three minutes prior to propofol induction effectively reduced the injection pain."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Ranucci <i>et al.</i> , 1999, Italy ¹¹⁵	Prospective, randomized trial	60 Patients undergoing elective coronary revascularization Tramadol (85%, mean 61.8 y ± 10.2) Ketorolac (85%, mean 61.8 y ± 10) Propacetamol (85%, mean 59.4 y ± 9.2)	<ul style="list-style-type: none"> • Tramadol (20) • Ketorolac (20) • Propacetamol (20) 	Pain scores; arterial blood gases	"Both tramadol and ketorolac may be used as single drugs, but repeated doses of tramadol may exert a moderate respiratory depression. No adverse effect was observed with each one of the drugs investigated with regard to hemodynamic responses and bleeding."
Rashwan and Fathy El-Rahmawy, 2013, Egypt ³¹⁶	—	120 In-patients undergoing emergency or elective upper-limb unilateral orthopedic surgery Tramadol (88%, mean 29.6 y ± 9.7) Tramadol and acetaminophen (87%, mean 31.6 y ± 8.7)	<ul style="list-style-type: none"> • Tramadol plus acetaminophen (60) • Tramadol only (60) 	Tramadol consumption; hemodynamics; patient satisfaction; adverse events	"The addition of acetaminophen to a low dose tramadol iv PCA as a multimodal analgesic approach provided satisfactory pain control than tramadol iv PCA alone and reduced tramadol consumption after unilateral upper limb orthopedic surgeries under general anesthesia."
Ravishankar <i>et al.</i> , 1996, India ²⁸⁸	Randomized study	50 In-patients undergoing cesarean section (0%, age not specified)	<ul style="list-style-type: none"> • Group I: Pethidine (not reported) • Group II: Tramadol (not reported) 	Pain; side effects	"After decoding, it was observed that pain relief was similar in both groups till the third dose, after which it was significantly better in Group II (p < 0.05). No significant differences in guise rate, blood pressure, respiratory rate and ABG [arterial blood gas] values were identified. The less sedative action of Tramadol was not proved. There was no significant difference in the side effects between the two groups, including APGAR scoring of the newborn and mother-baby interaction."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Resim <i>et al.</i> , 2005, Turkey ²¹⁶	–	35 Out-patients undergoing ESWL (57.1%, range 18-58 y)	<ul style="list-style-type: none"> • Electro-acupuncture (EA; 17) • Midazolam plus tramadol (18) 	Number of shockwaves administered; pain scores; stone-free rates; duration of procedure; side effects	"Our study demonstrates that EA is an effective method for inducing sedation with analgesia and had no demonstrable side effects. However, a different experimental design and other studies with a much larger population would be required to establish its safety."
Rodriguez <i>et al.</i> , 1993, Spain ¹¹⁶	Randomized, double-blind study	160 In-patients undergoing abdominal hysterectomy (0%, mean 46 y ± 8)	<ul style="list-style-type: none"> • Tramadol (40) • Metamizole (40) • Ketorolac (40) • Lysine clonixinate (40) 	Overall efficacy; number of boluses required; need for supplemental analgesia; nausea/vomiting	"In conclusion, tramadol, an analgesic with a central action, was shown to be more effective in controlling postoperative pain than metamizole, ketorolac, or lysine clonixinate. Our results support the concept that central analgesics are superior to peripheral analgesics, at least in the management of postoperative pain."
Safavi <i>et al.</i> , 2012, Iran ¹¹⁷	Randomized, double-blind, placebo-controlled study	<p>96 In-patients undergoing open urologic surgery</p> <p>Tramadol 1 mg/kg (84%, mean 38.5 y ± 12)</p> <p>Tramadol 2 mg/kg (75%, mean 37.4 y ± 15.4)</p> <p>Control (66%, mean 42.9 y ± 15.6)</p>	<ul style="list-style-type: none"> • Tramadol 1 mg/kg (32) • Tramadol 2 mg/kg (32) • Control (32) 	Pain scores; time to first rescue analgesic; need for postoperative analgesia	"In conclusion, preincisional s.c. administration of tramadol at 2 mg/kg provides effective analgesia during the first 24 hour after open urologic surgeries without significant side effects. As, to the best of our knowledge, no study has evaluated the pharmacokinetics of locally infiltrated tramadol, this should be investigated in future studies. Nevertheless, our results are interesting in light of their potential clinical application to the other types of surgeries."
Sagiroglu <i>et al.</i> , 2012, Turkey ¹¹⁸	–	40 In-patients undergoing elective thoracotomy (gender and age not specified)	<ul style="list-style-type: none"> • PCIA tramadol • Continuous IV tramadol 	Pain scores; tramadol consumption; hypotension	"We concluded that tramadol given both intravenous methods was effective for analgesia after postthoracotomy pain."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Sahmeddini <i>et al.</i> , 2017, Iran ¹¹⁹	Double-blind randomized clinical trial	69 In-patients undergoing upper extremity surgery Tramadol (44%, mean 34 y ± 9.9) Magnesium sulfate (56%, mean 38.91 y ± 14.7) Control (52%, mean 34.17 y ± 15.71)	Lidocaine plus: <ul style="list-style-type: none"> • Tramadol (23) • Magnesium sulfate (23) • Control (23) 	Onset of sensory block; duration of analgesia; side effects; respiratory depression	"It seems that adding tramadol as an adjuvant to lidocaine during IVRA [intravenous regional anesthesia] in comparison to magnesium sulfate increases duration of postoperative analgesia and decreases analgesic consumption without increasing opioid-related side effects."
Saita <i>et al.</i> , 2004, Italy ³¹⁷	—	300 Patients undergoing extracorporeal shockwave lithotripsy (ESWL; gender not specified, mean 46 y)	Ketorolac and tramadol plus: <ul style="list-style-type: none"> • Luan treatment (120) • No Luan (180) 	Stone-free rate; energy of treatment	"For ESWL treatment of kidney stones of 20 mm or less and ureteral stones of 15 mm or less, we suggest local analgesia with topical Luan and intramuscular analgesia. This approach increases the success rate of ESWL and reduces the discomfort associated with treatment."
Salim <i>et al.</i> , 2011, Pakistan ²⁸⁹	Prospective randomized study	70 In-patients undergoing laparoscopic cholecystectomy (gender and age not specified)	<ul style="list-style-type: none"> • IV tramadol • Local tramadol 	Pain scores	"To be discussed on the day of presentation."
Samee <i>et al.</i> , 2004, Pakistan ²⁹⁰	Prospective study	60 In-patients undergoing elective lower segment cesarean section Buprenorphine (0%, mean 25 y ± 2) Pentazocine (0%, mean 26 y ± 1) Tramadol (0%, mean 23 y ± 3)	<ul style="list-style-type: none"> • Buprenorphine (20) • Pentazocine (20) • Tramadol (20) 	Respiratory rate; arterial blood gases	"Opioids have a respiratory depressant effect which manifested within 30-60 minute of IM administration, whereas Tramadol which is a non opioid, does not cause respiratory depression in equiv. potent doses."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Saracoglu <i>et al.</i> , 2010, Turkey ²⁶⁰	Prospective, double-blind, randomized study	60 In-patients undergoing elective cesarean section Fentanyl (0%, mean 26.32 y ± 8.69) Tramadol (0%, mean 28.06 y ± 11.47)	<ul style="list-style-type: none"> • Fentanyl (30) • Tramadol (30) 	Analgesic consumption; patient satisfaction	"The present study comparing fentanyl with tramadol did not find a significant difference in postoperative pain scores. The pain scores and PCA opioid consumption during the first 24 hours after surgery in patients who had undergone cesarean section were similar. Further studies can be performed with different types of opioids by IV, epidural or transdermal PCA."
Saracoglu <i>et al.</i> , 2012, Turkey ²⁶¹	Randomized, prospective study	90 In-patients undergoing cesarean section Spinal anesthesia and IV fentanyl (0%, mean 27.9 y ± 10.6) General anesthesia and IV fentanyl (0%, mean 29 y ± 9.3) General anesthesia and IV tramadol (0%, mean 29 y ± 11.8)	<ul style="list-style-type: none"> • Spinal anesthesia and IV fentanyl (30) • General anesthesia and IV fentanyl (30) • General anesthesia and IV tramadol (30) 	PCA use; need for additional analgesic; opioid consumption; patient satisfaction; side effects	"We found no discrepancy between fentanyl and tramadol for the groups following GA [general anesthesia]. Both the postoperative pain scores and the incidence of side effects were similar. These two agents can be used safely in the postoperative period. Further studies are needed to compare the postoperative pain scores and patient satisfaction following neuraxial anesthesia and GA with different opioids when used with IV or epidural PCA techniques."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Sarafraz <i>et al.</i> , 2016, Iran ²⁹¹	Randomized double-blind clinical trial	120 In-patients with chronic tonsillitis, undergoing tonsillectomy Lidocaine (26.7%, mean 8.53 y ± 3.2) Ketamine (36.7%, mean 9.23 y ± 2.4) Tramadol (26.7%, mean 8.5 y ± 2.9) Placebo (46.7%, mean 7.4 y ± 1.9)	<ul style="list-style-type: none"> • Lidocaine (30) • Ketamine (30) • Tramadol (30) • Placebo (30) 	Pain scores; surgery time; time to first analgesic requirement; hospital stay; beginning liquid diet	"In our study, no significant difference was observed between ketamine, tramadol, lidocaine, and placebo regarding pain volume, surgery time, time of first analgesic request, hospital stay, and time of liquid diet start."
Saryazdi <i>et al.</i> , 2009, Iran ¹²⁰	Double-blind randomized controlled trial	75 In-patients undergoing abdominal surgery (gender and age not specified)	<ul style="list-style-type: none"> • Subcutaneous tramadol (25) • IV tramadol (25) • Placebo (25) 	Pain score; opioid consumption; side effects	"Injection of tramadol subcutaneously is effective as IV injection. The subcutaneous tramadol is suggested for relieving postoperative pain after major surgery."
Schmieder <i>et al.</i> , 1993, Germany ²¹⁷	Multi-center, observer-blind, parallel-group study	74 Patients with acute biliary colic Metamizole (20%, mean 54.6 y ± 14.4) Tramadol (36%, mean 57.3 y ± 17.1) Butylscopolamine (29%, mean 60.5 y ± 13.5)	<ul style="list-style-type: none"> • Metamizole (25) • Tramadol (25) • Butylscopolamine (24) 	Pain score	"The pharmacological profile, the rapid onset of analgesic action and the prolonged analgesic effect of metamizole are the rationale for the use of this non-opioid analgesic as first-choice drug in the treatment of acute colic."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Shah <i>et al.</i> , 2013, Pakistan ¹²¹	–	50 Patients with impacted mandibular third molars Ketorolac plus tramadol (52%, mean 20.68 y ± 1.55) Control (44%, 20.8 y ± 1.47)	<ul style="list-style-type: none"> • Ketorolac plus tramadol (25) • Control (25) 	Pain scores; time to first rescue analgesic; total analgesic consumption; self-assessment of efficacy	“Preoperative ketorolac or tramadol in comparison to placebo resulted in a significantly better post-operative pain management. However as against tramadol, ketorolac is a better choice as a pre-emptive analgesic agent for the post-operative pain management following third molar surgery.”
Shah <i>et al.</i> , 2016, India ¹²²	Randomized clinical trial	100 Patients undergoing elective surgery Tramadol (34%, mean 31.94 y ± 17.59) Lignocaine (40%, mean 29.86 y ± 13.58)	<ul style="list-style-type: none"> • Tramadol (50) • Lignocaine (50) 	Pain	“The study concludes that there is no significant difference between pretreatment with tramadol or lignocaine, in relieving pain caused by propofol.”
Shahid <i>et al.</i> , 2015, India ²¹⁸	Prospective randomized clinical study	60 In-patients undergoing laparotomy (gender not specified) Paracetamol (mean 33.14 y ± 5.22) Tramadol (mean 37.6 y ± 7.12)	<ul style="list-style-type: none"> • Paracetamol (30) • Tramadol (30) 	Pain relief; nausea/vomiting	"IV paracetamol is a safer alternative to tramadol with less PONV in the postoperative period, which translates into the lesser duration of hospitalization and hence earlier discharge."
Shamim <i>et al.</i> , 2006, Pakistan ¹²³	Double-blind, randomized controlled trial	60 In-patients undergoing total abdominal hysterectomy Tramadol (0%, mean 45.86 y ± 3.94) Pethidine (0%, mean 46.5 y ± 4.42)	<ul style="list-style-type: none"> • Tramadol (30) • Pethidine (30) 	Pain relief; nausea/vomiting; sedation; drug consumption; total attempts/good attempts	“Tramadol can be used as a suitable alternative to pethidine in our setup when the classical opioids are not freely available.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Shankariah <i>et al.</i> , 2012, India ¹²⁴	–	50 In-patients undergoing maxillofacial surgery Ketorolac (68%, mean 30.1 y ± 13.1) Tramadol (76%, mean 33.4 y ± 13.2)	<ul style="list-style-type: none"> • Ketorolac (25) • Tramadol (25) 	Pain; adverse events	“To conclude, intramuscular Tramadol seemed useful in controlling pain following surgery, with better levels of tolerance than intramuscular Ketorolac. However, both the drugs produced mild side effects but did not appear to influence the outcome.”
Shen <i>et al.</i> , 2008, China ¹²⁵	Randomized, follow-up, double-blind and controlled study	299 In-patients undergoing lumpectomy (gender not specified) Preemptive tramadol (mean 32 y ± 11) Preventative tramadol (mean 34 y ± 13)	<ul style="list-style-type: none"> • Preemptive tramadol (148) • Preventive tramadol (151) 	Pain at rest; overall satisfaction; morphine consumption; side effects	"In conclusion, preemptive and preventive delivery of tramadol expressed analgesia of similar efficacy up to 24 h after lumpectomy. The additional morphine requirement, the overall satisfaction and the incidence of side effects all did not display statistically significant difference between the two groups. This implies that the administration of tramadol either before the start or before the end of the surgical procedures both can produce effective postoperative analgesia in the context of a lumpectomy."
Shetty <i>et al.</i> , 2014, India ¹²⁶	Prospective study	65 In-patients in active labor requesting analgesia Tramadol (0%, mean 27.15 y ± 2.99) Pentazocine (0%, mean 26.68 y ± 3.23)	<ul style="list-style-type: none"> • Pentazocine (25) • Tramadol (40) 	Pain; maternal and neonatal side effects	“Pentazocine or tramadol can be given for labor pain relief as an alternative to epidural analgesia in resource poor setting. Further studies with multidose regimen of these analgesics are worth looking into.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Shipton <i>et al.</i> , 2003, New Zealand ¹²⁷	Double-blind, randomized, placebo-controlled study	45 Out-patients impacted mandibular third molar Tramadol (36%, mean 29 y ± 12) Placebo (26%, mean 29 y ± 13)	<ul style="list-style-type: none"> • Tramadol (22) • Placebo (23) 	Pain; cardiovascular; respiratory; and sedative effects	"Thus, this pilot study demonstrated the potential use of intravenous tramadol with propofol in day-case dento-alveolar surgery."
Shirazi <i>et al.</i> , 2015, Iran ¹²⁸	Prospective, single-blind randomized clinical trial	120 Patients with acute renal colic Tramadol (57.5%, mean 39.1 y ± 8.9) Desmopressin (62.5%, mean 38.8 y ± 7.6) Indomethacin (55%, mean 36.7 y ± 9.2)	<ul style="list-style-type: none"> • Tramadol (40) • Desmopressin (40) • Indomethacin (40) 	Pain intensity; pain relief	"According to the results of the current study, rectal indomethacin, intramuscular tramadol and intranasal desmopressin are effective and safe routes of controlling pain in acute renal colic secondary to urolithiasis. Tramadol was the most effective agent in controlling the pain."
Siddiqui and Chohan, 2007, Pakistan ²¹⁹	Prospective randomized double blind study	70 Out-patients with pregnancies 12-14 weeks undergoing dilation and evacuation procedure (0%, age not specified)	<ul style="list-style-type: none"> • Tramadol (35) • Nalbuphine (35) 	Hemodynamic parameters; postoperative recovery	"Quality of analgesia was better in nalbuphine group but both drugs provide suitable analgesic supplementation to TIVA [total intravenous anesthesia]."
Silvasti <i>et al.</i> , 2000, Finland ²⁹²	–	53 In-patients undergoing microvascular breast reconstruction (0%, range 38-64 y)	<ul style="list-style-type: none"> • Tramadol (25) • Morphine (28) 	Pain relief; side effects; respiratory status; psychomotor recovery	"In women receiving intravenous PCA for analgesia after microvascular breast reconstruction tramadol and morphine provided comparable postoperative analgesia with similar sedative effects. However, tramadol was associated with a disturbingly high incidence of nausea and vomiting."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Silvasti <i>et al.</i> , 1999, Finland ²⁹³	Prospective, randomized and double-blind study	52 In-patients undergoing maxillofacial surgery Tramadol (67%, mean 30 y ± 10) Oxycodone (60%, mean 29 y ± 10)	<ul style="list-style-type: none"> • Tramadol (27) • Oxycodone (25) 	Pain at rest and during activity (mouth opening); respiratory depression; nausea	"No respiratory depression was identified. Tramadol was found to provide adequate analgesia after maxillofacial surgery without risk of respiratory depression. However, the incidence of nausea was slightly greater in the tramadol group than in the oxycodone group."
Singh <i>et al.</i> , 2016, India ²⁶²	Randomized, double-blind, placebo-controlled study	90 Patients undergoing elective surgery Placebo (43.33%, mean 39.07 y ± 13.39) Tramadol (33.33%, mean 37.43 y ± 13.80) Butorphanol (53.33%, mean 36.23 y ± 11.88)	<ul style="list-style-type: none"> • Placebo (30) • Tramadol (30) • Butorphanol (30) 	Pain; pruritus; erythema	"Thus, we conclude that pretreatment with perioperatively used opioids tramadol 50 mg or butorphanol 1 mg effectively reduced the pain of propofol injection with fewer self-limiting mild side effects such as pruritus and erythema. Though statistical significance could not be achieved among both study drugs, we propose future studies exploring use of both tramadol and butorphanol as a pretreatment in relieving pain on propofol injection in large samples of surgical population."
Singh <i>et al.</i> , 2009, India ¹²⁹	Randomized, double blind fashion	200 Patients receiving propofol injection (gender not specified, range 18-60 y)	<ul style="list-style-type: none"> • Lignocaine (50) • Tramadol (50) • Meperidine (50) • Normal saline (50) 	Pain score change; patient satisfaction	"Lignocaine and tramadol can significantly reduce pain during propofol injection."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Soltanimohammadi and Seyedi, 2007, Iran ²⁶³	Randomized, double blind, controlled trial	<p>70 In-patients scheduled for elective surgery</p> <p>Lidocaine (54.3%, mean 28.6 y ± 5.9)</p> <p>Tramadol (51.4%, mean 28.4 y ± 5.8)</p>	<ul style="list-style-type: none"> • Lidocaine (35) • Tramadol (35) 	Postoperative pain (VAS); patient satisfaction; local reactions; nausea; vomiting	<p>"In conclusion this study showed that subcutaneous administration of tramadol provided local anesthesia equal to lidocaine, longer pain-free period after operation but more nausea in the recovery room. Since tramadol increases pain free period after operation with severe pain (flank incision) and does not increase side effects significantly, it can be used for local anesthesia instead of lidocaine. Further studies may be required for evaluating the mechanisms of local anesthetic effect of tramadol and comparing it with other local anesthetics in different operations."</p>
Stamer <i>et al.</i> , 1999, Germany ³¹⁸	Prospective, randomized, double-blinded study	<p>180 In-patients recovering from abdominal surgery (gender not specified)</p> <p>Morphine responder (mean 45.9 y ± 11.8)</p> <p>Morphine non-responder (mean 42.8 y ± 9.7)</p> <p>Tramadol responder (mean 44.1 y ± 13.3)</p> <p>Tramadol non-responder (mean 44.9 y ± 11.7)</p> <p>Placebo responder (mean 48.7 y ± 13.8)</p> <p>Placebo non-responder (mean 45.3 y ± 10.3)</p>	<ul style="list-style-type: none"> • Morphine (54) • Tramadol (54) • Placebo (53) 	Pain score change; patient satisfaction	<p>"Responders, including the 11 placebo responders, revealed similar behavior concerning pain scores and loading doses, irrespective of the treatment they received. Non-responders demonstrated significantly higher pain scores over the subsequent 23 h, although they received morphine as rescue medication. Some 89.2% of the non-responders had already been identified after the initial loading dose. This primary response to the loading dose may be useful in predicting analgesic consumption during PCA treatment and in identifying patients at risk of insufficient pain relief."</p>

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Stamer <i>et al.</i> , 1997, Germany ¹³⁰	Double-blind, randomized, placebo and active drug-controlled study	158 In-patients recovering from gynecological or abdominal surgery (gender not specified) Tramadol (mean 44.4 y ± 12.4) Morphine (mean 46.1 y ± 11.4) Placebo (mean 44.9 y ± 11.2)	<ul style="list-style-type: none"> • Tramadol (60) • Morphine (60) • Placebo (60) 	Decrease in pain intensity; patient satisfaction	"This study confirmed that effective post-operative analgesia can be achieved by tramadol administration by PCA. The incidence of side effects, especially nausea and vomiting, was comparable between the treatment groups receiving tramadol, morphine or placebo. Tramadol proved to be safe and effective for post-operative PCA treatment following abdominal and gynecological surgery."
Stankov <i>et al.</i> , 1995, Germany ²²⁰	Observer-blind, multicenter trial	100 In-patients with acute postoperative pain (gender and age not specified)	<ul style="list-style-type: none"> • Dipyrone (51) • Tramadol (49) 	Pain reduction; Sum of Pain Intensity Differences on VAS; Sum of Pain Intensity Differences on Tursky pain adjective scale; total pain relief; mood	"We conclude that dipyrone is more effective than tramadol in reducing acute postoperative pain."
Staunstrup <i>et al.</i> , 1999, Denmark ²²¹	Randomized, double-blind study	Moderate to unbearable pain following arthroscopic reconstruction of the anterior cruciate ligament using the patella bone-tendon-bone technique Lornoxicam (50%, mean 26.1 y) Tramadol (60%, mean 27.3 y)	<ul style="list-style-type: none"> • Lornoxicam (38) • Tramadol (35) 	Analgesic efficacy; use of rescue medication; patient impression of efficacy; adverse events	"Thus, intramuscular lornoxicam offers a useful alternative to tramadol for the treatment of moderate to severe postoperative pain."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Stiller <i>et al.</i> , 2007, Sweden ²²²	Randomized, double blind clinical trial	63 In-patients with osteoarthritis of the knee, selected for primary total knee arthroplasty (TKA; 47.6%, range 42-79 y)	Morphine plus: <ul style="list-style-type: none"> • Tramadol (31) • Placebo (32) 	VAS pain score after first dose and during first postoperative day	"In conclusion, this controlled clinical trial demonstrated that neither intravenous morphine by PCA nor the combination of morphine by PCA with tramadol resulted in clinically acceptable pain relief in patients with pain after TKA surgery. The search for an optimal post-operative treatment for this patient group should continue."
Su <i>et al.</i> , 2012, China ²²³	–	200 In-patients with myasthenia gravis (MG) who underwent thymectomy Flurbiprofen (53.6%, mean 31.1 y ± 11.8) Tramadol (47.8%, mean 30.3 y ± 13.1)	<ul style="list-style-type: none"> • Flurbiprofen (110) • Tramadol (90) 	VAS pain score; heart rate; blood pressure; respiratory rate; pulse oximetry; adverse events	"Thus, slow intravenous administration of flurbiprofen axetil is safe for clinical use and is not associated with respiratory inhibition."
Sudheer <i>et al.</i> , 2007, UK ²²⁴	–	60 In-patients undergoing craniotomy (58.3%, range 23-74 y)	<ul style="list-style-type: none"> • Morphine PCA (20) • Tramadol PCA (20) • Codeine phosphate (20) 	Pain score; patient satisfaction; arterial carbon dioxide tension; sedation	"In conclusion, we believe that tramadol PCA cannot be recommended as an analgesic regimen following craniotomy. Although codeine produced adequate analgesia in most patients, in three patients the pain was so poorly controlled that they withdrew from the study. Our results suggest that morphine PCA can provide superior analgesia and patient satisfaction without increasing the risk of excess sedation, vomiting or changes in ventilation when compared with codeine."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Sun <i>et al.</i> , 2014, China ¹³¹	Randomized, double-blinded, controlled, exploratory study	60 In-patients undergoing radical correction of gastric cancer Morphine (55%, mean 47 y ± 8) Tramadol (60%, mean 43 y ± 7) Tramadol plus lornoxicam (50%, mean 44 y ± 7)	<ul style="list-style-type: none"> • Morphine (20) • Tramadol (20) • Tramadol plus lornoxicam (20) 	Analgesic efficacy (VAS and Bruggemann comfort scale); serum levels of the interleukins (IL) IL-2, IL-6, and IL-10; and soluble IL-2 receptor (sIL-2R)	"In conclusion, the combination of tramadol and lornoxicam administered by PCIA can provide identical analgesic efficacy with less influence on inflammatory cytokines than morphine or tramadol alone in patients undergoing gastric cancer surgery, suggesting PCIA with tramadol combined with lornoxicam serves as a better medication to relieve postoperative pain for patients with compromised immune function."
Suriya <i>et al.</i> , 2015, India ²²⁵	Prospective study	32 In-patients with pregnancy-induced hypertension and increased umbilical blood flow (0%, age not specified)	<ul style="list-style-type: none"> • Epidural ropivacaine plus fentanyl • Intramuscular tramadol 	Doppler vascular indices; neonatal outcome	"Continuous epidural ropivacaine infusion as labor analgesia improves uteroplacental blood flow in hypertensive pregnant women with abnormal umbilical artery Doppler indices. Thus epidural analgesia is a better option in women with compromised fetuses."
Tan <i>et al.</i> , 2001, Singapore ¹³²	Prospective, randomized, double-blind study	32 In-patients undergoing upper limb surgery (gender and age not specified)	<ul style="list-style-type: none"> • Lignocaine • Lignocaine plus tramadol 	Onset of sensory and motor block; VAS score for tourniquet pain	"There is a positive trend that tramadol might improve the quality of intravenous regional anesthesia."
Tarkkila <i>et al.</i> , 1997, Finland ¹³³	Placebo-controlled, double-blind randomized study	36 In-patients undergoing minor surgery with general anesthesia Oxycodone (50%, mean 43 y ± 11) Tramadol (33.3%, mean 44 y ± 11) Placebo (16.7%, mean 42 y ± 9)	<ul style="list-style-type: none"> • Oxycodone (12) • Tramadol (12) • Placebo (12) 	Respiratory effects; inspiratory and expiratory oxygen and end tidal carbon-dioxide concentrations; tidal volume; minute volume of ventilation; respiratory rate	"We conclude that the respiratory effects of tramadol are similar to those of placebo in spontaneously breathing anesthetized patients. Equianalgesic doses of oxycodone caused significant respiratory depression compared with tramadol in this setting."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Tejashree <i>et al.</i> , 2013, India ³³⁴ Thippeswamy <i>et al.</i> , 2016, India ²²⁶	Prospective, interventional, open label, parallel group study	120 In-patients who underwent elective cesarean section Piroxicam (0%, mean 23.32 y ± 3.43) Tramadol (0%, mean 22.03 y ± 2.017) The mean ages were reversed in the abstract	<ul style="list-style-type: none"> • Piroxicam (60) • Tramadol (60) 	Severity of pain (VAS); side effects; patient satisfaction	"Thus, intra-muscular injection of piroxicam can be used as an alternative to tramadol for treating acute pain following caesarean section as it has better analgesic effect and devoid of central depressive effects of opioids."
Topal <i>et al.</i> , 2017, Turkey ¹³⁴	Double blind, prospective study	60 In-patients undergoing tonsillectomy Control (60%, mean 6.4 y ± 2) Dexamethasone (60%, mean 5.5 y ± 2.2) Tramadol (60%, mean 6.7 y ± 2.2)	<ul style="list-style-type: none"> • Control (20) • Dexamethasone (20) • Tramadol (20) 	Pain scores; nausea; vomiting	"Tramadol was found to be more effective than the dexamethasone in post-operative pain control with long-lasting relief of pain."
Torres <i>et al.</i> , 2001, Spain ²⁹⁴	Randomized, double-blind, controlled, multicenter study	151 In-patients who underwent abdominal hysterectomy (0%, age not specified)	<ul style="list-style-type: none"> • Dipyrone (73) • Tramadol (78) 	Number of boluses used; use of rescue morphine; pain intensity; pain relief; adverse events	"In summary, dipyrone and tramadol administered at maximal predetermined daily doses of 8 g and 500 mg, respectively, showed a similar efficacy for early pain relief after abdominal hysterectomy. Both treatments administered by IV maintenance infusion in addition to on-demand boluses were well tolerated, but nausea and vomiting occurred more frequently in patients administered tramadol."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Tricarico <i>et al.</i> , 2009, Italy ²²⁷	Randomized trial	91 In-patients undergoing major knee surgery (gender and age not specified)	Spinal bupivacaine plus: <ul style="list-style-type: none"> • Epidural bupivacaine and morphine (40) • Femoral peripheral nerve blockade with bupivacaine and tramadol plus IV ketorolac (51) 	Pain scores; nausea; vomiting; arterial hypotension; morphine consumption; headache; pruritus; patient satisfaction and rehabilitation indices	"Continuous femoral blockade represents the best balance between analgesia and side effects as a choice of postoperative analgesic technique for major knee surgery, especially as the risk of injury to the neuraxis is negligible. Overall, however, we believe that there is no sufficient evidence that lumbar epidural analgesia should not be used routinely."
Tuncer <i>et al.</i> , 2007, Turkey ¹³⁵	–	60 In-patients undergoing elective arthroscopic surgery of the knee End of procedure bupivacaine (25%, mean 45.4 y ± 15.6) End of procedure bupivacaine and tramadol (35%, mean 43.0 y ± 12.1) Before procedure tramadol and end of procedure bupivacaine (50%, mean 40.6 y ± 14.3)	<ul style="list-style-type: none"> • End of procedure bupivacaine (20) • End of procedure bupivacaine and tramadol (20) • Before procedure tramadol and end of procedure bupivacaine (20) 	Analgesic duration; total analgesic consumption; postoperative VAS pain scores; patient satisfaction	"In conclusion, preemptive ia tramadol provided effective and reliable pain control after arthroscopic knee surgeries and may be preferred to postoperative administration."
Turker <i>et al.</i> , 2005, Turkey ¹³⁶	Prospective, randomized, double-blind, clinical study	40 In-patients undergoing elective muscle-sparing thoracotomy Tramadol (66.7%, mean 56 y ± 15) Morphine (73.7%, mean 58 y ± 16)	<ul style="list-style-type: none"> • Tramadol (20) • Morphine (20) 	Analgesia onset time; duration of analgesia; pain scores at rest and during coughing; sedation scores	"The findings suggest that tramadol is a safe alternative to morphine for lumbar epidural analgesia in thoracic surgery patients."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Tuzuner <i>et al.</i> , 2007, Turkey ²⁶⁴	–	36 In-patients undergoing orthognathic surgery (69.4%, range 17-23 y)	<ul style="list-style-type: none"> • Tramadol (12) • Diclofenac sodium (12) • Placebo (12) 	Postoperative pain intensity; postoperative opioid consumption; hemodynamic variables; postoperative complications	“There is no significant difference between tramadol and diclofenac with regard to analgesic effectiveness and adverse effect profile; however, studies comprising more patients with different regimens are required.”
Ugur <i>et al.</i> , 2013, Turkey ¹³⁷	Prospective randomized double-blind controlled study	<p>75 In-patients undergoing adenotonsillectomy</p> <p>Tramadol (76%, mean 5.2 y ± 1.6)</p> <p>Ketamine (36%, mean 5.4 y ± 1.7)</p> <p>Control (68%, mean 5.2 y ± 1.6)</p>	<ul style="list-style-type: none"> • Tramadol (25) • Ketamine (25) • Control (25) 	<p>Pain; during operation heart rate; oxygen saturation; average mean blood pressures.</p> <p>Operation; anesthesia and the time that Alderete scores 9–10; patient satisfaction; analgesic requirements.</p> <p>Postoperatively nausea; vomiting; sedation; dysphagia; bleeding scores</p>	“We concluded that preincisional injection of ketamine and tramadol prior to tonsillectomy is safe, effective method and equivalent for post-tonsillectomy pain, patient satisfaction, postoperative nausea, vomiting, and dysphagia.”
Ugur <i>et al.</i> , 2008, Turkey ¹³⁸	Double blind, randomized, placebo-controlled clinical trial	<p>45 In-patients undergoing tonsillectomy</p> <p>Infiltration (66.7%, mean 8.4 y ± 1.6)</p> <p>IM (60%, mean 8.2 y ± 1.7)</p> <p>Placebo (60%, mean 8.5 y ± 2.1)</p>	<ul style="list-style-type: none"> • Peritonsillar injection of tramadol with epinephrine (15) • IM tramadol (15) • Placebo (15) 	VAS pain; heart rate; mean arterial pressure	“Peritonsillar infiltration with tramadol provided good intraoperative analgesia, less postoperative pain on awakening and lower analgesic requirement within the first hour after surgery.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Umuroğlu <i>et al.</i> , 2004, Turkey ²²⁸	Randomized, prospective, double-blind and placebo-controlled	<p>60 In-patients undergoing adenotonsillectomy</p> <p>Ketamine (66.7%, mean 6.9 y ± 2.1)</p> <p>Morphine (40%, mean 7.13 y ± 2.51)</p> <p>Tramadol (53.3%, mean 6.06 y ± 2.51)</p> <p>Placebo (53.3%, mean 6.96 y ± 2.08)</p>	<ul style="list-style-type: none"> • Ketamine (15) • Morphine (15) • Tramadol (15) • Placebo (15) 	Postoperative analgesia requirements; pain; side effects	“Morphine hydrochloride 0.1 mg*kg-1 i.v. administered during induction of anesthesia provides efficient pain relief in children undergoing adenotonsillectomy.”
Ünlügenç <i>et al.</i> , 2002, Turkey ³¹⁹	Double-blind randomized study	<p>66 Patients undergoing major abdominal surgery</p> <p>Tramadol (62%, mean 47 y ± 2)</p> <p>Tramadol and magnesium (52%, mean 48 y ± 2)</p> <p>Tramadol and ketamine (59%, mean 48 y ± 4)</p>	<ul style="list-style-type: none"> • Tramadol only (21) • Tramadol + magnesium (23) • Tramadol + ketamine (22) 	Discomfort; sedation; pain scores; total and bolus PCA tramadol consumption; side effects	"In conclusion, adding magnesium or ketamine to tramadol gave better analgesia, good patient comfort and a decrease in bolus dose requirement for post-operative pain management after major abdominal surgery. The most probable explanation for our findings is that ketamine possibly exerts a synergistic interaction between tramadol and NMDA [N-methyl-D-aspartate] antagonists. Magnesium too may have a synergistic interaction via NMDA antagonists and/or by preventing hypomagnesemia. Further research is likely to be needed to support this relationship."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Unlugenc <i>et al.</i> , 2009, Turkey ³²⁰	Prospective, double blind, controlled study	133 In-patients undergoing major abdominal surgery (gender and age not specified)	<ul style="list-style-type: none"> • Morphine (not reported) • Morphine plus remifentanil (not reported) • Tramadol (not reported) • Tramadol plus remifentanil (not reported) 	Discomfort; sedation; pain scores; side effects; and total and bolus tramadol and morphine consumption	"After major abdominal surgery, adding remifentanil to PCA tramadol resulted in better pain scores, lower analgesic consumption, and fewer side effects compared to tramadol alone. However, the addition of remifentanil to morphine did not improve analgesic outcomes."
Unlugenc <i>et al.</i> , 2008, Turkey ³²¹	Double-blind, controlled, randomized trial	62 In-patients undergoing major abdominal surgery (12.9%, range 47.0-55.7 y)	<ul style="list-style-type: none"> • Tramadol (32) • Tramadol plus remifentanil (30) 	Discomfort; sedation; pain scores; side effects; and total and bolus tramadol consumption	"In conclusion, after major abdominal surgery, adding remifentanil (0.2µg kg-1) to tramadol (0.2 mg kg-1), with 10-min lockout times, for PCA provided better analgesia and patient comfort without causing any sedation or respiratory depression. The most likely explanation for our findings includes summation of analgesia and synergistic interaction between remifentanil and tramadol. Further studies are required to clarify the analgesic efficacy and relative safety of remifentanil addition to PCA tramadol and to explore the possible additive or synergistic effects of combination therapy with other drugs."
Unlugenc <i>et al.</i> , 2008, Turkey ¹³⁹	Prospective, randomized, double-blind study	126 In-patients undergoing abdominal hysterectomy Morphine (0%, mean 50 y ± 11) Pethidine (0%, mean 47.2 y ± 13.1) Tramadol (0%, mean 46.4 y ± 8.3)	<ul style="list-style-type: none"> • Morphine (42) • Pethidine (42) • Tramadol (42) 	Cumulative analgesic consumption, supplementary fentanyl dose, hemodynamic variables	"In conclusion, in patients who underwent abdominal hysterectomy, morphine, pethidine, and tramadol administration resulted in equivalent pain scores and side effects, but group T [tramadol] required more rescue analgesic doses of fentanyl. However, tramadol might be indicated in patients for whom morphine and pethidine are contraindicated."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Uzun <i>et al.</i> , 2010, Turkey ²⁶⁵	-	68 Patients undergoing vaso-occlusive sickle cell pain crisis Meperidine (76%, mean 24.9 y ± 6.45) Tramadol (68%, mean 24.8 y ± 5.8)	<ul style="list-style-type: none"> • Meperidine (34) • Tramadol (34) 	Hemodynamic parameters, pain intensity, pain relief, sedation	"The results of our study demonstrated that either meperidine or tramadol is useful for initial ED treatment in patients with severe acute sickle cell pain crisis. Avoiding meperidine injections as recommended with previous guidelines needs to be carefully considered especially when low doses are mentioned. Rather than totally abandoning meperidine use, a combined approach involving a shift from meperidine to morphine derivatives may be considered as an option in patients with a severe and a long-lasting crisis. More controlled trials are needed to compare the safety and efficacy of these agents in management of acute sickle cell painful crisis."
Vahabi and Akhlaghi, 2011, Iran ³³⁵ Vahabi <i>et al.</i> , 2011, Iran ¹⁴⁰	-	70 Out-patients undergoing minor surgery (gender not specified, range 20-50 y)	<ul style="list-style-type: none"> • Tramadol (35) • Lidocaine (35) 	Pain scores; nausea; need for additional analgesic	"Tramadol 2mg/kg has local anesthetic and post-operative analgesic effect equal to lidocaine 1 mg/kg in minor surgeries performed subcutaneously. Therefore, we concluded that tramadol can be used as an alternative drug to lidocaine in local anesthesia and has the ability to decrease the demand for post operative analgesics."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Van Den Berg <i>et al.</i> , 1999, Saudi Arabia ²⁶⁶	Prospective, double-blind, randomized, controlled study	152 Patients undergoing tonsillectomy Saline (68%, mean 13 y ± 15) Tramadol (54%, mean 14 y ± 15) Pethidine (68.5%, mean 16 y ± 14) Nalbuphine (59%, mean 15 y ± 14)	<ul style="list-style-type: none"> • Saline (37) • Tramadol (38) • Pethidine (38) • Nalbuphine (39) 	Hemodynamic variables; time to recovery of spontaneous respiration; time to awakening; sedation; emesis	"In conclusion, these data reveal that tramadol 3 mg/kg given with induction of anesthesia confers little anti-nociceptive benefit during surgery but improves recovery conditions, whereas pethidine 1.5 mg/kg and nalbuphine 0.3 mg/kg are effective. These data suggest that the dose of tramadol may be inadequate and suggests the need for a dose-response study."
Verchère <i>et al.</i> , 2002, France ²²⁹	Randomized, blind, controlled study	64 In-patients undergoing supratentorial craniotomy Paracetamol (62.5%, mean 50 y ± 7) Paracetamol plus tramadol (38%, mean 48.8 y ± 15) Paracetamol plus nalbuphine (48%, mean 45 y ± 18)	<ul style="list-style-type: none"> • Paracetamol plus tramadol (29) • Paracetamol plus nalbuphine (27) • Paracetamol only (8) 	Pain scores; adverse effects	"In conclusion, postoperative pain in neurosurgical patients undergoing supratentorial craniotomy with remifentanyl cannot be managed with paracetamol alone. Addition of tramadol or nalbuphine allows the patient to maintain VAS scores less than 30 mm. However, this objective is fulfilled more rapidly and for a longer period with nalbuphine. In all patients, nausea and vomiting are a matter of concern and must be prevented and/or treated as well as pain."
Vimesh <i>et al.</i> , 2019, India ¹⁴¹	Prospective, double-blind, randomized study	63 In-patients undergoing thoracotomy (gender and age not specified)	<ul style="list-style-type: none"> • 1 mg/kg tramadol (21) • 2 mg/kg tramadol (21) • 3 mg/kg tramadol (21) 	Onset and duration of analgesia; side effects	"It is concluded that 2 mg/kg body weight thoracic epidural Tramadol is optimum dose for postoperative analgesia without significant side effects and in dose 3 mg/kg body weight, can be used with appropriate anti-emetics to reduce the incidence of nausea and vomiting."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Wahdan and Seleem., 2017, Egypt ¹⁴²	Double-blind, randomized prospective study	120 Patients undergoing hernioplasty Control (100%, mean 44 y ± 7.8) Bupivacaine (100%, mean 43 y ± 7.1) Tramadol (100%, mean 43.1 y ± 8.1)	<ul style="list-style-type: none"> Control (40) Bupivacaine (40) Tramadol (40) 	Postoperative pain score; time to first analgesic requirement; total meperidine consumption	"Our study concludes that an improved intra-operative and postoperative pain relief is provided by locally infiltrated tramadol in inguinal canal as well as incision line for hernia surgery under general anesthesia as compared to bupivacaine 0.25%, thus decreasing the need of postoperative analgesic agents and consequently reducing the side effects associated with narcotics."
Wali <i>et al.</i> , 2012, Pakistan ³²⁶ Wali <i>et al.</i> , 2014, Pakistan ¹⁴³	Double blind randomized trial	231 In-patients in active labor Tramadol (0%, mean 25.2 y ± 4.3) Pentazocine (0%, mean 24.5 y ± 4.4)	<ul style="list-style-type: none"> Tramadol (114) Pentazocine (117) 	Maternal vital signs; nausea/vomiting; sedation; duration of labor; mode of delivery; Apgar scores; neonatal intensive care unit (NICU) admissions; need for naloxone	"Tramadol and Pentazocine were found to be safe and equally effective for labor analgesia with comparable maternal and neonatal outcomes. So, either drug can be used for analgesia and labor."
Wang <i>et al.</i> , 2009, China ¹⁴⁴	Double-blind, randomized controlled trial	189 In-patients undergoing hysterectomy Saline (0%, mean 44 y ± 9) Tramadol (0%, mean 43 y ± 6)	Postoperative tramadol infusion and morphine PCA with preoperative: <ul style="list-style-type: none"> Saline (95) Tramadol (94) 	Pain at rest and during movement;	"In conclusion, bolus premedication of tramadol (100 mg) combined with the postoperative continuous small-dose iv infusion of tramadol adjunct to standard morphine PCA after total abdominal hysterectomy highlighted a superior analgesic effect, fewer incidence of side effects, higher satisfaction ratings, and less morphine consumption than the same analgesic regimen that omitted the preemptive tramadol."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Wang <i>et al.</i> , 2005, China ¹⁴⁵	Randomized, double-blinded, placebo-controlled study	40 In-patients with lung cancer undergoing pulmonary lobectomy Tramadol (85%, mean 52.7 y ± 9.9) Saline (80%, mean 56.6 y ± 7.6)	<ul style="list-style-type: none"> • Tramadol (20) • Saline (20) 	IL-6 and IL-10 levels	"IV infusion of tramadol does not seem to alter IL-6/IL-10 cytokine response to pulmonary lobectomy. Tramadol was associated with increased IL-2 levels and delayed enhancement of sIL-2R, suggesting that it may attenuate, to some extent, an impaired immune response in pulmonary lobectomy and may have a beneficial role in immunomodulation after surgery in cancer patients."
Wang <i>et al.</i> , 2016, China ¹⁴⁶	–	57 Patients undergoing transurethral prostate resection Flurbiprofen and tramadol (100%, mean 65.8 y ± 8.6) Control (100%, mean 68.6 y ± 9.1)	<ul style="list-style-type: none"> • Flurbiprofen and tramadol (29) • Control (28) 	Characteristics of spinal anesthesia; blood pressure; heart rate; analgesic requirement; pain scores; overall satisfaction	"We conclude that preoperative administration of flurbiprofen axetil and tramadol can prolong time to the first analgesic requirement without an influence on motor blockade. It is possible that preoperative flurbiprofen axetil and tramadol provide these benefits by blunting pain perception, so motor block is not affected."
Wiebalck <i>et al.</i> , 2000, Germany ¹⁴⁷	Prospective, double-blind, randomized study	20 Patients experiencing severe postoperative pain Tramadol (80%, mean 39.6 y ± 12.56) Morphine (90%, mean 49 y ± 21.88)	<ul style="list-style-type: none"> • Tramadol (10) • Morphine (10) 	Pain intensity; side effects	"Both tramadol and morphine reduce extremely severe postoperative pain successfully. However, higher drug dosages than usually administered are necessary. Tramadol patients presented with no severe side effects. In contrast, in the morphine group, one patient each presented with severe sedation and respiratory depression. Tramadol may therefore have an advantage over morphine in patients with severe postoperative pain."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Wilder-Smith <i>et al.</i> , 1999, Switzerland ²⁹⁵	Randomized, double-blinded, prospective study	50 In-patients undergoing abdominal surgery (gender not specified) Morphine (mean 45 y ± 8) Tramadol (mean 46 y ± 9)	<ul style="list-style-type: none"> • Morphine (25) • Tramadol (25) 	Pain intensity; pain tolerance; gastric emptying; motility and sensory parameters	"In conclusion, pain control with morphine and tramadol infusions was very effective. During morphine and tramadol infusions, pain tolerance thresholds as markers of antinociception were increased. The significant sensitization seen only after morphine discontinuation may be due to convergent visceral input. Gut motility was prolonged significantly by visceral surgery itself and also by morphine."
Wilder-Smith <i>et al.</i> , 1998, Switzerland ²³⁰	Double-blind, randomized, placebo-controlled 5-day trial	40 In-patients scheduled for elective knee or hip replacement Tramadol 20 mg (30%, mean 53 y ± 20) Tramadol 50 mg (40%, mean 64 y ± 11) Tramadol 100 mg (60%, mean 62 y ± 16) Placebo (50%, mean 63 y ± 14)	<ul style="list-style-type: none"> • Tramadol 20 mg (10) • Tramadol 50 mg (10) • Tramadol 100 mg (10) • Placebo (10) 	Pain scores; time to first PCA use; total use and duration of PCA; side effects	"In conclusion, the preoperative adjuvant epidural use of tramadol did not improve clinical measures of postoperative analgesia. Low-dose tramadol resulted in anti-analgesia and was associated with more post-operative side-effects. Only tramadol 100 mg depressed perioperative pain processing, but this was not reflected in better clinical pain parameters in our study."
Wong and Cheong, 2001, Singapore ²⁶⁷	Randomized, double-blind study	90 Patients undergoing surgery Placebo (47%, mean 39.3 y ± 15.8) Tramadol (50%, mean 37.4 y ± 15.1) Lignocaine (57%, mean 36.2 y ± 12.9)	<ul style="list-style-type: none"> • Placebo (30) • Tramadol (30) • Lignocaine (30) 	Injection pain	"In conclusion, we have found tramadol to have a peripheral site of action and it is as effective as lignocaine in reducing the incidence and severity of pain on propofol injection. Further studies with different doses of tramadol may be useful to determine if there is a dose-dependent effect on the incidence and severity of pain on propofol injections as well as perioperative pain relief."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Wyles <i>et al.</i> , 2010, UK ²³¹	–	32 Patients undergoing a sleeve gastrectomy or gastric bypass (gender and age not specified)	<ul style="list-style-type: none"> • IV tramadol (16): <ul style="list-style-type: none"> ○ Post sleeve (8) ○ Post bypass (8) • Sublingual tramadol group (16) <ul style="list-style-type: none"> ○ Post sleeve (5) ○ Post bypass (11) 	Pain score via a visual analogue score both as rest and at movement before and analgesia	"This study shows that sub-lingual Zamadol [tramadol] is as effective as IV Tramadol as post-operative analgesia for the post-operative bariatric patient. It should be considered as a valuable alternative, as not only is it significantly cheaper and increases patient comfort without additional needle pricks, but also it can be taken without water, and can minimize potential topical infections or serious drug errors and clinical incidents associated with the IV route."
Xu <i>et al.</i> , 2013, China ²³²	Randomized controlled, double-blind trial	<p>99 In-patients scheduled for elective major abdominal surgery</p> <p>Parecoxib and control (67.9%, mean 45.7 y ± 14.7)</p> <p>Parecoxib and celecoxib (42.9%, mean 41.6 y ± 11.2)</p> <p>Tramadol and control (42.9 %, mean 41.6 y ± 11.2)</p> <p>Tramadol and tramadol (35.7%, mean 48.7 y ± 14.5)</p>	<p>First 3 days after surgery of first medication via IV followed by 4 days of the second medication via oral route:</p> <ul style="list-style-type: none"> • Parecoxib plus control (25) • Parecoxib plus celecoxib (24) • Tramadol plus control (24) • Tramadol plus tramadol (26) 	Measured resting energy expenditure	"In addition, intravenous parecoxib (IV 40 mg bid) followed by oral celecoxib (PO 0.2 g bid) is as effective as intravenous tramadol (IV 0.1 g tid) with continued oral tramadol (PO 0.1 g tid). Considering the potential little gastrointestinal adverse effects of tramadol and the beneficial effects on inflammation of COX-2 selective inhibitor, parecoxib followed by oral celecoxib seems to be an attractive option after abdominal surgery."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Yarramalle <i>et al.</i> , 2018, India ³²²	Randomized prospective study	50 In-patients with various organ involvements requiring analgesia Tramadol plus ondansetron (44%, mean 44.2 y ± 9.88) Tramadol (60%, mean 44.72 y ± 8.97)	<ul style="list-style-type: none"> • Tramadol plus ondansetron (25) • Tramadol (25) 	Hemodynamic parameters along with pain assessment using Verbal Rating Scale (VRS); analgesic efficacy; side effects	"We conclude that co-administration of ondansetron with tramadol can be practiced in medical ICU patients with lesser doses without any side effects such as nausea, vomiting, and sedation. More number of studies with large study population along with the determination of plasma concentrations of O-demethyltramadol is required before a conclusion can be elucidated."
Yektas <i>et al.</i> , 2014, Turkey ³³⁶ Yektas <i>et al.</i> , 2016, Turkey ¹⁴⁸	–	60 Patients undergoing hand surgery Lidocaine plus IVRA tramadol (45%, mean 36.55 y ± 11.82) Lidocaine plus systemic tramadol (70%, mean 41.65 y ± 12.47) Lidocaine (65%, mean 44.1 y ± 13.09)	<ul style="list-style-type: none"> • Lidocaine plus IVRA tramadol (20) • Lidocaine plus systemic tramadol (20) • Lidocaine-only (20) 	Onset and duration of anesthesia; analgesic requirement	"In conclusion, administration of tramadol as an adjunct showed some clinical benefits by providing a shorter onset time of sensory and motor block, decreasing pain and analgesic requirement, and improving intraoperative conditions during IVRA."
Yenigun <i>et al.</i> , 2015, Turkey ²³³	Randomized controlled study	120 Patients undergoing tonsillectomy (56.6%) Peritonsillar ketamine (mean 7.4 y ± 3.2) Rectal ketamine (mean 7.23 y ± 1.92) IV ketamine (mean 7.67 y ± 2.59) IV tramadol (mean 6.25 y ± 1.96)	<ul style="list-style-type: none"> • Peritonsillar ketamine (30) • Rectal ketamine (30) • IV ketamine (30) • IV tramadol (30) 	Pain scores; sedation	"Ketamine and tramadol hydrochloride were found to be equally effective in terms of sedation scoring, and no complications developed. It is seen as an advantage that ketamine can be administered in different routes at analgesic dosage and has a low incidence of adverse effects. Ketamine is considered as an alternative for administration to postoperative analgesic drugs such as the opioids, nonopioids, and nonsteroidal anti-inflammatory drugs."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Yilmaz <i>et al.</i> , 2015, Turkey ¹⁴⁹	Randomized prospective study	60 In-patients undergoing lumbar disc surgery (gender not specified) Paracetamol (mean 48.1 y ± 14.1) Tramadol (mean 43.8 y ± 9.8)	<ul style="list-style-type: none"> • Paracetamol (30) • Tramadol (30) 	Hemodynamic parameters; sedation; patient satisfaction; pain scores; nausea/vomiting; need and time to additional analgesic	"Paracetamol alone was not able to provide effective analgesia, and tramadol was more effective in the treatment of postoperative pain after lumbar disc surgery."
Yousef, 2009, Egypt ¹⁵⁰ Yousef, 2010, Egypt ³³⁷	–	80 Patients undergoing open thoracotomy (gender and age not specified)	<ul style="list-style-type: none"> • Epidural morphine (20) • Epidural tramadol (20) • IV morphine (20) • IV tramadol (20) 	Pain scores; stress response; nausea/vomiting	"Tramadol when used in proper dose provides adequate analgesia in post-thoracotomy pain without the adverse effects associated with morphine infusion."
Zahedi <i>et al.</i> , 2012, Iran ²³⁴	Randomized prospective double-blinded and placebo-controlled study	135 Patients undergoing elective eye surgery (60%, range 16-80 y)	<ul style="list-style-type: none"> • Tramadol (45) • Ondansetron (45) • Saline (45) 	Incidence and severity of pain	"In conclusion, ondansetron pretreatment provides a simple and safe method of reducing propofol injection pain with the advantage of preventing PONV and avoiding the administration of other drugs that may be undesirable in certain circumstances."
Zeidan <i>et al.</i> , 2008, Lebanon ¹⁵¹	Prospective, randomized, double-blind study	90 Patients undergoing elective arthroscopy Bupivacaine (57%, mean 34 y ± 11) Tramadol (53%, mean 32.9 y ± 10.4) Bupivacaine and tramadol (50%, mean 36.6 y ± 11.6)	<ul style="list-style-type: none"> • Bupivacaine (30) • Tramadol (30) • Bupivacaine plus tramadol (30) 	Pain scores; duration of analgesia; rescue analgesic consumption; time to ambulation; time to discharge; side effects	"The IA admixture of tramadol 100 mg with bupivacaine 0.25% provides a pronounced prolongation of analgesia compared with either drug alone in patients undergoing day care arthroscopic knee surgery."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Zheng <i>et al.</i> , 2015, China ²³⁵	Prospectively randomized	30 Pediatric in-patients undergoing costal cartilage harvest (gender and age not specified)	<ul style="list-style-type: none"> • Intercostal nerve block (15) • IV tramadol (15) 	Pain scores; time to first rescue analgesia; side effects	"Ultrasound-guided intercostal nerve block after Costal cartilage harvest with 2 ml 0.25% ropivacaine each intercostal provided efficient analgesia in pediatrics."

Abbreviations: “–”, not mentioned; ABG, arterial blood gas; ACL, anterior cruciate ligament; AP, acute pancreatitis; AUC, area under the curve; BIS, bispectral index; CABG, coronary artery bypass graft; CDH, chronic daily headaches; CNS, central nervous system; CPB, continuous paravertebral block; CPP, cerebral perfusion pressure; CRO, controlled-release oxycodone; CRP, C-reactive protein; ED, emergency department; ESP, erector spinae plane; ESWL, extracorporeal shockwave lithotripsy; GA, general anesthesia; GAN, greater auricular nerve; HANS, Han’s Acupoint nerve stimulator; HSG, hysterosalpingography; IA, intra-articular; ICP, intracranial pressure; ICU, intensive care unit; IL, interleukin; IM, intramuscular; IP, intraperitoneal; IT, intrathecal; ITM, intrathecal morphine; IV, intravenous; IVRA, intravenous regional anesthesia; LC, laparoscopic cholecystectomy; MAP, mean arterial pressure; MG, myasthenia gravis; NDPH, new daily persistent headaches; NICU, neonatal intensive care unit; NRS, numeric rating scale; NSAID, nonsteroidal anti-inflammatory drug; PACU, postoperative care unit; PCA, patient-controlled analgesia; PCEA, patient-controlled epidural analgesia; PCIA, patient-controlled intravenous analgesia; PCNL, percutaneous nephrolithotomy; PONV, postoperative nausea and vomiting; PMPS, post mastectomy pain syndrome; PVB, paravertebral block; QoR, quality of postoperative recovery; RCT, randomized controlled trial; SA, spinal anesthesia; SC, subcutaneous; SAPB, serratus anterior plane block; SCP, superficial cervical plexus; SCD, sickle cell disease; sIL-2R, soluble IL-2 receptor; SWL, shockwave lithotripsy; TAP, transversus abdominis plane; TRUS, transrectal ultrasonography; TRUSP, transrectal ultrasound-guided biopsy of the prostate; TFEI, transforaminal epidural injection; TIVA, total intravenous anesthesia; TKA, total knee arthroplasty; TNF- α , tumor necrosis factor- α ; VAPS, visual analogue pain scale; VAS, visual analogue scale; VATS, video-assisted thoracoscopic surgery; VOC, vaso-occlusive crisis.

^aAs defined by authors.

Appendix 3.1. Survey instrument for professional medical associations

Welcome. We want to understand your clinical use of compounded tramadol hydrochloride. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

If you have additional questions or concerns about this study, please email:
compounding@rx.umaryland.edu.

If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Thank you,

Dr. Ashlee Mattingly
Principal Investigator
The University of Maryland School of Pharmacy

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

2. Do you prescribe or administer tramadol hydrochloride to your patients?

- Yes
- No

3. Do you prescribe or administer tramadol hydrochloride by any of the following dosage forms and/or routes of administration? (check all that apply)

- Solution for injection
- None of the above

4. I prescribe or administer tramadol hydrochloride for the following conditions or diseases: (check all that apply)

- Moderate to severe pain
- Other (please explain) _____

5. I use compounded tramadol hydrochloride because: (check all that apply)
- Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
 - Patient allergies prevent me from using commercially available products. (please explain) _____
 - Patient conditions prevent me from using commercially available products. (please explain) _____
 - There are no commercially available products containing tramadol hydrochloride.
 - Other (please explain) _____
6. Do you stock non-patient-specific compounded tramadol hydrochloride at your practice?
- Yes
 - No
 - I'm not sure
7. I obtain compounded tramadol hydrochloride from the following: (check all that apply)
- Compound myself at my practice
 - Have the product compounded by an in-house pharmacy
 - Purchase, or have a patient purchase, from a compounding pharmacy
 - Purchase, or have a patient purchase, from an outsourcing facility
 - Other (please explain) _____
8. What is your practice setting? (check all that apply)
- Physician office/private practice
 - Outpatient clinic
 - Hospital/health system
 - Academic medical center
 - Emergency room
 - Operating room
 - Other (please describe) _____
9. What degree do you hold? (check all that apply)
- Doctor of Medicine (MD)
 - Doctor of Osteopathic Medicine (DO)
 - Doctor of Medicine in Dentistry (DMD/DDS)
 - Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
 - Naturopathic Doctor (ND)
 - Nurse Practitioner (NP)
 - Physician Assistant (PA)
 - Other (please describe) _____

Appendix 3.2. Survey instrument for Ambulatory Surgery Center Association

Welcome. We want to understand your clinical use of compounded drugs. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in bulk compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

If you have additional questions or concerns about this study, please email:
compounding@rx.umaryland.edu.

If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Thank you,

Dr. Ashlee Mattingly
Principal Investigator
The University of Maryland School of Pharmacy

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

2. Do you utilize a 503B outsourcing facility to acquire compounded drugs?

- Yes. If yes, why? _____
- No. If no, why not? _____

3. Do you obtain any of the following products from a 503B outsourcing facility? (check all that apply)

- I do not obtain any compounded drugs from 503B outsourcing facilities
- Amitriptyline / Ketoprofen / Oxymetazoline
- Budesonide
- Calcium gluconate
- Droperidol
- Epinephrine
- Epinephrine for ophthalmic administration
- Epinephrine / Lidocaine for ophthalmic administration
- Epinephrine / Bupivacaine / Fentanyl
- Fentanyl
- Flurbiprofen
- Flurbiprofen for ophthalmic administration
- Hydromorphone
- Ipamorelin
- Ketoprofen / Nifedipine
- Lidocaine / Epinephrine / Tetracaine HCl
- Meperidine
- Morphine
- Naloxone
- Neomycin
- Phentolamine
- Promethazine

- Remifentanyl
- Sufentanyl
- Tramadol
- None of the above

4. What type of specialty procedures are performed in your facility? (check all that apply)

- Dental
- Dermatology
- Endoscopy
- Neurosurgery
- Obstetrics/gynecology
- Ophthalmology
- Otolaryngology
- Orthopedics
- Pain
- Plastics
- Podiatry
- Other (please describe) _____

Appendix 4. Survey distribution to professional associations

Specialty	Association^a	Agreed/Declined, Reason for Declining
Allergy/Immunology	American Academy of Allergy, Asthma, and Immunology (AAAAI)	Declined – survey not approved
Anesthesiology	American Society of Regional Anesthesia and Pain Medicine (ASRA)	Declined – failed to respond
	Society for Ambulatory Anesthesia (SAMBA)	Declined – failed to respond
	Society for Neuroscience in Anesthesiology and Critical Care	Declined – failed to respond
Critical Care	Critical Care Societies Collaborative	Declined – failed to respond
Dentistry & Oral Medicine	Academy of General Dentistry (AGD)	Declined – provided interview referrals
	American Dental Association (ADA)	Declined – failed to respond
Dermatology	American Academy of Dermatology (AAD)	Agreed
	American Osteopathic College of Dermatology (AOCD)	Declined – not interested
Endocrinology	The Endocrine Society (ENDO)	Agreed
	Pediatric Endocrine Society	Agreed
Gastroenterology	American Gastroenterological Association (AGA)	Declined – failed to respond
	Obesity Medicine Association (OMA)	Declined – did not have anyone to contribute to research
Hematology	American Society of Hematology (ASH)	Declined – does not distribute surveys
Infectious Disease	American Academy of HIV Medicine (AAHIVM)	Declined – failed to respond
Medicine	American Medical Association (AMA)	Declined – failed to respond

Naturopathy	American Association of Naturopathic Physicians (AANP)	Agreed
	The Oncology Association of Naturopathic Physicians (OncANP)	Agreed
Nephrology	American College of Clinical Pharmacists: Nephrology Practice Network	Agreed
	American Society of Nephrology (ASN)	Declined – provided interview referrals
Nutrition	American Society for Parenteral and Enteral Nutrition (ASPEN)	Declined – provided interview referrals
Obstetrics and Gynecology	American Gynecological and Obstetrical Society (AGOS)	Declined – failed to respond
	Nurse Practitioners in Women’s Health	Agreed
Ophthalmology	American Academy of Ophthalmology (AAO)	Agreed
Otolaryngology	American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS)	Declined – survey not approved
Pain Management	American Academy of Pain Medicine (AAPM)	Declined – survey not approved
	American Academy of Physical Medicine and Rehabilitation	Declined – failed to respond
Pediatrics and Neonatology	American Academy of Pediatrics (AAP)	Agreed
Primary Care	American College of Physicians (ACP)	Declined – failed to respond
Psychiatry	American Academy of Clinical Psychiatrists	Declined – failed to respond
	American Association for Geriatric Psychiatry	Declined – failed to respond
Rheumatology	American College of Rheumatology (ACR)	Agreed

Surgery	Ambulatory Surgery Center Association (ASCA)	Agreed
	American Academy of Orthopaedic Surgeons (AAOS)	Declined – no interest in participation from members
	American Association of Hip and Knee Surgeons (AAHKS)	Declined – only send surveys from members
	American College of Surgeons (ACS)	Agreed
	American Society for Metabolic and Bariatric Surgery (AMBS)	Declined – only send surveys from members
	The Association of Bone and Joint Surgeons	Declined – failed to respond
	Physician Assistants in Orthopaedic Surgery	Declined – failed to respond
	Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)	Declined – failed to respond
	Society of Gynecologic Surgeons (SGS)	Declined – policy limits number of surveys per year and do not have a method to identify if any of the SGS members are using ipamorelin
Toxicology	American Academy of Environmental Medicine (AAEM)	Declined – failed to respond
Urology	Sexual Medicine Society of North America (SMSNA)	Agreed

^aAssociations that declined in Year 1 were not contacted in Year 2.