Anna Dizner-Golab[1], Dariusz Kosson[1, 2], Barbara Lisowska[3]

[1]1st Department of Anesthesiology and Intensive Care, Medical University of Warsaw, Poland
[2]Department of Anesthesiology and Intensive Care Education, Faculty of Health Sciences, Medical University of Warsaw, Poland
[3]Anaesthesiology Department, Carolina Medical Centre, Warsaw, Poland

Metamizole (dipyrone) for multimodal analgesia in postoperative pain in adults

Abstract

Background: Metamizole (dipyrone) is a non-opioid analgesic used in perioperative analgesia in some countries. The drug has analgesic, antipyretic, and spasmolytic effects. The complex mechanism has not been fully explained yet. Presumably, the analgesic effect is based on the inhibition of the activity of COX-1 and COX-2 cyclooxygenases and prostaglandin synthesis. Moreover, the activation of the opioidergic, cannabinoid, and endovanilloid systems also plays an important role. Metamizole is a relatively safe analgesic, although it is not completely free of adverse effects. Among them, the most serious and controversial are myelotoxicity, idiosyncratic drug-induced liver injury (DILI), and allergic reactions. The aim and objective is to present data on the use of metamizole for treating acute postoperative pain in adults.

Methods: The search, which included PubMed/Medline, Web of Science, and Scopus databases, has been performed to find information about the use of metamizole in perioperative pain management.

Results: The data on the role of metamizole in perioperative pain management seems to be insufficient. Moreover, most studies concerning the use of metamizole focus on postoperative administration regimens. The use of metamizole in preventive and multimodal analgesia is represented by sparse or controversial data.

Conclusions: There is some evidence in the literature of the effectiveness of metamizole in the treatment of postoperative pain. Moreover, experience based on clinical practice indicates the high usefulness of metamizole as a perioperative analgesic. Thus metamizole could be considered an important part of multimodal analgesia. Although this drug could be a dominant component of multimodal analgesia, its use is limited by the occurrence of serious adverse reactions. Therefore, special precautions should be taken when using it. However, there is a need for further research, especially to determine its effectiveness in multimodal and preventive analgesia regimens.

Palliat Med Pract

Keywords: metamizole (dipyrone), preventive/preemptive analgesia, postoperative pain, multimodal analgesia

Address for correspondence:
Anna Dizner-Golab
1st Department of Anesthesiology and Intensive Care, Medical University of Warsaw, Lindley 4, 02–005, Warsaw, Poland
e-mail: adizner@gmail.com

Palliative Medicine in Practice

DOI: 10.5603/pmp.101971

Received: 13.08.2024 Accepted: 23.09.2024 Early publication date: 7.11.2024

Introduction

Metamizole (dipyrone) is a non-opioid analgesic that shows efficacy for moderate-to-severe pain and can be used for postoperative pain management. The substance has been known for more than 100 years. Metamizole was synthesized in Germany in 1920 (Hoechst AG) and brought to market in 1922 under the brand Novalgin® [1, 2]. The efficacy of metamizole as a postoperative analgesic has been evaluated for more than 50 years.

In some countries, metamizole is widely used and considered a safe and sufficient analgesic [1]. However, in certain countries, the drug has been removed from the market because of its association with life-threatening myelotoxicity (Canada — 1963, the United States — 1977, and Sweden — 1974 and 1999) [2, 3]. Moreover, metamizole has been revoked from use in the United Kingdom, Australia, Japan, Norway, India, and other countries [2, 3].

According to data from the European Medicines Agency (EMA), metamizole-containing medicines are available in several countries of the European Union (EU), including Austria, Belgium, Bulgaria, Croatia, the Czech Republic, Finland, Germany, Hungary, Italy, Latvia, Lithuania, Luxembourg, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, and Spain. The drug has been withdrawn for human use in Denmark, Estonia, France, Greece, Ireland, and Sweden [4].

Metamizole can be administered through different routes [intravenous (*i.v.*, *intravenosa*), intramuscular (*i.m.*, *intramuscularis*), oral (*p.o.*, *per os*), and rectal (*p.r.*, *per rectum*)]. After oral administration, metamizole is easily absorbed from the gastrointestinal tract and then, after hepatic metabolism, mainly by glucuronidation and sulfation, it is excreted by the kidneys [5]. The volume of distribution and the clearance of metamizole decrease in an age-dependent fashion [6].

Metamizole has strong analgesic, antipyretic, and spasmolytic effects. Although some animal studies showed that metamizole could inhibit pro-inflammatory response after surgery [7], its anti-inflammatory effects are considered irrelevant in humans [5].

Metamizole, a derivative of pyrazolone, is a prodrug [8]. The pharmacological activity of metamizole is determined by two active metabolites: N-methyl-4-aminoantipyrine (4-MAA) and 4-aminoantipyrine (4-AA) [9]. The complex mechanism of the analgesic effect is based on the inhibition of COX-1 and COX-2 cyclooxygenases and decreasing the synthesis of prostaglandins. This effect occurred by a different mechanism than classical non-steroidal anti-inflammatory drugs (NSAIDs). The pharmacologically active metabolites target the initiation of the catalytic reaction of both COX isoforms by reducing the higher oxidation states of COX or sequestering activating peroxides [10]. Therefore, metamizole is no longer considered a member of NSAIDs.

Moreover, metamizole activates the opioidergic (kappa receptors), cannabinoid (CB1, CB2), and endovanilloid (TRPA1, TRPV1) systems [9, 11–13]. 4-MAA and 4-AA activate and sensitize the nociceptive ion channels TRPA1 and TRPV1 in a redox-dependent manner [14]. Active metabolites of metamizole probably act through the central and peripheral nervous system [15].

The antipyretic effect is most likely based on the inhibition of both prostaglandin (PG)-dependent and PG-independent febrile pathways [16]. The spasmolytic effect of metamizole is also probably complex. Several mechanisms have been proposed. Metamizole opens adenosine triphosphate (ATP)-sensitive potassium channels and inhibits smooth muscle contractions induced by angiotensin II in rats [17]. Moreover, smooth muscle relaxation is caused by a decrease in the intracellular calcium ions ($Ca2+$) concentration as a result of the synthesis of inositol phosphate. The synthesis of inositol phosphate depends on the activity of phospholipase C. Active metabolites of metamizole can act in two ways: directly inhibit the activity of the enzyme or indirectly inhibit G protein-coupled receptors that activate phospholipase C. This results in a reduction of intracellular $Ca2+$ levels [18, 19].

Furthermore, some data [20, 21] showed direct β2-adrenoceptor activation induced by active metabolites of metamizole. However, the evaluation of these mechanisms requires further research.

Metamizole seems a relatively safe analgesic for certain ethnic populations, but it is not completely free of adverse reactions. Among them, the most serious and controversial is myelotoxicity [22, 23], drug-induced idiosyncratic liver injury (DILI) [24, 25], and the risk of severe allergic reactions, including anaphylactic shock [26]. Some data also showed delayed postoperative allergic reactions to metamizole, mainly in the form of a rash [27].

This review aims to present available data on the use of metamizole (dipyrone) in postoperative pain management in adults including benefits and threats.

Methods

The literature search included PubMed/Medline, Web of Science, and Scopus search engines. The search has been performed up to the end of April 2024 and included the following keywords: "metamizole", "dipyrone", "preventive/preemptive analgesia", "postoperative pain" and "multimodal analgesia". The results

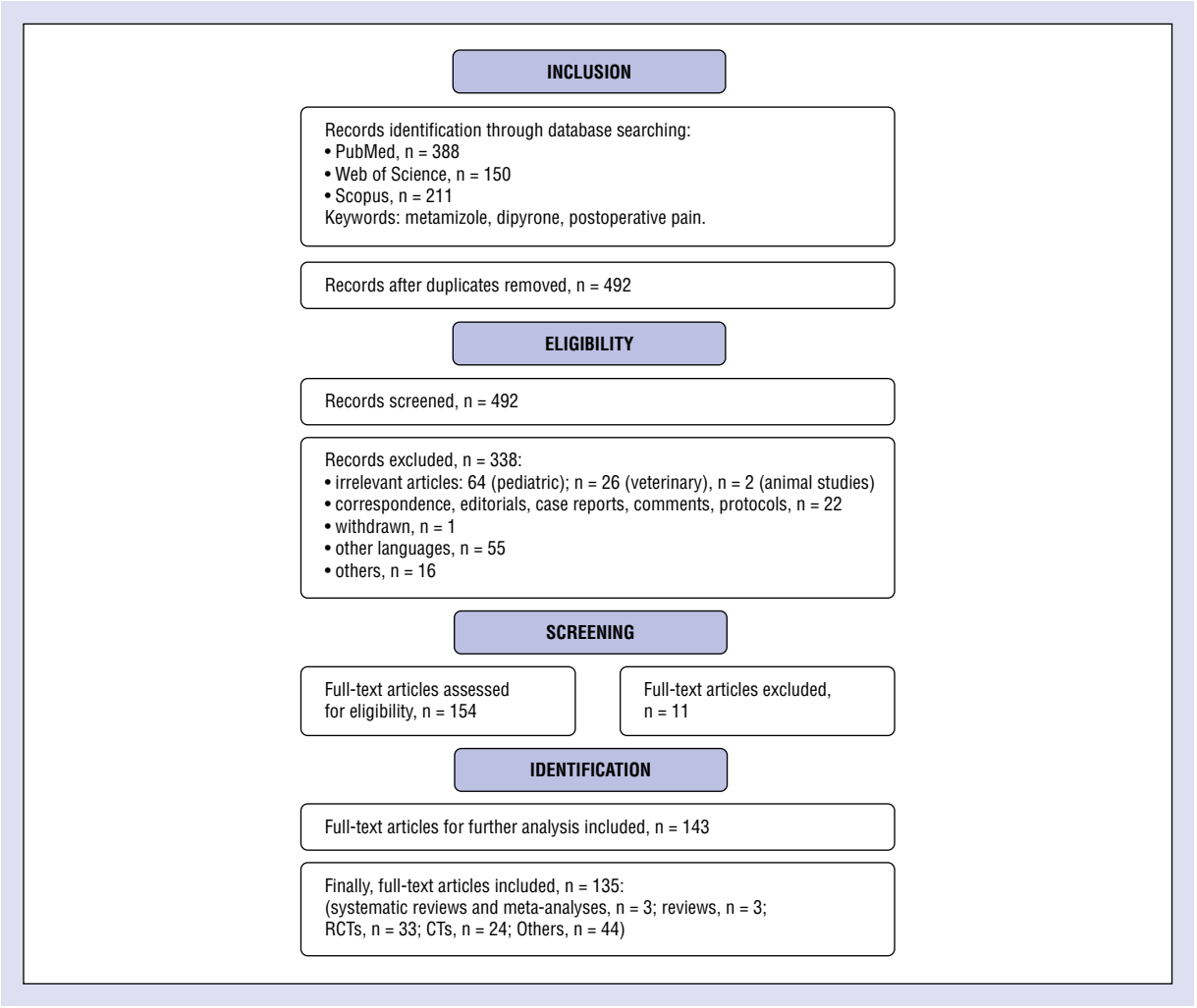

Figure 1. Flow chart of literature search

have brought a total number of 749 publications (PubMed/Medline — 388, Web of Science — 150, and Scopus — 211 respectively). The removal of duplicates and off-topic articles limited references to 492. A thorough review of the publications has been performed. The most relevant types of articles were included in further analysis, such as Clinical Trials, Meta-Analyses, Randomized Controlled Trials, Reviews, and Systematic Reviews. The methodology of the search has been presented in Figure 1. Finally, the authors selected 135 articles.

Results of search

Metamizole as a non-opioid analgesic showed valuable analgesic efficacy in comparison with placebo in several early studies [28–32]. The authors managed to find data comparing the analgesic potential of metamizole with other analgesics showing its effectiveness in preemptive analgesia regimens and use in multimodal analgesia (MMA). The authors intentionally did not specify the time frame of the analyzed data from the literature, which covered more than 40 years. The search results are described below.

Comparison with other analgesics

In several studies, metamizole has been compared with acetylsalicylic acid (ASA). Blendinger et al. [33] showed lysine salicylate more effective analgesic than metamizole, but the results were not statistically significant. Additionally, the study was limited by a small patient sample. In contrast, in a double-blind controlled trial, Mukherjee et al. [28] studied patients with moderate to severe pain following episiotomy. The comparison of *p.o.* metamizole with acetylsalicylic acid and placebo showed significant advantages of both analgesics over placebo. Moreover, pain relief with metamizole was of significantly longer duration than that of acetylsalicylic acid. Mehta et al. [29] in a randomized double-blind

placebo-controlled study of patients with postoperative pain following closed reduction of fractured long bones showed that metamizole produced significantly greater pain relief than acetylsalicylic acid.

A comparison of the analgesic efficiency of metamizole versus paracetamol also brought controversial results. Gómez-Jiménez et al. [34], in two studies of pain after episiotomy and tooth extraction, showed higher effectiveness of metamizole than paracetamol and placebo. In another double-blind, placebo-controlled trial of post-episiotomy pain, Daftary et al. [30] presented similar results with metamizole being significantly more effective than paracetamol and placebo. On the contrary, Landwehr et al. [35], in the randomized, double-blinded, placebo-controlled study of patients undergoing retinal surgery, showed no difference in analgesic potency between paracetamol and metamizole administered *i.v.* for postoperative analgesia. Similar results have been presented in the other randomized, double-blinded study of patients undergoing surgery for breast cancer, performed by Kampe et al. [36].

Patel et al. [37] compared *i.m.* administration of metamizole with pethidine in a double-blind parallel-group study for postoperative pain following abdominal surgery. The results showed similar effectiveness of both drugs.

Rodriguez et al. [38] in a randomized, double-blind study of 160 patients undergoing abdominal hysterectomy compared the analgesic efficacy and safety of tramadol, metamizole, ketorolac, and lysine clonixinate in the control of postoperative pain. The analgesic efficacy of tramadol was found to be greater than the other three analgesics. However, the number of patients requiring additional analgesia was lower with metamizole compared to the other two non-opioid analgesics.

Planas et al. [31] assessed the efficacy of metamizole (doses of 1 g and 2 g) in pain relief after surgical extraction of the lower third molar. Metamizole has been compared with ibuprofen (600 mg) and placebo. The study demonstrated that the analgesic efficacy of *p.o.* metamizole in a higher dose (2 g) was significantly more effective than that of ibuprofen 600 mg or placebo. Metamizole 1 g and ibuprofen 600 mg showed a similar therapeutic effect.

Bagán et al. [39] evaluated 125 patients with moderate to severe pain after surgical removal of one impacted third molar. The patients were randomly assigned to receive dexketoprofen trometamol 12.5 or 25 mg or metamizole 575 mg. Both doses of dexketoprofen trometamol had higher pain relief scores than metamizole and the differences were statistically significant. On the other hand, Saray et al. [40] revealed a statistically significant advantage of metamizole over diclofenac in the reduction of postoperative pain after plastic surgery.

In the study of patients who underwent abdominal or urological surgery, Tempel et al. [32] compared the influence of metamizole and placebo on the use of morphine patient-controlled analgesia (PCA). The results showed a reduction in morphine consumption while maintaining postoperative pain relief with a low incidence of side effects.

Rawal et al. [41] in a prospective, randomized, double-blinded study of the analgesic efficacy of three drugs: tramadol, metamizole, and paracetamol in patients scheduled for ambulatory hand surgery with *i.v.* regional anesthesia showed the advantage of tramadol over other analgesics in postoperative pain treatment. However, metamizole turned out to be more effective than paracetamol, and fewer side effects were observed after tramadol administration.

The study on the efficacy and safety of metamizole in comparison with tramadol used in early postoperative pain following abdominal hysterectomy performed by Torres et al. [42] showed results of similar efficacy for early pain relief for both drugs.

Grundmann et al. [43] in the prospective, double-blind, randomized, placebo-controlled study compared the efficacy of three *i.v.* non-opioid analgesics (parecoxib, paracetamol, metamizole) in postoperative pain relief after lumbar microdiscectomy. The results of the study suggested that metamizole was superior to the other drugs, and placebo.

In a randomized, single-blind study, Jovic et al. [44] compared the analgesic efficacy and safety of ketoprofen and metamizole after major head and neck surgery. The efficacy of ketoprofen as a postoperative analgesic was comparable to that of metamizole in the first 48 hours, while ketoprofen was more effective than metamizole from the 3rd day after surgery.

Soltesz et al. [45] compared the analgesic efficacy of parecoxib and metamizole administered *i.v.* for 48 hours after a transvaginal hysterectomy. Patients were divided into two groups depending on the analgesic used: the parecoxib group and the metamizole group, respectively. Visual Analogue scale (VAS) scores did not differ between groups with one exception. Twelve hours after surgery, the parecoxib group had lower VAS scores than the metamizole group (1 and 2, respectively; $p < 0.05$). No significant differences in cumulative piritramide administration have been observed between groups. Postoperative pain relief was equal in both groups during the first 48 hours after surgery.

Sener et al. performed two studies [46, 47] to compare lornoxicam with other non-opioid

analgesics. In the first study, which included patients who underwent septoplasty, analgesics (lornoxicam, diclofenac, ketoprofen, metamizole) and placebo were administered *i.m*. The results showed the advantages of all drugs over placebo and their analgesic efficacy has been similar [46].

In the second study [47], authors compared *i.v.* lornoxicam *vs.* metamizole in postoperative patient-controlled analgesia after elective septorhinoplasty. The results showed the superiority of lornoxicam only at 8 h ($p = 0.016$) postoperatively. The lornoxicam group required fewer rescue analgesics (*vs.* metamizole, $p = 0.046$; *vs.* placebo, $p = 0.001$). Moreover, patients in the metamizole group also have diminished requirements for rescue analgesics compared with placebo ($p = 0.008$).

Noronha et al. [48] in the randomized-controlled study compared the analgesic effect of lysine clonixinate, paracetamol, and metamizole after lower third molar extraction. The results did not show any significant differences in postoperative pain control between the studied drugs.

Korkmaz Dilmen et al. [49] in the prospective, placebo-controlled, randomized, double-blind study compared the effects of *i.v.* metamizole, paracetamol, and lornoxicam on postoperative pain control, morphine consumption, and adverse effects after lumbar disc surgery. The results showed more effective analgesia of metamizole and paracetamol over lornoxicam.

Karaman et al. [50] in the prospective, double-blind, randomized study compared the efficacy of three *i.v.* non-opioid analgesics (dexketoprofen trometamol, metamizole, paracetamol) for postoperative pain relief after ear, nose and throat (ENT) surgery. The pain scores were significantly lower in the dexketoprofen trometamol group compared with the other groups ($p < 0.05$). The pethidine requirement was found to be significantly higher in the groups of paracetamol and metamizole ($p < 0.05$).

Brodner et al. [51] in the double-blind, placebo-controlled study compared the efficacy of *i.v.* paracetamol, metamizole and parecoxib as part of a multimodal concept analgesia. Patient-controlled piritramide was administered as rescue medication. All of the studied drugs showed equivalent efficacy.

Abdulla et al. in three studies [52–54] compared the efficiency of three non-opioid analgesics (parecoxib, metamizole, and paracetamol) on piritramide consumption in the postoperative period. In the first study [52] of postoperative pain management following laparoscopic cholecystectomy, the results showed that metamizole significantly reduced piritramide consumption compared to the other analgesics upon discharge from the post-anesthesia care unit (PACU). On the other hand, the overall, cumulative piritramide consumption was only slightly lower in the metamizole group and statistically not significant. A significantly lower postoperative pain intensity was only found in the parecoxib group at 24 h after surgery compared to the metamizole group.

The second study of Abdulla et al. [53], a randomized, double-blind trial of the synergistic action of *i.v.* parecoxib, metamizole, or paracetamol on postoperative piritramide consumption in patients after total thyroidectomy resulted in no significant differences between groups. Similarly to the study described above, pain relief scores at 24 h were significantly higher in the parecoxib group as compared to metamizole and paracetamol ($p < 0.01$).

In conclusion, the studies showed that the efficacy of tested adjunct medications on piritramide consumption and pain relief was weak. However, parecoxib seemed to be superior regarding pain level scores and piritramide consumption.

In the third study [54] authors compared the aforementioned analgesics in patients recovering from arthroscopic knee surgery. The results showed an advantageous, statistically significant analgesic effect of parecoxib over metamizole and paracetamol. The cumulative consumption of piritramide in the parecoxib group was significantly lower than that in the placebo group at 6 and 12 hours after surgery. After the immediate postoperative period in the PACU, cumulative piritramide consumption in both paracetamol and metamizole groups also remained lower compared to the placebo. However, this observation was statistically not significant. A reason for the missing clear-cut opioid-sparing effect in the metamizole and paracetamol groups might be due to the nonequivalent doses of these nonopioid analgesics administered in the study. Moreover, the study has been performed in patients who underwent remifentanil-based anesthesia. This type of anesthesia is associated with postoperative hyperalgesia, even after a short-term exposure [55].

Oreskovic et al. [56] in a prospective, randomized, double-blind study compared the analgesic effects of *i.v.* metamizole or *i.v.* paracetamol in combination with morphine PCA during the first 24 hours following total hip arthroplasty. In this study, the authors showed excellent efficacy of paracetamol and metamizole combined with opioids, but metamizole proved to be a better analgesic than paracetamol.

The study of patients scheduled for elective supratentorial craniotomy performed by Dilmen et al. [57] did not demonstrate a statistically significant effect of supplemental analgesics on morphine consumption. The results showed that it was lower in dexketoprofen

and metamizole groups than the control group but not statistically significant.

In turn, in a prospective cohort study, Geißler et al. [58] compared the analgesic effect of metamizole and etoricoxib in the treatment of postoperative pain after tonsillectomy with no statistically significant differences between analgesics. However, the study has a limitation because of more severe initial, preoperative pain in the metamizole group ($p = 0.001$).

In another clinical trial of 83 patients who underwent tonsillectomy (TE), Gostian et al. [59] compared the analgesic efficiency of metamizole and ibuprofen in four-staged escalating analgesic protocols. Metamizole showed statistically significant superiority over ketoprofen. The authors recommended metamizole as a basic medication that alleviates pain in patients after tonsillectomy (TE).

The main findings have been summarized in Table 1.

Table 1. Metamizole — comparison with other analgesics

Author	Year	Study	Population	Patient number, groups	Treatment doses, routes	Outcome
Blendinger	1980	CT	Gynecological procedures	17.2	Lysine salicylate 1.8 g (= ASA 1.0 g) *i.v.* Metamizole 1.0 g *i.v.*	Lysine salicylate > metamizole Small number of patients
Gómez--Jiménez	1980	CT	Episiotomy	264.3	Metamizole 1.0 *p.o.* Paracetamol 1.0 *p.o.* Placebo *p.o.*	Metamizole > paracetamol > placebo
Gómez--Jiménez	1980	CT	Tooth extraction	90.2	Metamizole 1.0 *p.o.* Paracetamol 1.0 *p.o.*	Metamizole > paracetamol
Patel	1980	CT	Laparotomy	100.2	Metamizole 2.5 g *i.m.* Pethidine 100 mg *i.m.*	Metamizole = pethidine
Mukherjee	1980	CT	Episiotomy	267.3	Metamizole 0.5 *p.o.* Acetylsalicylic acid 0.5 *p.o.* Placebo	Metamizole > acetylsalicylic acid > placebo
Daftary	1980	CT	Episiotomy	299.3	Metamizole 0.5 *p.o.* Paracetamol 0.5 *p.o.* Placebo	Metamizole > paracetamol > placebo
Mehta	1986	CT	Orthopedic surgery (closed reduction fracture)	254.3	Metamizole 0.5 *p.o.* Acetylsalicylic acid 0.5 *p.o.* Placebo	Metamizole > acetylsalicylic acid > placebo
Rodriguez	1993	CT	Abdominal hysterectomy	160.4	Tramadol, metamizole, ketorolac, lysine clonixinate Analgesics were administered using continuous infusion plus patient-controlled analgesia	Tramadol > metamizole, Tramadol > ketorolac, Tramadol > lysine clonixinate
Tempel	1996	CT	Laparotomy/ /urological surgery	103.2	Metamizole (initially 2.0 g *i.v.* and 1.0 g/2 mL *i.v.* at 4, 8 and 16 h) Placebo (saline)	Metamizole > placebo Metamizole reduces on-demand morphine (PCA) consumption
Planas	1998	CT	Third molar extraction	253.4	Metamizole 1 g *p.o.* Metamizole 2 g *p.o.* Ibuprofen 600 mg *p.o.* Placebo *p.o.*	Metamizole 2 g > metamizole 1 g = ibuprofen 600 > placebo
Bagán	1998	CT	Third molar extraction	125.2	Dexketoprofen trometamol 12.5 or 25 mg Metamizole 575 mg	Dexketoprofen > metamizole
Saray	2001	RCT	Plastic surgery	166.2	Metamizole 1 g *i.m.* every 8 hours Diclofenac 75 mg *i.m.* every 12 hours	Metamizole > diclofenac

→

Table 1. cont. Metamizole — comparison with other analgesics

Author	Year	Study	Population	Patient number, groups	Treatment doses, routes	Outcome
Rawal	2001	RCT	Hand surgery	120.3	Tramadol 100 mg every 6 h Metamizole 1 g every 6 h Paracetamol 1 g every 6 h	Tramadol > metamizole (SS) Tramadol > paracetamol (SS) Metamizole > paracetamol (NS)
Torres	2001	CT	Hysterectomy	151.2	Metamizole 2 g *i.v.* over 15 min., followed by continuous infusion of 166 mg/h and demand doses of 333 mg up to a maximum of 6 bolus injections in 24 hours (8 g/24 h!) Tramadol 100 mg *i.v.* over 15 min., followed by continuous infusion of 12.5 mg/h and demand doses of 16.5 mg up to a maximum of 6 bolus injections in 24 hours (500 mg/24 h)	Metamizole = tramadol
Landwehr	2005	CT	Retinal surgery	38.3	Paracetamol 1 g/100 mL Metamizole 1 g/100 mL Placebo (100 mL of saline solution) 30 min before arrival in the recovery area and every 6 h up to 24 h postoperatively	Metamizole = paracetamol
Grundmann	2006	RCT	Lumbar micro-discectomy	80.4	Parecoxib 40 mg *i.v.* Paracetamol 1 g *i.v.* Metamizole 1 g *i.v.* placebo *i.v.*	Metamizole > parecoxib, Metamizole > paracetamol, Metamizole > placebo
Kampe	2006	RCT	Breast cancer surgery	40.2	Metamizole 1 g/100 mL *i.v.* 30 min before arrival in the recovery area and every 6 h up to 24 h postoperatively Paracetamol 1 g/100 mL *i.v.* 30 min before arrival in the recovery area and every 6 h up to 24 h postoperatively	Metamizole = paracetamol
Jovic	2008	RCT	Head and neck tumor operation	60.2	Ketoprofen 100 mg *i.v.* every 8 h Metamizole 2.5 g *i.v.* every 8 h	Ketoprofen > metamizole (in 3 day) $p < 0.05$
Soltesz	2008	RCT	Hysterectomy	50.2	Parecoxib 40 mg *i.v.* intraoperatively and every 12 h postoperatively Metamizole 2.5 g *i.v.* intraoperatively and 1.0 *i.v.* every 6 h	Parecoxib = metamizole
Sener	2008	RCT	Septoplasty	200.5	Lornoxicam 8 mg (twice daily) *i.m.*, diclofenac 75 mg (twice daily) *i.m.*, ketoprofen 100 mg (twice daily) *i.m.*, metamizole 1 g (three times daily) *i.m.*, Placebo (twice daily) *i.m.*	Lornoxicam = diclofenac = ketoprofen = metamizole > placebo
Sener	2008	RCT	Septorhino-plasty	105.3	Lornoxicam (24 mg/day) Metamizole (5 g/day) placebo	Lornoxicam > metamizole

→

Table 1. cont. Metamizole — comparison with other analgesics

Author	Year	Study	Population	Patient number, groups	Treatment doses, routes	Outcome
Noronha	2009	RCT	Third molar extraction	90.3	Lysine clonixinate 125 mg *p.o.* Metamizole 500 mg *p.o.* Paracetamol 750 mg *p.o.*	Lysine clonixinate = metamizole = paracetamol
Korkmaz Dilmen	2010	RCT	Lumbar disc surgery	80.4	Metamizole 1 g *i.v.*, Paracetamol 1 g *i.v.* Lornoxicam 8 mg *i.v.* 0.9% NaCl *i.v.*	Metamizole > paracetamol > Lornoxicam > 0.9% NaCl
Karaman	2010	CT	Elective ENT surgery	100.3	Dexketoprofen trometamol 50 mg *i.v.* 3×/day, Paracetamol 1 g *i.v.* 4×/day Metamizole 1 g *i.v.* 3×/day	Dexketoprofen > paracetamol Dexketoprofen > metamizole
Brodner	2011	RCT	Various types of surgical procedures	196.4	Intravenous infusions: Paracetamol (1 g every 6 h) Metamizole (1 g every 6 h) Parecoxib (40 mg every 12 h) + 2 doses of placebo (normal saline) Normal saline (every 6 h)	Paracetamol = metamizole = parecoxib
Abdulla	2012	RCT	Laparoscopic cholecystectomy	120.4	Intravenous infusions: Parecoxib 40 mg twice daily, metamizole 1 g three times daily, paracetamol 1 g three times daily) Normal saline	Parecoxib > metamizole (at 24 h post operation) Metamizole significantly reduced piritramide consumption
Abdulla	2012	RCT	Total thyroidectomy	120.4	Parecoxib 40 mg twice daily *i.v.* Metamizole 1 g three times daily *i.v.* Paracetamol 1 g *i.v.* three times daily Placebo (0.9% NaCl) *i.v.*	Parecoxib > metamizole > paracetamol NS differences between groups in piritramide consumption
Abdulla	2012	RCT	Arthroscopic knee surgery	120.4	Parecoxib 40 mg twice daily *i.v.* Metamizole 1 g three times daily *i.v.* Paracetamol 1 g *i.v.* three times daily Placebo (0.9% NaCl) *i.v.*	Parecoxib > metamizole Parecoxib > paracetamol SS opioid-saving effect only by administering parecoxib
Chaparro	2012	RCT	Herniorrhaphy	162.2	Metamizole 15 mg/kg Metamizole 40 mg/kg	Metamizole 40 mg/kg > metamizole 15 mg/kg
Oreskovic	2014	RCT	Hip arthroplasty	110.2	Paracetamol 1g *i.v.* every 8h Metamizole 1.5 g *i.v.* every 8h	Metamizole > paracetamol ($p = 0.038$)
Dilmen	2016	RCT	Elective supratentorial craniotomy	75.4	Dexketoprofen 50 mg *i.v.* Paracetamol 1g *i.v.* Metamizole 1g *i.v.* Placebo *i.v.*	Dexketoprofen = paracetamol= metamizole = placebo ($p = 0.741$) Morphine consumption. was lower in dexketoprofen and metamizole groups ($p > 0.05$)
Geißler	2019	CT	Tonsilectomy	124.2	Etoricoxib 90 mg *p.o.* Metamizole 1g *i.v.* every 6 h	Etoricoxib = metamizole
Gostian	2020	CT	Tonsilectomy	83.2	Ibuprofen 600 mg every 8 h Metamizole 1 g *p.o.* every 6 h	Ibuprofen < metamizole

ASA — acetylsalicylic acid; CT — clinical trial; ENT — ear, nose, throat; *i.m.* (*intramuscularis*) — intramuscular; *i.v.* (*intravenosa*) — intravenous; NS — non statistically significant; *p.o.* (*per os*) — oral; PS — pilot study; RCT — randomized controlled trial; RT — randomized trial; SS — statistically significant

Metamizole in preemptive analgesia regimens

Early works of Steffen et al. from 1996–1997 showed the beneficial effect of metamizole administered preemptively, solely [60] or with diclofenac coadministration [61] in comparison with placebo on intensity of postoperative pain. Moreover, a decrease in postoperative buprenorphine consumption has been observed [60, 62].

In the study of Srebrzyński et al. [63], an evaluation of the analgesic effect of metamizole administered *i.v.* has been performed in patients who underwent multinodular goiter surgery. The authors showed that an administration of an additional dose of metamizole before the surgery (preemptive analgesia) resulted in postoperative pain relief and reduced demand for opioid analgesics.

Ohnesorge et al. [64] compared paracetamol, metamizole, and placebo used in a preemptive regimen in the study of patients undergoing elective breast surgery. The authors did not notice any significant difference in total morphine consumption between these groups. Administration of paracetamol, but not metamizole resulted in a significant reduction in the number of patients needing opioid analgesics.

Lauretti et al. [65] in the study of patients scheduled for minor orthopedic surgery treated with epidural administration of dexamethasone showed that *i.v.* metamizole in contrast to parecoxib enhanced the level of postoperative analgesia.

The study of postoperative pain in women undergoing surgery for breast neoplasm performed by Węgorowski et al. [66] demonstrated the effectiveness of tramadol ($p = 0.004$) and ketoprofen ($p = 0.039$) administered half an hour before the beginning of surgery, but metamizole did not show the same effect ($p = 1.0$).

In the work of Neychev et al. [67] in patients who underwent surgical removal of impacted mandibular third molars, the preventive use of metamizole was more effective than placebo but less effective than nimesulide.

In a pilot study of third molars surgery conducted by Favarini et al. [68], metamizole was preemptively administered (study group) for the extraction of two third molars on the same side and, in a second surgical procedure, metamizole was administered in the immediate postoperative period (control group). The authors concluded that preemptive administration of metamizole is more beneficial.

In another clinical trial, Suljević et al. [69] compared the analgesic effects of preemptively administered tramadol and metamizole after an elective hysterectomy with adnexectomy and showed that preemptively administered tramadol is significantly more favorable than metamizole. However, metamizole showed better effect than placebo.

Stessel et al. [70] in a randomized trial of 110 patients who underwent arthroscopic shoulder surgery found no benefits of the addition of metamizole to preemptive treatment of postoperative pain with ibuprofen and paracetamol.

Stasiowski et al. [71] in a study of patients who underwent vitreoretinal surgery showed the improved efficiency of preemptive coadministration of metamizole and paracetamol.

All of the results are presented in Table 2.

Table 2. Metamizole in preemptive analgesia

Author	Year	Study	Population	Patient number, groups	Treatment doses, routes	Outcome
Steffen	1996	RCT	Various types of surgical procedures including laparoscopies	117.2	Metamizole 1 g *i.v.* (PA) Placebo	Metamizole (PA) > placebo Metamizole significantly lowers buprenorphine requirements
Steffen	1997	RCT	Orthopedic surgery	74.2	Metamizole 1 g *i.v.* + diclofenac 100 mg *p.r.* (PA) Placebo	Metamizole + diclofenac > placebo
Steffen	1997	RCT	Laparoscopic surgery	40.2	Metamizole 1 g *i.v.* (PA) Placebo	Metamizole (PA) > placebo Metamizole significantly lowers buprenorphine requirements

→

Table 2. cont. Metamizole in preemptive analgesia

Author	Year	Study	Population	Patient number, groups	Treatment doses, routes	Outcome
Srebrzyński	2008	CT	Nodular goiter surgery	114.4	Metamizole 1 g *i.v.* every 6 hours Metamizole 1 g *i.v.* every 6 hours + surgical wound was injected with 10 mL of bupivacaine 0.25% Metamizole 1 g *i.v.* every 6 hours (preemptive analgesia) Ketoprofen 0.1 g every 6 hours	Metamizole (PA) > metamizole + bupivacaine > ketoprofen > metamizole (postoperatively)
Ohnesorge	2009	RCT	Elective breast surgery	87.3	Paracetamol 1 g *i.v.* Metamizole 1 g *i.v.* Placebo	Paracetamol > metamizole Administration of paracetamol resulted in a significant reduction in the number of patients needing opioid analgesics to achieve adequate postoperative pain relief
Lauretti	2014	CT	Minor orthopedic surgery, epidural anesthesia with dexamethasone	91.7	Parecoxib 40 mg *i.v.* Metamizole 1 g *i.v.*	Analgesia secondary to epidural dexamethasone was exacerbated by *i.v.*_metamizole
Wegorowski	2016	CT	Breast tumor surgery	100.4	Tramadol Ketoprofen Metamizole Placebo	Metamizole = placebo (p = 1.00) Tramadol > placebo (p = 0.004) Ketoprofen > placebo (p = 0.036)
Neychev	2017	RCT	Impacted mandibular third molars surgery	80.3	Nimesulide 100 mg *p.o.* Metamizole 500 mg *p.o.* Placebo *p.o.*	Nimesulide > metamizole > placebo
Favarini	2018	PS	Third molar surgery	25.2	Metamizole 1 g (PA) Metamizole 1 g (postoperatively)	Metamizole (PA) > metamizole
Suljević	2020	CT	Hysterectomy with adnexectomy	90.3	Tramadol 1mg/kg *i.m.* Metamizole 30 mg/kg *i.m.* Placebo	Tramadol > metamizole > placebo
Stessel	2023	RT	Arthroscopic shoulder surgery	110.2	MIP (metamizole 1000 mg *p.o.* 3 × 1 + ibuprofen 600 mg *p.o.* 3 × 1 + paracetamol 1 g *p.o.* 4 × 1 for 4 days) IP (placebo 3 × 1 + ibuprofen 600 mg *p.o.* 3 × 1 + paracetamol 1 g *p.o.* 4 × 1 for 4 days	Metamizole + ibuprofen + paracetamol (MIP) = placebo + ibuprofen + paracetamol (PIP) The first dose of studied medications or placebo was given 30 min before surgery
Stasiowski	2024	RT	Vitreoretinal surgery	153.3	Paracetamol 1 g *i.v.* + Metamizole 2.5 g *i.v.* Paracetamol 1 g *i.v.* Metamizole 2.5 g *i.v.*	Paracetamol + metamizole > paracetamol Paracetamol + metamizole > metamizole Preemptive paracetamol administration diminished the requirement for intravenous FNT

CT — clinical trial; GA — general anesthesia; *i.m.* (*intramuscularis*) — intramuscular; *i.v.* (*intravenosa*) — intravenous; FNT — fentanyl; NS — non statistically significant; PA — preemptive analgesia; PBB — preprocedural peribulbar block; *p.o.* (*per os*) — oral; PS — pilot study; RCT — randomized controlled trial; RT — randomized trial; SPI — surgical pleth index; SS — statistically significant; TA — topical anesthesia

Multimodal analgesia

Multimodal analgesia (MMA) is a method involving the administration of two or more analgesic drugs with different mechanisms of action. The goal of MMA is to improve analgesia while reducing the need for opioids and reducing opioid-related adverse effects. Moreover, perioperative MMA can be used for the prevention of chronic postoperative pain [72]. Combined analgesic regimens can produce sufficient analgesia by additive or synergistic effects.

Striebel et al. [73] in the randomized, prospective double-blind study of 60 female patients who underwent vaginal hysterectomy comparing tramadol/metamizole and tramadol/ibuprofen in postoperative analgesia showed that satisfactory pain reduction occurred rather late despite high doses of drugs.

Schneider et al. [74] in a randomized, placebo-controlled, cross-over study of 35 patients undergoing bilateral lower third molar extraction combined metamizole and ibuprofen in treatment.

The results showed superior pain control compared to ibuprofen or metamizole alone. Unfortunately, the premature study-termination might overestimate this effect.

Stessel et al. [75] in a double-blind randomized controlled trial compared metamizole and paracetamol versus ibuprofen and paracetamol in treating pain at home after painful day-case surgery. The results showed that both combinations of drugs are equally effective with comparable patient satisfaction levels.

The study performed by Samulak et al. [76] included patients treated for acute postoperative pain after gynecological oncology surgery. The study covered 128 patients who were randomly divided into two groups with two different postoperative pain therapy regimens. Patients in the first group received morphine (*s.c.*, *subcutaneous*), paracetamol *i.v.*, and naproxen *p.r.* Patients in the second group were administered metamizole instead of paracetamol. The pain intensity level was checked using the numeric rating scale (NRS). When pain rates exceeded 5, patients were additionally given ketoprofen *i.v*. The results showed that the use of metamizole with morphine (without ketoprofen) was less effective than paracetamol with morphine. The combination of morphine, paracetamol, and ketoprofen, or morphine, metamizole, and ketoprofen, gave comparable satisfactory pain relief.

Uzun et al. [77] investigated the metamizole, paracetamol, and morphine combination in postoperative pain treatment after lumbar disc surgery. The authors concluded that the addition of metamizole to paracetamol along with *i.v.* morphine PCA offered an advantage over single *i.v.* morphine PCA and paracetamol. The level of early postoperative pain decreased, which increased patients' satisfaction.

The evidence for the positive role of multimodal analgesia in a systematic review and meta-analysis has been performed by Martinez et al. [78], who compared 135 randomized trials to establish the effectiveness of analgesics other than morphine (AOM) in several configurations for postoperative pain treatment after different procedures of major surgery. A combination of analgesics was superior to most AOM used alone, in reducing morphine consumption. For AOM used alone, efficacy was best with three of them: α-2 agonists, NSAIDs, and COX-2 inhibitors: 0.7 (95% CI: 0.6––0.8), 0.36 (0.18–0.79), 0.41(0.15–0.64), respectively. Moreover, network meta-analysis found morphine consumption reduction to be the greatest with the combination of two AOM (acetaminophen + nefopam, acetaminophen + NSAID, and tramadol + metamizole): −23.9 (95% CI −40; −7.7), −22.8 (−31.5; −14) and −19.8 (35.4; −4.2), respectively. The studies concerning the use of metamizole in multimodal analgesia have been summarized in Table 3.

Adverse effects and unfavorable actions

According to the Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring, the number of adverse effects registered in the years 1968-2024 (April) for metamizole was 38,444 [79]. In comparison, a similar search was performed for the years 1978–2009 (March) and revealed 14,441 cases [80].

Despite the above data, a comparison of the risk profile of side effects of metamizole with other non-opioid analgesics appears to be favorable for it. The risk of hepatotoxicity, nephrotoxicity, bleeding, and cardiovascular adverse reactions is less common than with NSAIDs [81].

There is a slightly elevated risk of gastrointestinal hemorrhage after metamizole administration, but this risk appears to be smaller than with the use of NSAIDs [82]. Metamizole is better tolerated by the gastrointestinal tract and has a wide therapeutic index compared to paracetamol and NSAIDs. Moreover, there is currently insufficient evidence for nephrotoxicity caused by metamizole administered perioperatively. Hence, the drug seems to be rather safe for patients with coexisting kidney diseases [82]. Furthermore, metamizole has not yet been associated with cardiovascular adverse effects. In a study on non-opioid analgesics (NOPA) and cardiovascular events, there was no increased risk of myocardial infarction for

Table 3. Metamizole in multimodal analgesia

Author	Year	Study	Population	Patient number, groups	Treatment doses, routes	Outcome
Striebel	1992	CT	Vaginal hysterectomy	60.2	Tramadol + metamizole (*i.v.* infusion) + placebo (*supp.*) Tramadol + placebo (*i.v.* infusion) + ibuprofen (*supp.*)	Both regimens seem to be insufficient because of the very slow onset of action and the high failure rate
Grossman	2007	OS	Awake craniotomy	40.1	Wound infiltration with lidocaine and bupivacaine Conscious sedation using remifentanil and propofol Single dose of metamizole for postoperative pain control	The results suggest the possible role of local intradermal infiltration of the scalp combined with a single dose of metamizole to control postoperative pain in patients undergoing craniotomy
Samulak	2011	RCT	Gynecological oncology surgery	128.2	Group I: morphine (*s.c.*) + acetaminophen (*i.v.*) + naproxen (*p.r.*) (if NRS > 5 additional dose of ketoprofen *i.v.*) Group II: morphine (*s.c.*) + metamizole (*i.v.*) + naproxen (*p.r.*) (if NRS > 5 additional dose of ketoprofen *i.v.*)	Acetaminofen + morphine > metamizole + morphine Morphine + acetaminophen + ketoprofen = morphine + metamizole + ketoprofen
Schneider	2022	RCT	Lower third molar extraction	35.2 (repeating the procedure in the same group of patients)	Each patient received three applications of 1000 mg metamizole + 400 mg ibuprofen for surgery on one side and either 1000 mg metamizole + placebo or 400 mg ibuprofen + placebo on the other side	Metamizole + ibuprofen > metamizole Metamizole + ibuprofen > ibuprofen
Stessel	2023	RT	Arthroscopic shoulder surgery	110.2	MIP (metamizole 1000 mg *p.o.* 3 × 1 + ibuprofen 600 mg *p.o.* 3 × 1 + paracetamol 1 g *p.o.* 4 × 1 for 4 days) IP (placebo 3×1 + ibuprofen 600 mg *p.o.* 3 × 1+ paracetamol 1 g *p.o.* 4 × 1 for 4 days	Metamizole + ibuprofen + paracetamol (MIP) = placebo + ibuprofen + paracetamol (PIP) The first dose of studied medications or placebo was given 30 min before surgery

CT — clinical trial; GA — general anesthesia; *i.m.* (*intramuscularis*) — intramuscular; *i.v.* (intravenosa) — intravenous; NS — non statistically significant; PA — preemptive analgesia; PBB — preprocedural peribulbar block; *p.o.* (*per os*) — oral; *p.r.* (*per rectum*) — rectal; PS — pilot study; RCT — randomized controlled trial; RT — randomized trial; s.c. (*subcutanea*) — subcutaneous; SPI — surgical pleth index; SS — statistically significant; TA — topical anesthesia

patients with low, intermediate, or high cardiovascular risk on long-term therapy with metamizole [83].

However, some adverse effects of metamizole can be harmful. One of the disadvantages of the use of parenteral metamizole in perioperative pain management is transient hypotension. Clinical data and animal studies indicate a possible vasodilator action of metamizole. Hoenicka et al. [84, 85] investigated the effects of metamizole on human artery and vein tone in an *ex vivo* model to assess potential contributions to venous pooling. Metamizole and its metabolites displayed counteracting effects on blood vessel tone *ex vivo*. The vasoconstrictor effect was probably mediated by cyclooxygenase-derived products. In contrast, the net effect seemed to be site-specific, resulting in a selective venous vasodilator action. These changes could exacerbate unwanted venous pooling during postoperative pain therapy [84, 85].

Hemodynamic adverse effects of single doses of three non-opioid analgesics (metamizole 2 g, ketorolac 30 mg, and propacetamol 1 g) have been studied during postoperative pain treatment and in critically ill

patients in the intensive care unit (ICU) [86]. Metamizole produced a 10% decrease in the left ventricular work index. This effect has not been clinically significant in hemodynamically stable patients [85]. However, caution is advised in hemodynamically unstable patients.

The observational trial of Hoenicka et al. [85] showed that metamizole exerted a significant influence on postoperative fluid balances in cardiac surgery patients. Especially, rapid *i.v.* administration of metamizole can lead to dose-dependent critical hypotension. In order to avoid serious complications, a prolonged infusion of the drug is recommended (approximately 20–30 minutes) under monitoring of the circulatory system.

A serious adverse effect caused by metamizole is undoubtedly agranulocytosis. In general, agranulocytosis is defined as a decrease in the neutrophil count of less than < 500/μL. Metamizole-induced agranulocytosis (MIA) is probably manifested as a dose-independent idiosyncratic reaction [87]. Moreover, in rare cases, also pancytopenia after metamizole administration can be induced [88].

Metamizole-induced agranulocytosis is estimated to occur in about one case per million inhabitants per year [81]. In the Berlin Case-Control Surveillance Study [87], the prevalence of metamizole-induced agranulocytosis has been estimated as 0.96 [95% confidence interval (CI) 0.95–0.97] cases per million per year. However, this risk appears to be relatively low compared to other drugs, such as antithyroid drugs and ticlopidine [81].

The etiology of MIA is still unexplained. Accordingly, with available data, MIA appears to be more common in females (woman: man ratio 2:1) and older age patients [23]. Thus, different levels of acetylation and clearance of the drug's active metabolites based on gender and age could explain the suspected difference in incidence and risk of MIA in those groups [89]. On the contrary, other analyses of available MIA reports failed to identify individual risk factors [22].

Some viral infections [including severe-acute-respiratory-syndrome-related coronavirus 2 (SARS-CoV-2), hepatitis C virus (HCV), human immunodeficiency virus (HIV), herpes simplex virus (HSV), human herpesvirus (HHV), Epstein–Barr virus (EBV), cytomegalovirus (CMV) and others] could predispose to adverse drug reactions. This also applies to MIA, but the mechanism is not fully clear [90]. Most cases of immune-mediated agranulocytosis are thought to be caused by drug-dependent antibodies. Active drug metabolites, acting as immunogenic haptens, activate the T-cell response and destroy neutrophils [89]. Increased risk of MIA could be also connected with specified human leukocyte antigens (HLA) region characteristics, but insufficient data supported this thesis [91, 92].

Despite attempts at population research, it has not yet been possible to obtain data explaining the mechanisms of MIA [93]. Hence, further studies are needed to fully understand them.

In all cases of suspected MIA, treatment with metamizole should be immediately paused and followed by a prompt blood cell count examination. Detection of metamizole-specific antibodies against granulocytes via indirect immunofluorescence could alleviate the diagnosis of MIA [89]. However, the clinical significance of this method is highly limited because of the unclear etiology of the disease.

Metamizole-induced agranulocytosis can lead to high mortality due to the increased risk of infection. Management of these patients should include isolation, diagnosis of potential infections (blood cultures, swabs, infection parameters), and empirical therapy with broad-spectrum antibiotics. Currently, there are no clear guidelines regarding the use of granulocyte colony-stimulating factor (G-CSF) in the treatment of drug-induced agranulocytosis. Although, the use of G-CSF has brought benefits in the treatment of agranulocytosis caused by other drugs [94, 95]. However, the potential risks of this therapy [myalgia, nausea, acute respiratory distress syndrome (ARDS), and capillary leak syndrome], indicate the limitation to patients with severe course and poor prognosis [89].

Another potentially life-threatening adverse effect of metamizole is drug-induced liver injury (DILI). The incidence of DILI in the general population is rare and estimated at 14–19 cases per 100,000 inhabitants (< 1% of acute liver injury ALI) [96]. Unfortunately, this complication is the cause of most cases of acute liver failure with a mortality rate of up to 50% [97] and the need for emergent liver transplantation. There are only a few metamizole-associated DILI cases (n = 61) described in the literature [97]. A liver transplantation procedure has been reported in 6 cases [97].

Weber et al. [98] investigated a case series comprising 32 patients with suspected metamizole-induced DILI. Suspected metamizole-DILI was characterized by a female predominance, a hepatocellular pattern of injury, and a high proportion of antinuclear antibody positivity (ANA). The predominance of eosinophilic cell infiltration and necrosis has been observed in the histopathological analysis. Furthermore, jaundice was frequently observed in these patients and has been associated with a worse prognosis.

Sebode et al. [25] described metamizole as the second most frequent cause of DILI (23 of all 154 DILI cases, 14,9%). In another study, Reike-Kunze et al. [99] also showed similar results (11%). Courses of liver

injury associated with metamizole have been similar in the described cases. In all cases, the mean values of ALT and bilirubin levels were highly elevated with a high prevalence of hepatocellular changes. The model for end-stage liver disease (MELD) score ≥ 18 at the time of admission was a prediction of poor outcome [24]. Thus, metamizole therapy should be used with a high level of caution, especially in patients with decompensated cirrhosis [100].

Drug interactions are also an important aspect when using metamizole. Metamizole acts as a potent inductor of cytochrome P450 isoenzymes [101]. The interaction profile is especially important in the treatment of chronic pain syndromes frequently co-occurring with depression. Thus, the interaction between metamizole and sertraline leads to insufficiently low sertraline drug concentrations, which may be dangerous in these patients [102]. Therefore, meticulous analysis of potential drug interactions should be considered before therapy initiation.

Severe allergic reactions have been described after metamizole use. The cases include anaphylactic shock [26], Kounis syndrome [103], and Stevens–Johnson syndrome [104].

Anaphylactic or anaphylactoid reactions after the use of metamizole have been described with a frequency of 1:5000. Patients with analgesic asthma, analgesic intolerance of the urticarial angioedema type, bronchial asthma, chronic urticaria, and intolerance to alcohol, colorings and preservatives (*e.g.* benzoates) are particularly at risk. Delayed hypersensitivity with characteristic maculopapular exanthema after metamizole administration has been observed [27].

Discussion

Multimodal analgesia (MMA) involves the use of several analgesic and/or coanalgesic (adjuvant) drugs and regional anesthesia techniques targeting different pain sites [72]. This approach increases the level of analgesia and reduces the risk of adverse effects by decreasing the amount of opioids. Such a method is referred to as the opioid-sparing effect [105] and has been applied with the use of metamizole in postoperative pain treatment [32]. Although metamizole has had well-documented efficiency as a sole analgesic for moderate to severe postoperative pain (Table 2), the drug also has additive and synergistic interactions with other non-opioid analgesics (paracetamol, NSAIDs) and opioids (morphine, tramadol) (Table 2, 3). Therefore, metamizole has been used in multimodal, non-opioid, or opioid-sparing therapies for the treatment of acute postoperative pain. Moreover, some randomized controlled trials (RCTs) cited in this review brought evidence for sufficient analgesic activity of metamizole, comparable with opioid analgesic potency with a simultaneous lack of typical adverse effects (Table 2, 3). Metamizole as a component of multimodal treatment, could enhance the analgesic effect, which has been shown in some experimental and clinical studies (Table 3).

The drug has been used in preemptive /preventive models of intraoperative analgesia (Table 2) and has shown promising but controversial results [106]. Some authors presented similar preemptive efficacy of metamizole in comparison with other analgesics [71]. Preemptive use of metamizole in the third molar surgery could reduce the perception and intensity of postoperative pain [68] but is not such prominent as after NSAIDS administration. Other studies showed there was no evidence of preemptive use [66, 69]. Unfortunately, data on the preemptive use of metamizole is not very extensive. Therefore, it seems too early to draw firm conclusions.

The effectiveness of metamizole in postoperative analgesia varies, depending on the specific surgical procedures. Thus, the use of this analgesic should be determined individually. Moreover, additional studies will be needed to evaluate these differences [56–59]. Achieving these goals could be facilitated by the use of standardized and validated perioperative assessment.

Metamizole seems to be relatively safe for postoperative pain treatment after consideration of some limitations caused by potential adverse effects (MIA, DILI, and allergic reactions). Therefore, metamizole therapy, especially at high doses, should only be used with a high level of caution [100].

Among others, critical hypotension as a consequence of rapid *i.v.* administration should be considered in clinical practice. The hypotension after metamizole use is possibly dose-dependent and particularly affects hemodynamically unstable patients [85, 86]. Therefore, a prolonged infusion of the drug (20–30 minutes) with simultaneous circulatory monitoring is recommended [86]. Because of the above reasons, metamizole use should be critically assessed, especially in prolonged treatment during the postoperative period.

Number-need-to-treat (NNT) is a standardized measure of efficacy that allows for the comparison of analgesics across trials. Lower values indicate higher pain relief with the use of a specific analgesic.

This method has been popular as a tool for the evaluation of analgesic efficacy in chronic pain treatment. NNT has been used to compare treatments and help clinical decision-making. However, there are some controversies about its use because of unrepeatable data achieved [107]. Thus, NNT is associated with

specific limitations regarding the method of calculation and interpretation. Nevertheless, this parameter may be useful for the evaluation of analgesic potency in clinical practice. Metamizole has been shown as a quite potent analgesic (Table 4).

In the latest available data from the 2016 Cochrane review, Hearn et al. [108] assessed the analgesic efficacy and associated adverse effects of a single dose of metamizole in the treatment of moderate to severe acute postoperative pain. The analysis

Table 4. Efficiency of selected non-opioid analgesics (NOA) [134, 135]

Drug	Number of patients	Dose [mg]*	NNT	95% CI
Aspirin	4965	600/650	4.2	3.8–4.6
Aspirin	249	1200	2.4	1.9–3.2
Celecoxib	705	200	4.2	3.4–5.6
Celecoxib	722	400	2.6	2.3–3.0
Dexketoprofen	452	10/12.5	3.6	2.8–5.0
Dexketoprofen	523	20/25	3.2	2.6 – 4.1
Diclofenac	284	50	6.6	4.2–17.0
Diclofenac (fast acting)	486	100	2.4	2.0–3.0
Etoricoxib	798	120	1.8	1.7–2.0
Ibuprofen	316	50	4.7	3.3–8.0
Ibuprofen	396	100	4.3	3.2–6.4
Ibuprofen	2103	200	2.9	2.7–3.2
Ibuprofen	6475	400	2.5	2.4–2.6
Ibuprofen	203	600	2.7	2.0–4.2
Ketoprofen	274	12.5	2.4	1.9–3.1
Ketoprofen	535	25	2.0	1.8–2.3
Ketoprofen	624	50	3.3	2.7–4.3
Ketoprofen	321	100	2.1	1.7–2.6
Ketorolac	790	10	2.6	2.3–3.1
Ketorolac	69	20	1.8	1.4–2.5
Ketorolac	359	30 (*i.m.*)	3.4	2.5–4.9
Ketorolac	116	60 (*i.m.*)	1.8	1.5–2.3
Metamizole	**288**	**500**	**2.3**	**1.9–3.1**
Metamizole	**113**	**1000**	**1.6**	**1.3–2.2**
Naproxen	202	200/220	3.4	2.4–5.8
Naproxen	334	400/440	2.7	2.2–3.5
Naproxen	784	500/550	2.7	2.3–3.3
Paracetamol	561	500	3.5	2.2–13.3
Paracetamol	3232	975/1000	3.6	3.2–4.1
Paracetamol	138	1500	3.7	2.3–9.5
Parecoxib	170	20 (*i.v.*)	3.0	2.3–4.1
Parecoxib	173	40 (*i.v.*)	2.2	1.8–2.7
Piroxicam	30	40	1.9	1.2–4.3
Valdecoxib**	101	20	1.7	1.4–2.0
Valdecoxib**	279	40	1.6	1.4–1.8

*Oral route unless otherwise specified; **drug was withdrawn in 2005 from the market due to potential increased risk for serious cardiovascular side events and increased risk of serious skin reactions; CI — confidence interval; *i.m.* — *intramuscularis*; *i.v.* — intravenosa; NNT — number-need-to-treat

included eight studies (7 studies with *p.o.* route and 1 study with *i.m.* route of metamizole administration) involving 809 participants. The results showed 50% pain relief in 70% of patients treated with *p.o.* metamizole *vs.* 30% in the control group (placebo). NNT for metamizole was 2.4 (95% CI 1.8 to 3.1). Moreover, the need for additional analgesia appears to be less often for the metamizole group in comparison with the control group (7% and 34% respectively). Unfortunately, other routes of drug administration, especially *i.v.*, are represented by insufficient data to draw binding conclusions.

In the literature review, Konijnenbelt-Peters et al. [82] discussed whether metamizole could be an alternative to classical NSAIDs and opioids in postoperative pain management. The authors showed that metamizole causes fewer gastric and duodenal ulcers than nonselective NSAIDs with a lower risk for gastrointestinal (GI) bleeding. Then, metamizole could be used as an alternative in patients with an increased risk for gastric or renal diseases. There is, however, no evidence for higher safety in comparison with the usage of nonselective NSAIDs combined with a proton pump inhibitor.

The survey conducted by Lux et al. [109] showed the important role of metamizole in the management of acute and postoperative pain in the outpatient setting. The analysis included a total of 86,616 patients treated with analgesics in the postoperative period. In the perioperative period, 62% of respondents took metamizole (compared to 66% taking NSAIDs, 41% paracetamol and 73% opioids, respectively). Another survey of anesthesiologists performed by Reist et al. [110] in German-speaking countries showed that metamizole is the preferred non-opioid analgesic for the treatment of acute and chronic pain. Moreover, Vilcane et al. [111] in their survey of emergency services in Germany, presented metamizole as one of the important non-opioid analgesics in prehospital pain treatment.

In a multicentered survey study performed by Ponholzer et al. [112] in thoracic surgery units, the authors described the heterogeneity in postoperative pain treatment after video-assisted thoracic surgery (VATS) procedures, including anatomic lung resections. The results showed that the most used medication was metamizole. However, the use of regional anesthesia in the perioperative period, recommended by enhanced recovery after surgery (ERAS) programs, was not utilized uniformly. There are no contraindications to combining both techniques and obtaining an optimal therapeutic effect. In an earlier observational study of 40 patients undergoing awake craniotomy for the removal of brain tumors, Grossman et al. [113] used local intradermal infiltration of the scalp combined with a single dose of metamizole to improve the treatment of postoperative pain. Despite promising results, metamizole has not been recommended yet for pain management in patients undergoing craniotomy because of the lack of procedure-specific evidence [114].

The oral use of analgesics in the treatment of postoperative pain seems to be safe and is recommended by many authors. However, parenteral analgesia remains to be more effective and convenient for some perioperative schedules. Parenteral ready-to-use fixed-dose combinations of non-opioid analgesics have been introduced to the market and seem to be a convenient way to improve postoperative pain treatment regimens [115]. Therefore, metamizole combined with NSAIDs and paracetamol in ready-to--use formulas could be advantageous as multimodal and parenteral analgesia.

Some data showed that the efficacy of metamizole in a period of high inflammatory response after surgery is poorer than after other COX inhibitors (both selective/nonselective) [39, 44, 45, 47]. These findings suggest the lower anti-inflammatory effect of metamizole than classical NSAIDs. In the meta-analysis of the effectiveness of preemptive analgesia with non-steroidal anti-inflammatory drugs (NSAIDs) in third-molar surgery, Costa et al. [116] showed no significant benefit of preemptive analgesia in reducing postoperative pain. However, the authors concluded that there could be a probable direct relationship between the effectiveness of NSAIDs in preemptive analgesia and its selectivity for cyclooxygenase-2 (COX-2). The different mechanisms of metamizole's action and low anti-inflammatory effect could be the reason for failed studies on its preemptive efficacy. There is evidence of drug ineffectiveness in 2^{nd}–3^{rd} postoperative days when the main pain component seems to be secondary inflammation. Thus, metamizole should not be considered as a sole analgesic but rather has to be combined with other NOPA to get the most optimal analgesic effect.

Despite the above conclusions, some studies showed the potential, neuroprotective role of metamizole which could alleviate processes of neuroinflammation in central and peripheral nervous systems. Maytalman et al. [117] observed an increase in NGF and nestin (neuroepithelial stem cell protein) mRNA expressions under the influence of metamizole. Moreover, metamizole can cause an increase in gonadotropin hormone-releasing hormone (GnRH) mRNA expression [117]. These findings could reveal some potential role of metamizole in the prevention of the chronification of pain.

Chronic postoperative pain (CPOP) occurs as the result of persistent neuroplastic changes after activation by nociceptive stimulation [118]. Alterations in neurotransmission are triggered by neurotrophic factors. Their influences on interactions between neurons and microglia have interfered with inhibitory modulation of nociception [119]. Microglia intracellular signaling has undergone continuous up-regulation leading to permanent stimulation of neurons (central sensitization) followed by perception and chronification of pain [118]. In a model of acute pain, Schumacher et al. [120] showed that peripheral injury-induced inflammation becomes persistent through repeated cycles of TRP channel modification, Sp4-dependent overexpression of TRP channels, and ongoing production of inflammatory mediators. Thus, metamizole could potentially prevent the onset of chronic postoperative pain (CPOP) by its impact on TRP channels.

Nestin, as mentioned before, is a cytoskeletal intermediate filament initially found in neural and mesenchymal stem cells. Nestin+ cells with progenitor and/or regulatory functions are localized in other tissues, including bone marrow [117, 121]. Thus, this mechanism could explain the potency of metamizole for the arising of agranulocytosis. Currently, nestin+ cells are under research in preclinical models of neurodegenerative diseases and bone marrow malignancies [121].

Additionally, some gender-dependent differences in the metabolism of metamizole have been observed [122]. Thus, analgesic therapy with the use of metamizole could be more effective in the female population. On the other side, statistically significant differences in the degree of metamizole's demethylation have not been observed between sexes [123]. Gender and functional polymorphisms are strongly related to the metabolic profiles of metamizole [122]. Moreover, as mentioned above, Maytalman et al. [117] in the study of GT1-7 mouse hypothalamic GnRH neuronal cell line showed an increase in GnRH mRNA expression after metamizole application.

Therefore, assessing the gender-dependent effectiveness of metamizole requires further research. Another important observation made in the study of Chapparo et al. [124] have shown metamizole dose-dependent increase in analgesic effect. This issue is particularly noteworthy because of the potential increased risk of the drug's adverse effects with higher doses. The observation also requires confirmation with a study on a larger population.

Evidence-based medicine (EBM) indicates the validity of using multimodal analgesia in the treatment of postoperative pain. The results showed the necessity of at least 2 different nonopioid analgesic drug classes (cyclooxygenase inhibitors, acetaminophen, nefopam, or metamizole) to provide meaningful pain relief (> 30%) [125]. Therefore, it can be concluded that the multimodal use of non-opioid analgesics, including metamizole, seems to be essential in the effective treatment of postoperative pain. In countries with approval for use, metamizole is recommended for postoperative analgesia including MMA [126–128].

Identification of the optimal treatment based on MMA remains challenging. Multiple analgesic options are available, but comparisons of outcomes are limited by a lack of comparable trials. Methods for assessing pain in the intra- and postoperative period have been proposed to optimize perioperative procedures. These methods are integral parts of international initiatives such as ERAS® (enhanced recovery after surgery) and PROSPECT (procedure-specific postoperative pain management) aimed at optimizing perioperative management. Another project has also been introduced, using multi-criteria decision analysis (MCDA) to quantify and compare the efficacy and safety data of various drugs [129]. Moreover, for optimum patient care, the implementation of evidence-based schedules in recommendations could improve the quality of postoperative pain management [130].

The use of artificial intelligence (AI) to predict pain intensity may be useful in establishing sufficient therapeutic regimens. The practitioners usually used two or more analgesics for better control of postoperative pain. These regimens are based on the potential synergistic effects of administered drugs. In the study, Fritsch et al. [131] used artificial intelligence algorithms to predict the efficacy of analgesic cocktails used for postoperative treatment of orthopedic surgical procedures and showed their beneficiary effects. All these cocktails contained metamizole.

Moreover, some studies show the opioid-sparing effect of metamizole. Patients treated with tramadol in emergency departments have a higher risk of opioid use at the one-year follow-up than those treated with NSAIDs or metamizole [132]. Therefore, metamizole could be used as an alternative in patients potentially susceptible to opioids [133].

In summary, due to limited data, the studies on the perioperative use of metamizole presented above are of rather low quality. Moreover, an analysis of insufficiency and/or adverse events accompanying therapy was impossible due to the lack of consistent data. However, the reliable assessment of metamizole efficacy requires further evaluation due to the small number of well-designed studies on its effectiveness, particularly in multimodal and preemptive/preventive analgesia protocols.

Conclusions and further perspectives

Metamizole as one of the potentially effective nonopioid analgesics is an important component of multimodal perioperative analgesia. Some data indicates a relatively high level of safety. Metamizole appears to be the preferred analgesic in patients with concomitant cardiovascular and renal disease. Unfortunately, the drug is considered controversial due to its serious adverse reactions. Thus, it is probably the reason, why there are no extensive studies on its use in postoperative pain treatment. Indications for metamizole should be determined individually, taking into account the patient's characteristics including type of surgery and combination with other analgesics for the best therapeutic effects. Moreover, special cautions have to be taken, referring to potentially serious adverse effects such as myelotoxicity, DILI, and allergic reactions. For that reason, standardized treatment regimens should be implemented to prevent potential severe complications of metamizole use. Therefore, because of the limited availability of data regarding the use of metamizole in perioperative multimodal and preemptive analgesia, this requires further research, which should be carried out taking into account appropriate precautions while obtaining sufficiently extensive data.

Article information and declarations

Acknowledgments
None.

Author contributions
ADG is the first author of the publication and mainly participated in the tasks of conceptualization, methodology, and writing (original draft preparation). DK end BL participated in review and editing. All authors have read and agreed to the published version of the manuscript.

Conflict of interest
The authors declare that there is no conflict of interest.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Supplementary material
The Supplementary Material for this article can be found online at https://journals.viamedica.pl/palliative_medicine_in_practice/article/view/101971.

References

1. Kötter T, da Costa BR, Fässler M, et al. Metamizole-associated adverse events: a systematic review and meta-analysis. PLoS One. 2015; 10(4): e0122918, doi: 10.1371/journal.pone.0122918, indexed in Pubmed: 25875821.
2. Lutz M. Metamizole (dipyrone) and the liver: a review of the literature. J Clin Pharmacol. 2019; 59(11): 1433–1442, doi: 10.1002/jcph.1512, indexed in Pubmed: 31433499.
3. Andrade S, Bartels DB, Lange R, et al. Safety of metamizole: a systematic review of the literature. J Clin Pharm Ther. 2016; 41(5): 459–477, doi: 10.1111/jcpt.12422, indexed in Pubmed: 27422768.
4. European Medicines Agency. https://www.ema.europa.eu/en/homepage (13.08.2024).
5. Levy M, Zylber-Katz E, Rosenkranz B. Clinical pharmacokinetics of dipyrone and its metabolites. Clin Pharmacokinet. 1995; 28(3): 216–234, doi: 10.2165/00003088-199528030-00004, indexed in Pubmed: 7758252.
6. Zylber-Katz E, Granit L, Stessman J, et al. Effect of age on the pharmacokinetics of dipyrone. Eur J Clin Pharmacol. 1989; 36(5): 513–516, doi: 10.1007/BF00558078, indexed in Pubmed: 2753071.
7. Hong GS, Stein K, Lysson M, et al. A comparative study about the immunomodulatory effects of tramadol and metamizole in a murine model of postoperative ileus. Lab Anim. 2019; 53(6): 610–618, doi: 10.1177/0023677219832919, indexed in Pubmed: 30907232.
8. Brogden RN. Pyrazolone derivatives. Drugs. 1986; 32 Suppl 4: 60–70, doi: 10.2165/00003495-198600324-00006, indexed in Pubmed: 3552586.
9. Rogosch T, Sinning C, Podlewski A, et al. Novel bioactive metabolites of dipyrone (metamizol). Bioorg Med Chem. 2012; 20(1): 101–107, doi: 10.1016/j.bmc.2011.11.028, indexed in Pubmed: 22172309.
10. Pierre SC, Schmidt R, Brenneis C, et al. Inhibition of cyclooxygenases by dipyrone. Br J Pharmacol. 2007; 151(4): 494–503, doi: 10.1038/sj.bjp.0707239, indexed in Pubmed: 17435797.
11. dos Santos GG, Dias EV, Teixeira JM, et al. The analgesic effect of dipyrone in peripheral tissue involves two different mechanisms: neuronal K(ATP) channel opening and CB(1) receptor activation. Eur J Pharmacol. 2014; 741: 124–131, doi: 10.1016/j.ejphar.2014.07.019, indexed in Pubmed: 25058903.
12. Gonçalves Dos Santos G, Vieira WF, Vendramini PH, et al. Dipyrone is locally hydrolyzed to 4-methylaminoantipyrine and its antihyperalgesic effect depends on CB and kappa-opioid receptors activation. Eur J Pharmacol. 2020; 874: 173005, doi: 10.1016/j.ejphar.2020.173005, indexed in Pubmed: 32057719.
13. Russo S, de Azevedo WF. Computational analysis of dipyrone metabolite 4-aminoantipyrine as a cannabinoid receptor 1 agonist. Curr Med Chem. 2020; 27(28): 4741–4749, doi: 10.2174/0929867326666190906155339, indexed in Pubmed: 31490743.
14. Schenk SA, Dick F, Herzog C, et al. Active metabolites of dipyrone induce a redox-dependent activation of the ion channels TRPA1 and TRPV1. Pain Rep. 2019; 4(3): e720, doi: 10.1097/PR9.0000000000000720, indexed in Pubmed: 31583344.
15. Maione S, Radanova L, De Gregorio D, et al. Effects of metabolites of the analgesic agent dipyrone (metamizol) on rostral ventromedial medulla cell activity in mice. Eur J Pharmacol. 2015; 748: 115–122, doi: 10.1016/j.ejphar.2014.12.022, indexed in Pubmed: 25557763.
16. Malvar Dd, Soares DM, Fabrício ASC, et al. The antipyretic effect of dipyrone is unrelated to inhibition of PGE(2)

synthesis in the hypothalamus. Br J Pharmacol. 2011; 162(6): 1401–1409, doi: 10.1111/j.1476-5381.2010.01150.x, indexed in Pubmed: 21133897.
17. Valenzuela F, García-Saisó S, Lemini C, et al. Metamizol acts as an ATP sensitive potassium channel opener to inhibit the contracting response induced by angiotensin II but not to norepinephrine in rat thoracic aorta smooth muscle. Vascul Pharmacol. 2005; 43(2): 120–127, doi: 10.1016/j.vph.2005.05.003, indexed in Pubmed: 15958287.
18. Gulmez SE, Gurdal H, Tulunay FC. Airway smooth muscle relaxations induced by dipyrone. Pharmacology. 2006; 78(4): 202–208, doi: 10.1159/000096688, indexed in Pubmed: 17077647.
19. Gulmez SE, Celik G, Misirligil Z, et al. Dipyrone improves small airway function in asthmatic patients with moderate obstruction. J Investig Allergol Clin Immunol. 2007; 17(4): 242–248, indexed in Pubmed: 17694696.
20. Vinagre AM, Collares EF. Effect of selective β-adrenoceptor blockade and surgical resection of the celiac-superior mesenteric ganglion complex on delayed liquid gastric emptying induced by dipyrone, 4-aminoantipyrine, and antipyrine in rats. Braz J Med Biol Res. 2016; 49(3), doi: 10.1590/1414-431X20155011, indexed in Pubmed: 26840714.
21. Collares EF, Troncon LEA. Effects of dipyrone on the digestive tract. Braz J Med Biol Res. 2019; 52(2): e8103, doi: 10.1590/1414-431X20188103, indexed in Pubmed: 30652827.
22. Stammschulte T, Ludwig WD, Mühlbauer B, et al. Metamizole (dipyrone)-associated agranulocytosis. An analysis of German spontaneous reports 1990–2012. Eur J Clin Pharmacol. 2015; 71(9): 1129–1138, doi: 10.1007/s00228-015-1895-y, indexed in Pubmed: 26169297.
23. Hoffmann F, Bantel C, Jobski K. Agranulocytosis attributed to metamizole: An analysis of spontaneous reports in EudraVigilance 1985–2017. Basic Clin Pharmacol Toxicol. 2020; 126(2): 116–125, doi: 10.1111/bcpt.13310, indexed in Pubmed: 31449718.
24. Björnsson ES. Liver injury associated with the analgetic drug metamizole. Br J Clin Pharmacol. 2020; 86(7): 1248–1250, doi: 10.1111/bcp.14294, indexed in Pubmed: 32400058.
25. Sebode M, Reike-Kunze M, Weidemann S, et al. Metamizole: an underrated agent causing severe idiosyncratic drug-induced liver injury. Br J Clin Pharmacol. 2020; 86(7): 1406–1415, doi: 10.1111/bcp.14254, indexed in Pubmed: 32080881.
26. Blanca-López N, Pérez-Sánchez N, Agúndez JA, et al. Allergic reactions to metamizole: immediate and delayed responses. Int Arch Allergy Immunol. 2016; 169(4): 223–230, doi: 10.1159/000444798, indexed in Pubmed: 27224978.
27. Lopes A, Paulino M, Spínola Santos A, et al. Delayed postoperative reactions to metamizole: a diagnostic challenge. Eur Ann Allergy Clin Immunol. 2023 [Epub ahead of print], doi: 10.23822/EurAnnACI.1764-1489.317, indexed in Pubmed: 38054601.
28. Mukherjee S, Sood S. A controlled evaluation of orally administered aspirin, dipyrone and placebo in patients with post-operative pain. Curr Med Res Opin. 1980; 6(9): 619–623, doi: 10.1185/03007998009109498, indexed in Pubmed: 6996932.
29. Mehta SD. A randomized double-blind placebo-controlled study of dipyrone and aspirin in post-operative orthopaedic patients. J Int Med Res. 1986; 14(2): 63–66, doi: 10.1177/030006058601400202, indexed in Pubmed: 3516752.
30. Daftary SN, Mehta AC, Nanavati M. A controlled comparison of dipyrone and paracetamol in post-episiotomy pain. Curr Med Res Opin. 1980; 6(9): 614–618, doi: 10.1185/03007998009109497, indexed in Pubmed: 6996931.
31. Planas ME, Gay-Escoda C, Bagán JV, et al. Oral metamizol (1 g and 2 g) versus ibuprofen and placebo in the treatment of lower third molar surgery pain: randomised double-blind multi-centre study. Cooperative Study Group. Eur J Clin Pharmacol. 1998; 53(6): 405–409, doi: 10.1007/s002280050400, indexed in Pubmed: 9580448.
32. Tempel G, von Hundelshausen B, Reeker W. The opiate-sparing effect of dipyrone in post-operative pain therapy with morphine using a patient-controlled analgesic system. Intensive Care Med. 1996; 22(10): 1043–1047, doi: 10.1007/BF01699225, indexed in Pubmed: 8923067.
33. Blendinger I, Eberlein HJ. Comparison of intravenous acetylsalicylic acid and dipyrone in postoperative pain: an interim report. Br J Clin Pharmacol. 1980; 10 Suppl 2(Suppl 2): 339S–341S, doi: 10.1111/j.1365-2125.1980.tb01819.x, indexed in Pubmed: 7437274.
34. Gómez-Jiménez J, Franco-Patino R, Chargoy-Vera J, et al. Clinical efficacy of mild analgesics in pain following gynaecological or dental surgery: report on multicentre studies. Br J Clin Pharmacol. 1980; 10 Suppl 2(Suppl 2): 355S–358S, doi: 10.1111/j.1365-2125.1980.tb01823.x, indexed in Pubmed: 7437277.
35. Landwehr S, Kiencke P, Giesecke T, et al. A comparison between IV paracetamol and IV metamizol for postoperative analgesia after retinal surgery. Curr Med Res Opin. 2005; 21(10): 1569–1575, doi: 10.1185/030079905X61857, indexed in Pubmed: 16238896.
36. Kampe S, Warm M, Landwehr S, et al. Clinical equivalence of IV paracetamol compared to IV dipyrone for postoperative analgesia after surgery for breast cancer. Curr Med Res Opin. 2006; 22(10): 1949–1954, doi: 10.1185/030079906x132659, indexed in Pubmed: 17022854.
37. Patel CV, Koppikar MG, Patel MS, et al. Management of pain after abdominal surgery: dipyrone compared with pethidine. Br J Clin Pharmacol. 1980; 10 Suppl 2(Suppl 2): 351S–354S, doi: 10.1111/j.1365-2125.1980.tb01822.x, indexed in Pubmed: 7437276.
38. Rodriguez MJ, Torre MRD, Perez-Iraola P, et al. Comparative study of tramadol versus NSAIDS as intravenous continuous infusion for managing postoperative pain. Current Therapeutic Research. 1993; 54(4): 375–383, doi: 10.1016/s0011-393x(05)80639-3.
39. Bagán JV, López Arranz JS, Valencia E, et al. Clinical comparison of dexketoprofen trometamol and dipyrone in postoperative dental pain. J Clin Pharmacol. 1998; 38(S1): 55S–64S, doi: 10.1002/jcph.1998.38.s1.55, indexed in Pubmed: 29023870.
40. Saray A, Büyükkocak U, Cinel I, et al. Diclofenac and metamizol in postoperative analgesia in plastic surgery. Acta Chir Plast. 2001; 43(3): 71–76, indexed in Pubmed: 11692987.
41. Rawal N, Allvin R, Amilon A, et al. Postoperative analgesia at home after ambulatory hand surgery: a controlled comparison of tramadol, metamizol, and paracetamol. Anesth Analg. 2001; 92(2): 347–351, doi: 10.1097/00000539-200102000-00013, indexed in Pubmed: 11159230.
42. Torres LM, Rodríguez MJ, Montero A, et al. Efficacy and safety of dipyrone versus tramadol in the management of pain after hysterectomy: a randomized, double-blind, multicenter study. Reg Anesth Pain Med. 2001; 26(2): 118–124, doi: 10.1053/rapm.2001.21437, indexed in Pubmed: 11251134.
43. Grundmann U, Wörnle C, Biedler A, et al. The efficacy of the non-opioid analgesics parecoxib, paracetamol and metamizol for postoperative pain relief after lumbar microdiscectomy. Anesth Analg. 2006; 103(1): 217–222, doi: 10.1213/01.ane.0000221438.08990.06, indexed in Pubmed: 16790656.

44. Jovic R, Dragicevic D, Komazec Z, et al. Ketoprofen is superior to metamizole in relieving postoperative pain after head and neck tumor operation. J BUON. 2008; 13(4): 519–523, indexed in Pubmed: 19145673.
45. Soltesz S, Gerbershagen MU, Pantke B, et al. Parecoxib versus dipyrone (metamizole) for postoperative pain relief after hysterectomy : a prospective, single-centre, randomized, double-blind trial. Clin Drug Investig. 2008; 28(7): 421–428, doi: 10.2165/00044011-200828070-00003, indexed in Pubmed: 18544002.
46. Sener M, Yilmazer C, Yilmaz I, et al. Efficacy of lornoxicam for acute postoperative pain relief after septoplasty: a comparison with diclofenac, ketoprofen, and dipyrone. J Clin Anesth. 2008; 20(2): 103–108, doi: 10.1016/j.jclinane.2007.09.009, indexed in Pubmed: 18410864.
47. Sener M, Yilmazer C, Yilmaz I, et al. Patient-controlled analgesia with lornoxicam vs. dipyrone for acute postoperative pain relief after septorhinoplasty: a prospective, randomized, double-blind, placebo-controlled study. Eur J Anaesthesiol. 2008; 25(3): 177–182, doi: 10.1017/S0265021507002827, indexed in Pubmed: 17953792.
48. Noronha VRS, Gurgel GdS, Alves LC, et al. Analgesic efficacy of lysine clonixinate, paracetamol and dipyrone in lower third molar extraction: a randomized controlled trial. Med Oral Patol Oral Cir Bucal. 2009; 14(8): e411–e415, indexed in Pubmed: 19415056.
49. Korkmaz Dilmen O, Tunali Y, Cakmakkaya OS, et al. Efficacy of intravenous paracetamol, metamizol and lornoxicam on postoperative pain and morphine consumption after lumbar disc surgery. Eur J Anaesthesiol. 2010; 27(5): 428–432, doi: 10.1097/EJA.0b013e32833731a4, indexed in Pubmed: 20173643.
50. Karaman Y, Çukurova I, Demirhan E, et al. Efficacy of dexketoprofen trometamol for acute postoperative pain relief after ENT surgery: acomparision with paracetamol and metamizole. Nobel Medicus. 2010; 6(2): 47–52.
51. Brodner G, Gogarten W, Van Aken H, et al. Efficacy of intravenous paracetamol compared to dipyrone and parecoxib for postoperative pain management after minor-to-intermediate surgery: a randomised, double-blind trial. Eur J Anaesthesiol. 2011; 28(2): 125–132, doi: 10.1097/EJA.0b013e32833fedfa, indexed in Pubmed: 20890207.
52. Abdulla S, Eckhardt R, Netter U, et al. A randomized, double-blind, controlled trial on non-opioid analgesics and opioid consumption for postoperative pain relief after laparoscopic cholecystectomy. Acta Anaesthesiol Belg. 2012; 63(1): 43–50, indexed in Pubmed: 22783709.
53. Abdulla S, Eckhardt R, Netter U, et al. Efficacy of three IV non-opioid-analgesics on opioid consumption for postoperative pain relief after total thyroidectomy: a randomised, double-blind trial. Middle East J Anaesthesiol. 2012; 21(4): 543–552, indexed in Pubmed: 23327027.
54. Abdulla S, Eckhardt R, Netter U, et al. Randomized, double-blind, placebo-controlled study to assess the efficacy of nonopioid analgesics on pain following arthroscopic knee surgery. Pain Res Treat. 2012; 2012: 305821, doi: 10.1155/2012/305821, indexed in Pubmed: 23213511.
55. Santonocito C, Noto A, Crimi C, et al. Remifentanil-induced postoperative hyperalgesia: current perspectives on mechanisms and therapeutic strategies. Local Reg Anesth. 2018; 11: 15–23, doi: 10.2147/LRA.S143618, indexed in Pubmed: 29670398.
56. Oreskovic Z, Bicanic G, Hrabac P, et al. Treatment of postoperative pain after total hip arthroplasty: comparison between metamizol and paracetamol as adjunctive to opioid analgesics-prospective, double-blind, randomised study. Arch Orthop Trauma Surg. 2014; 134(5): 631–636, doi: 10.1007/s00402-014-1979-7, indexed in Pubmed: 24676651.
57. Dilmen OK, Akcil EF, Tunali Y, et al. Postoperative analgesia for supratentorial craniotomy. Clin Neurol Neurosurg. 2016; 146: 90–95, doi: 10.1016/j.clineuro.2016.04.026, indexed in Pubmed: 27164511.
58. Geißler K, Ducke M, Volk GF, et al. Pain on the first postoperative day after tonsillectomy in adults: a comparison of metamizole versus etoricoxib as baseline analgesic. PLoS One. 2019; 14(8): e0221188, doi: 10.1371/journal.pone.0221188, indexed in Pubmed: 31412091.
59. Gostian AO, Loeser J, Tholen C, et al. Postoperative pain after tonsillectomy - the value of standardized analgesic treatment protocols. Auris Nasus Larynx. 2020; 47(6): 1009–1017, doi: 10.1016/j.anl.2020.05.011, indexed in Pubmed: 32536501.
60. Steffen P, Schuhmacher I, Weichel T, et al. [Differential administration of non-opioids in postoperative analgesia, I. Quantification of the analgesic effect of metamizole using patient-controlled analgesia]. Anasthesiol Intensivmed Notfallmed Schmerzther. 1996; 31(3): 143–147, doi: 10.1055/s-2007-995890, indexed in Pubmed: 8672615.
61. Steffen P, Seeling W, Reiser A, et al. [Differential indications for non-opioids for postoperative analgesia III. Analgesic effect of perioperative administration of metamizole plus diclofenac after spinal anesthesia]. Anasthesiol Intensivmed Notfallmed Schmerzther. 1997; 32(8): 496–501, doi: 10.1055/s-2007-995098, indexed in Pubmed: 9376465.
62. Steffen P, Seeling W, Kunz R, et al. [Postoperative analgesia after endoscopic abdominal operations. A randomized double-blind study of perioperative effectiveness of metamizole]. Chirurg. 1997; 68(8): 806–810, doi: 10.1007/s001040050275, indexed in Pubmed: 9377992.
63. Srebrzyński A, Ziółkowski R, Płużańska K, et al. Analiza przeciwbólowego działania metamizolu u chorych operowanych z powodu wola [Analysis of the analgesic effect of metamizole sodium in patients operated on for goitre]. Polish J Surgery. 2008; 80(5): 466–479, doi: 10.2478/v10035-008-0034-1.
64. Ohnesorge H, Bein B, Hanss R, et al. Paracetamol versus metamizol in the treatment of postoperative pain after breast surgery: a randomized, controlled trial. Eur J Anaesthesiol. 2009; 26(8): 648–653, doi: 10.1097/EJA.0b013e328329b0fd, indexed in Pubmed: 19487950.
65. Lauretti GR, Righeti CCf, Kitayama AT. Analgesia after epidural dexamethasone is further enhanced by IV dipyrone, but not IV parecoxibe following minor orthopedic surgery. Korean J Pain. 2014; 27(4): 345–352, doi: 10.3344/kjp.2014.27.4.345, indexed in Pubmed: 25317284.
66. Węgorowski P, Stanisławek A, Domżał-Drzewicka R, et al. The effect of pre-emptive analgesia on the level of postoperative pain in women undergoing surgery for breast neoplasm. Contemp Oncol (Pozn). 2016; 20(2): 158–164, doi: 10.5114/wo.2016.60071, indexed in Pubmed: 27358596.
67. Neychev D, Chenchev I, Simitchiev K, et al. Analysis of postoperative pain after extraction of impacted mandibular third molars and administration of preemptive analgesia.

J of IMAB. 2017; 23(3): 1697–1701, doi: 10.5272/jimab.2017233.1697.
68. Favarini VT, Lima CA, da Silva RA, et al. Is dipyrone effective as a preemptive analgesic in third molar surgery? A pilot study. Oral Maxillofac Surg. 2018; 22(1): 71–75, doi: 10.1007/s10006-018-0669-y, indexed in Pubmed: 29353426.
69. Suljević I, Hadžiavdić M, Šurković I, et al. The preemptive effect of tramadol and metamizole on the intensity of postoperative pain. Med Glas (Zenica). 2020; 17(2): 285–289, doi: 10.17392/1118-20, indexed in Pubmed: 32483957.
70. Stessel B, Lambrechts M, Evers S, et al. Additive or synergistic analgesic effect of metamizole on standard pain treatment at home after arthroscopic shoulder surgery: a randomised controlled superiority trial. Eur J Anaesthesiol. 2023; 40(3): 171–178, doi: 10.1097/EJA.0000000000001792, indexed in Pubmed: 36632758.
71. Stasiowski MJ, Lyssek-Boroń A, Zmarzły N, et al. The adequacy of anesthesia guidance for vitreoretinal surgeries with preemptive paracetamol/metamizole. Pharmaceuticals (Basel). 2024; 17(1): 129, doi: 10.3390/ph17010129, indexed in Pubmed: 38256962.
72. Joshi GP. Rational multimodal analgesia for perioperative pain management. Curr Pain Headache Rep. 2023; 27(8): 227–237, doi: 10.1007/s11916-023-01137-y, indexed in Pubmed: 37405552.
73. Striebel HW, Hackenberger J. [A comparison of a tramadol/metamizole infusion with the combination tramadol infusion plus ibuprofen suppositories for postoperative pain management following hysterectomy]. Anaesthesist. 1992; 41(6): 354–360, indexed in Pubmed: 1636921.
74. Schneider T, Mauermann E, Ilgenstein B, et al. Analgesic benefit of metamizole and ibuprofen vs. either medication alone: a randomized clinical trial. Minerva Anestesiol. 2022; 88(6): 448–456, doi: 10.23736/S0375-9393.22.16346-7, indexed in Pubmed: 35416465.
75. Stessel B, Boon M, Pelckmans C, et al. Metamizole vs. ibuprofen at home after day case surgery: A double-blind randomised controlled noninferiority trial. Eur J Anaesthesiol. 2019; 36(5): 351–359, doi: 10.1097/EJA.0000000000000972, indexed in Pubmed: 30946703.
76. Samulak D, Michalska M, Gaca M, et al. Efficiency of postoperative pain management after gynecologic oncological surgeries with the use of morphine + acetaminophen + ketoprofen versus morphine + metamizol + ketoprofen. Eur J Gynaecol Oncol. 2011; 32(2): 168–170, indexed in Pubmed: 21614906.
77. Uzun S, Aycan IO, Erden IA, et al. The addition of metamizole to morphine and paracetamol improves early postoperative analgesia and patient satisfaction after lumbar disc surgery. Turk Neurosurg. 2010; 20(3): 341–347, doi: 10.5137/1019-5149.JTN.3081-10.3, indexed in Pubmed: 20669107.
78. Martinez V, Beloeil H, Marret E, et al. Non-opioid analgesics in adults after major surgery: systematic review with network meta-analysis of randomized trials. Br J Anaesth. 2017; 118(1): 22–31, doi: 10.1093/bja/aew391, indexed in Pubmed: 28039239.
79. VigiAccess WHO. https://www.vigiaccess.org/ (13.08.2024).
80. Zukowski M, Kotfis K. [Safety of metamizole and paracetamol for acute pain treatment]. Anestezjol Intens Ter. 2009; 41(3): 170–175, indexed in Pubmed: 19999607.
81. Sittl R, Bäumler P, Stumvoll AM, et al. [Considerations concerning the perioperative use of metamizole]. Anaesthesist. 2019; 68(8): 530–537, doi: 10.1007/s00101-019-00637-0, indexed in Pubmed: 31435718.
82. Konijnenbelt-Peters J, van der Heijden C, Ekhart C, et al. Metamizole (dipyrone) as an alternative agent in postoperative analgesia in patients with contraindications for nonsteroidal anti-inflammatory drugs. Pain Pract. 2017; 17(3): 402–408, doi: 10.1111/papr.12467, indexed in Pubmed: 27346584.
83. Stamer UM, Erlenwein J, Freys SM, et al. [Perioperative analgesia with nonopioid analgesics : Joint interdisciplinary consensus-based recommendations of the German Pain Society, the German Society of Anaesthesiology and Intensive Care Medicine and the German Society of Surgery]. Chirurg. 2021; 92(7): 647–663, doi: 10.1007/s00104-021-01421-w, indexed in Pubmed: 34037807.
84. Hoenicka M, Gorki H, Traeger K, et al. Selective venous vasodilator properties of the analgesic metamizole (dipyrone) in a human ex vivo model-implications for postoperative pain management. Naunyn Schmiedebergs Arch Pharmacol. 2017; 390(5): 519–526, doi: 10.1007/s00210-017-1347-6, indexed in Pubmed: 28144710.
85. Hoenicka M, Stahl L, Datzmann T, et al. Effect of the analgesic metamizole (dipyrone) on volume balance and vasopressor use in cardiac surgery patients. Minerva Anestesiol. 2022; 88(12): 1073–1074, doi: 10.23736/S0375-9393.22.16722-2, indexed in Pubmed: 36445249.
86. Avellaneda C, Gómez A, Martos F, et al. The effect of a single intravenous dose of metamizol 2 g, ketorolac 30 mg and propacetamol 1 g on haemodynamic parameters and postoperative pain after heart surgery. Eur J Anaesthesiol. 2000; 17(2): 85–90, doi: 10.1046/j.1365-2346.2000.00607.x, indexed in Pubmed: 10758451.
87. Huber M, Andersohn F, Sarganas G, et al. Metamizole-induced agranulocytosis revisited: results from the prospective Berlin case-control surveillance study. Eur J Clin Pharmacol. 2015; 71(2): 219–227, doi: 10.1007/s00228-014-1777-8, indexed in Pubmed: 25378038.
88. Stamer UM, Stammschulte T, Erlenwein J, et al. [Recommendations for the perioperative use of dipyrone : Expert recommendation of the working group on acute pain of the German Pain Society, the scientific working group on pain medicine of the German Society for Anesthesiology and Intensive Care Medicine and the surgical working group on acute pain of the German Society for Surgery with participation of representatives of the Drug Commission of the German Medical Association]. Schmerz. 2019; 33(4): 287–294, doi: 10.1007/s00482-019-0389-8, indexed in Pubmed: 31342162.
89. Tomidis Chatzimanouil MK, Goppelt I, Zeissig Y, et al. Metamizole-induced agranulocytosis (MIA): a mini review. Mol Cell Pediatr. 2023; 10(1): 6, doi: 10.1186/s40348-023-00160-8, indexed in Pubmed: 37589909.
90. Lerman TT, Sagi M, Shafir Y, et al. A possible increased risk of metamizole-associated neutropenia among COVID-19 patients. Br J Clin Pharmacol. 2021; 87(7): 2902–2906, doi: 10.1111/bcp.14703, indexed in Pubmed: 33332642.
91. Shah RR. Metamizole (dipyrone)-induced agranulocytosis: does the risk vary according to ethnicity? J Clin Pharm Ther. 2019; 44(1): 129–133, doi: 10.1111/jcpt.12768, indexed in Pubmed: 30311250.
92. Cismaru AL, Grimm L, Rudin D, et al. EuDAC Collaborators. High-Throughput sequencing to investigate associations between HLA genes and metamizole-induced agranulocytosis. Front Genet. 2020; 11: 951, doi: 10.3389/fgene.2020.00951, indexed in Pubmed: 32973882.
93. Cismaru AL, Rudin D, Ibañez L, et al. Genome-Wide Association study of metamizole-induced agranulocytosis

in european populations. Genes (Basel). 2020; 11(11): 1275, doi: 10.3390/genes11111275, indexed in Pubmed: 33138277.
94. Kamitani F, Nishioka Y, Koizumi M, et al. Antithyroid drug-induced leukopenia and G-CSF administration: a long-term cohort study. Sci Rep. 2023; 13(1): 19336, doi: 10.1038/s41598-023-46307-5, indexed in Pubmed: 37935745.
95. Couto L, Goulart A, Valadão I, et al. Ceftriaxone-induced agranulocytosis. Eur J Case Rep Intern Med. 2021; 8(1): 002215, doi: 10.12890/2021_002215, indexed in Pubmed: 33585342.
96. Hosack T, Damry D, Biswas S. Drug-induced liver injury: a comprehensive review. Therap Adv Gastroenterol. 2023; 16: 17562848231163410, doi: 10.1177/17562848231163410, indexed in Pubmed: 36968618.
97. Pohl J, Bischoff P, Oellinger R, et al. Liver transplantation for metamizole induced acute liver failure. Transplant Proc. 2022; 54(7): 1854–1858, doi: 10.1016/j.transproceed.2022.04.028, indexed in Pubmed: 35933233.
98. Weber S, Benesic A, Neumann J, et al. Liver injury associated with metamizole exposure: features of an underestimated adverse event. Drug Saf. 2021; 44(6): 669–680, doi: 10.1007/s40264-021-01049-z, indexed in Pubmed: 33638811.
99. Reike-Kunze M, Zenouzi R, Hartel J, et al. Drug-induced liver injury at a tertiary care centre in Germany: model for end-stage liver disease is the best predictor of outcome. Liver Int. 2021; 41(10): 2383–2395, doi: 10.1111/liv.14985, indexed in Pubmed: 34152686.
100. Schulte B, Tergast TL, Griemsmann M, et al. Metamizole-associated risks in decompensated hepatic cirrhosis. Dtsch Arztebl Int. 2022; 119(41): 687–693, doi: 10.3238/arztebl.m2022.0280, indexed in Pubmed: 35912424.
101. Bachmann F, Meyer Zu Schwabedissen HE, Duthaler U, et al. Cytochrome P450 1A2 is the most important enzyme for hepatic metabolism of the metamizole metabolite 4-methylaminoantipyrine. Br J Clin Pharmacol. 2022; 88(4): 1885–1896, doi: 10.1111/bcp.15108, indexed in Pubmed: 34648192.
102. Watermeyer F, Gaebler AJ, Neuner I, et al. Metamizole but not ibuprofen reduces the plasma concentration of sertraline: Implications for the concurrent treatment of pain and depression/anxiety disorders. Br J Clin Pharmacol. 2021; 87(3): 1111–1119, doi: 10.1111/bcp.14471, indexed in Pubmed: 32652557.
103. Lameiras C, Corte-Real A, Órfão A, et al. Metamizole-induced type I Kounis syndrome. Eur J Case Rep Intern Med. 2021; 8(3): 002249, doi: 10.12890/2021_002249, indexed in Pubmed: 33768068.
104. Gomes Ferreira S, Fernandes L, Santos S, et al. Dipyrone (metamizole)-induced Stevens-Johnson syndrome. Cureus. 2024; 16(1): e53122, doi: 10.7759/cureus.53122, indexed in Pubmed: 38420072.
105. Jipa M, Isac S, Klimko A, et al. Opioid-sparing analgesia impacts the perioperative anesthetic management in major abdominal surgery. Medicina (Kaunas). 2022; 58(4): 487, doi: 10.3390/medicina58040487, indexed in Pubmed: 35454326.
106. Cetira-Filho EL, Martins-Filho PR, de Barros Silva PG, et al. Is coadministration of preemptive medications an effective strategy for reducing inflammatory clinical events and the need for rescue medication after mandibular third molar surgery? A systematic review of randomized clinical trials. Inflammopharmacology. 2023; 31(4): 1561–1575, doi: 10.1007/s10787-023-01258-1, indexed in Pubmed: 37306939.
107. Katz N, Paillard FC, Van Inwegen R. A review of the use of the number needed to treat to evaluate the efficacy of analgesics. J Pain. 2015; 16(2): 116–123, doi: 10.1016/j.jpain.2014.08.005, indexed in Pubmed: 25419989.
108. Hearn L, Derry S, Moore RA. Single dose dipyrone (metamizole) for acute postoperative pain in adults. Cochrane Database Syst Rev. 2016; 4(4): CD011421, doi: 10.1002/14651858.CD011421.pub2, indexed in Pubmed: 27096578.
109. Lux EA, Stamer U, Meissner W, et al. [Postoperative pain management after ambulatory surgery. A survey of anaesthesiologists]. Schmerz. 2011; 25(2): 191–194, 197–198, doi: 10.1007/s00482-011-1022-7, indexed in Pubmed: 21424335.
110. Reist L, Erlenwein J, Meissner W, et al. Dipyrone is the preferred nonopioid analgesic for the treatment of acute and chronic pain. A survey of clinical practice in German-speaking countries. Eur J Pain. 2018; 22(6): 1103–1112, doi: 10.1002/ejp.1194, indexed in Pubmed: 29377479.
111. Vilcane S, Scharonow O, Weilbach C, et al. Application of analgesics in emergency services in Germany: a survey of the medical directors. BMC Emerg Med. 2023; 23(1): 104, doi: 10.1186/s12873-023-00878-8, indexed in Pubmed: 37710177.
112. Ponholzer F, Schweiger T, Ghanim B, et al. Analysis of pain management after anatomic VATS resection in austrian thoracic surgery units. J Clin Med. 2023; 13(1): 80, doi: 10.3390/jcm13010080, indexed in Pubmed: 38202087.
113. Grossman R, Ram Z, Perel A, et al. Control of postoperative pain after awake craniotomy with local intradermal analgesia and metamizol. Isr Med Assoc J. 2007; 9(5): 380–382, indexed in Pubmed: 17591378.
114. Mestdagh FP, Lavand'homme PM, Pirard G, et al. PROSPECT Working Group of the European Society of Regional Anaesthesia and Pain Therapy (ESRA). Pain management after elective craniotomy: a systematic review with procedure-specific postoperative pain management (PROSPECT) recommendations. Eur J Anaesthesiol. 2023; 40(10): 747–757, doi: 10.1097/EJA.0000000000001877, indexed in Pubmed: 37417808.
115. Silva F, Costa G, Veiga F, et al. Parenteral ready-to-use fixed-dose combinations including nsaids with paracetamol or metamizole for multimodal analgesia-approved products and challenges. Pharmaceuticals (Basel). 2023; 16(8): 1084, doi: 10.3390/ph16081084, indexed in Pubmed: 37630999.
116. Costa FW, Esses DF, de Barros Silva PG, et al. Does the preemptive use of oral nonsteroidal anti-inflammatory drugs reduce postoperative pain in surgical removal of third molars? A meta-analysis of randomized clinical trials. Anesth Prog. 2015; 62(2): 57–63, doi: 10.2344/0003-3006-62.2.57, indexed in Pubmed: 26061574.
117. Maytalman E, Nemutlu Samur D. Neuroendocrine modulation by metamizole and indomethacin: investigating the impact on neuronal markers and GnRH release. Endocrine. 2024; 85(3): 1327–1336, doi: 10.1007/s12020-024-03822-3, indexed in Pubmed: 38625503.
118. Ji RR, Nackley A, Huh Y, et al. Neuroinflammation and central sensitization in chronic and widespread pain. Anesthesiology. 2018; 129(2): 343–366, doi: 10.1097/ALN.0000000000002130, indexed in Pubmed: 29462012.
119. Fuller AM, Bharde S, Sikandar S. The mechanisms and management of persistent postsurgical pain. Front Pain Res (Lausanne). 2023; 4: 1154597, doi: 10.3389/fpain.2023.1154597, indexed in Pubmed: 37484030.

120. Schumacher MA. Peripheral neuroinflammation and pain: how acute pain becomes chronic. Curr Neuropharmacol. 2024; 22(1): 6–14, doi: 10.2174/1570159X21666230808111908, indexed in Pubmed: 37559537.
121. Bernal A, Arranz L. Nestin-expressing progenitor cells: function, identity and therapeutic implications. Cell Mol Life Sci. 2018; 75(12): 2177–2195, doi: 10.1007/s00018-018-2794-z, indexed in Pubmed: 29541793.
122. Martínez C, Andreu I, Amo G, et al. Gender and functional CYP2C and NAT2 polymorphisms determine the metabolic profile of metamizole. Biochem Pharmacol. 2014; 92(3): 457–466, doi: 10.1016/j.bcp.2014.09.005, indexed in Pubmed: 25241292.
123. Szałek E, Spychala A, Kozanecka P, et al. The metabolic conversion of metamizole (Dipyrone) in male and female patients after total gastrectomy for stomach cancer. Acta Poloniae Pharmaceutica - Drug Research. 2022; 79(3): 401–407, doi: 10.32383/appdr/152216.
124. Chaparro LE, Lezcano W, Alvarez HD, et al. Analgesic effectiveness of dipyrone (metamizol) for postoperative pain after herniorrhaphy: a randomized, double-blind, dose-response study. Pain Pract. 2012; 12(2): 142–147, doi: 10.1111/j.1533-2500.2011.00463.x, indexed in Pubmed: 21507197.
125. Baca Q, Marti F, Poblete B, et al. Predicting acute pain after surgery: a multivariate analysis. Ann Surg. 2021; 273(2): 289–298, doi: 10.1097/SLA.0000000000003400, indexed in Pubmed: 31188202.
126. Misiołek H, Zajączkowska R, Daszkiewicz A, et al. Postoperative pain management — 2018 consensus statement of the Section of Regional Anaesthesia and Pain Therapy of the Polish Society of Anaesthesiology and Intensive Therapy, the Polish Society of Regional Anaesthesia and Pain Therapy, the Polish Association for the Study of Pain and the National Consultant in Anaesthesiology and Intensive Therapy. Anaesthesiol Intensive Ther. 2018; 50(3): 173–199, doi: 10.5603/AIT.2018.0026, indexed in Pubmed: 30124229.
127. Wordliczek J, Zajączkowska R, Dziki A, et al. Postoperative pain relief in general surgery — recommendations of the Association of Polish Surgeons, Polish Society of Anaesthesiology and Intensive Therapy, Polish Association for the Study of Pain and Polish Association of Regional Anaesthesia and Pain Treatment. Pol Przegl Chir. 2019; 91(1): 47–68, doi: 10.5604/01.3001.0013.1088, indexed in Pubmed: 30919814.
128. Stamer UM, Erlenwein J, Freys SM, et al. [Perioperative analgesia with nonopioid analgesics : Joint interdisciplinary consensus-based recommendations of the German Pain Society, the German Society of Anaesthesiology and Intensive Care Medicine and the German Society of Surgery]. Anaesthesist. 2021; 70(8): 689–705, doi: 10.1007/s00101-021-01010-w, indexed in Pubmed: 34282481.
129. Schug S, Pogatzki-Zahn E, Phillips LD, et al. Multi-Criteria decision analysis to develop an efficacy-safety profile of parenteral analgesics used in the treatment of postoperative pain. J Pain Res. 2020; 13: 1969–1977, doi: 10.2147/JPR.S255921, indexed in Pubmed: 32801852.
130. Dusch M. [Perioperative pain management — patient information, informed consent and discharge management]. Anasthesiol Intensivmed Notfallmed Schmerzther. 2021; 56(9): 574–585, doi: 10.1055/a-1188-2591, indexed in Pubmed: 34507381.
131. Fritsch G, Steltzer H, Oberladstaetter D, et al. Artificial intelligence algorithms predict the efficacy of analgesic cocktails prescribed after orthopedic surgery. PLoS One. 2023; 18(2): e0280995, doi: 10.1371/journal.pone.0280995, indexed in Pubmed: 36730239.
132. Machado-Alba JE, Serna-Echeverri LS, Valladales-Restrepo LF, et al. Use of tramadol or other analgesics in patients treated in the emergency department as a risk factor for opioid use. Pain Res Manag. 2020; 2020: 8847777, doi: 10.1155/2020/8847777, indexed in Pubmed: 33273995.
133. Keane A, Jardine K, Goldenberg D, et al. Opioid versus non-opioid postoperative pain management in otolaryngology. BMC Anesthesiol. 2023; 23(1): 291, doi: 10.1186/s12871-023-02213-x, indexed in Pubmed: 37626331.
134. Barden J, Edwards JE, McQuay HJ, et al. Oral valdecoxib and injected parecoxib for acute postoperative pain: a quantitative systematic review. BMC Anesthesiol. 2003; 3(1): 1, doi: 10.1186/1471-2253-3-1, indexed in Pubmed: 12854974.
135. Schug SA, Scott DA, Mott JF, Halliwell R, Palmer GM, Alcock M. Working Group of the Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine. Acute pain management: scientific evidence (5th edition). ANZCA & FPM, Melbourne 2020.