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BETWEEN EFFICACY AND RISK: A CRITICAL APPRAISAL OF METAMIZOLE'S PHARMACOLOGY, CLINICAL USE AND REGULATORY STATUS

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ABSTRACT

This review critically assesses metamizole's pharmacology, clinical efficacy, and safety profile, with particular focus on its widespread over-the-counter (OTC) availability in Poland versus more restrictive approaches elsewhere. The primary research objective was to evaluate whether the clinical benefits of metamizole outweigh its well-documented risks, especially severe adverse effects such as agranulocytosis and immune-mediated liver injury. During the research PubMed, Google Scholar, and institutional sources were used, applying keywords: "pyralgin," "metamizole," "analgesic," "side effects," "synergy," and "combination". Publications from 2000 to 2025 were screened for relevance, with a primary focus on articles in English and Polish. Abstracts were initially analyzed, followed by full-text review; 20 pertinent sources were ultimately selected for appraisal, comparing indications, mechanisms, and interactions with other analgesics, notably paracetamol, NSAIDs, opioids, and gabapentin. Findings demonstrate that metamizole shows unique spasmolytic, analgesic, and antipyretic properties, and offers therapeutic synergism with various analgesic combinations, aiding multimodal pain management when minimizing opioid or NSAID use is preferred. However, serious adverse events, while infrequent, are potentially fatal and unpredictable, with no effective preventive measures or reliable individual risk prediction identified. The review concludes that the unrestricted OTC availability and mass media promotion of metamizole pose disproportionate public health risks. It recommends limiting access to prescription-only status and ending promotional advertising for common ailments, given the availability of safer first-line analgesics.

KEYWORDS

Metamizole, Pyralgin, Analgesic, Side Effects, Synergy, Adverse Effects

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Introduction and Objectives

Metamizole (also known as Dipyrone) is a non-opioid, nonsteroidal, antipyretic and analgesic agent that was introduced into clinical practice in 1922 - at first under the names Novalgin and Analgin [1, 2]. Initially gained popularity and widespread use. Nevertheless, due to documented cases of agranulocytosis, its marketing authorization was first revoked in the United States, followed by similar regulatory actions in the United Kingdom, Canada, France, Japan, Australia and India. Although metamizole remains banned in several countries, including the United States of America, the United Kingdom, Japan, Australia, Sweden—with its use in the U.S. even prohibited in food-producing animals—it continues to be widely used worldwide. In some countries, such as Greece, Italy, and Spain, it is available only by prescription, while in others, including Germany, Poland, Mexico, China, Russia, and most South American nations, it can be obtained over the counter [2,3,4,5]. In contrast to a cautious regulatory approach, in Poland metamizole is at times promoted through mass media- including television and internet advertisements- as an appropriate remedy for common ailments such as headaches, abdominal pain, or back pain in everyday situations. Looking from a strictly European perspective, Pharmaceuticals containing metamizole are approved in many EU countries: Austria, Luxembourg, Croatia, Czech Republic, Belgium, Netherlands, Bulgaria, Germany, Hungary, Italy, Latvia, Lithuania, Poland, Portugal, Spain, Romania, Slovakia, and Slovenia.. In Finland, the only authorised metamizole-containing medicine is being recalled [6]. The aim of this review is to answer the question of whether the clinical benefits of metamizole use outweigh its well-documented, potentially serious adverse effects, and to reflect on the appropriateness of its over-the-counter availability and promotion.

Materials and Methods

To conduct this review we searched through Pubmed and Google Scholar databases as well as institutional documents using various combinations of keywords: “pyralgin”, “metamizole”, “analgesic”, “side effects”, “synergy” and “combination”. Publications from the years 2000 to 2025 were considered. No language criteria were implied, but majorly articles in English and Polish were included. The selection of articles was based on an individual approach depending on relevance to the topic. Primarily, the analysis of abstracts was performed, followed by full-text review. Ultimately, 20 sources were analyzed and reviewed.

Description of The State of Knowledge

Classification

Chemically, metamizole is classified as a pyrazolone derivative - more specifically, sodium N-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)-N-methylamino methanesulphonate. Pharmacologically it was long misclassified as a non-steroidal anti-inflammatory drug (NSAID). It is now recognized that embedding it in one group together with paracetamol (acetaminophen) and referring to it as a non-opioid analgesic and antipyretic drug is more accurate, as its anti-inflammatory activity is minimal and significantly weaker than that of typical NSAIDs [1, 5].

Although metamizole and paracetamol are often considered similar in terms of their therapeutic use and are therefore grouped together, it is important to recognize that they differ significantly in their mechanisms of action, clinical indications, contraindications, and potential drug interactions. The most and instantly notable difference between these drugs is that unlike paracetamol, metamizole shows a spasmolytic effect [1, 2, 5]. Metamizole is a pharmaceutical agent indicated for the treatment of moderate to severe pain and fever, and is available in oral, rectal, and parenteral formulations [6].

Mechanism of Action and Metabolism

Metamizole is a non-opioid analgesic and antipyretic, whose broad mechanism of action involves inhibition of prostaglandin synthesis, modulation of the endocannabinoid system, and interference with pain signal transmission at the spinal level [7].

Metamizole metabolites inhibit prostaglandin synthesis, mainly by suppressing the activity of cyclooxygenase enzymes COX-1 and COX-2. They also inhibit substance P-induced nociceptive signaling. Additionally, modulating the endocannabinoid system contributes to its analgesic and antipyretic properties. Its interaction with the cannabinoid system, together with the inhibition of adenosine reuptake in the central nervous system, underlies its spasmolytic action—particularly beneficial in the treatment of colicky and visceral pain, so especially that associated with the gastrointestinal, biliary, or urinary systems [8]. Moreover, The broad mechanism of action of the agent, which engages both peripheral and central pathways, creates room for a wide spectrum of its pharmacological effects, including its capacity to exhibit synergistic interactions with other analgesics. This synergism is multifactorial in nature, resulting from the diverse actions of metamizole and its active metabolites, which complement and potentiate the effects of co-administered analgesic agents.

The primary active metabolite of metamizole is 4-N-methylaminoantipyrine (MAA). Following oral administration, the drug undergoes rapid hydrolysis, resulting in high bioavailability of approximately 90%, with food having no significant effect on absorption. MAA is subsequently metabolized in the liver via oxidation, demethylation, and acetylation. In addition to MAA, its metabolite 4-aminoantipyrine (AA) also contributes to the clinical effects, though to a lesser extent. In contrast, the metabolites 4-N-acetyl aminoantipyrine (AAA) and 4-N-formylaminoantipyrine (FAA) are considered pharmacologically inactive. Plasma protein binding is approximately 58% for MAA, 48% for AA, 18% for FAA, and 14% for AAA. Consequently, the displacement of other compounds from such binding sites, which is often implicated in numerous drug interactions, does not represent a clinically significant concern in the case of metamizole [9,17].

Metamizole crosses the placental barrier, and at therapeutic doses, its metabolites are excreted into human breast milk. Therefore, its use is not recommended during pregnancy and lactation due to potential risks to the fetus and the nursing infant. In animal studies, metamizole demonstrated adverse effects on reproduction but did not exhibit teratogenic properties. According to the Polish Summary of Product Characteristics, breastfeeding should be discontinued during treatment with metamizole-containing medicinal products and for at least 48 hours after the last dose [9,10].

Research maintained by David J. Brinkman et al. indicates that metamizole functions as a moderate to strong inducer of the cytochrome P450 enzymes CYP3A4, CYP2B6, and CYP2C19, while exhibiting weak induction of CYP2C9 and moderate inhibition of CYP1A2. The use of metamizole is characterized by a low potential for interactions with concurrently administered medications. Co-administration with acetylsalicylic acid has been shown to attenuate the antiplatelet effect of the latter. Therefore, caution is advised when administering metamizole to patients receiving low-dose acetylsalicylic acid for cardioprotective purposes. Due to its potential to induce agranulocytosis, metamizole should be used with caution when combined with other agents known to affect bone marrow function. Furthermore, when combined with cyclosporine, regular monitoring of cyclosporine blood levels is recommended because of possible pharmacokinetic interactions and clinical relevance. In cases of high-dose therapy (e.g., 1,000 mg administered three to four times daily for over one day), these pharmacokinetic and pharmacodynamic considerations become particularly important. [1, 8, 11].

Synergism

In the context of analgesics, synergism represents a clinically valuable property. In pain management, it refers to the phenomenon where the combined use of two drugs produces a greater analgesic effect than the sum of their individual effects. This allows for improved therapeutic outcomes—more effective pain relief—while potentially reducing the required doses and minimizing adverse effects. Metamizole has been shown to exert synergistic effects when combined with NSAIDs, paracetamol, opioids, and gabapentin [8].

Numerous studies have demonstrated a synergistic interaction between metamizole and other analgesics. One such study, conducted by López-Muñoz et al. (2008), provided evidence that the interaction between metamizole and morphine exhibits a superadditive synergistic effect. The co-administration of both drugs resulted in a significantly enhanced antinociceptive response compared to either drug administered alone or to the expected additive effect based on their individual actions. These findings support the presence of a superadditive interaction between metamizole and morphine [12].

Examples of synergism in practice:

Paracetamol and metamizole: Although both agents share similar, yet distinct mechanisms of action, their combined use has been shown to enhance analgesic efficacy. This supports their role in multimodal analgesic therapy, where the combination produces a greater effect than either drug used alone [13, 14].

NSAIDs and metamizole: metamizole combined with nonsteroidal anti-inflammatory drugs (NSAIDs) may produce a synergistic effect, enhancing overall analgesic efficacy. This approach is particularly recommended in cases of severe pain where monotherapy proves inadequate [14].

Opioids and metamizole: The addition of metamizole to opioid therapy (e.g., morphine, buprenorphine) enables a reduction in the required opioid dose to achieve effective analgesia, thereby lowering the risk of opioid-related adverse effects. Studies have demonstrated that combining metamizole with morphine results in a synergistic analgesic effect without exacerbating morphine-induced constipation. Similar synergistic benefits have also been observed with buprenorphine and tramadol [13].

In a 1:1 volume ratio of administered solutions—metamizole (1,000 mg in 100 ml) and tramadol (100 mg in 100 ml)—Montes et al. observed synergism in a study involving 101 women undergoing hysterectomy. This synergism was noted not only in terms of enhanced analgesic efficacy but also in the side effect profile, although the latter was not clinically significant [15]. The addition of metamizole to morphine accelerates the achievement of satisfactory analgesia and facilitates improved pain control, even after metamizole discontinuation [13].

Gabapentin and metamizole: Evidence suggests that the addition of metamizole to gabapentin therapy may enhance the effectiveness of neuropathic pain management, particularly in alleviating symptoms such as allodynia and hyperalgesia [13].

Dipyrone exhibits an additive spasmolytic effect when combined with both musculotropic agents, such as papaverine and drotaverine, as well as with anticholinergic compounds like hyoscine butylbromide [14].

In both acute and chronic pain therapy, a multimodal approach involving metamizole is widely recommended—especially in clinical scenarios where minimizing the use of opioids or NSAIDs is desired.

Table. 1. Clinically Relevant Combinations of Metamizole with Other Analgesics and Their Observed Synergistic Effects

Agents Combination	Clinical Outcome / Type of Synergism	Source
Metamizole + Morphine	Superadditive synergy; enhanced analgesia; no exacerbation of opioid-induced constipation	Study by López-Muñoz et al.; clinical trial data
Metamizole + Paracetamol	Enhanced analgesic efficacy; supports multimodal pain therapy	Study by Wordliczek J, Zajączkowska R, Dziki A, et al.; Postoperative pain relief in general surgery
Metamizole + Tramadol	Demonstrated synergy in perioperative settings; improved efficacy and tolerability	Montes et al.; hysterectomy study
Metamizole + Gabapentin	Improved control of neuropathic pain symptoms (e.g., allodynia, hyperalgesia)	Study by Krzyżak-Jankowicz M, Jankowicz R.
Metamizole + NSAIDs	Increased overall analgesic effectiveness, especially in severe pain where monotherapy is insufficient	Study by Wordliczek J, Zajączkowska R, Dziki A, et al.; Postoperative pain relief in general surgery

The mechanism underlying the synergistic effect of metamizole with other analgesics is multifactorial and stems from the diverse pharmacological actions of metamizole and its active metabolites, which complement and enhance the effects of co-administered analgesic agents. Several mechanisms have been proposed to explain the synergism between metamizole and other analgesics, including:

Activation of the endocannabinoid and opioid systems: Metamizole and its metabolites activate CB1 and CB2 receptors within the spinal cord and brain, contributing to analgesia and modulation of pain pathways. The study by Topuz et al. provides growing evidence supporting the role of the endocannabinoid system—particularly CB1 receptors—in dipyrone-induced antinociception. Studies suggest that its metabolites exert antihyperalgesic effects through CB1 receptor activation and neuronal KATP channel opening. Computational models also identify 4-methylaminoantipyrine, a dipyrone metabolite, as a CB1 agonist.Concurrently, metamizole promotes the release of endogenous opioid peptides and interacts with both central and peripheral μ-opioid receptors, which accounts for its synergistic effects when combined with opioids such as morphine and tramadol [7, 16, 17].

Opening of ATP-sensitive potassium (KATP) channels: Metamizole activates the L-arginine–nitric oxide (NO) synthesis pathway, which results in the opening of neuronal KATP channels. This leads to neuronal hyperpolarization and a subsequent reduction in the transmission of pain signals [17].

Inhibition of nociceptors and pain signal transmission: Metamizole inhibits TRPA1 channels (commonly referred to as "wasabi receptors") in peripheral sensory neurons, which are involved in mediating pain and thermal hyperalgesia. This inhibition contributes to its analgesic effects [17].

Inhibition of prostaglandin synthesis via selective COX-2 and COX-3 modulation: Metamizole exhibits minimal inhibitory activity on COX-1 but acts more selectively on COX-2 and COX-3 isoforms within the central nervous system. This selective inhibition leads to reduced synthesis of prostaglandins involved in pain perception and inflammatory responses [16].

Activation of the descending antinociceptive pathways: Metamizole stimulates neuronal activity in the periaqueductal gray (PAG) matter of the midbrain, thereby enhancing endogenous pain-inhibitory mechanisms within the central nervous system [17].

Spasmolytic effect: Metamizole exerts smooth muscle relaxant properties, which are particularly beneficial in the management of colicky pain. This action can complement and enhance the analgesic efficacy of co-administered drugs [17].

Safety Profile and Adverse Effects

Numerous adverse effects have been described in association with metamizole use; however, their incidence remains relatively low. According to the Polish Summary of Product Characteristics (ChPL), the most frequently reported adverse events are categorized as "uncommon," corresponding to a frequency of ≥1/1,000 to <1/100. This frequency primarily refers to the occurrence of hypotensive reactions during or after administration of the product, which are likely pharmacologically mediated and are not typically accompanied by signs of anaphylactic or anaphylactoid responses. What is important, the risk of such reactions is notably increased when the drug is administered intravenously at an excessively rapid rate. Subsequently, adverse reactions classified as “rare” (with an incidence of ≥ 1/10,000 to < 1/1,000) are identified. These include leukopenia, anaphylactoid or anaphylactic reactions—including severe and life-threatening forms—as well as skin rashes, such as maculopapular eruptions. The third frequency category is classified as “very rare,” referring to an incidence of less than 1 in 10,000. This group encompasses serious complications such as agranulocytosis (including fatal cases), thrombocytopenia, Stevens–Johnson syndrome, toxic epidermal necrolysis, sudden decline in renal function, acute renal failure, oliguria, proteinuria, anuria, interstitial nephritis, asthma exacerbations, and analgesic-induced asthma. In addition to well-defined frequency categories, a considerable number of adverse effects are classified as having an unknown incidence. These include: hemolytic anemia, aplastic anemia, bone marrow suppression, headache, dizziness, nausea, vomiting, abdominal pain, gastrointestinal irritation, diarrhea, dry mouth, hepatic injury, jaundice, elevated liver enzymes, and anaphylactic shock [9]. However, according to other sources, adverse events such as nausea, vomiting, headache, fatigue, fever, abdominal pain, somnolence, vertigo, muscle spasms, neutropenia, renal dysfunction, and rash are reported as common [2]. It is worth noting that a substantial proportion of these adverse effects may be attributable to overdose. Symptoms indicative of metamizole overdose include: abdominal pain, nausea, vomiting, impaired renal function, and acute renal failure (e.g., due to interstitial nephritis). Less commonly, central nervous system manifestations such as dizziness, somnolence, coma, and seizures may occur, as well as hypotension—occasionally progressing to shock—and tachycardia. Also, it should be kept in mind that at higher doses, excretion of the metabolite rubazonic acid may result in red discoloration of the urine [9]. It should also be emphasized that the development of agranulocytosis or thrombocytopenia associated with metamizole therapy is likely immunologically mediated. Notably, these reactions may occur even in individuals who have previously tolerated metamizole without adverse effects. The risk of agranulocytosis appears to increase with treatment durations exceeding seven days, but is not related to the drug dosage. This immunological etiology renders the phenomenon particularly hazardous, as effective preventive measures are essentially unattainable and susceptibility is highly individual. Consequently, any exposure to metamizole—especially for periods longer than seven days - entails a significant risk [9, 18]. Yet, cohort and observational studies indicate that metamizole-induced agranulocytosis is a rare event, with an incidence rate comparable to that associated with other nonsteroidal analgesics [8].

Prior to 2019, reports of metamizole-induced liver injury were exceptionally rare. This changed with two German case series documenting hepatotoxicity, including fatal outcomes. Subsequent reassessments by the European Medicines Agency followed the accumulation of over 40 reported cases. Within a relatively short period, more than 50 instances of clinically apparent liver injury linked to metamizole were described. The clinical presentation of these cases has been heterogeneous, with some exhibiting hyperacute onset characterized by fever, rash, and jaundice shortly after the initial or early doses. Such manifestations may reflect severe hypersensitivity reactions, including hepatic involvement in DRESS syndrome, Stevens-Johnson syndrome, or toxic epidermal necrolysis.

Metamizole-induced liver injury is believed to result primarily from immune-mediated mechanisms, exhibiting both immediate hypersensitivity and delayed adaptive immune responses. While metamizole may trigger hypersensitivity reactions without hepatic involvement—such as urticaria, rash, Stevens-Johnson syndrome, and toxic epidermal necrolysis—patients who develop agranulocytosis often present with concurrent, typically mild liver dysfunction, which is usually secondary to the hematologic manifestations [2].

Regarding renal effects, findings from the study by Calvo et al indicate that triple therapy (TW) regimens incorporating an NSAID may be associated with a reduced risk of acute kidney injury (AKI)-related

hospitalization and mortality compared to those including metamizole, despite no significant differences observed in renal function parameters. Further studies are warranted to validate these observations [19].

On the other hand, in comparison to opioids, in a study by Thomas Kötter et al., 79 trials involving nearly 4,000 patients with short-term metamizole use (less than two weeks) were selected from an initial pool of 696 potentially eligible studies. The analysis revealed fewer adverse events with metamizole compared to opioids (RR = 0.79; 95% CI: 0.79–0.96), while no significant differences were observed in comparison to placebo, paracetamol, or NSAIDs. Serious adverse events were infrequently reported, with no significant difference between metamizole and other analgesics. Notably, no cases of agranulocytosis or death were identified. However, the reliability of the findings was constrained by the generally low methodological quality of the included trials [20].

Table. 2. Frequency and Examples of Adverse Effects Associated with Metamizole Use

Frequency Category	Examples of Adverse Effects
Uncommon (≥1/1,000 to <1/100)	Hypotensive reactions (especially with rapid IV administration), not typically linked to anaphylaxis
Rare (≥1/10,000 to <1/1,000)	Leukopenia, anaphylactoid or anaphylactic reactions (including severe), maculopapular rash
Very rare (<1/10,000)	Agranulocytosis (including fatal cases), thrombocytopenia, Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute renal failure, interstitial nephritis, analgesic-induced asthma
Unknown frequency	Hemolytic anemia, aplastic anemia, bone marrow suppression, dizziness, gastrointestinal disturbances (e.g., nausea, vomiting, abdominal pain, diarrhea), hepatic injury, jaundice, liver enzyme elevation, anaphylactic shock

Summary

Although the use of metamizole is associated with certain adverse effects, their actual incidence appears to be lower than the controversy surrounding the drug might suggest. A major advantage of metamizole is its suitability for combination therapy, along with a low risk of clinically significant drug–drug interactions [8]. On the other hand, it can be observed that the use of metamizole is associated with a number of relatively rare, yet potentially very serious adverse effects. Therefore, it may be concluded that the true risk linked to the administration of this drug arises not from the high probability of such events occurring, but from the severity of the potential complications.

Considering the documented occurrence of severe adverse events associated with metamizole—some of which may result in death or serious health consequences—and recognizing that these complications are primarily immune-mediated hypersensitivity reactions for which current knowledge does not allow effective prevention or reliable individual risk prediction, it is imperative to mitigate such risks by minimizing exposure to this drug. The OTC availability of metamizole is unwarranted, given that its indications predominantly pertain to hospital settings or conditions of sufficient severity to justify prescription-only distribution under specialist supervision. Restricting access to prescription status would likely reduce the incidence of overdose and chronic unsupervised use. Moreover, the promotion of metamizole through mass media—including television and internet advertisements—portraying it as appropriate for common ailments such as headaches, abdominal pain, or back pain in everyday contexts is ethically questionable. Such advertising unnecessarily exposes patients to rare but unpredictable and potentially fatal complications. Considering the availability of analgesics with more favorable safety profiles that are better suited as first-line treatments for these common pain conditions, the unrestricted OTC use and advertising of metamizole represent a disproportionate public health risk.

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