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Article

Comparative safety profile of Metamizole, Viminol, and Tapentadol: a prospective observational study on adverse reactions

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The most potent analgesics cause serious Adverse Drug Reactions (ADRs), so medications such as metamizole, viminol, and tapentadol may be alternatives. However, the safety of these analgesics still needs to be better understood. This study aims to assess prospective ADRs associated with these analgesics in a pain clinic. We followed up with the patients who had used these medicines for 45 days, classified the ADRs according to severity (mild, moderate or severe), mechanism (type A or type B), and incidence (very common, common, uncommon, and rare), and determined the causality. Among 240 patients, three ADRs to metamizole, seven to viminol, and 11 to tapentadol alone were documented. Additionally, 22 suspected ADRs were attributed to potential drug interactions among these analgesics and other medications. The ADRs were categorized as mild to moderate, type A, and common or uncommon. Causality was categorized as certain or possible. The ADRs induced by viminol were associated with age, with each year of age leading to a 6% increase in risk of ADRs, according to a logistic regression model applied specifically to this drug. No other association was found between tapentadol or viminol and comorbidities. It was not possible to analyze the metamizole data due to its low incidence. Overall, metamizole was the safest, reinforcing its safety profile and its valuable indication in the treatment of pain.

Keywords: Analgesics. Pharmacovigilance. Drug-Related Side Effects and Adverse Reactions. Drug Monitoring. Adverse Drug Reactions (ADRs). Safety Monitoring or Risk Management.

INTRODUCTION

Managing chronic pain presents a substantial challenge in clinical practice, primarily due to the significant adverse drug reactions (ADRs), such as liver and kidney failure, physical and psychological dependence, and withdrawal syndrome, often associated with prolonged analgesic use (David-Pereira, Dickenson, 2019). The effectiveness of analgesics largely depends on the pain's origin and type, and the safety of these drugs is not always well established. Analgesics are frequently contraindicated for long-term use due to their associated risks: non-steroidal anti-inflammatory drugs (NSAIDs), the most common non-opioid analgesics, are linked to gastrointestinal tract injuries and hemorrhage (Bindu, Mazumder, 2020), while opioids are known for their addictive properties (Volkow, Blanco, 2021).

The indiscriminate use of opioids has contributed to the global opioid crisis, underscoring the need for a more rational approach to medication use (Dalal, Bruera, 2019). In addition to guidelines for the appropriate use of painkillers, it is crucial to explore alternatives that can replace or complement opioids to reduce their dosage. Metamizole is a widely used analgesic in several countries, particularly in Latin America and much of the European Union (Kötter *et al*., 2015) but faces controversy due to the risk of agranulocytosis and other serious ADRs, as well as its ban in Sweden, the United Kingdom, and the United States (Lupu, Bel, Andrei, 2022). Despite its extensive use, metamizole is not listed in the World Health Organization's Model List of Essential Medicines, which also omits other analgesics like viminol and

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tapentadol. Viminol, approved by the Brazilian Health Regulatory Agency (ANVISA) since 1999 (ANVISA, 2024), is less studied, with limited evidence available from the 1970s and 1980s suggesting its efficacy and safety as an analgesic with minimal risk of addiction and ADRs (Shook, Kallman, Dewey, 1994). Tapentadol, approved by the FDA in 2008 for acute pain and in extended-release form in 2011 for chronic pain, is characterized as a norepinephrine reuptake inhibitor and a μ-opioid receptor agonist (Tzschentke *et al*., 2007). Its moderate μ-opioid receptor activity is thought to contribute to reduced nausea, vomiting, and constipation (Tzschentke, Christoph, Kögel, 2014).

Thus, monitoring ADRs related to these three analgesics highlights the ongoing importance of pharmacovigilance. This field supports safer use of analgesics by tracking medications already in use and helping identify ADRs that may not emerge during pre-marketing trials (Crestan *et al*., 2020). It also helps refine existing knowledge on adverse drug events and clarify their occurrence in real-world settings (Montané, Santesmases, 2020). In this study, we evaluated ADRs associated with metamizole, viminol, and tapentadol in patients treated at a pain clinic, aiming to address specific gaps in the literature and offer evidence that may guide safer clinical choices.

MATERIAL AND METHODS

The study employed an observational, analytical, longitudinal, and prospective design, conducted at the Pain Medicine Clinic of a reference hospital of Alfenas, Minas Gerais state, in the southeast region of Brazil (coordinates: 21.4255° S, 45.9477° W), from January 2022 to October 2023. The Pain Medicine Clinic is an outpatient unit specialized in pain management. It primarily serves patients referred from Internal Medicine, Palliative Care, Traumatology, Geriatrics, Arthroscopy, and Anesthesiology. Ethical approval was obtained from the Research Ethics Committee of the Federal University of Alfenas (UNIFAL-MG) (CAAE 51321921.1.0000.5142), and the study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Participants

A total of 240 participants were enrolled based on a sample size calculation using the binomial test for exact proportions, targeting a difference from the null hypothesis of 10% ADR incidence. Under the null hypothesis of 0.1, the calculated sample size of 240 participants provided 95.2% power with a significance level of 4%. Eligible participants were 18 years or older, experiencing chronic pain, and only those who signed the Free and Informed Consent Form (*Termo de Consentimento Livre e Esclarecido* - TCLE, in Portuguese) and completed initial contact were included in the study. All participants were undergoing mono or polydrug therapy with at least one of the study drugs – metamizole, viminol hydroxybenzoate, or tapentadol hydrochloride. Participants who could not be contacted by telephone were excluded from the study.

Experimental design

The study design is outlined in Figure 1. During routine consultations at the Pain Medicine Clinic, the responsible physician invited eligible participants. After signing the TCLE, participants/guardians were contacted by phone five days later by members of the Pharmacovigilance Center of UNIFAL-MG (CEFAL). Participant information, including personal health history (diabetes, cancer, cardiovascular disease and Alzheimer's) and any ADEs, was collected using a standardized form from the VIGIMED® system (Figure 2), a computerized tool managed by ANVISA. This form contains essential information for the notification and analysis of ADRs.

Participants who reported ADRs during the first contact were followed up within seven days to assess their clinical condition. If ADRs persisted or other ADEs were mentioned, the case was referred to the prescriber. Participants who did not report ADRs were contacted

every 15 days for 45 days to monitor the potential onset of latent ADRs. ADRs were documented either during the initial contact or at subsequent follow-up calls, depending on when symptoms appeared. No minimum duration of medication use was required for inclusion; however, the treatment period typically aligned with the 45-day follow-up window established in the study design.

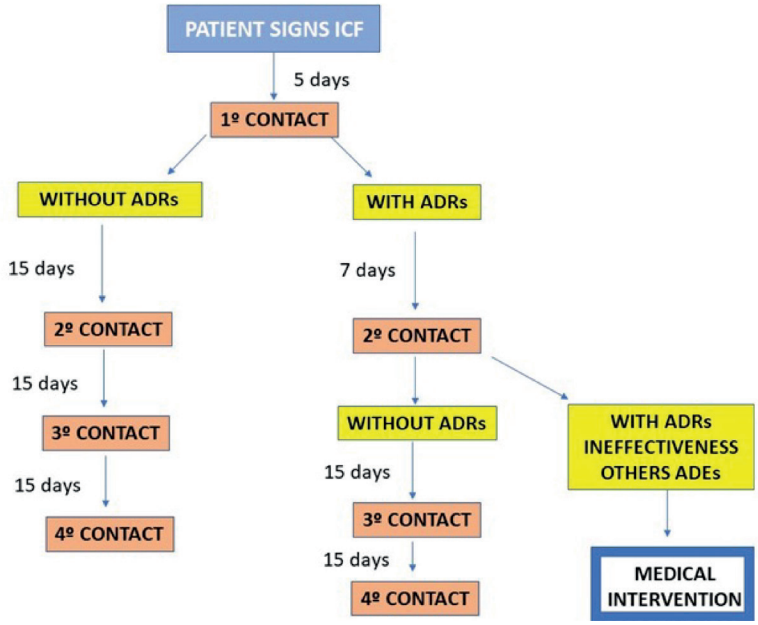

FIGURE 1 - Experimental design - contact with the patients via phone call according to the manifestation of ADRs.

MEDICATION USER DATA
1- Full name
2- Gender
3- Weight
4- Date of birth
5- Age at time of ADR
6- Color or race
7- Height
8- Country
9- Municipality of residence
10- Hospitalized ( ) yes ( ) No
11- Health problems and personal history
12- User email
13- User phone

MEDICINE DATA
1- Name of the medicine
2- Lot
3- Expiration date
4- Treatment start date
5- Continuation of treatment ( ) yes ( ) No
6- Manufacturer industry
7- Description of ADR
8- ADR start date
9- ADR end date
10- Consequence of ADR
( ) Death
( ) Life risk
( ) Persistent or significant disability
( ) Caused or prolonged hospitalization
( ) Anomaly or malformation of the newborn
( ) Other clinically important situations
( ) Not applicable
11- Communication to the industry about what happened ( ) yes ( ) No
12- ADR disappeared or improved after drug withdrawal ( ) yes ( ) No
13- ADR reappeared after drug reintroduction ( ) yes ( ) No
14- Use other medications ( ) yes ( ) No Which _____

FIGURE 2 - VIGIMED® form for notification of ADRs.

Classification and causality of ADRs

All ADRs were classified using the Medical Dictionary for Regulatory Activities (MedDRA), a standardized terminology developed to support international pharmacovigilance. Two independent researchers performed the classification to ensure consistency. ADRs related to metamizole, viminol, or tapentadol were classified by severity - mild (does not require drug treatment), moderate (requires hospitalization), or severe (requiring intensive care unit admission) (Hartwig, Siegel, Schneider, 1992) - and by mechanism of action as type A (dose-dependent, exaggerated effect) or type B (dose-independent, unpredictable) (Rawlins, Thompson, 1977). At the end of the proposed period, the frequency of ADRs was categorized as very common (≥10%), common (≥1% but <10%), uncommon (≥ 0.1% but <1%), and rare (≥0.01% but <0.1%) (Meyboom, Egberts, 1999). The presence and incidence of ADRs and the possible association with drug interactions were verified in the respective monographs, on the website drugs.com (https://www.drugs.com), and in the electronic clinical resource tool UpToDate® (http://www.uptodate.com). To determine the causality of ADRs, a standardized scale from the World Health Organization-Uppsala Monitoring Centre (WHO-UMC, 2005) criteria was used (World Health Organization, 2005). Reactions were categorized as certain, probable, possible, unlikely, conditional, or unclassifiable. Causality was also determined based on the VIGIMED® questions required for the notification of ADEs and clinical judgment, considering the following criteria: temporality between the event and drug use; previous description of ADRs in scientific literature; the association between ADRs and the drug's mechanism of action, exclusion of confounding variables, and subjective and objective impressions of the prescriber. CEFAL researchers were trained to standardize ADR causality assessments and were responsible for reporting and referring cases to the competent authorities.

Statistical analysis

Descriptive statistics were applied to summarize population characteristics such as sex, age, race, primary diagnoses associated with pain, comorbidities, and incidence of ADRs. Additionally, a descriptive survey of drug interactions and ADR classification was conducted.

To assess the association between ADR occurrence and categorical variables, the Chi-square test was used. A significance level of 5% ($P<0.05$) was adopted to reject the null hypothesis.

The relationship between ADR manifestation and sex was investigated using a Chi-square test of independence, while the association with age was analyzed using the T test. Logistic regression models were also performed to predict ADRs for each study drug, both in isolation and in drug interactions, with sex, age, and comorbidities as predictor variables.

Therefore, the present analyses were performed using the free software R (R version 4.2.2). For associations with the occurrence of adverse effects, the chi-square or Fisher's exact tests were used, depending on the assumption of a maximum of 20% of expected values lower than five to verify the association between adverse effects and categorical variables, and the Mann-Whitney test to verify the difference in age and number of medications in patients who did or did not have adverse effects. A 5% significance level was adopted, indicating that when $p<0.05$ we should reject the null hypothesis (of independence or equality of distributions, respectively).

RESULTS

Population characteristic

Between January 2022 and October 2023, a total of 413 prescriptions were issued for 364 different individuals. Of these, 124 (34.07%) did not respond to follow-up calls, leaving 240 participants who agreed to take part in the study by signing the TCLE, and were contacted four times throughout the study.

Of the 240 participants, 84 (35%) were male and 156 (65%) female. The average age was 58.19 (standard deviation 13.62) years. Among the participants, 62 (25.83%) reported experiencing ADRs related to the administration of the study drugs (ADRs) at the time of contact with the patient, with 42 (67.74%) of these being female and 20 (32.26%) male. Most participants identified as white (61.20%), while 17.74% identified as mixed-race, 9.68% as black, and 11.29% did not report their race. There was no significant association between ADR manifestation and sex ($\chi^2(1) = 0.14$; P=0.711) or age ($t(91) = 1.39$; P=0.168). It is important to note that this t-test analysis was applied to the full sample (n = 240), regardless of the drug used. In contrast, a significant association between age and ADR was observed in the logistic regression model applied only to the viminol group, as detailed in the following section (Predictors Associated with ADRs).

The primary diagnoses associated with pain among participants reporting ADRs were cancer-related pain 22 (35.50%); back pain (lumbar, cervical, and thoracic) 17 (27.40%); osteoarthritis 8 (12.90%); legs and feet pain 4 (6.50%); fibromyalgia 3(4.80%); arthritis 2 (3.20%); shoulders, arms, and forearms pain 3 (4.80%); hip pain 2 (3.20%); tendinitis 2 (3.20%); and other conditions 6 (9.67%).

The most frequent comorbidities were hypertension 10 (16.10%), hypertension combined with diabetes 9 (14.50), thyroid disorders 5 (8.10%), depression and anxiety 4 (6.50%), heart disease 4 (6.50%), diabetes 3 (4.80%); respiratory disorders 3 (4.80%), and other conditions 9 (14.52%).

Classification and causality of ADRs

Pregabalin, tapentadol, and viminol were the drugs most frequently associated with ADRs and drug interactions. These three medications alone accounted for 47.83%, 15.94%, and 10.15% of ADR occurrences, respectively (Table I). Table II shows that 183, 147, and 105 drug interactions were detected for pregabalin, viminol, and tapentadol, respectively, when combined with other medications (drug interactions).

TABLE I - Frequency of isolated drugs related to adverse drug reactions (ADRs)

DRUG	FREQUENCY	RELATIVE FREQUENCY (%)	CUMULATIVE FREQUENCY N (%)
Pregabalin	33	47.83	33 (47.83)
Tapentadol	11	15.94	44 (63.77)
Viminol	7	10.14	51 (73.91)
Duloxetine	6	8.70	57 (82.61)
Metamizole	3	4.35	60 (86.96)
Tramadol	3	4.35	63 (91.30)
Topiramate	2	2.90	65 (94.20)
Indomethacin	1	1.45	66 (95.65)
Escitalopram	1	1.45	67 (97.10)
Quetiapine	1	1.45	68 (98.55)
Tizanidine	1	1.45	69 (100.00)

TABLE II - Frequency of drug interactions

DRUG	FREQUENCY	RELATIVE FREQUENCY (%)	95% CI FREQUENCY (%)
Pregabalin	183	76.25	(69.62; 80.79)
Viminol	147	61.25	(54.26; 66.88)
Tapentadol	105	43.75	(37.10; 49.89)
Duloxetine	17	7.08	(4.27; 11.21)
Escitalopram	3	1.25	(0.32; 3.88)
Amitriptyline	3	1.25	(0.32; 3.88)
Buprenorphine	3	1.25	(0.32; 3.88)
Alprazolam	2	0.83	(0.14; 3.28)
Sertraline	2	0.83	(0.14; 3.28)
Metoprolol	2	0.83	(0.14; 3.28)
Tizanidine	2	0.83	(0.14; 3.28)
Methadone	2	0.83	(0.14; 3.28)
Furosemide	2	0.83	(0.14; 3.28)
Lactulose	1	0.41	(0.02; 2.64)
Hidroclorothiazide	1	0.41	(0.02; 2.64)
Omeprazole	1	0.41	(0.02; 2.64)
Nimesulide	1	0.41	(0.02; 2.64)
Pantoprazole	1	0.41	(0.02; 2.64)
Espironolactone	1	0.41	(0.02; 2.64)
Nebivolol	1	0.41	(0.02; 2.64)
Metamizole	1	0.41	(0.02; 2.64)

Focusing on the three analgesics under study, a total of 43 ADRs were detected among 22 participants, with 21 ADRs linked to a single drug and 22 resulting from drug interactions. A database analysis identified a total of 253 drug interactions involving these analgesics with other medications, however, only 22 (8.69%) of these interactions resulted in ADRs.

The incidence of ADRs for isolated tapentadol, viminol, and metamizole was 10.78% (11/102), 4.76% (7/147), and 1.60% (3/187), respectively (Table III). For tapentadol, the ADRs were classified as mild or moderate (constipation and vomiting), type A, common or uncommon, and certain. For viminol, the ADRs were classified as mild or moderate (dizziness), type A, common (asthenia) or uncommon, and certain. For metamizole, the ADRs were classified as mild, type A, uncommon and certain (Table III). It is important to highlight that no patient with an ADR to metamizole presented with non-specific symptoms related to agranulocytosis, such as sore throat, fever and chills, ulcerative lesions in the mouth, gum inflammation, change in heartbeat, and muscle weakness.

TABLE III - Adverse Drug Reactions (ADRs) associated with isolated tapentadol, viminol, and metamizole

ADRs	N (%)	95% CI Frequency (%)	Severity	Mechanism of action	Incidence*	Causality
TAPENTADOL						
Anorexia	2 (18.18)	[3.21; 52.25]	Mild	Type A	Common	Certain
Lip paresthesia	2 (18.18)	[3.21; 52.25]	Mild	Type A	Common	Certain
Blurred vision	2 (18.18)	[3.21; 52.25]	Mild	Type A	Common	Certain
Constipation	1 (9.09)	[0.48; 42.88]	Moderate	Type A	Uncommon	Certain
Lack of concentration	1 (9.09)	[0.48; 42.88]	Mild	Type A	Uncommon	Certain
Restlessness	1 (9.09)	[0.48; 42.88]	Mild	Type A	Uncommon	Certain
Somnolence	1 (9.09)	[0.48; 42.88]	Mild	Type A	Uncommon	Certain
Vomiting	1 (9.09)	[0.48; 42.88]	Moderate	Type A	Uncommon	Certain
VIMINOL						
Asthenia	3 (42.86)	[11.81; 79.76]	Mild	Type A	Common	Certain
Rash	1 (14.29)	[0.75; 57.99]	Mild	Type A	Uncommon	Certain
Somnolence	1 (14.29)	[0.75; 57.99]	Mild	Type A	Uncommon	Certain
Dizziness	1 (14.29)	[0.75; 57.99]	Moderate	Type A	Uncommon	Certain
Tremors	1 (14.29)	[0.75; 57.99]	Mild	Type A	Uncommon	Certain

Asthenia was the predominant complaint resulting from the interaction of viminol with other drugs. Among participants taking tapentadol, in addition to asthenia, somnolence was also a common ADR, as shown in Table IV. For tapentadol, ADRs were classified as mild or moderate (mental confusion and dizziness; drowsiness and difficulty with motor coordination), type A, common or uncommon, and possible. For viminol, ADRs were classified as mild, type A, common or uncommon (tremor), and possible. No ADRs related to drug interactions were reported for metamizole (Table IV).

TABLE IV - Adverse Drug Reactions (ADRs) related to drug interactions of tapentadol and viminol

ADRs	N (%)	95% CI Frequency (%)	Severity	Mechanism of action	Incidence*	Causality
TAPENTADOL						
Asthenia	3 (2.86)	[0.74; 8.73]	Mild	Type A	Common	Possible
Somnolence	3 (2.86)	[0.74; 8.73]	Mild	Type A	Common	Possible
Sweating and cold extremities	2 (1.90)	[0.33; 7.38]	Mild	Type A	Common	Possible
Mental confusion and dizziness	1 (0.95)	[0.05; 5.96]	Moderate	Type A	Uncommon	Possible
Constipation	1 (0.95)	[0.05; 5.96]	Mild	Type A	Uncommon	Possible
Epigastric discomfort	1 (0.95)	[0.05; 5.96]	Mild	Type A	Uncommon	Possible
Dyspnea	1 (0.95)	[0.05; 5.96]	Mild	Type A	Uncommon	Possible
Drowsiness and difficulty with motor coordination	1 (0.95)	[0.05; 5.96]	Moderate	Type A	Uncommon	Possible
Dizziness	1 (0.95)	[0.05; 5.96]	Mild	Type A	Uncommon	Possible
VIMINOL						
Asthenia	3 (2.04)	[0.53; 6.3]	Mild	Type A	Common	Possible
Somnolence	2 (1.36)	[0.24; 5.33]	Mild	Type A	Common	Possible
Dizziness	2 (1.36)	[0.24; 5.33]	Mild	Type A	Common	Possible
Tremor	1 (0.68)	[0.04; 4.30]	Mild	Type A	Uncommon	Possible

* Incidence calculated considering the 102 patients who received tapentadol; and 147 patients who received viminol.

Predictors Associated with ADRs

A logistic regression analysis was conducted to identify predictors associated with the occurrence of ADRs for tapentadol and viminol separately, as shown in Table V. Due to the low incidence of ADRs with metamizole, it was not possible to analyze the data for this drug. For the viminol group, the results indicated that ADRs were significantly associated with age, with each additional year increasing the risk of ADRs by 6.0% (OR = 1.06; P = 0.041). No other significant associations were found between ADRs for tapentadol or viminol and factors such as sex, hypertension, arrhythmia, and anxiety and/or depression.

TABLE V - Predictors associated with Adverse Drug Reactions (ADRs) of tapentadol and viminol (*continues*)

CARACTERISTIC	OR	95% CI Frequency	P value
TAPENTADOL			
Sex			
F	—	—	
M	0.70	0.19; 2.29	0.6
Hypertension			
No	—	—	
Yes	0.41	0.08; 1.72	0.2
Diabetes			
No	—	—	
Yes	2.16	0.38; 11.20	0.4
Arrhythmia			
No	—	—	
Yes	0.84	0.04; 5.84	0.9
Anxiety and/or depression			
No	—	—	
Yes	0.46	0.10; 1.66	0.3
Age	0.98	0.93; 1.02	0.3

TABLE V - Predictors associated with Adverse Drug Reactions (ADRs) of tapentadol and viminol (*continuation*)

CARACTERISTIC	OR	95% CI Frequency	P value
VIMINOL			
Sex			
F	—	—	
M	0.85	0.20; 3.13	0.8
Hypertension			
No	—	—	
Yes	1.53	0.39; 6.13	0.5
Diabetes			
No	—	—	
Yes	0.31	0.02; 1.94	0.3
Arrhythmia			
No	—	—	
Yes	0		>0.9
Anxiety and/or depression			
No	—	—	
Yes	0.78	0.19; 2.79	0.7
Age	1.06	1.00; 1.12	0.041

OR: Odds Ratio

DISCUSSION

Given the widespread use of analgesics, a significant number of ADRs are expected among users. According to Jo *et al*. (2021), analgesics constitute the third class of medications with the highest rate of ADRs (4.0%), following antibacterials (20.3%) and antimycobacterials (5.4%). Similar results were observed by Sakuma *et al*. (2020), with 4.5% of their study population reporting ADRs related to analgesics, particularly among the elderly. The present study found that despite the frequent use of tapentadol and viminol, these drugs presented a relatively low incidence of ADRs. Among the three drugs studied, metamizole demonstrated the safest profile, corroborating findings from previous research and real-world evidence, as

mentioned by Sznejder *et al*. (2022), which supported metamizole's safety in the Brazilian population.

Previous studies have consistently shown that ADRs are most frequent in female patients (Sznejder *et al.*, 2022; Al-Qurain *et al*., 2020; Cazacu*et al*., 2018). Franconi *et al.* (2012) reported that women have a 50 to 70% higher risk of experiencing ADRs, which may be attributed to differences in pharmacokinetics, pharmacodynamics, and hormonal factors. For instance, Lopes *et al.* (2021) demonstrated a significant disparity in opioid-related ADRs between the sexes, with 6.5% of female participants reporting ADRs compared to 3.4% of males. Tramadol, in particular, was associated with gastrointestinal, dermatological, and neurological ADRs in women. However, in contrast to these findings, the present study did not reveal any statistically significant influence of sex on ADR occurrence. This discrepancy may be related to methodological differences between the studies, since Lopes *et al*. (2021) performed a retrospective study incorporating pharmacogenomic genotyping, which may have influenced the detection of sex-related effects.

Comorbidities can play a crucial role in the development of ADRs (Zazzara *et al*., 2021). In this study, 13 participants who experienced ADRs had comorbidities, such as hypertension and/or diabetes. The presence of comorbidities is often linked to polypharmacy, which increases the risk of drug-drug interactions and subsequent ADRs (Ognibene *et al*., 2018). Polypharmacy, combined with non-specific symptoms, presents a diagnostic challenge in identifying the exact cause of ADRs, highlighting the importance of detailed data collection and analysis (Woo *et al*., 2020). It worth noting that while 253 drug interactions were detected across the three analgesics under investigation, only 22 (8.69%) were associated with ADRs. Tapentadol and viminol were most frequently implicated in drug interactions, yet these interactions did not result in significant clinical consequences, mirroring the findings of Riera *et al*. (2022), who also reported safe drug interactions involving analgesics without clinical implications.

Related to the drugs studied, metamizole emerged as the most prescribed, used, and tolerated analgesic. This is consistent with the results of Reist *et al.* (2018) who found that metamizole was the most frequently prescribed analgesic by anesthesiologists and pain specialists in German-speaking countries. The authors observed that 93.8% of 2,237 patients received metamizole, either alone (19.9%) or in combination with other analgesics (76.7%) for chronic pain management. Although they reported a 3.5% incidence of metamizole-associated agranulocytosis, it was not possible to definitively attribute the agranulocytosis to metamizole, as patients were also using other medications. Indeed, various drugs, including antipsychotic, antibiotic, antithyroid agents, and antiplatelet medications, have been implicated in agranulocytosis (Mijovic, MacCabe, 2020). Moreover, studies evaluating agranulocytosis related to metamizole often fail to clearly distinguish between neutropenia, agranulocytosis, and aplastic anemia (Klose *et al.*, 2020). Lobo *et al.* (2013) found that 20% of ADRs reported in a hospital in northern Brazil were linked to metamizole, but did not specify the nature of these effects, attributing the high incidence to the frequency of metamizole use in the study population. The ADRs identified in this study - namely asthenia, hypotension, and gastric discomfort - were not reported in previous studies, though they were mild and consistent with the drug's label. Despite its demonstrated safety, as noted by Sznejder *et al*. (2022), who supported metamizole's safety in the Brazilian population, metamizole remains banned in many countries, possibly due to geopolitical factors rather than scientific evidence.

Viminol, in contrast, lacks recent studies on its efficacy and safety. Between 1985 and 2019, only 20 ADRs related to viminol were reported in the Americas, with symptoms including dizziness, abdominal pain, nausea and vomiting, malaise, asthenia, withdrawal syndrome, ataxia, coma, peripheral neuropathy, mental confusion, dyspnea, urticaria, and skin tissue disorders. The majority of ADRs are manifested in males, in young adults, aged between 18 and 44 years (DIVIDOL, 2020). Historical studies, such as those by

Foschi, Ventresca, Lodola (1985) observed sedation as an ADR related to viminol, while Martinetti *et al*. (1970) reported dizziness and sedation, and Frigerio *et al.* (1974) asthenia, dizziness, and skin rashes. In the current study, dizziness, drowsiness, asthenia, tremors, and skin rashes were the most frequently reported ADRs, observed in both male and female participants with a mean age of 65.2 years. Importantly, this is the first study to highlight that in participants over 55 years of age, each additional year increased the risk of ADRs by 6%, underscoring the need for cautious prescription in older adults.

Tapentadol was the analgesic most frequently associated with ADRs in this study. Previous meta-analyses have demonstrated that tapentadol is generally safe, with constipation being the most commonly reported ADR (Freynhagen *et al.*, 2021). Abeyaratne *et al*. (2018) also identified gastrointestinal issues as common, but reported that psychiatric disorders constituted 50% of tapentadol-related. Coluzzi, Ruggeri (2014) found that tapentadol prolonged-release formulations reduced ADR-related discontinuations compared to oxycodone/naloxone. In a study by Mateos *et al.* (2021) involving 81 patients with chronic knee and lower back pain, 18.1% of patients experienced ADRs likely related to extended-release tapentadol and 8.4% discontinued treatment due to ADRs.

Monitoring and reporting ADRs during analgesic treatment are critical for improving pain management and patient outcomes (Planelles *et al.*, 2019). Studies like the present reinforce pharmacovigilance efforts by providing essential data to support regulatory agencies' decision-making. Many medications, including analgesics, have been withdrawn from the market due to safety concerns, often without a systematic investigation to establish a clear cause-effect relationship for ADRs (Onakpoya, Heneghan, Aronson, 2018). Pharmacovigilance also plays a key role in strategies such as including drugs in the World Health Organization's list of essential medicines, where safety data help determine the optimal cost-benefit ratio. The findings of this study suggest that analgesics like metamizole could be strong candidates for inclusion in this list, especially in resource-limited settings where safe and effective pain management options are crucial.

The results of this study clearly demonstrate that metamizole, viminol, and tapentadol are safe analgesics, with a low incidence of adverse drug reactions (ADRs) and no severe side effects reported. This prospective assessment addresses significant gaps in the literature by providing current safety data on these three analgesics in a clinical setting. Among the three, metamizole emerged as the safest and most frequently prescribed, making it a valuable option for pain management, particularly in settings where the need for non-opioid, low-risk analgesics is critical. Viminol and tapentadol also exhibited favorable safety profiles, supporting their inclusion in therapeutic protocols for both acute and chronic pain. These findings highlight the potential of these drugs to serve as safer alternatives or adjuncts to analgesics with higher ADR rates and dependency risks, and underscore the importance of further studies to inform clinical practice and regulatory decisions.

Regarding possible biases in the study, the diagnosis of acute pain was excluded, since the pathophysiology, duration, and treatment are different from chronic pain. In addition, the high loss of follow-up was related to the fact that patients did not answer phone calls, contrary to what was proposed in the methodology, and therefore was considered an exclusion factor. Thus, we conclude that there is a limitation in the methodology, as its complete execution depends on patient adherence.

Additionally, these exclusion criteria may have introduced selection bias. By excluding patients with acute pain, our findings are limited to populations with chronic pain and cannot be generalized to broader clinical contexts. Furthermore, the high loss to follow-up (34.07%) – primarily due to unanswered phone contacts – may have disproportionately excluded certain profiles, such as older adults, individuals with cognitive impairments, or those less responsive to follow-up procedures, potentially affecting the sociodemographic balance and representativeness of the final sample.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

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