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Review Article

Safety of metamizole: a systematic review of the literature

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SUMMARY

What is known and objective: **Metamizole was withdrawn from the market in the United States and several European countries following reports of fatal agranulocytosis among users, but is still available in many countries in Europe, South America and Asia. Over the past several decades, a number of epidemiologic studies have been conducted to quantify the risk of agranulocytosis and other adverse effects associated with metamizole and other non-narcotic analgesics. The objective of this study was to perform a systematic review of the safety of metamizole.**

Methods: **Epidemiologic studies published between 1 January 1980 and 15 December 2014 were identified through systematic searches of PubMed and Google Scholar; the reference sections of selected articles were also reviewed to identify potentially relevant studies. Studies included in this review focused on the safety of metamizole, that is on outcomes such as haematologic abnormalities, gastrointestinal bleeding, anaphylaxis and hepatotoxicity. Two study investigators independently reviewed the abstracts and articles to determine relevant studies according to prespecified criteria.**

Results and discussion: **A total of 22 articles met the criteria for evaluation. The majority of studies that evaluated agranulocytosis indicated an increased risk associated with metamizole, with relative risk (RR) estimates ranging from 1·5 (95% CI, 0·8–2·7) to 40·2 (95% CI, 14·7–113·3). Findings of three case–control studies do not suggest an association between metamizole and aplastic anaemia. Of the five case–control studies that evaluated the risk of upper gastrointestinal bleeding, four found a statistically significant increased risk associated with metamizole (RR estimates ranging from 1·4 to 2·7). There is insufficient evidence to determine whether metamizole increases the risk of other outcomes (e.g. hepatic effects, anaphylaxis, congenital anomalies). Few studies evaluated the effects of dose, route of administration or duration of therapy.**

What is new and conclusion: **Published studies reported differences in the magnitude of risk of adverse outcomes associated with metamizole use and often had small sample sizes and a number of other limitations that may have biased the results. Further research is needed to better quantify the potential risks associated with metamizole compared to other non-narcotic analgesics.**

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WHAT IS KNOWN AND OBJECTIVE

Metamizole is a pyrazolone derivative that is an effective non-narcotic analgesic and antipyretic agent.[1,2] Metamizole was withdrawn from the market in the United States and several European countries following reports of fatal agranulocytosis among users, but is still available by prescription and/or over-the-counter (OTC) in many countries in Europe, South America and Asia.[3] There is still considerable controversy surrounding its safety, which has led to varying levels of use and regulatory restrictions across countries.

Since the 1970s when metamizole was initially banned in several countries, a number of non-interventional epidemiologic studies have evaluated the safety of metamizole and other non-narcotic medications, including non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen – medications with similar indications, but varying side effects profiles. A previously published comparative safety evaluation of non-narcotic analgesics based upon epidemiologic evidence reported that the estimated excess mortality associated with short-term treatment with metamizole was similar to acetaminophen, and approximately 7-fold lower than aspirin and 23-fold lower than diclofenac.[4] However, the assessment, which identified epidemiologic studies published from 1970 to 1995, was based upon limited evidence, given that only four epidemiologic studies were published that evaluated adverse outcomes associated with metamizole and met selection criteria. A recent meta-analysis of randomized clinical trials that provided data to evaluate the safety of metamizole found no differences in reported adverse effects between metamizole and placebo, acetaminophen, or NSAIDs.[5] However, too few patients were enrolled in the trials included in the review to provide information on rare, serious adverse outcomes associated with non-narcotic analgesics, such as agranulocytosis and hospitalizations for upper gastrointestinal bleeding.

The primary objective of this study was to conduct a systematic literature review of the safety of metamizole. Specifically, we focused on epidemiologic (observational) studies of non-narcotic analgesics that evaluated outcomes associated with significant morbidity and mortality (e.g. haematologic abnormalities, gastrointestinal bleeding, anaphylaxis, renal failure and hepatotoxicity).

METHODS

Search strategy

A general search strategy was developed to conduct a primary PubMed search to identify original epidemiologic studies

describing the safety of metamizole and a secondary PubMed search to identify relevant review articles related to the safety of metamizole. The reference sections of identified original studies and review articles were examined to determine other potentially relevant original studies that were not identified by the primary PubMed search. A third search, using Google Scholar, was then performed to identify original epidemiologic studies that had cited relevant review articles identified by the PubMed searches. The search strategy, which included terms to identify both specific adverse outcomes associated with non-narcotic analgesics and non-specific terms to identify overall drug safety, is summarized in Table 1.

The PubMed searches were conducted on 16 December 2014 and the Google Scholar Search on 8 January 2015.

Abstract review

Two members of the study team (SA and MES) independently reviewed the abstracts to identify potentially relevant articles for retrieval, including those describing epidemiologic studies where the safety of metamizole (dipyrone) was assessed. Articles identified as potentially relevant by either investigator were retrieved. Articles describing case reports, case series, the analysis of spontaneous reports or clinical trials were not included.

For original studies (PubMed Search 1 and Google Scholar search; Table 1), specific exclusion criteria included the following:

1) the study included non-human population(s) only
2) the abstract did not describe an evaluation of metamizole
3) the study was not an epidemiologic study

Table 1. Search strategy for the systematic review of the safety of metamizole

Search	Criteria[a]
PubMed Search 1 (Original Articles)	Search terms included the following: (dipyrone OR metamizole) AND (agranulocytosis OR blood OR anemia OR gastrointestinal OR haemorrhage OR bleeding OR anaphylaxis OR renal OR kidney OR hepatotoxicity OR liver OR hepatic OR 'adverse drug event' OR 'adverse drug reaction' OR 'drug safety'). The search was restricted to human studies.
PubMed Search 2 (Review Articles)	Search terms included (dipyrone OR metamizole), restricted to review studies and human studies.
Google Scholar search (Studies Citing Relevant Review Articles)	A Google Scholar search was performed to identify articles that cited a published review article authored by one of the investigators (SA) related to the safety of non-narcotic analgesics[4] and other relevant review articles identified in the PubMed searches that were specifically related to metamizole (e.g. not general review articles related to a disease or condition).

[a]Searches were performed to identify articles published between 1 January 1980 and 15 December 2014. The reference sections of all identified articles were examined to determine other potentially relevant original studies that were not identified by the original searches.

For review articles (PubMed Searches 1 and 2), specific exclusion criteria included the following:

1) the study was not specific to metamizole or non-narcotic analgesics as a class (e.g. article was a general review of a specific disease or condition)
2) the review did not describe drug safety
3) the article described a review of randomized clinical trials only
4) the article described a review of intoxication or overdose only

Abstracts identified in both PubMed searches were searched to identify review articles using the above criteria.

Exclusion criteria were applied sequentially (e.g. if an abstract was excluded based upon the first criterion, no other criterion were documented).

Full-text review

Two investigators (SA and JG) independently reviewed the full-text articles with a goal of identifying epidemiologic studies where the safety of metamizole was described. The reference sections of all identified articles were also examined to determine other potentially relevant original studies that were not identified by the original searches. Non-English language full-text articles were translated into English for review.

Specific exclusion criteria included the following:

1) the study did not evaluate metamizole
2) the study was not an epidemiologic study (e.g. treatment with analgesics was assigned by the investigators)
3) the results of the evaluation did not report estimates for metamizole individually (i.e. data for metamizole were grouped in a category with other analgesics)
4) no comparison group was included
5) the article described case reports or a case series
6) the study design or methods were ambiguous
7) the article reported statistics (e.g. preliminary data) from the same study population as another study included in the literature review

Exclusion criteria were applied sequentially and documented. Discrepancies regarding the inclusion of a study for the review report were resolved by consensus following the independent reviews.

A single investigator abstracted information from qualifying articles using a database designed to capture information on the data source, study design and population, analysis, results, strengths and limitations for each study. In addition to extracting data for metamizole, estimates for other non-narcotic analgesics with similar indications (i.e. acetaminophen, aspirin, ibuprofen, naproxen and diclofenac) were documented. When relevant, prior articles cited by the authors which described the study design or methods were reviewed to obtain the information. The data were confirmed by a second investigator for accuracy. Based upon the specific outcomes reported, we categorized studies by the following outcomes: agranulocytosis, aplastic anaemia, upper gastrointestinal bleeding, congenital anomalies and other pregnancy outcomes associated with *in utero* exposure, childhood cancer associated with *in utero* exposure, hepatic effects, anaphylaxis and bleeding complications. When estimates of association are presented (odds ratios [ORs] and relative risks [RRs]), the reference group is no exposure to the medication of interest, unless otherwise stated.

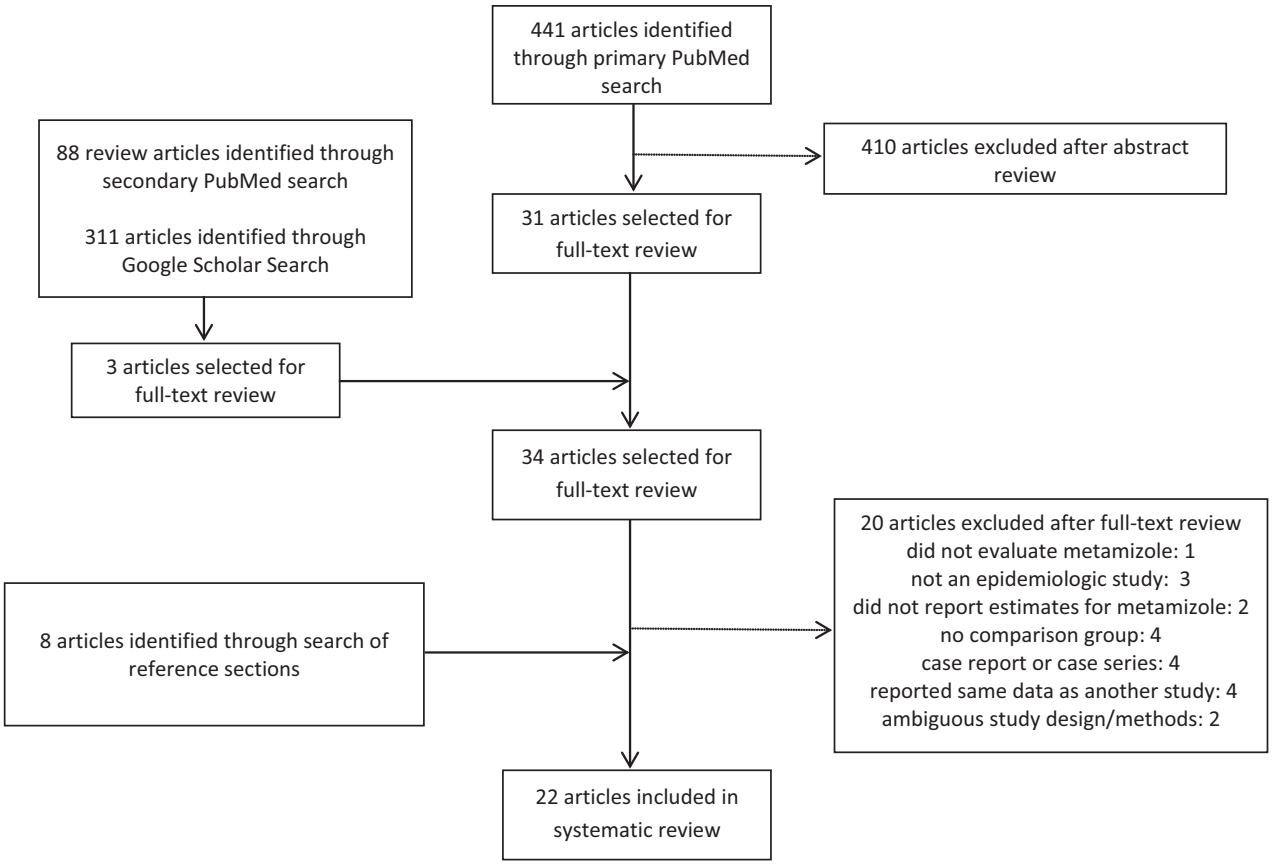

Fig. 1. Abstract and article review process.

RESULTS AND DISCUSSION

Abstract reviews

Figure 1 describes the abstract and article review process. A total of 441 abstracts were identified in the primary PubMed search (PubMed Search 1): 31 original studies were selected for full-text review. Eighty-eight abstracts were identified in the secondary PubMed search (PubMed Search 2); 19 review articles were selected for full-text review (11 of which were also identified by PubMed Search 1). Eight relevant review articles[3,5–11] identified in PubMed Searches 1 and 2 were used to identify citations of interest in the Google Scholar search. Overall, 311 citations were identified in the Google Scholar search; eight original studies were selected for full-text review (five of which were identified in PubMed Search 1 or through the search of the reference sections of articles identified in PubMed searches).

Thus, the primary and secondary PubMed searches and Google Scholar search identified a total of 34 unique original studies and 23 unique review articles for full-text review.

Full-text reviews

Of the 34 full-text articles retrieved, 14 were included in this review.[12–25] Reviewers identified 20 citations for review from the reference sections of review articles and original studies. Of these, eight were included in the literature review.[26–33]

Thus, of the 22 qualifying studies included in this review, 12 were identified from the primary PubMed search, eight were identified through references of articles that underwent full-text review, and two were identified through the Google Scholar search. Six studies evaluated agranulocytosis;[15,16,20,23,28,33] three evaluated aplastic anaemia;[31–33] five evaluated upper gastrointestinal bleeding;[13,18,24,29,30] two evaluated congenital anomalies and birth outcomes associated with *in utero* exposure;[12,27] three evaluated childhood cancer associated with *in utero* exposure;[21,25,26] one evaluated hepatic effects;[19] one evaluated anaphylaxis;[15] one evaluated bleeding complications after percutaneous liver biopsy,[22] and one evaluated the severity of dengue virus infection.[14]

Description of study methods and results

A description of the study methods, results, strengths and limitations for each outcome is summarized below and in Table 2 and the Online Appendix.

Agranulocytosis. Five case–control studies[15,16,20,28,33] and one case-cohort study[23] evaluated the association between metamizole and agranulocytosis. The reported estimates of relative risk (ORs) vary

Table 2. Epidemiologic studies evaluating the safety of metamizole

Citation	Study design	Study population and time period	Country	Data source	Results	Strengths and limitations
Agranulocytosis						
Hamerschlak *et al.*[28]	Case–control	Cases and controls were identified from hospitals/haematology clinics including seven sites in Brazil and two sites in Argentina and Mexico, 2002–2005	Brazil, Argentina, Mexico	Active surveillance of hospitals/haematology clinics, patient interviews, medical records, physicians	30 confirmed cases and 120 controls were included in the case–control analysis. Estimates of the odds ratios and 95% CIs: Metamizole: 2·4 (0·8–6·7) Diclofenac: 4·0 (0·5–29·9) Acetaminophen: 1·9 (0·3–12·1) Aspirin: 1·4 (0·2–6·8)	Strengths • validation of cases by a committee of haematologists • non-prescription drug use could be identified Limitations • small number of cases identified • large proportion of confirmed cases not included in the case–control analysis • potential for missed cases (low access to medical care) • potential information/recall bias • potential residual confounding • estimates did not account for duration of therapy, dose or previous therapy
Huber *et al.*[15]	Case–control	Cases and controls were identified from an adult population served by all 51 Berlin hospitals, 2000–2010	Germany	Active surveillance of hospitals, patient interviews	48 cases and 755 controls were included in the case–control analysis. Odds ratios and 95% CIs for the 'simple' assessment (adjusting for age and sex) were as follows: Metamizole 28·4 (11·6–72·4) Diclofenac 1·9 (0·4–5·9) Aspirin 0·7 (0·2–1·8) Aspirin in combination 2·7 (0·8–7·6) Acetaminophen 5·1 (1·6–14·5) Odds ratios, 'joint' assessment (adjusting for age, sex and other drugs): Metamizole 40·2 (14·7–113·3) Acetaminophen 5·1 (1·02–20·4)	Strengths • active surveillance of all 51 Berlin hospitals • non-prescription use could be identified Limitations • small sample size • potential recall/information bias • potential for missed cases (e.g. if died without receiving medical care) • potential selection bias with controls • potential residual confounding • estimates did not account for the duration of therapy, dose or prior therapy
Ibanez *et al.*[16]	Case–control	Cases and controls were identified from all hospitals in the Metropolitan Area of Barcelona, 1980 to 2001	Spain	Active surveillance of haematology laboratory units of hospitals, patient interviews. Centre participated in the International Agranulocytosis and Aplastic Anemia	177 cases and 586 controls were included in the conditional logistic regression analysis. The odds ratio and 95% CI estimates were as follows: Metamizole: 25·76 (8·39–79·12)	Strengths • active surveillance of all Barcelona metropolitan area hospitals • non-prescription use could be identified Limitations • potential information/recall bias

(continued)

Table 2 (continued)

Citation	Study design	Study population and time period	Country	Data source	Results	Strengths and limitations
				Study (IAAAS) between 1980 and 1986. Data collection and data analysis continued using the same methods.	Aspirin: 1·39 (0·67–2·88) Acetaminophen: 1·54 (0·68–3·52) Diclofenac: 3·86 (1·00–15·00) Other NSAIDs: 1·39 (0·41–4·77) 245 cases and 1530 controls were included in the unconditional regression analysis. The odds ratio estimates were as follows: Metamizole: 20·53 (11·45–36·81) Aspirin: 1·66 (1·01–2·73) Acetaminophen: 1·41 (0·83–2·41) Diclofenac: 2·90 (1·12–7·54) Other NSAIDs: 2·40 (0·94–6·08)	• potential for missed cases (e.g. if died without receiving medical care) • a large proportion of cases were excluded from the case–control analysis • potential residual confounding • estimates did not account for duration of therapy, dose or previous therapy • data for 1980 to 1986 previously analysed as part of the IAAAS
Kaufman *et al.*[33]	Case–control	Cases and controls were identified from hospitals in Israel; Barcelona, Spain; Ulm, West Germany; West Berlin; Milan, Italy; Budapest, Hungary; Sofia, Bulgaria; Stockholm/Uppsala, Sweden, 1980–1986	Israel, Spain, West Germany, Italy, Hungary, Bulgaria, Sweden	Active surveillance of hospitals in designated regions, patient interviews	270 community-acquired cases were included in the case–control analysis. The multivariate relative risk estimates and 95% CIs for any use in the week before the index day were as follows: Metamizole: Ulm, West Germany/West Berlin/Barcelona: 16 (6·9–38) Israel/Budapest/Sofia/Milan: 1·5 (0·8–2·7) Salicylates (aspirin and other salicylates): 2·0 (1·3–3·2) Acetaminophen: 1·2 (0·7–2·0) No consistent trend was found for duration of therapy. Estimates of the excess risk per million were 0·6 for metamizole (Ulm/Berlin/Barcelona) and 0·06 for salicylates.	Strengths • large, population-based study • validation of cases by a committee of haematologists • non-prescription use could be identified Limitations • potential information/recall bias • potential for missed cases (e.g. if died without receiving medical care) • a large proportion of cases were excluded from the case–control analysis • potential residual confounding • estimates did not account for dose
Shapiro *et al.*[20]	Case–control	Cases and controls identified from all hospitals in Bangkok, 1990–1994	Thailand	Active surveillance of hospitals in Bangkok, medical records, patient interviews	25 cases and 529 controls were included in the case–control analysis. One case and three controls were exposed to metamizole. No statistically significant associations were found for any of the analgesics of interest.	Strengths • active surveillance of all Bangkok hospitals • validation of cases by a committee of haematologists • non-prescription use could be identified

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Table 2 (continued)

Citation	Study design	Study population and time period	Country	Data source	Results	Strengths and limitations
						Limitations • small sample size • potential recall/information bias • potential for missed cases (e.g. if died without receiving medical care) • potential for confounding • estimates did not account for duration of therapy, dose or previous therapy
Van der Klauw *et al.*[23]	Case-cohort	The base cohort consisted of all persons in the Netherlands; all pharmacy dispensing data from a representative sample of pharmacies were considered as an exposure sample from the base cohort (reference cohort), 1987–1990	Netherlands	Pharmaco Morbidity Record Linkage System (PHARMO exposure database; dispensed drugs); nationwide computerized register of hospital diagnoses (Dutch Centre for Health Care Information, Ultrecht); contact with the general practitioner, pharmacist, patient record	75 cases that occurred out of hospital were included in the analysis. Adjusted RR and 95% Cis estimates were as follows: Metamizole: 26·4 (4·4–111·1) Acetaminophen: 2·4 (1·1–5·2) Salicylates: 3·6 (1·3–9·3) NSAIDs: 2·5 (1·3–4·9) Estimates of the excess risk per million were as follows: Metamizole: 1·36 Acetaminophen: 0·07 Salicylates: 0·14 NSAIDs: 0·08	Strengths • design avoids recall bias • validation of cases by a committee of haematologists Limitations • potential for underascertainment of cases • proportion of potential cases for which records were sent containing sufficient information • reference cohort was not a random sample from the total study population • small number of cases exposed to medications of interest (e.g. only 2 cases were exposed to metamizole) • potential for residual confounding • estimates did not account for duration of therapy, dose or previous therapy
Aplastic Anaemia Kaufman *et al.*[33]	Case–control	Cases and controls were identified from hospitals in Israel; Barcelona, Spain; Ulm, West Germany; West Berlin; Milan, Italy; Budapest, Hungary; Sofia, Bulgaria; Stockholm/Uppsala, Sweden, 1980–1986	Israel, Spain, West Germany, Italy, Hungary, Bulgaria, Sweden	Active surveillance of hospitals in designated regions, patient interviews	152 community-acquired cases were interviewed and included in the case–control analysis. The multivariate relative risk estimates and 95% CIs for any use in days 29 to 180 before admission were as follows: Metamizole: 0·5 (0·3–0·9) Salicylates: 1·2 (0·8–1·8) Acetaminophen: 1·4 (0·9–2·3) Diclofenac: 4·2 (1·6–11)	Strengths • large, population-based study • validation of cases by a committee of haematologists • non-prescription use could be identified Limitations • potential information/recall bias • potential for missed cases (e.g. if died without receiving medical care) • a large proportion of cases were excluded from the case–control analysis

(continued)

Table 2 (continued)

Citation	Study design	Study population and time period	Country	Data source	Results	Strengths and limitations
					The estimate of excess risk per 1 million was 2·6 for diclofenac.	• potential residual confounding • estimates did not account for duration of exposure
Maluf *et al.*[31]	Case–control	Cases and controls were identified from hospitals/ haematology clinics including seven sites in Brazil and two sites in Argentina and Mexico, 2002–2005	Brazil, Argentina, Mexico	Active surveillance of haematology; patient interviews, medical records, physicians	173 cases and 692 controls were used in the case–control analysis. The odds ratio estimate for metamizole was 0·8 (95% CI, 0·54–1·14)	Strengths • validation of cases by a committee of haematologists • non-prescription use could be identified Limitations • potential information/recall bias • long period for assessment of exposure • potential for missed cases (e.g. if died without receiving medical care) • a large proportion of cases were excluded from the case–control analysis • potential residual confounding • estimates did not account for dosage or duration of exposure
Mary *et al.*[32]	Case–control	Cases and controls were identified from the catchment areas of medical centres in France, 1985–1988	France	Population-based registry from 83 medical centres in designated regions, patient interviews	147 cases, 287 hospital controls and 108 community controls were included in the study. Estimates of odds ratios and 95% CIs for exposure in the last 5 years) were as follows: Metamizole (and derivatives): 1·6 (0·6–4·4) Acetaminophen: 1·8 (1·1–3·0) Diclofenac: 1·1 (0·6–1·9) Salicylates: 1·8 (1·2–2·6) Estimates of ORs and 95% CIs in the last 1 year) were as follows: Metamizole (and derivatives): - Acetaminophen: 2·0 (1·0–3·8) Diclofenac: 1·4 (0·6–3·5) Salicylates: 1·9 (1·1–3·2)	Strengths • non-prescription drug use could be identified Limitations • potential information/recall bias • long period for assessment of exposure which included the time period up to the diagnosis • potential for missed cases (e.g. if died without receiving medical care) • a large proportion of cases were excluded from the case–control analysis • potential residual confounding • estimates did not account for dosage or duration of exposure
Upper gastrointestinal bleeding						
De Abajo *et al.*[13]	Case–control	Cases and controls were identified from the population aged 40 to 90 years included in Base de datos para la Investigación	Spain	Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria (BIFAP) database which is a computerized,	1193 cases and 10 000 controls were included in the analysis. Odds ratio and 95% CI estimates for current use were as follows: Metamizole: 1·52 (1·09–2·13)	Strengths • large population-based study • assigned index date for cases was the earlier of the date of first signs or first diagnosis (rather than admission date)

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Table 2 (continued)

Citation	Study design	Study population and time period	Country	Data source	Results	Strengths and limitations
		Farmacoepidemiológica en Atención Primaria (BIFAP), 2001–2005		population-based database of anonymized longitudinal medical records of patients attended by general practitioners and primary paediatricians in Spain	Diclofenac: 1·32 (0·87–1·98) Ibuprofen: 1·33 (0·94–1·89) Naproxen: 2·14 (1·03–4·47) Aspirin: 1·85 (1·51–2·28) Low-dose aspirin: 1·74 (1·37–2·21) Medium–high dose: 3·29 (1·42–7·62) Acetaminophen: 1·00 (0·82–1·23) For overall NSAID use, ORs were higher for high dose current use and within the first 30 days of treatment. No dose effect was found for acetaminophen.	Limitations • no information on non-recorded non-prescription drug use • potential residual confounding/ confounding by indication • estimates did not account for the duration of therapy (except for overall NSAIDs) or dose (except for aspirin and overall NSAID use)
Lanas *et al.*[30]	Case–control	Cases and controls were identified from a network of general hospitals within Spain, 2001–2004	Spain	Network of general hospitals integrated within the Spanish Association of Gastroenterology, patient interviews, clinical records	2777 cases and 5532 controls were included in the analysis. Odds ratio and 95% CI estimates for current use were as follows: Metamizole: 1·4 (1·0–2·0) Diclofenac: 3·1 (2·3–4·2) Ibuprofen: 4·1 (3·1–5·3) Naproxen: 7·3 (4·7–11·4) Aspirin: 5·3 (4·5–6·3) Acetaminophen: 0·9 (0·7–1·1) For aspirin and non-aspirin NSAIDs, ORs were higher for higher dosages and were higher for shorter durations of use.	Strengths • large population-based study • non-prescription drug use could be identified • assigned index date for cases was the date of first signs (rather than admission date) Limitations • potential information/recall bias • control selection • potential residual confounding/ confounding by indication • estimates for specific NSAIDs, acetaminophen and metamizole did not account for duration of therapy or dose
Lanas *et al.*[24]	Case–control	Cases and controls were identified from areas encompassed by four general hospitals in Spain, 1995–1998	Spain	Four general hospitals in Spain; patient interviews, medical charts	1122 cases and 2231 controls were included in the analysis. Odds ratio and 95% CI estimates for current use were as follows: Metamizole: 2·7 (1·3–5·4) Diclofenac: 5·1 (3·1–8·4) Naproxen: 5·3 (2·6–10·8) Aspirin: 6·6 (5·2–8·2) Acetaminophen: 0·6 (0·4–1·0)	Strengths • non-prescription drug use could be identified Limitations • potential information/recall bias • control selection • use of hospital admission date as index date • potential residual confounding/ confounding by indication • estimates did not account for duration of therapy or dose • secondary analysis of data from a previous study (not primary objective of the study)

(continued)

Table 2 (continued)

Citation	Study design	Study population and time period	Country	Data source	Results	Strengths and limitations
Laporte *et al.*[18]	Case–control	Cases and controls were identified from a population participating hospitals in Barcelona and Palma de Mallorca, 1987–1988	Spain	Participating hospitals in Barcelona and Palma de Mallorca; patient interviews	A total of 875 cases and 2682 controls were included in the analysis. Odds ratio estimates and 95% confidence intervals were as follows: Aspirin 7·2 (5·4-9·6) Acetaminophen 1·5 (0·8-2·5) Metamizole 1·6 (0·8-3·1) Diclofenac 7·9 (4·3-14·6) Naproxen 6·5 (2·2-19·6)	Strengths • non-prescription drug use could be identified • assigned index date for cases was the date of first signs (rather than admission date) Limitations • potential information/recall bias • potential residual confounding/ confounding by indication • control selection • estimates did not account for duration of therapy or dose
Laporte *et al.*[29]	Case–control	Cases and controls > 18 years were identified from 18 hospitals in Spain and Italy, 1998–2001	Spain, Italy	Eighteen hospitals in Spain and Italy; patient interviews	2813 cases and 7193 controls were included in the analysis. Odds ratio and 95% CI estimates for current use were as follows: Metamizole: 1·9 (1·4–2·6) Diclofenac: 3·7 (2·6–5·4) Ibuprofen: 3·1 (2·0–4·9) Naproxen: 10·0 (5·7–17·6) Aspirin: 8·0 (6·7–9·6) Acetaminophen: 1·2 (1·0–1·5) For aspirin and non-aspirin NSAIDs, ORs were higher for higher dosages. No dose-related trend was found for acetaminophen.	Strengths • non-prescription drug use could be identified • assigned index date for cases was the date of first signs (rather than admission date) Limitations • potential information/recall bias • potential residual confounding/ confounding by indication • control selection • estimates did not account for duration of therapy
Congenital anomalies and birth outcomes associated with *in utero* exposure						
Banhidy *et al.*[12]	Case–control	Cases and controls were identified in the Hungarian Case-Control Surveillance of Congenital Abnormalities study dataset (covering the population of Hungary), 1980–1996	Hungary	Hungarian Case-Control Surveillance of Congenital Abnormalities dataset (Hungarian Congenital Abnormality Registry and Hungarian Birth Registry of the Central Statistical Office), patient questionnaires/ interviews, antenatal log books	22 843 cases with congenital abnormalities, 38 151 matched population controls without congenital abnormalities and 834 malformation controls were identified. Among the 25 congenital abnormality group evaluated, 3 congenital abnormality groups (cardiovascular [OR 1·3, 95% CI 1·0–1·7], diaphragmatic [OR 2·7, 95% CI 1·0–6·8] and other isolated congenital abnormalities [OR 1·8, 95% CI 1·1–2·9]) were associated with metamizole (compared to	Strengths • large, population-based study • non-prescription drug use could be identified • malformation controls available to minimize/assess recall bias Limitations • potential for information/recall bias: more active follow-up for non-respondent cases compared to population controls and the period between the end of pregnancy and return of the questionnaire was different between the case and population control groups • several important confounders were not used in the analysis (e.g.

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Table 2 (continued)

Citation	Study design	Study population and time period	Country	Data source	Results	Strengths and limitations
					population controls). No statistically significant associations were found in models with the malformation controls as the referent group.	obesity, smoking, alcohol use) • large number of comparisons
Bar-Oz *et al.*[27]	Cohort	Women who called one of four participating teratogen information services (TIS): Assaf Harofeh Teratogen Information Center (Zerifin, Israel), The National Teratogen Information Center (Jerusalem, Israel), Beilinson Teratogen Information Center (Petach Tikva, Israel) and the TIS in Padova, Italy	Israel, Italy	Four participating teratogen information services; follow-up telephone interviews	108 women who received metamizole and 108 women who received acetaminophen were included in the analysis. There was no significant difference between the groups in the rate of major malformations (OR 1·55 (95% CI, 0·26–9·05) or other pregnancy outcomes, including live births, spontaneous abortions and elective abortions, gestational age at birth, prematurity rate and birthweight and foetal distress. There was a significantly higher rate of Caesarean section among the metamizole-exposed women compared to the acetaminophen group.	Strengths • non-prescription drug use could be identified Limitations • small sample size • outcomes reported by women (no follow-up examination by a study physician) • representativeness of comparison group (from one centre only) • many potential confounders not accounted for (e.g. obesity) • generalizability of findings
Childhood cancer associated with *in utero* exposure						
Alexander *et al.*[26]	Case–control	Cases and controls were identified from catchment areas of hospitals in Italy, Greece, Egypt, Brazil, Chile, mainland China, Hong Kong, Japan	Italy, Greece, Egypt, Brazil, Chile, mainland China, Hong Kong, Japan	Hospitals in designated regions, patient interviews	136 cases and 266 controls were recruited for study. The odds ratio and 95% CI estimates for metamizole were as follows: Overall infant leukaemia: 2·83 (1·15–6·99) MLL+ve: 5·84 (2·09–16·30) MLL -ve subgroup: 0·64 (0·08 –5·41)	Strengths • non-prescription drug use could be identified Limitations • small sample size • pilot study • potential for information/recall bias (majority of interviews > 12 months after child's birth) • inconsistent criteria for control selection across sites • representativeness of controls • MLL status unknown for a large proportion of cases • potential residual confounding
Couto *et al.*[25]	Case–control	Cases and controls were identified from	Brazil	Hospitals in designated regions, patient interviews	176 children with acute lymphocytic leukaemia (ALL) and 55 with acute myeloid	Strengths • non-prescription drug use could be identified

(continued)

Table 2 (continued)

Citation	Study design	Study population and time period	Country	Data source	Results	Strengths and limitations
		hospitals in 11 states in Brazil, 1999–2007			leukaemia (AML) cases, and 411 controls were included in the analysis. The odds ratio (OR) and 95% CI estimates were as follows: ALL Metamizole only: Overall 1·41 (0·92–2·16) Preconception period 1·63 (1·06–2·53) First trimester 1·36 (0·90–2·05) Second trimester 1·35 (0·89–2·04) Third trimester 1·20 (0·71–1·99) Breastfeeding 2·00 (1·18–3·39) Acetaminophen only Overall 0·53 (0·28–1·02) Preconception period 0·80 (0·37–1·73) First trimester 0·38 (0·16–0·87) Second trimester 0·34 (0·15–0·80) Third trimester 0·56 (0·28–1·11) Breastfeeding 0·67 (0·30–1·54) Aspirin Overall 1·37 (0·52–3·69) Preconception period 1·32 (0·39–4·49) First trimester 1·54 (0·44–5·37) Second trimester 0·54 (0·11–2·74) Third trimester 0·49 (0·10–2·48) Breastfeeding 0·42 (0·05–3·79) AML Metamizole only: Overall 1·13 (0·55–2·35) Preconception period 1·13 (0·55–2·35) First trimester 1·24 (0·62–2·47) Second trimester 1·12 (0·56–2·23)	Limitations • potential information/recall bias • potential selection bias/ representativeness of controls • potential residual confounding

(continued)

Table 2 (continued)

Citation	Study design	Study population and time period	Country	Data source	Results	Strengths and limitations
					Third trimester 0·99 (0·40–2·46) Breastfeeding 0·90 (0·32–2·55) Acetaminophen only Overall 0·48 (0·16–1·43) Preconception period 0·48 (0·16–1·43) First trimester 0·44 (0·12–1·63) Second trimester 0·20 (0·04–1·08) Third trimester 0·50 (0·16–1·62) Breastfeeding 0·61 (0·16–2·27) Aspirin Overall 2·28 (0·47–11·08) Preconception period 5·33 (1·02–27·87) First trimester 1·10 (0·09–12·86) Second trimester 0·79 (0·07–8·36) Third trimester 0·83 (0·07–9·10) Breastfeeding 2·32 (0·21–25·28)	
Sharpe *et al.*[21]	Case–control	Cases and controls were identified from hospitals in four cities in Brazil, 1987–1989	Brazil	Hospitals in four cities in Brazil, patient interviews	The study included 109 cases of Wilms' tumour (100 incident cases and 9 recently diagnosed cases returning for treatment) and 218 controls. Odds ratios and 95% CIs were as follows: Metamizole, Low income: 10·89 (2·38–49·9) Metamizole, Medium income: 0·66 (0·17–2·60) Metamizole, High income: 2·56 (0·72–9·12) NSAIDs: 0·91 (0·27–3·12) Analgesics: 1·33 (0·72–2·45)	Strengths • non-prescription drug use could be identified Limitations • exploratory investigation with multiple associations evaluated • small sample size • potential information/recall bias • potential selection bias • potential residual confounding • association with metamizole only indicated in subgroup analysis for low-income families
Hepatic Effects Sabate *et al.*[19]	'Case population study' (estimation of risk/incidence)	Population 15 years of age or older identified from a collaborating network, including 12 hospitals covering a population of 2·7 million inhabitants, 1993–1999	Spain	A collaborating network, including 12 hospitals in Barcelona, Spain; medical records, patient interviews	126 patients fulfilled inclusion criteria. Relative risk estimates and 99% CIs were for the association with acute liver injury: Metamizole: 3·1 (0·4–11·4) Acetaminophen: 7·0 (3·3–13·9) Aspirin: 5·4 (2·0–12·3) Diclofenac: 7·6 (1·8–22·0)	Strengths • non-prescription drug use could be identified • cases based upon clinical criteria (independent from exposure status) Limitations • small sample size • potential information/recall bias

(continued)

Table 2 (continued)

Citation	Study design	Study population and time period	Country	Data source	Results	Strengths and limitations
						• crude estimates reported, based upon assumptions on drug consumption in the population • potential confounding • estimates did not account for duration of therapy or dose
Anaphylaxis International Collaborative Study of Severe Anaphylaxis[17]	Risk estimation for various medications (case–control data collection but not analysis)	Cases and controls were identified from hospitals in Budapest Hungary; Barcelona, Spain; Mumbai and Pune, India; and five cities in Sweden, 1992–1997	Hungary, Spain, India, Sweden	Hospital medical records, patient interviews, in some cases physicians and nurses	There were 184 inpatient cases of anaphylaxis who met the criteria for anaphylaxis: 120 were classified as definite, 33 as probable and 31 as possible cases. Estimates of incidence per 10 000 exposed patients (95% CI) were as follows: Metamizole (parenteral) 7·0 (3·0–16) Metamizole (oral) 8·1 (3·5–19) Diclofenac (parenteral) 9·0 (2·7–30) Diclofenac (oral) 7·2 (2·6–20) Acetaminophen (oral) 4·5 (2·1–9·7) Aspirin (oral) 2·1 (0·7–6·5)	Strengths • cases validated by clinicians blinded to exposures • use of medical records avoids recall bias Limitations • small sample size • crude estimates of risk based upon various assumptions to extrapolate exposure data (no control for potential confounders) • estimates did not account for the duration of therapy or previous therapy with the medications under study
Bleeding Complications Terjung *et al.*[22]	Cohort	Patients who underwent a diagnostic percutaneous liver biopsy at Department of Internal Medicine I at the University of Bonn, Germany, 1993–1996	Germany	Department of Internal Medicine I at the University of Bonn, Germany, medical charts	72 of 629 patients experienced bleeding complications. The adjusted odds ratio (95% CI) for metamizole was 2·8 (1·1–7·4).	Strengths • use of medical records avoids recall bias Limitations • large number of risk factors were assessed • potential for residual confounding/confounding by indication • generalizability of the results • estimates did not account for dose and duration of use

(continued)

Table 2 (continued)

Citation	Study design	Study population and time period	Country	Data source	Results	Strengths and limitations
Severity of Dengue Infection						
Diaz-Quijano *et al.*[14]	Cohort	Patients over the age of 12 with a confirmed diagnosis of dengue, who were treated at health institutions in the metropolitan area of Bucaramanga, 2003–2004	Colombia	Physical examination and follow-up assessments of patients treated at health institutions	Of the 110 patients meeting eligibility criteria, 17 were exposed to metamizole. Overall, 7 patients developed DHF (6·36%), 17 had plasma leakage and 3 had platelet counts below 50 000/μL. The estimates of relative risk (RR) and 95% CIs for the association between each outcome and metamizole (compared to unexposed patients) were as follows: Haemorrhagic fever: 7·29 (1·79–29·72) Plasma leakage: 2·28 (0·92–5·64) Platelets <50 000: 10·94 (1·05–114·05) There was no statistically significant association between exposure to diclofenac and the risk of developing DHF (RR: 0·67; 95% CI: 0·14–3·31). None of the 16 patients exposed to ibuprofen developed DHF. Exposure to NSAIDs was not associated with thrombocytopenia or plasma leakage.	Strengths • use of medical records avoids recall bias • WHO criteria used to defined outcome of interest Limitations • small number of users of metamizole were assessed • crude estimates were calculated (potential for confounding) • estimates did not account for dose and duration of use

substantially across studies, ranging from 1·5 (95% CI, 0·8–2·7) to 40·2 (95% CI, 14·7–113·3) for the overall association with metamizole; one study[19] conducted in Thailand had too few cases to adequately evaluate the association with metamizole (25 overall cases; 1 case was exposed to metamizole). Associations between acetaminophen, aspirin/salicylates, diclofenac, or other NSAIDs and agranulocytosis were inconsistently found across studies, with the risks generally substantially lower for these non-narcotic agents compared to metamizole.

The International Agranulocytosis and Aplastic Anemia Study (IAAAS) was the first large-scale case–control study to evaluate the association between agranulocytosis and metamizole.[31] The OR estimates for the association between agranulocytosis and metamizole varied by region, with the adjusted OR associated with metamizole use being 16 (95% CI, 6·9–38) for the regions of Ulm, West Germany/West Berlin/Barcelona compared to an adjusted OR of 1·5 (95% CI, 0·8–2·7) in Israel/Budapest/Sofia/Milan. The adjusted ORs were 1·2 (95% CI, 0·7–2·0) for acetaminophen and 2·0 (95% CI, 1·3–3·2) for salicylates across all regions. The risks of agranulocytosis for durations of use <5 days vs. ≥5 days were assessed; no consistent trend across non-narcotic agents or for the different regions among metamizole users was found. Estimates of the excess risk per million were reported for medications associated with an increased risk of agranulocytosis; the excess risk was 0·6 for metamizole (Ulm/Berlin/Barcelona) and 0·06 for salicylates.

Ibanez *et al.* reported the results of a case–control study from one centre which had participated in the IAAAS (Barcelona) between 1980 and 1986.[16] Including data collected between 1980 and 2001, investigators reported an OR of 25·76 (95% CI, 8·39–79·12) for exposure to metamizole. The adjusted ORs were 1·54 (95% CI, 0·68–3·52) for acetaminophen, 1·39 (95% CI, 0·67–2·88) for aspirin and 3·86 (95% CI, 1·00–15·00) for diclofenac. Ibanez *et al.* conducted additional analyses on the association between metamizole and agranulocytosis including an assessment of the effect of dose and duration of exposure.[34] The adjusted OR was higher when the length of exposure (determined as the time between the first and the last dose) was between 22 and 31 days (OR 167·7; 95% CI, 19·6–2567·7), compared to other time periods (ORs of 14·7 for 1 day, 34·4 for 2–10 days, and 12·4 for 31–180 days), although the confidence intervals were wide and overlapped. The number of days of exposure was higher in cases compared to controls, with 66% of cases and 40% of controls having more than 2 days of exposure.

A case-cohort study conducted in the Netherlands during the period 1987 to 1990 identified potential cases using the Dutch Centre for Health Care Information.[23] Exposure to medications in the 10-day window preceding symptom onset was identified through contact with the general practitioner or pharmacist of the patient or the patient record. The reference cohort consisted of all people in the catchment area of all pharmacies included in the Pharmaco Morbidity Record Linkage System (PHARMO RLS). The adjusted RR associated with metamizole was 26·4 (95% CI 4·4–111·1). The adjusted ORs were 2·4 (95% CI, 1·1–5·2) for acetaminophen, 3·6 (95% CI, 1·3–9·3) for salicylates and 2·5 (95% CI, 1·3–4·9) for other NSAIDs. Estimates of the excess risk per million were 1·36 for metamizole, 0·07 for acetaminophen, 0·14 for salicylates and 0·08 for NSAIDs.

The Latin Study identified 30 cases of agranulocytosis and 120 controls in haematology clinics and hospitals in Brazil, Argentina and Mexico during 2002 to 2005.[28] Exposure to medications in the 10-day period before symptom onset was identified through patient interviews. Metamizole was not associated with a significantly increased risk of agranulocytosis (OR 2·4, 95% CI, 0·8–6·7). The adjusted ORs were 1·9 (95% CI, 0·3–12·1) for acetaminophen, 1·4 (95% CI, 0·2–6·8) for aspirin and 4·0 (95% CI, 0·5–29·9) for diclofenac.

Huber *et al.* conducted a recent case–control study identifying cases and controls from an adult population served by all 51 Berlin hospitals.[15] Medication exposures during the 7-day period before symptom onset were identified through patient interviews. Adjusting for patient sex, age, and other medication exposures, the OR was 40·2 (95% 14·7–113·3) for metamizole. The OR for acetaminophen was 5·1 (95% CI, 1·02–20·4); no statistically significant association was found for aspirin or diclofenac.

Aplastic anaemia. Three case–control studies evaluated the association between metamizole and aplastic anaemia, with medication use identified through patient interviews. Findings of these studies do not suggest an association between metamizole and aplastic anaemia, with OR estimates ranging from 0·5 (95% CI, 0·3–0·9) to 1·6 (95% CI, 0·6–4·4).[31–33] No consistent associations were found between acetaminophen, aspirin/salicylates, or diclofenac and aplastic anaemia.

Upper gastrointestinal bleeding. Of the five case–control studies that evaluated the risk of upper gastrointestinal bleeding,[13,18,24,29,30] four found a statistically significant increased risk associated with metamizole, with the risk generally reported to be less than that found for aspirin and non-aspirin NSAIDs and slightly higher than the risk found for acetaminophen. Estimates of ORs associated with metamizole in these studies ranged from 1·4 to 2·7, compared to 0·6 to 1·5 for acetaminophen, 1·8 to 8·0 for aspirin, 1·3 to 4·1 for ibuprofen, 2·1 to 10·0 for naproxen and 1·3 to 7·9 for diclofenac.

Four of the five case–control studies identified information on medication exposures through patient interviews.[18,24,29,30] The other study by de Abajo *et al.* identified medication exposures in the Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria (BIFAP) database, which is a computerized, population-based database of anonymized longitudinal medical records of patients in Spain.[13] This latter study, which did not identify non-recorded non-prescription medication use and included an older study population than other case–control studies, reported the lowest OR estimates for aspirin and non-aspirin NSAIDs, which were similar to the OR for metamizole (OR of 1·52, 95% CI, 1·09–2·13 for metamizole). In contrast, the OR estimates for aspirin and non-aspirin NSAIDs were approximately 2-fold higher or more than metamizole in the 4 case–control studies that collected medication exposure information through patient interviews.

Information from these studies indicates that the risk of upper gastrointestinal bleeding is higher for increased doses of aspirin and non-aspirin NSAIDs[13,29,30] and early in therapy (duration <30 days).[13,30] The impact of dosage and duration of use among users of metamizole were not evaluated.

Congenital anomalies and birth outcomes associated with in utero exposure. One case–control study[12] and one cohort study[27] evaluated the risk of congenital anomalies and/or other pregnancy outcomes associated with metamizole. The results of the studies do not provide evidence to suggest a strong association with specific outcomes, but the studies have a number of limitations.

Banhidy *et al.* conducted an evaluation of the risk of congenital anomalies associated with metamizole using data from the Hungarian Case–Control Surveillance of Congenital Abnormalities data set.[12] Exposure to medication use during pregnancy was

identified through patient questionnaires or interviews and antenatal log books. Among the 25 congenital abnormality groups evaluated, 3 congenital abnormality groups (cardiovascular, diaphragmatic and other isolated congenital abnormalities) were associated with metamizole compared to population controls. No statistically significant associations were found using the malformation controls as the referent group.

Bar-Oz *et al.* evaluated the risk of congenital anomalies and other pregnancy outcomes among women telephoning four participating teratogen information services in Israel and Italy.[27] Follow-up telephone interviews were conducted to determine outcomes. There was no statistically significant difference between the groups in the rate of major malformations [OR 1·55 (95% CI, 0·26–9·05)] or other pregnancy outcomes, including live births, spontaneous abortions and elective abortions, gestational age at birth, prematurity rate and birthweight, and foetal distress.

Childhood cancer associated with in utero exposure. Two case–control studies evaluated childhood leukaemia[25,26] and one case–control study[21] evaluated Wilms' tumour associated with *in utero* exposures.

Alexander *et al.* conducted a multinational pilot case–control study to assess the association between medications and infant leukaemia.[26] Exposures were identified through maternal interviews. The OR estimate for metamizole was 2·83 (95% CI, 1·15–6·99). Couto *et al.* conducted a case–control study in Brazil to evaluate risk factors associated with childhood leukaemia.[25] A total of 176 acute lymphocytic leukaemia (ALL) cases, 55 acute myeloid leukaemia (AML) cases and 411 controls were included in the analysis. No statistically significant associations were found for AML or ALL for any of the non-narcotic medications evaluated (metamizole, acetaminophen only (with no use of metamizole) or aspirin).

Sharpe *et al.* reported an exploratory evaluation of the association between metamizole and Wilms' tumour using a subset of patients who were enrolled in a nationwide therapy trial by the Brazilian Wilms' Tumor Study Group and nine additional cases that were not eligible for the clinical trial.[21] Paediatricians who were trained as interviewers selected controls. Exposure to medications during pregnancy was identified through parental interviews; interviewers were not blinded to case status. Estimates of the ORs were 10·89 (95% CI, 2·38–49·9) among low-income users of metamizole, 0·66 (95% CI, 0·17–2·60) among medium-income users and 2·56 (95% CI, 0·72–9·12) among high-income users. The OR estimate for NSAID use was 0·91 (95% CI, 0·27–3·12).

Hepatic effects. One study evaluated hepatic effects associated with metamizole.[19] Sabate *et al.* identified cases of acute liver injury in a population 15 years of age or older identified from a network of 12 hospitals in Barcelona, Spain.[19] Drug exposures within 15 days (hepatocellular pattern) or 30 days (acute cholestatic or mixed pattern) before the onset of the symptoms of liver disease were identified through patient interviews. RR estimates were 3·1 (99% CI, 0·4–11·4) for metamizole, 7·0 (99% CI, 3·3–13·9) for acetaminophen, 5·4 (99% CI, 2·0–12·3) for aspirin and 7·6 (99% CI, 1·8–22·0) for diclofenac.

Anaphylaxis. One published study evaluated the risk of anaphylaxis among patients in participating hospitals in Hungary, Spain, India and Sweden.[17] The study reported crude risks for a number of medications administered in the hospital setting based upon various assumptions to extrapolate exposure data. The estimates of incidence of anaphylaxis per 10,000 exposed patients were 8·1 (95% CI, 3·5–19) for metamizole, 4·5 (95% CI, 2·1–9·7) for acetaminophen, 2·1 (95% CI, 0·7–6·5) for aspirin and 7·2 (95% CI, 2·6–20) for diclofenac.

Bleeding Complications. Terjung *et al.* evaluated risk factors for bleeding complications among patients who underwent a diagnostic percutaneous liver biopsy at the Department of Internal Medicine I at the University of Bonn, Germany.[22] Information on exposure to medications was identified through chart review. The adjusted OR between metamizole and bleeding complications was 2·8 (95% CI, 1·1–7·4).

Severity of dengue infection. Diaz-Quijano *et al.* reported the results of a prospective cohort study that evaluated the risk of dengue haemorrhagic fever (DHF) and other indicators of the severity of dengue infection associated with metamizole.[14] Of the 110 patients meeting eligibility criteria, 17 were exposed to metamizole. The RR for the association between metamizole and DHF was 7·29 (95% CI 1·79–29·72). There was no statistically significant association between exposure to diclofenac or ibuprofen and the risk of developing DHF or other indicators of the severity of dengue infection.

Strengths and limitations of published studies

Agranulocytosis. The identified epidemiologic studies provided estimates for validated cases of agranulocytosis.

Limitations of the case–control studies include the potential for information and recall bias due to identification of exposures through patient interviews and the potential selection bias related to control selection. Alternatively, while the case-cohort study by Van der Klauw *et al.*[25] avoided recall bias through use of pharmacy dispensing data, the reference cohort was not a random sample from the total study population. In addition, in this study, a small number of cases were exposed to medications of interest (e.g. only two cases were exposed to metamizole). Two of the case–control studies also encompassed small study populations (≤30 total cases).[20,28]

A limitation of most published studies was the lack of assessment of the impact of dose, duration of therapy, route of administration or previous therapy with the medications of interest. As non-constant hazards of agranulocytosis are likely over time, the relative risk estimates for most medications may be underestimated. The ability to compare the risks associated with the different non-narcotic drugs or determine whether risks vary across regions may also be limited, given potential differential patterns of use. Route of administration was not specifically addressed in studies; however, studies evaluated community-acquired cases, suggesting most exposures would be to oral, rather than parenteral, formulations.

In addition, the representativeness of the cases for included studies is questionable, given that studies generally reported a large proportion of cases were not interviewed or complete medical records were not available. Potential underascertainment of cases without adequate access to treatment, milder cases that were not diagnosed and/or admitted to hospitals, or more severe cases that result in death are possible for all epidemiologic studies.

Aplastic anaemia. The identified case–control studies provided estimates for validated cases of aplastic anaemia. The use of

patient interviews allowed identification of both prescription and non-prescription medication exposures.

Limitations of each of the case–control studies evaluating aplastic anaemia and metamizole include the potential for information and recall bias due to identification of exposures through patient interviews, particularly with the extended risk windows being evaluated, and the potential selection bias related to control selection. The representativeness of the cases is questionable, given that studies reported a large proportion of identified cases were not included in the case–control analyses. Another limitation was the lack of assessment of the impact of dose, duration of therapy, route of administration or previous therapy with the medications of interest.

Upper gastrointestinal bleeding. Most studies include estimates adjusted for important confounders, although some did not adjust for smoking status[24] or alcohol use.[13,24,30] All but one study assigned the index day of the cases as the date of the first signs or diagnosis date; the study by Lanas *et al.*[24] assigned the index day as the hospital admission date, which could potentially lead to misclassification of exposure. Limitations of the case–control studies that used patient interviews to collect exposure information include the potential for information and recall bias. Conversely, the study by de Abajo *et al.*[13] which identified medication exposure information through a medical records database did not include information on non-recorded non-prescription medication use and on whether or not the patient actually took the prescribed medications.

Information from two studies indicates that the risk of upper gastrointestinal bleeding is higher early in therapy (duration <30 days) for aspirin and non-aspirin NSAIDs,[13,30] suggesting that ORs not accounting for duration of therapy may be underestimated due to the depletion of patients susceptible to the outcome when including patients on long-term therapy. The impact of dosage and duration of use among users of metamizole was not evaluated.

Congenital anomalies and birth outcomes. The study by Banhidy *et al.* was a large, population-based study evaluating the association between congenital anomalies and *in utero* exposure to metamizole.[12] The use of patient interviews allowed identification of both prescription and non-prescription drug use. In addition, the inclusion of malformation controls provided data to minimize/assess recall bias. Limitations of the study included the potential for recall/information bias, more active follow-up of non-respondent cases compared to population controls, and the period between the end of pregnancy and return of the questionnaire was different between the case and population control groups. Several important confounders were not used in the analysis (e.g. obesity, smoking, alcohol use, febrile illness). There were also a large number of comparisons (assessment of the association with 25 abnormality groups), potentially leading to spurious findings due to multiple comparisons.

The study by Bar-Oz *et al.* allowed assessment of a variety of pregnancy outcomes, as well as the assessment of both prescription and non-prescription medication use.[27] Limitations of the study included the small sample size, the outcomes were reported by the women through a follow-up telephone call (no follow-up examination by a study physician was performed), use of a comparison group from one centre only, and many potential confounders were not accounted for (e.g. febrile illness, obesity). Inclusion of women telephoning teratogen information services also limits the generalizability of findings.

Childhood cancer. Studies evaluating the association between metamizole and childhood cancer were exploratory and had a number of limitations. Use of maternal interviews, often more than 12 months after the child's birth, may have led to information/recall bias. The lack of information on risk factors for these cancers suggests the potential for residual confounding. In addition, the study by Alexander *et al.*[26] included inconsistent criteria for control selection across sites.

Hepatic effects. The study by Sabate *et al.*[20] reported crude estimates and did not control for potential confounders. This study estimated risks based upon assumptions of drug consumption in the population, and the results may be prone to information/recall bias due to the use of patient interviews to identify exposures.

Anaphylaxis. The International Collaborative Study of Severe Anaphylaxis provided crude estimates of risk based upon various assumptions to extrapolate exposure data, with no control for potential confounders.[17] The estimates did not account for the duration of therapy or previous therapy with the medications under study. Estimates were reported for oral and parenteral formulations separately.

Bleeding complications. Identification of exposure to medications through chart review avoids recall bias; however, the timing of the administration of medications, whether the exposure occurred before or after the bleeding complications, was not specified in the study by Terjung *et al.*[22] Additional limitations of the study include the potential for residual confounding or confounding by indication and the potential for spurious findings given that a number of risk factors (approximately 50 factors) were evaluated for their association with bleeding complications. As the study was conducted at one institution, the results may not be generalizable to other populations/institutions.

Severity of dengue infection. The study design and methods used in the study by Diaz-Quijano *et al.*[14] avoid recall bias. However, this study provided crude estimates of relative risk, with no control for potential confounders, and included a small sample size. The estimates did not account for the dose or duration of therapy.

Discussion

Twenty-two epidemiologic studies which evaluated the safety of metamizole are included in this review. Overall, the evidence suggests an association with agranulocytosis, although the level of risk cannot be precisely concluded based upon the currently available data. In addition, studies indicate an increased risk of upper gastrointestinal bleeding associated with metamizole, a risk that has generally been reported to be lower than the risk for aspirin and non-aspirin NSAIDS. There is insufficient evidence to determine whether metamizole increases the risk of other outcomes (e.g. aplastic anaemia, congenital anomalies and other pregnancy outcomes, childhood cancer, hepatic effects, anaphylaxis, bleeding complications) as few studies have evaluated these outcomes, and these studies often had small sample sizes and a number of other limitations that may have biased the results.

Regulatory decisions related to metamizole have been based upon the risk of agranulocytosis associated with its use. Published epidemiologic studies have generally indicated a relatively low excess risk associated with short-term use of metamizole; however, these estimates may not relate to longer term use. For example, the

excess risk of agranulocytosis per million with 7 days of exposure was estimated to be 0·6 for metamizole in the study by Kaufman *et al.*[33], based upon the RR estimate of 16·0 determined for the regions of Ulm, West Germany/West Berlin/Barcelona. The estimated excess risk during 10 days of exposure to metamizole was slightly higher in the study by Van der Klauw *et al.*[23] (1·36 per million). Huber *et al.* further analysed data from the Berlin Case-Control Surveillance Study and reported a risk of 0·96 cases per million per year for metamizole-associated agranulocytosis.[35] These estimates are substantially lower than estimate of 1 case per 1400 metamizole-treated outpatients reported in a study conducted in Sweden that used spontaneous reports and pharmacy sales data.[36,37] In contrast, the estimates from two studies conducted in Poland suggest the risk of metamizole-associated agranulocytosis is approximately 0·2 cases per million person-days of use, based upon cases identified in haematology centres and medication sales data.[38,39] In another study based upon Swiss spontaneous safety reports, the minimal incidence rate of agranulocytosis associated with metamizole was reported to be 0·46 to 1·63 cases per million person-days of use.[40] While 44% of cases received metamizole for ≤7 days in this latter study, use of spontaneous report data (potential underreporting and missing data) and lack of information on usage patterns in the overall population are potential limitations in interpreting these results, Other than the estimate from the study conducted in Sweden, the risk of agranulocytosis attributable to metamizole use appears substantially lower than the excess risks of upper gastrointestinal bleeding associated with short-term use of metamizole or other non-narcotic analgesics.[4]

WHAT IS NEW AND CONCLUSION

Published studies reported differences in the magnitude of risk of adverse outcomes associated with metamizole use and often had small sample sizes and a number of other limitations that may have biased the results. Based upon the findings of this review, there is a need for future epidemiologic studies to better quantify the potential risks associated with metamizole compared to other non-narcotic analgesics. Well-designed epidemiologic studies would allow assessment of rare outcomes associated with significant morbidity and mortality which would be difficult to evaluate in randomized clinical trials, given the large populations needed for adequate statistical power to detect differences between populations receiving the agents. Unlike evaluations based upon spontaneous reports or case series, well-designed epidemiologic studies include a comparison group to allow estimates of relative and excess risks associated with individual agents. In addition to careful identification of exposures (both non-prescription and prescription drug use), outcomes and potential confounders, evaluation of the impact of differing patterns of use (duration of therapy, dose, prior therapy) and determination of patient groups which may be at higher risk of adverse outcomes is necessary. Given the differing side effects profiles of non-narcotic analgesics, the risks of all important outcomes associated with these agents should be determined and used to conduct a comprehensive review and comparative safety evaluation of non-narcotic analgesics in order to assist both regulators and providers in making informed decisions.

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CONFLICT OF INTERESTS

Dorothee B. Bartels and Robert Lange are employees of Boehringer Ingelheim GmbH, a manufacturer of metamizole. Drs Andrade and Gurwitz and Ms. Sandford have no conflict of interests.

REFERENCES

1. Barzaga AZ, Choonara I Balancing the risks and benefits of the use of over-the-counter pain medications in children. *Drug Saf*, 2012;**35**:1119–1125.
2. Schug SA, Manopas A. Update on the role of non-opioids for postoperative pain treatment. *Best Pract Res Clin Anaesthesiol*, 2007;**21**:15–30.
3. Arellano F, Sacristan JA. Metamizole: reassessment of its therapeutic role. *Eur J Clin Pharmacol*, 1990;**38**:617–619.
4. Andrade SE, Martinez C, Walker AM. Comparative safety evaluation of non-narcotic analgesics. *J Clin Epidemiol*, 1998;**51**:1357–1365.
5. Kötter T, da Costa BR, Fässler M *et al.* Metamizole-associated adverse events: a systematic review and meta-analysis. *PLoS ONE*, 2015;**10**:e0122918.
6. Brogden RN. Pyrazolone derivatives. *Drugs*, 1986;**32**(Suppl 4):60–70.
7. Fendrich Z. Metamizol–a new effective analgesic with a long history. Overview of its pharmacology and clinical use. *Casopis Lekaru Ceskych*, 2000;**139**:440–444.
8. Hamerschlak N, Cavalcanti AB. Neutropenia, agranulocytosis and dipyrone. *Sao Paulo Med J*, 2005;**123**:247–249.
9. Hassan K, Khazim K, Hassan F, Hassan S. Acute kidney injury associated with metamizole sodium ingestion. *Ren Fail*, 2011;**33**:544–547.
10. Jasiecka A, Maslanka T, Jaroszewski JJ. Pharmacological characteristics of metamizole. *Pol J Vet Sci*, 2014;**17**:207–214.
11. Koster HT, Avis HJ, Stevens MF, Hollmann MW. Metamizole in postoperative pain management. *Ned Tijdschr Geneeskd*, 2012;**156**:A4323.
12. Banhidy F, Acs N, Puho E, Czeizel AE. A population-based case-control teratologic study of oral dipyrone treatment during pregnancy. *Drug Saf*, 2007;**30**:59–70.
13. de Abajo FJ, Gil MJ, Bryant V, Timoner J, Oliva B, Garcia-Rodriguez LA. Upper gastrointestinal bleeding associated with NSAIDs, other drugs and interactions: a nested case-control study in a new general practice database. *Eur J Clin Pharmacol*, 2013;**69**:691–701.
14. Diaz-Quijano FA, Villar-Centeno LA, Martinez-Vega RA. Effectiveness of early dipyrone administration on severity of dengue virus infection in a prospective cohort. *Enferm Infecc Microbiol Clin*, 2005;**23**:593–597.
15. Huber M, Andersohn F, Bronder E *et al.* Drug-induced agranulocytosis in the Berlin case-control surveillance study. *Eur J Clin Pharmacol*, 2014;**70**:339–345.
16. Ibanez L, Vidal X, Ballarin E, Laporte JR. Population-based drug-induced agranulocytosis. *Arch Intern Med*, 2005;**165**:869–874.

17. International Collaborative Study of Severe Anaphylaxis. Risk of anaphylaxis in a hospital population in relation to the use of various drugs: an international study. *Pharmacoepidemiol Drug Saf*, 2003;**12**:195–202.
18. Laporte JR, Carne X, Vidal X, Moreno V, Juan J. Upper gastrointestinal bleeding in relation to previous use of analgesics and non-steroidal anti-inflammatory drugs. Catalan Countries Study on Upper Gastrointestinal Bleeding. *Lancet*, 1991;**337**:85–89.
19. Sabate M, Ibanez L, Perez E *et al.* Risk of acute liver injury associated with the use of drugs: a multicentre population survey. *Aliment Pharmacol Ther*, 2007;**25**:1401–1409.
20. Shapiro S, Issaragrisil S, Kaufman DW *et al.* Agranulocytosis in Bangkok, Thailand: a predominantly drug-induced disease with an unusually low incidence. Aplastic Anemia Study Group. *Am J Trop Med Hyg*, 1999;**60**:573–577.
21. Sharpe CR, Franco EL Use of dipyrone during pregnancy and risk of Wilms' tumor. Brazilian Wilms' Tumor Study Group. *Epidemiology*, 1996;**7**:533–535.
22. Terjung B, Lemnitzer I, Dumoulin FL *et al.* Bleeding complications after percutaneous liver biopsy. An analysis of risk factors. *Digestion*, 2003;**67**:138–145.
23. van der Klauw MM, Goudsmit R, Halie MR *et al.* A population-based case-cohort study of drug-associated agranulocytosis. *Arch Intern Med*, 1999;**159**:369–374.
24. Lanas A, Serrano P, Bajador E, Fuentes J, Sáinz R. Risk of upper gastrointestinal bleeding associated with non-aspirin cardiovascular drugs, analgesics and nonsteroidal anti-inflammatory drugs. *Eur J Gastro Hepatol*, 2003;**15**:173–178.
25. Couto AC, Ferreira JD, Pombo-de-Oliveira MS, Koifman S. Pregnancy, maternal exposure to analgesic medicines, and leukemia in Brazilian children below 2 years of age. *Eur J Cancer Prev*, 2015;**24**:245–252.
26. Alexander FE, Patheal SL, Biondi A *et al.* Transplacental chemical exposure and risk of infant leukemia with MLL gene fusion. *Cancer Res*, 2001;**61**:2542–2546.
27. Bar-Oz B, Clementi M, Di Giantonio E *et al.* Metamizol (dipyrone, optalgin) in pregnancy, is it safe? A prospective comparative study. *Eur J Obstet Gynecol Reprod Biol*, 2005;**119**:176–179.
28. Hamerschlak N, Maluf E, Biasi Cavalcanti A *et al.* Incidence and risk factors for agranulocytosis in Latin American countries–the Latin Study: a multicenter study. *Eur J Clin Pharmacol*, 2008;**64**:921–929.
29. Laporte JR, Ibanez L, Vidal X, Vendrell L, Leone R. Upper gastrointestinal bleeding associated with the use of NSAIDs: newer versus older agents. *Drug Saf*, 2004;**27**:411–420.
30. Lanas A, Garcia-Rodriguez LA, Arroyo MT *et al.* Risk of upper gastrointestinal ulcer bleeding associated with selective cyclooxygenase-2 inhibitors, traditional non-aspirin non-steroidal anti-inflammatory drugs, aspirin and combinations. *Gut*, 2006;**55**:1731–1738.
31. Maluf E, Hamerschlak N, Cavalcanti AB *et al.* Incidence and risk factors of aplastic anemia in Latin American countries: the LATIN case-control study. *Haematologica*, 2009;**94**:1220–1226.
32. Mary JY, Guiguet M, Baumelou E. Drug use and aplastic anaemia: the French experience. French Cooperative Group for the Epidemiological Study of Aplastic Anaemia. *Eur J Haematol Suppl*, 1996;**60**:35–41.
33. Kaufman DW. *The drug etiology of agranulocytosis and aplastic anemia*. New York: Oxford University Press, 1991.
34. Ibanez L, Vidal X, Ballarin E, Laporte JR. Agranulocytosis associated with dipyrone. *Eur J Clin Pharmacol*, 2005;**60**:821–829.
35. 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**:219–227.
36. Hedenmalm K, Spigset O. Agranulocytosis and other blood dyscrasias associated with dipyrone (metamizole). *Eur J Clin Pharmacol*, 2002;**58**:265–274.
37. Backstrom M, Hagg S, Mjorndal T, Dahlqvist R. Utilization pattern of metamizole in northern Sweden and risk estimates of agranulocytosis. *Pharmacoepidemiol Drug Saf*, 2002;**11**:239–245.
38. Basak GW, Drozd-Sokolowska J, Wiktor-Jedrzejczak W. Update on the incidence of metamizole sodium-induced blood dyscrasias in Poland. *J Int Med Res*, 2010;**38**:1374–1380.
39. Maj S, Lis Y. The incidence of metamizole sodium-induced agranulocytosis in Poland. *J Int Med Res*, 2002;**30**:488–495.
40. Blaser LS, Tramonti A, Egger P, Haschke M, Krähenbühl S, Rätz Bravo AE. Hematological safety of metamizole: retrospective analysis of WHO and Swiss spontaneous safety reports. *Eur J Clin Pharmacol*, 2015;**71**:209–217.

