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Use of metamizole and other non-opioid analgesics in Switzerland between 2014 and 2019: an observational study using a large health insurance claims database

Stephan Gut[ab], Marlene Rauch[ab], Manuel Haschke[c], Carola A. Huber[d], Jan Gaertner[e], Nadine Schur[f], Christoph R. Meier[ab], Julia Spoendlin[ab]

[a] Basel Pharmacoepidemiology Unit, Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland
[b] Hospital Pharmacy, University Hospital Basel, Basel, Switzerland
[c] Clinical Pharmacology & Toxicology, Department of General Internal Medicine, University Hospital Bern, University of Bern, Switzerland
[d] Department of Health Sciences, Helsana Group, Zurich, Switzerland
[e] Palliative care center Hildegard, Basel, Switzerland
[f] Institute of Pharmaceutical Medicine (ECPM), University of Basel, Basel, Switzerland

Summary

OBJECTIVE: To investigate claims patterns for metamizole and other non-opioid analgesics in Switzerland. To characterise users of these non-opioid analgesics regarding sex, age, comedications and canton of residence.

METHODS: We conducted a retrospective descriptive study using administrative claims data of outpatient prescribed non-opioid analgesics of the Swiss health insurance company Helsana between January 2014 and December 2019. First, we evaluated the number of claims and defined daily doses per year of metamizole, ibuprofen, diclofenac and paracetamol in adults aged 18 years or over. Second, we characterised new users of these non-opioid analgesics in terms of sex, age, claimed comedications and canton of residence.

RESULTS: From 2014 to 2019, among the investigated non-opioid analgesics, metamizole showed the highest increase in claims (+9545 claims, +50%) and defined daily doses (+86,869 defined daily doses, +84%) per 100,000 adults. Metamizole users had the highest median age (62 years [IQR: 44–77]) compared to ibuprofen (47 years [IQR: 33–62]), diclofenac (57 years [IQR: 43–71]) and paracetamol (58 years [IQR: 39–75]) users. Metamizole users also more frequently claimed proton pump inhibitors, anticoagulants, platelet aggregation inhibitors and antihypertensive drugs than users of other non-opioid analgesics. While metamizole was most frequently claimed in German-speaking regions of Switzerland, ibuprofen and paracetamol were most frequently claimed in the French-speaking regions and diclofenac in German- and Italian-speaking regions.

CONCLUSION: In Switzerland, metamizole was increasingly claimed between 2014 and 2019. Metamizole was most frequently claimed by older adults and patients with comedications suggestive of underlying conditions, which can be worsened or caused by use of nonsteroidal anti-inflammatory drugs. The lack of studies regarding the effectiveness and safety of metamizole in this population warrants further investigation.

Julia Spoendlin, PhD, MPH
Basel Pharmacoepidemiology Unit
Division of Clinical Pharmacy and Epidemiology
Department of Pharmaceutical Sciences
University of Basel
Schanzenstrasse 9
CH-4031 Basel
julia.spoendlin[at]usb.ch

Introduction

Metamizole is a controversial non-opioid analgesic drug due to its potential toxicity. In various countries, including France, the US, England and Sweden, metamizole has not been approved or has been withdrawn from the market due to the risk of drug-induced agranulocytosis. However, the reported absolute risk of metamizole-induced agranulocytosis varies between 1 per 1439 and 1.1 per million metamizole prescriptions across different studies [1–13]. Agranulocytosis is defined as a rapid decrease of peripheral neutrophil granulocytes, leading to an increased susceptibility to serious infections with a mortality of approximately 5% [13, 14]. Additionally, European drug authorities have recently warned about a potentially increased risk of drug-induced liver injury (DILI) associated with metamizole [15–17].

In Switzerland, metamizole is approved for the treatment of severe pain or fever if other treatments have failed [18]. Despite these potential adverse drug events and the restricted label, the number of claims for metamizole in Switzerland has increased from 4018 per 100,000 people in 2006 to 13,729 per 100,000 people in 2013 (+ 242%) [19]. Moreover, metamizole has been listed by a large Swiss health insurance company (Helsana) as one of the 10 most frequently claimed medications since 2014 [20]. Possible reasons may be that many physicians presume that metamizole has a more favourable safety profile and fewer drug-drug interactions than non-steroidal anti-inflammatory drugs (NSAIDs), especially in older adults and in those with advanced, progressive diseases [21, 22]. These patients are more susceptible to the adverse drug reactions

of NSAIDs, such as gastroduodenal bleeding, cardiovascular events or renal toxicity [23–32]. However, it remains unknown which non-opioid analgesic drugs are preferably claimed by older adults in Switzerland.

This study aimed to investigate the use of metamizole and the three other most frequently claimed non-opioid analgesic drugs in Switzerland (ibuprofen, diclofenac and paracetamol) between 2014 and 2019 in subgroups comparing sex, age and region (canton) of its users.

Methods

Study design and data source

We conducted a retrospective descriptive study using outpatient administrative claims data from the Swiss health insurance company Helsana for the period from January 2014 to December 2019. In Switzerland, basic health insurance is mandatory and insurance companies must accept all applicants for basic insurance coverage. Patients can choose between various private insurance companies, but all of them have to cover the same catalogue of health services. The Helsana claims database provides anonymised basic health insurance data of approximately 1.2 million individuals across all Swiss cantons (approximately 15% of the overall Swiss population for the year 2019) and thus provides information on a representative sample of the Swiss population [33]. The Helsana claims database captures longitudinal records of patients, comprising demographics and all reimbursed dispensations of outpatient prescription drugs, including information on the Anatomical Therapeutic Chemical (ATC) Classification System, dose, route of administration and pack size.

Study population

In the first part of this study we evaluated the number of claims, defined daily doses and geographical regions (cantons) of the claims of the four non-opioid analgesic drugs of interest in Switzerland [34]. We included all claims (based on recorded ATC codes) between 1 January 2014 and 31 December 2019 of metamizole, ibuprofen, diclofenac and paracetamol by adults aged 18 years or older (ATC codes in table S1 in the appendix). In the second part of the study, we characterised new users of these non-opioid analgesic drugs over a 1-year period. Therefore, we categorised users who had at least one claim of a non-opioid analgesic drug of interest in 2019 into four groups (i.e. metamizole, ibuprofen, diclofenac or paracetamol). New users had to have been continuously insured for at least 180 days before the first claim of interest, during which they must not have had any recorded claims for the respective non-opioid analgesic drug. If new users had claims of different non-opioid analgesic drugs of interest, they were included in each respective group.

Ethical approval and consent to participate

According to the Swiss Law of Human Research, this study did not require ethical approval since data were anonymised. We conducted the study following the principles of Good Clinical Practice and in accordance with the Declaration of Helsinki.

Variables

We identified all drugs of interest based on their respective ATC codes. The non-opioid analgesic drugs of interest were metamizole, ibuprofen, diclofenac and paracetamol (without combination products). We captured the canton in which these non-opioid analgesic drugs were claimed. Additionally, we used comedications as proxies for underlying comorbidities since outpatient diagnoses were not systematically recorded in a standardised manner in the Swiss outpatient setting. Pre-existing cardiovascular, gastrointestinal and renal comorbidities might influence the choice of non-opioid analgesic drug given the known cardiovascular risk associated with NSAIDs, which might result in channelling of non-opioid analgesic drug users. We identified claims of anticoagulants, platelet aggregation inhibitors, lipid-modifying drugs, antihypertensive drugs and antidiabetics within 180 days before the first non-opioid analgesic drug claim of interest (ATC codes in table S1 in the appendix).

Statistical analysis

We applied descriptive statistics and reported results as counts and proportions. In the first analysis, we assessed the number of claims per year and the number of dispensed defined daily doses per year per non-opioid analgesic drug of interest per 100,000 adults during the study period. To calculate the number of claimed defined daily doses per non-opioid analgesic drug of interest per year, we summed the dispensed cumulative dose of each claimed non-opioid analgesic drug of interest per year and divided it by the defined daily dose of the respective drug. The World Health Organization defines a defined daily dose as the average maintenance dose per day for a drug used for its main indication in adults [35]. We analysed the number of adults with at least one metamizole claim per calendar year between 2014 and 2019 overall and stratified by age. Additionally, we calculated the number of claims per 100,000 adults of each non-opioid analgesic drug of interest per canton and assessed its percentage difference compared to the Swiss average number of claims per 100,000 adults of the respective non-opioid analgesic drug of interest in the year 2019.

In the second analysis, we characterised new users of each non-opioid analgesic drug of interest in the year 2019 regarding age (median and interquartile range [IQR] as well as age groups 18–45, 46–65, 66–75, 76–85 and ≥85 years), sex and comedications. We calculated the median and IQR of the number of claims of metamizole per metamizole user per calendar year overall and within each age group during the study period. We performed all analyses using SAS 9.4 software (SAS Institute, Cary, NC, USA).

Results

We identified an average annual total of 955,638 adults in the Helsana claims database between 2014 and 2019 (total number of adults per year are displayed in table S2 in the appendix). Paracetamol was the most frequently claimed non-opioid analgesic drug of interest in 2014 (50,596 claims/100,000 adults), followed by ibuprofen (22,533/100,000 adults), metamizole (19,297/100,000 adults) and diclofenac (18,128/100,000 adults). However, we observed

the largest increase in claims between 2014 and 2019 for metamizole (+ 50%) followed by ibuprofen (+ 30%). Claims for diclofenac decreased by 30% during the same period, whereas claims for paracetamol slightly increased (+ 7%, figure 1). Absolute numbers of claims (per 100,000 adults) per non-opioid analgesic drug of interest and year are displayed in table S2.

Paracetamol had the highest number of claimed defined daily doses with 827,684 claimed defined daily doses per 100,000 adults in 2014, followed by diclofenac (456,199), ibuprofen (366,166) and metamizole (103,630). However, between 2014 and 2019, we observed the largest increase in claimed defined daily doses per 100,000 adults for metamizole (+84%), followed by ibuprofen (+22%) and paracetamol (+6%). The number of claimed defined daily doses per 100,000 adults of diclofenac decreased during this period (–22%) (figure 2). Absolute values of defined daily doses (per 100,000 adults) per non-opioid analgesic drug of interest and year are displayed in table S2. Our post hoc analysis showed that the number of adults with at least one claim of metamizole increased by 33% overall and by 47% in adults aged over 85 years between 2014 and 2019 (table S3 in the appendix).

Figure 3 displays the relative difference between the number of metamizole claims per 100,000 adults per canton and the Swiss average in 2019 (28,843 metamizole claims per 100,000 adults). Compared to the Swiss average, the French- and Italian-speaking cantons of Switzerland showed much lower use of metamizole (e.g. Geneva: –94%, Ticino: –37%, Fribourg: –49%). On the other hand, in most German-speaking cantons, more metamizole was claimed compared to the Swiss average, with the highest use of metamizole in Basel-Land, Zürich, St Gallen and Glarus (all at least +25% compared with the Swiss average) In the French-speaking part of Switzerland, ibuprofen and paracetamol were claimed more frequently, whereas diclofenac was more often claimed in the German- and Italian-speaking parts of Switzerland, compared with the Swiss average (table S4 and figure S1 in the appendix).

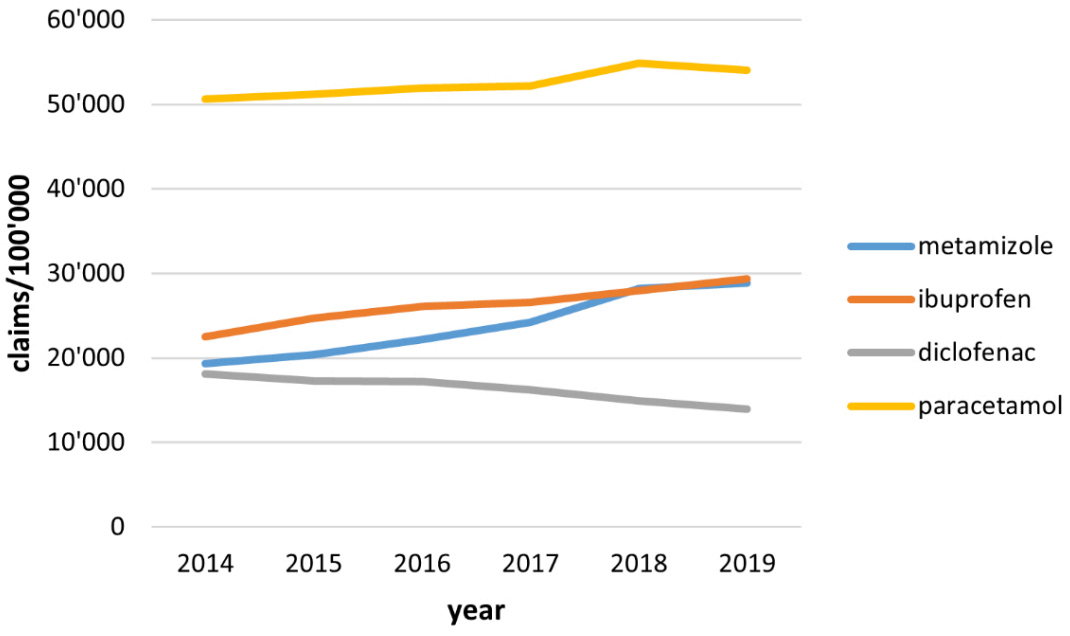
In 2019, new users of metamizole had the highest median age (62 years) and the highest percentage of elderly users aged 65 years or over (46%) followed by paracetamol (58 years; ≥65 years: 40%), diclofenac (57 years; ≥65 years: 36%) and ibuprofen users (47 years; ≥65 years: 22%, table 1).

Overall, new users of metamizole claimed more comedications of interest in the preceding 180 days, with paracetamol users showing the most similar pattern of comedications. In total, 40% of new metamizole users previously claimed at least one antihypertensive drug (vs 36% paracetamol, 32% diclofenac, 22% ibuprofen users), 13% claimed at least one anticoagulant (vs 10% paracetamol, 6% diclofenac, 5% ibuprofen users) and 11% claimed at least one antidiabetic drug (vs 10% paracetamol, 8% diclofenac, 6% ibuprofen users). The median number of claims of metamizole per metamizole user per calendar year did not increase in our study period, independent of age (table S5 in the appendix).

Discussion

The present study investigated the claims pattern of metamizole, ibuprofen, diclofenac and paracetamol in Switzerland between 2014 and 2019. Paracetamol was the most frequently claimed non-opioid analgesic drug of interest during this 6-year period, but metamizole showed the largest increase in claims and defined daily doses per 100,000 adults (+50%; +84%), followed by ibuprofen (+30%; +22%) and paracetamol (+7%; +6%), whereas diclofenac claims and defined daily doses declined (–30%; –22%). The median number of claims of metamizole per

Figure 1: Number of claims per 100,000 adults between 2014 and 2019.



metamizole user per calendar year did not change, either overall or stratified by age group, between 2014 and 2019. On the other hand, the number of adults with at least one metamizole claim increased by 33% overall and by 47% in adults older than 85 years of age during this time period. This suggests that the observed increase in metamizole claims is mainly driven by an increase in the number of adults using metamizole and not by individual adults using more metamizole. We found that metamizole users were older than NSAID (ibuprofen, diclofenac) or paracetamol users (median ages in 2019: 62 vs 47, 57, 58 years) and more often had claims of PPIs, anticoagulants and platelet

Figure 2: Number of claimed defined daily doses (DDD) per 100,000 adults between 2014 and 2019.

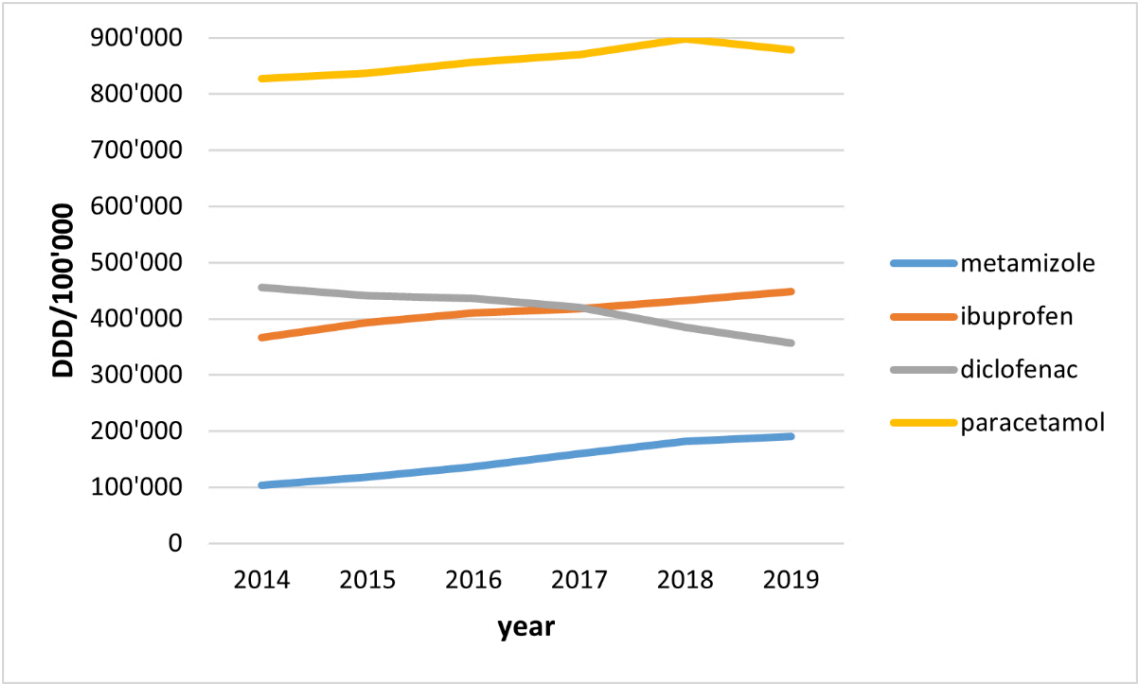
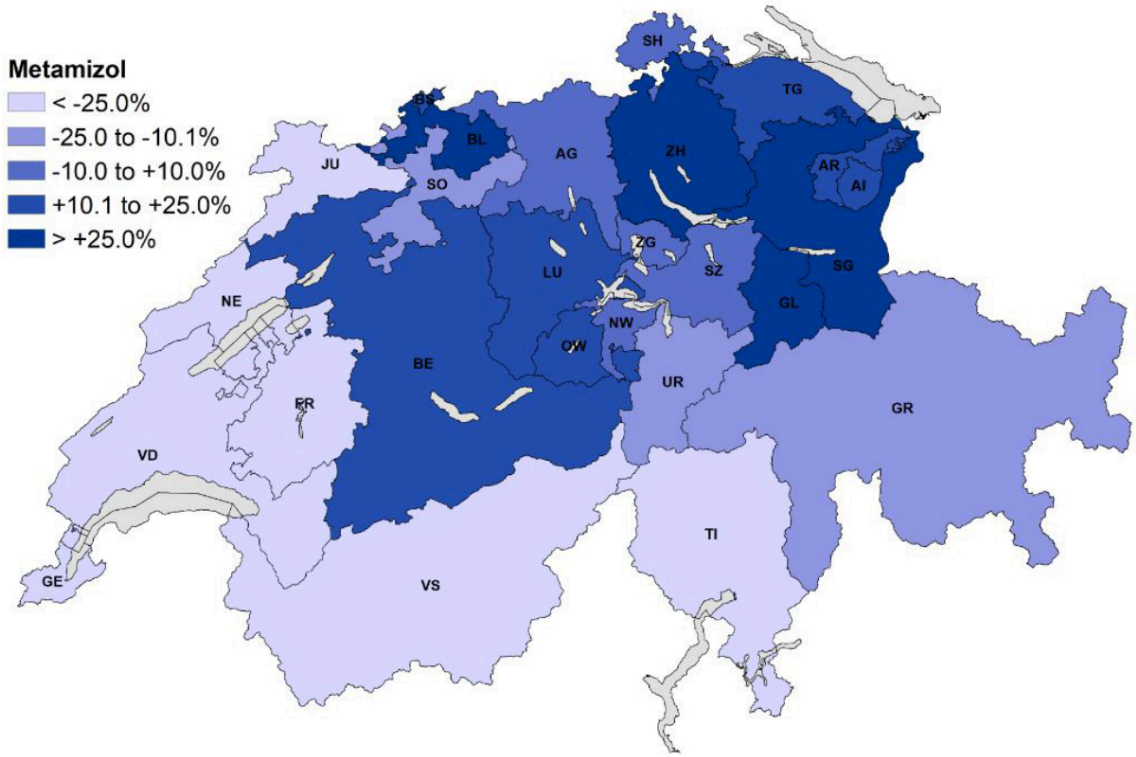


Figure 3: Relative differences between the number of claims of metamizole per 100,000 adults per canton and the Swiss average. Abbreviations: AG: Aargau, AI: Appenzell Innerrhoden, AR: Appenzell Ausserrhoden, BE: Bern, BL: Basel-Land, BS: Basel-Stadt, FR: Fribourg, GE: Geneva, GL: Glarus, GR: Graubünden, JU: Jura, LU: Luzern, NE: Neuchâtel, NW: Nidwalden, OW: Obwalden, SG: St Gallen, SH: Schaffhausen, SO: Solothurn, SZ: Schwyz, TG: Thurgau, TI: Ticino, UR: Uri, VD: Vaud, VS: Valais, ZG: Zug, ZH: Zürich.



aggregation inhibitors than NSAID and paracetamol users. Metamizole was less often claimed in French- and Italian-speaking Switzerland than in German-speaking regions of Switzerland, whereas the number of claims of ibuprofen and paracetamol was highest in the French-speaking regions and that of diclofenac in Italian- and German-speaking regions.

A previous study conducted with Helsana claims data found increasing popularity of metamizole and showed a similar pattern of non-opioid analgesic drug claims although with an even steeper increase in claims per 100,000 adults of metamizole (+242%) between 2006 and 2013 (vs ibuprofen [+68%], paracetamol [+32%], diclofenac [–2.7%]) [19]. Given its similar methodology, the increase of claims of metamizole might have slowed down since 2013. Also, in Germany, an increase in metamizole prescriptions was reported between 2009 and 2018 (2009: 115 million defined daily doses; 2018: 225 million defined daily doses) [36]. We observed that metamizole had the largest increase in claims of all non-opioid analgesic drugs, whereas ibuprofen increased less steeply and use of diclofenac dropped. In addition to its rather potent antipyretic and analgesic effects, the increasing use of metamizole may be due to increasing awareness of potential risks associated with NSAID use. NSAIDs are associated with gastrointestinal (e.g. dyspepsia, gastroduodenal bleeding), cardiovascular (e.g. myocardial infarction, worsening of heart failure, hypertension) and renal (e.g. worsening of renal function) adverse drug events [23–32]. In particular, diclofenac (more than ibuprofen) has been associated with cardiovascular events over the past years, which might explain a certain shift from diclofenac towards metamizole and ibuprofen over time [26]. These adverse drug events are especially problematic in older adults, who have more comorbidities such as hypertension, heart failure, atherosclerosis and chronic renal failure [37]. Consequently, older adults are often exposed to polypharmacy, which can further increase the risk of developing adverse drug reactions when taking NSAIDs (e.g. increased risk of gastroduodenal bleeding in combination with anticoagulants, antiplatelet drugs, serotonergic antidepressants) [38, 39]. Therefore, the American Geriatrics Society recommends avoiding chronic NSAID use in older adults (aged > 65 years) and many classifications of drug appropriateness for older people recommend that NSAIDs should be avoided in older adults [40–43]. Paracetamol is not associated with gastrointestinal, cardiovascular or renal toxicity, but is a less effective analgesic especially for certain indications such as lower back pain or arthritis, and therefore is not always a viable treatment option [44, 45].

Metamizole users were older than ibuprofen, diclofenac or paracetamol users (median age in 2019: 62 vs 47, 57, 58 years), which is also supported by the "Fit for The Aged" (FORTA) expert consensus list [41]. Metamizole users also claimed more comedications, such as PPIs, indicating possible underlying comorbidities. PPIs are often prescribed as prophylaxis to prevent gastroduodenal bleeding in adults with risk factors thereof, such as advanced age and/or comedication with anticoagulants or platelet aggregation inhibitors [39, 46]. Metamizole users also had more claims of antihypertensive and lipid-modifying drugs than ibuprofen and diclofenac users, which are commonly prescribed in adults with cardiovascular diseases such as hypertension, heart failure and myocardial infarction, conditions which can be worsened or caused by NSAIDs [30, 47, 48]. Metamizole users had slightly more claims for antidiabetics than NSAID users. Adults with diabetes often develop renal and heart failure among other cardiovascular diseases [49]. Since NSAIDs can worsen existing renal or heart failure, they may not be a viable treatment option in these patients either [31, 48, 50]. Interestingly, metamizole seems to be used for shorter treatment periods than ibuprofen or diclofenac. Metamizole claims per 100,000 adults were higher than diclofenac claims and almost equalled ibuprofen claims in 2019 (metamizole: 28,843 vs ibuprofen: 29,354 per 100,000 adults), but the number of claimed

Table 1:
Characteristics of non-opioid analgesic drug users in 2019 regarding sex, age and number of claimed oral comedications.

		Metamizole	Ibuprofen	Diclofenac	Paracetamol
N		98,910	159,705	74,902	215,770
Female sex (%)		59,086 (60%)	98,430 (62%)	40,563 (54%)	132,644 (61%)
Age, median (IQR)		62 (44–77)	47 (33–62)	57 (43–71)	58 (39–75)
Age groups (%)	18–45 years	25,078 (25%)	71,940 (45%)	20,292 (27%)	67,667 (31%)
	46–65 years	28,261 (29%)	52,492 (33%)	27,328 (36%)	60,612 (28%)
	66–75 years	15,985 (16%)	18,742 (12%)	13,791 (18%)	32,268 (15%)
	76–85 years	17,114 (17%)	12,286 (7%)	10,316 (14%)	32,713 (15%)
	>85 years	12,472 (13%)	4245 (3%)	3175 (4%)	22,510 (10%)
Claimed oral comedications (%)	PPIs	47,592 (48%)	58,704 (37%)	33,744 (45%)	82,818 (38%)
	Anticoagulants	13,100 (13%)	7984 (5%)	4764 (6%)	21,896 (10%)
	Platelet aggregation inhibitors	17,815 (18%)	13,118 (8%)	9511 (13%)	34,759 (16%)
	Lipid-modifying drugs	19,573 (20%)	17,633 (11%)	12,921 (17%)	40,374 (19%)
	Antihypertensive drugs	40,036 (40%)	34,972 (22%)	24,255 (32%)	78,266 (36%)
	RAAS inhibitors	30,451 (31%)	26,587 (17%)	19,065 (25%)	59,846 (28%)
	Calcium-channel blockers	14,849 (15%)	11,516 (7%)	8125 (11%)	27,812 (13%)
	Diuretics	22,726 (23%)	16,171 (10%)	11,827 (16%)	42,304 (20%)
	Beta blockers	19,226 (19%)	14,218 (9%)	9786 (13%)	36,369 (17%)
	Antidiabetics	10,401 (11%)	9505 (6%)	6007 (8%)	21,699 (10%)
	Metformin	7259 (7%)	7315 (5%)	4785 (6%)	15,846 (7%)
	SGLT-2 inhibitors	1459 (1%)	1557 (1%)	999 (1%)	3099 (1%)
	GLP-1 receptor agonists (subcutaneous application)	1175 (0%)	1091 (1%)	648 (1%)	2211 (1%)
	Other antidiabetics	3070 (3%)	2244 (1%)	1552 (2%)	6168 (3%)

defined daily doses of metamizole per 100,000 adults was markedly lower than that of ibuprofen and diclofenac during the whole study period. This suggests that metamizole is claimed in smaller pack sizes or dosages than ibuprofen or diclofenac.

Additionally, we observed regional differences in the claiming patterns of metamizole and the other non-opioid analgesic drugs of interest. These regional differences might be present because French- and Italian-speaking cantons might more often use pharmaceutical and medical information from France and Italy, both countries in which metamizole is not approved.

Some limitations of this study need to be considered. Firstly, in Switzerland, ibuprofen, diclofenac and paracetamol can also be purchased over the counter, which is not captured in administrative Helsana claims data. Moreover, use of non-opioid analgesic drugs in the inpatient setting is also not captured as they are reimbursed as part of bundled Diagnosis-Related Groups. Therefore, we likely underestimated the real extent of use of ibuprofen, diclofenac and paracetamol during the study period. Secondly, the data is based on 1.2 million Swiss insured by the Helsana basic health insurance scheme and is approximately representative for the general Swiss population. The insured population may have a slightly higher proportion of women and people aged 65 years or older than the Swiss population [34]. Thirdly, we had no information on diagnoses of non-opioid analgesic drug users, which is why we used the main indication of claimed medications as proxies for potential underlying chronic diseases. Since medications are also used for conditions other than their main indications, we cannot be certain that the claimed medications were always a good proxy for the underlying diseases. Fourthly, we had no information about the socioeconomic status of the insured people, a factor that could influence the amount of claimed health services and medications.

The presented results strengthen the assumption that metamizole is preferably used in older, frailer adults in whom comorbidities and comedications may prevent the use of NSAIDs owing to their safety profile, and paracetamol may not be effective enough. In the future, metamizole claims may further increase due to ageing of the population. In Switzerland, 19% of the population were 65 years or older in 2020, and it is assumed that by 2050 this percentage will increase to 25.6% [51, 52]. Despite the increasing use of metamizole, which may even be more pronounced in the future, little is known about its safety profile apart from the rare risk of blood disorders [53]. Recently, warnings have been issued by European drug authorities, associating metamizole use with drug-induced liver injuries [16, 17, 54]. To date, no increased cardiovascular risk associated with metamizole use has been reported, but studies on this safety outcome are scarce [55]. Although one study reported that short-term use of metamizole did not affect renal function in healthy adults [56], little is known about the nephrotoxic potential of metamizole. In view of its growing popularity, it is important to further investigate the safety profile of metamizole in future studies, especially in older adults with comorbidities and comedications.

Conclusion

We observed increasing use of metamizole between 2014 and 2019, mainly in the German-speaking parts of Switzerland. Metamizole users were older and claimed more comedications, suggesting that metamizole is preferably prescribed to patients with contraindications to NSAIDs. Given that the safety profile of metamizole remains incompletely understood, studies to evaluate its effectiveness and safety in this patient population are needed.

Availability of data

Study data cannot be shared due to strict laws of privacy protection, which requires presence of legal agreements and contracts for data provision.

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Potential competing interests
All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest related to the content of this manuscript was disclosed.

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Appendix

Table S1.

ATC codes of investigated non-opioid analgesic drugs and oral comedications

Non-opioid analgesic drugs of interest	
N02BB02	metamizole
M01AE01	ibuprofen
M01AB05, M01AB55	diclofenac
N02BE01	paracetamol
Proton pump inhibitors	
A02BC01	omeprazole
A02BC02	pantoprazole
A02BC03	lansoprazole
A02BC04	rabeprazole
A02BC05	esomeprazole
A02BC06	dexlansoprazole
Anticoagulants	
B01AA07	acenocoumarol
B01AA04	phenprocoumon
B01AE07	dabigatran etexilate
B01AF01	rivaroxaban
B01AF02	apixaban
B01AF03	edoxaban
Platelet aggregation inhibitors	
B01AC04	clopidogrel
B01AC06	acetylsalicylic acid
B01AC07	dipyridamole
B01AC22	prasugrel
B01AC24	ticagrelor
B01AC30	combinations
Antihypertensive drugs	
RAAS inhibitors	
C09AA01	captopril
C09AA02	enalapril

C09AA03	lisinopril
C09AA04	perindopril
C09AA05	ramipril
C09AA06	quinapril
C09AA08	cilazapril
C09CA01	losartan
C09CA02	eprosartan
C09CA03	valsartan
C09CA04	irbesartan
C09CA06	candesartan
C09CA07	telmisartan
C09CA08	olmesartan medoxomil
C09CA09	azilsartan medoxomil
C09BA02	enalapril and diuretics
C09BA03	lisinopril and diuretics
C09BA04	perindopril and diuretics
C09BA05	ramipril and diuretics
C09BA06	quinapril and diuretics
C09BA08	cilazapril and diuretics
C09BA09	fosinopril and diuretics
C09BB02	enalapril and lercanidipine
C09BB04	perindopril and amlodipine
C09BB10	trandolapril and verapamil
C09BX01	perindopril, amlodipine and indapamide
C09BX02	perindopril and bisoprolol
C09BX03	ramipril, amlodipine and hydrochlorothiazide
C09BX04	perindopril, bisoprolol and amlodipine
C10BX11	atorvastatin, amlodipine and perindopril
C10BX15	atorvastatin and perindopril
C09DA01	losartan and diuretics
C09DA02	eprosartan and diuretics
C09DA03	valsartan and diuretics
C09DA04	irbesartan and diuretics
C09DA06	candesartan and diuretics
C09DA07	telmisartan and diuretics
C09DA08	olmesartan medoxomil and diuretics

C09DA09	azilsartan medoxomil and diuretics
C09DB01	valsartan and amlodipine
C09DB02	olmesartan medoxomil and amlodipine
C09DB04	telmisartan and amlodipine
C09DB07	candesartan and amlodipine
C09DX01	valsartan, amlodipine and hydrochlorothiazide
C09DX03	olmesartan medoxomil, amlodipine and hydrochlorothiazide
C09DX04	valsartan and sacubitril
C09XA02	aliskiren
C09XA52	aliskiren and hydrochlorothiazide
Calcium-channel blockers (dihydropyridine type)	
C07FB02	metoprolol and felodipine
C07FB07	bisoprolol and amlodipine
C08CA01	amlodipine
C08CA02	felodipine
C08CA03	isradipine
C08CA04	nicardipine
C08CA05	nifedipine
C08CA06	nimodipine
C08CA13	lercanidipine
C09BB02	enalapril and lercanidipine
C09BB04	perindopril and amlodipine
C09BB10	trandolapril and verapamil
C10BX03	atorvastatin and amlodipine
C09BX01	perindopril, amlodipine and indapamide
C09BX03	ramipril, amlodipine and hydrochlorothiazide
C09BX04	perindopril, bisoprolol and amlodipine
C09DB01	valsartan and amlodipine
C09DB02	olmesartan medoxomil and amlodipine
C09DB04	telmisartan and amlodipine
C09DB07	candesartan and amlodipine
C09DX01	valsartan, amlodipine and hydrochlorothiazide
C09DX03	olmesartan medoxomil, amlodipine and hydrochlorothiazide
C10BX11	atorvastatin, amlodipine and perindopril
Diuretics	
C03AA03	hydrochlorothiazide

C03AA04	chlorothiazide
C03BA11	indapamide
C03CA01	furosemide
C03CA04	torasemide
C03DA01	spironolactone
C03DA04	eplerenone
C03EA01	hydrochlorothiazide and potassium-sparing agents
C03EB01	furosemide and potassium-sparing agents
C07BB07	bisoprolol and thiazides
C07BB12	nebivolol and thiazides
C07CB03	atenolol and other diuretics
C09BA02	enalapril and diuretics
C09BA03	lisinopril and diuretics
C09BA04	perindopril and diuretics
C09BA05	ramipril and diuretics
C09BA06	quinapril and diuretics
C09BA08	cilazapril and diuretics
C09BA09	fosinopril and diuretics
C09BX01	perindopril, amlodipine and indapamide
C09BX03	ramipril, amlodipine and hydrochlorothiazide
C09DA01	losartan and diuretics
C09DA02	eprosartan and diuretics
C09DA03	valsartan and diuretics
C09DA04	irbesartan and diuretics
C09DA06	candesartan and diuretics
C09DA07	telmisartan and diuretics
C09DA08	olmesartan medoxomil and diuretics
C09DA09	azilsartan medoxomil and diuretics
C09DX01	valsartan, amlodipine and hydrochlorothiazide
C09DX03	olmesartan medoxomil, amlodipine and hydrochlorothiazide
C09XA52	aliskiren and hydrochlorothiazide
Beta-blocking drugs	
C07AA05	propranolol
C07AA06	timolol
C07AA07	sotalol
C07AB02	metoprolol

C07AB03	atenolol
C07AB07	bisoprolol
C07AB08	celiprolol
C07AB12	nebivolol
C07AG01	labetalol
C07AG02	carvedilol
C07BB07	bisoprolol and thiazides
C07BB12	nebivolol and thiazides
C09BX02	perindopril and bisoprolol
C09BX04	perindopril, bisoprolol and amlodipine
C07CB03	atenolol and other diuretics
C07FB02	metoprolol and felodipine
C07FB07	bisoprolol and amlodipine
Lipid-modifying drugs	
C10AA01	simvastatin
C10AA02	lovastatin
C10AA03	pravastatin
C10AA04	fluvastatin
C10AA05	atorvastatin
C10AA06	cerivastatin
C10AA07	rosuvastatin
C10AA08	pitavastatin
C10AX16	inclisiran
C10BA02	simvastatin and ezetimibe
C10BA04	simvastatin and fenofibrate
C10BA05	atorvastatin and ezetimibe
C10BX03	atorvastatin and amlodipine
C10BX11	atorvastatin, amlodipine and perindopril
C10BX15	atorvastatin and perindopril
C10AX09	ezetimibe
C10AX13	evolocumab
C10AX14	alirocumab
C10BA10	bempedoic acid and ezetimibe
Metformin	
A10BA02	metformin
A10BD05	metformin and pioglitazone

A10BD07	metformin and sitagliptin
A10BD08	metformin and vildagliptin
A10BD10	metformin and saxagliptin
A10BD11	metformin and linagliptin
A10BD13	metformin and alogliptin
A10BD15	metformin and dapagliflozin
A10BD16	metformin and canagliflozin
A10BD20	metformin and empagliflozin
A10BD23	metformin and ertugliflozin
SGLT-2 inhibitors	
A10BK01	dapagliflozin
A10BK02	canagliflozin
A10BK03	empagliflozin
A10BK04	ertugliflozin
A10BD15	metformin and dapagliflozin
A10BD16	metformin and canagliflozin
A10BD19	linagliptin and empagliflozin
A10BD20	metformin and empagliflozin
A10BD21	saxagliptin and dapagliflozin
A10BD23	metformin and ertugliflozin
A10BD24	sitagliptin and ertugliflozin
GLP-1 receptor agonists	
A10BJ01	exenatide
A10BJ02	liraglutide
A10BJ03	lixisenatide
A10BJ05	dulaglutide
A10BJ06	semaglutide
A10AE56	insulin degludec and liraglutide
A10AE54	insulin glargine and lixisenatide
Blood glucose-lowering drugs	
A10BA01	phenformin
A10BB01	glibenclamide
A10BB07	glipizide
A10BB09	gliclazide
A10BB12	glimepiride
A10BD19	linagliptin and empagliflozin

A10BD21	saxagliptin and dapagliflozin
A10BD24	sitagliptin and ertugliflozin
A10BG03	pioglitazone
A10BH01	sitagliptin
A10BH02	vildagliptin
A10BH03	saxagliptin
A10BH04	alogliptin
A10BH05	linagliptin
A10BX02	repaglinide

We investigated only oral forms of non-opioid analgesic drugs of interest and comedications, except for GLP-1 receptor agonists, of which most are only available as subcutaneous injections.

Table S2.

Number of adults per year and number of claims and defined daily doses per 100,000 adults from 2014 to 2019.

Nº adults	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**
	978,055	**981,594**	**955,931**	**906,016**	**934,412**	**977,817**
Claims/100,000 adults						
Metamizole	19,297	20,382	22,217	24,243	28,197	28,843
Ibuprofen	22,533	24,699	26,096	26,587	27,930	29,354
Diclofenac	18,128	17,300	17,191	16,254	14,889	13,926
Paracetamol	50,596	51,225	51,956	52,203	54,837	54,066
defined daily doses/100,000 adults						
Metamizole	103,630	118,732	136,068	159,273	181,362	190,500
Ibuprofen	366,116	393,789	410,691	417,564	432,160	448,961
Diclofenac	456,199	441,456	436,605	420,181	384,718	357,233
Paracetamol	827,684	837,537	857,237	870,262	898,585	878,561

Table S3.

Number of adults with at least one metamizole claim between 2014 and 2019, stratified by age.

Age groups	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**
Overall	76,094	82,723	87,701	89,346	95,388	101,723
18–45 years	19,896	22,361	23,910	22,993	24,736	26,906
46–65 years	22,201	23,933	25,213	25,606	27,389	29,081
66–75 years	12,700	13,680	14,280	14,776	15,398	16,078
76–85 years	12,798	13,522	14,410	15,228	16,293	17,166
>85 years	8499	9227	9888	10,743	11,572	12,492

Table S4.

Number of claims of non-opioid analgesic drugs of interest, stratified by canton.

	Metamizole			Ibuprofen			Diclofenac			Paracetamol		
	total claims	**per 100,000**	**difference [%]**	**total claims**	**per 100,000**	**difference [%]**	**total claims**	**per 100,000**	**difference [%]**	**total claims**	**per 100,000**	**difference [%]**
Switzerland	282,031	28,843		287,028	29,354		136,172	13,926		528,666	54,066	
Aargau	30,822	28,338	–2%	31,879	29,309	0%	13,794	12,682	–9%	43,321	39,829	–26%
Appenzell Innerhoden	371	33,758	+17%	199	18,107	–38%	217	19,745	+42%	586	53,321	–1%
Appenzell Ausserhoden	1844	32,109	+11%	1247	21,713	–26%	1086	18,910	+36%	2172	37,820	–30%
Bern	39,800	33,631	+17%	34,749	29,363	0%	16,886	14,269	+2%	57,586	48,660	–10%
Basel Land	8389	36,635	+27%	7451	32,539	+11%	2117	9245	–34%	10,191	44,504	–18%
Basel Stadt	3853	33,727	+17%	4070	35,627	+21%	987	8,640	–38%	4955	43,374	–20%
Fribourg	3133	14,828	–49%	7303	34,564	+18%	2954	13,981	0%	13,645	64,579	+19%
Geneva	969	1749	–94%	24,811	44,771	+53%	4803	8667	–38%	44,810	80,858	+50%
Glarus	1849	36,679	+27%	1952	38,722	+32%	717	14,223	+2%	2529	50,169	–7%
Graubünden	5739	24,977	–13%	5588	24,320	–17%	3649	15,881	+14%	8183	35,614	–34%
Jura	318	10,714	–63%	1040	35,040	+19%	231	7783	–44%	2105	70,923	+31%
Luzern	11,926	34,330	+19%	8946	25,752	–12%	6004	17,283	+24%	15,724	45,263	–16%

Neuchâtel	1968	13,232.92	–54%	4570	30,729	+5%	1182	7948	–43%	10,962	73,709	+36%
Nidwalden	1076	29,375	+2%	705	19,247	–34%	863	23,560	+69%	1524	41,605	–23%
Obwalden	1053	32,420	+12%	704	21,675	–26%	636	19,581	+41%	1439	44,304	–18%
St Gallen	15,284	38,992	+35%	9272	23,654	–19%	7655	19,529	+40%	19,429	49,566	–8%
Schaffhausen	3409	29,444	+2%	2659	22,966	–22%	1900	16,410	+18%	4823	41,657	–23%
Solothurn	10,211	24,143	–16%	13985	33,067	+13%	7157	16,922	+22%	17,782	42,045	–22%
Schwyz	3963	28,938	0%	3440	25,119	–14%	2359	17,225	+24%	5830	42,570	–21%
Thurgau	9137	32,654	+13%	5697	20,360	–31%	4863	17,380	+25%	11,569	41,346	–24%
Ticino	10,777	18,112	–37%	14,106	23,706	–19%	12,562	21,112	+52%	42,255	71,013	+31%
Uri	1563	24,614	–15%	1530	24,094	–18%	1394	21,953	+58%	2601	40,961	–24%
Vaud	4031	5,944	–79%	25,753	37,978	+29%	4166	6143.55	–56%	49,904	73,593	+36%
Valais	2914	9098	–68%	11,336	35,393	+21%	2574	8036	–42%	20,947	65,400	+21%
Zug	3512	26,772	–7%	2760	21,040	–28%	1697	12,936	–7%	5124	39,061	–28%
Zürich	104,120	44,893	+56%	61,276	26,420	–10%	33,719	14,538	+4%	128,670	55,478	+3%

Table S5.

The median number of claims of metamizole in metamizole users overall and in each age group from 2014 to 2019.

	Claims, median (IQR)					
Age groups	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**
Overall	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)
18–45 years	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)
46–65 years	1 (1–5)	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)
66–75 years	1 (1–3)	1 (1–3)	1 (1–2)	1 (1–3)	1 (1–3)	1 (1–3)
76–85 years	2 (1–4)	2 (1–3)	2 (1–4)	2 (1–3)	2 (1–3)	2 (1–3)
> 85 years	2 (1–5)	2 (1–5)	2 (1–5)	2 (1–5)	2 (1–5)	2 (1–5)

Figure S1. The relative differences between the number of claims of ibuprofen, diclofenac and paracetamol per 100,000 adults per canton and the Swiss average.