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NSAID prescribing and adverse outcomes in common infections: a population-based cohort study

Beth Stuart [1,2] Roderick Venekamp [3] Hilda Hounkpatin [2] Sam Wilding,[4] Michael Moore [2] Paul Little [2] Martin C Gulliford [5]

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[1]Wolfson Institute of Population Health, Queen Mary University of London, London, UK
[2]Primary Care Research Centre, University of Southampton Faculty of Medicine, Southampton, UK
[3]Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, Utrecht, Netherlands
[4]Southampton Clinical Trials Unit, University of Southampton, Southampton, UK
[5]King's College London, UK, London, UK

Correspondence to
Professor Beth Stuart;
b.l.stuart@qmul.ac.uk

ABSTRACT

Objectives Infections in primary care are often treated with non-steroidal anti-inflammatory drugs (NSAIDs). This study evaluates whether NSAID prescribing is associated with adverse outcomes for respiratory (RTIs) or urinary track (UTI) infections.

Objectives To determine whether there is an association between NSAID prescribing and the rate of adverse outcomes for infections for individual consulting in primary care.

Design Cohort study of electronic health records.

Setting 87 general practices in the UK Clinical Practice Research Datalink GOLD.

Participants 142 925 patients consulting with RTI or UTI.

Primary and secondary outcome measures Repeat consultations, hospitalisation or death within 30 days of the initial consultation for RTI or UTI. Poisson models estimated the associations between NSAID exposure and outcome. Rate ratios were adjusted for gender, age, ethnicity, deprivation, antibiotic use, seasonal influenza vaccination status, comorbidities and general practice. Since prescribing variations by practice are not explained by case mix—hence, less impacted by confounding by indication—both individual-level and practice-level analyses are included.

Results There was an increase in hospital admission/death for acute NSAID prescriptions (RR 2.73, 95% CI 2.10 to 3.56) and repeated NSAID prescriptions (6.47, 4.46–9.39) in RTI patients, and for acute NSAID prescriptions for UTI (RR 3.03; 1.92 to 4.76). Practice-level analysis, controlling for practice population characteristics, found that for each percentage point increase in NSAID prescription, the percentages of hospital admission/death within 30 days increased by 0.32 percentage points (95% CI 0.16 to 0.47).

Conclusions In this non-randomised study, prescription of NSAIDs at consultations for RTI or UTIs in primary care is infrequent but may be associated with increased risk of hospital admission. This supports other observational and limited trial data that NSAID prescribing might be associated with worse outcomes following acute infection and should be prescribed with caution.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study uses a large and representative primary care database, validated for quality and accuracy of coding.
⇒ We were able to explore associations at both the individual and practice levels.
⇒ There is a potential for missed cases of infection, since this study only include those unwell enough to consult their General Practitioner.
⇒ While we have controlled for potential confounding factors available in the dataset, there is a possibility for residual confounding, particularly with respect to the severity of illness at the initial consultation, which is not routinely coded.
⇒ Non-steroidal anti-inflammatory drugs (NSAID) prescribing data can only be expected to detect a signal and not provide a full picture of the impact of NSAIDs since patients can access NSAIDs over-the-counter themselves.

BACKGROUND

Consultations for respiratory tract infections (RTIs) are common in primary care. A recent study using Clinical Practice Research Datalink (CPRD) practices found a consulting rate of 217 consultations per 1000 person years.[1] Urinary tract infection (UTI) are also common, with 11% of women experiencing at least one episode each year.[2] Most patients are be advised to self-manage infections at home and many use analgesics such as paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) for symptom relief.[3 4] However, observational studies suggest that the use of NSAIDs during RTIs may be associated with increased risk of acute cardiovascular events,[5] and cyclooxygenase-2 inhibitors or non-selective NSAIDs may be associated with a further increase in risk.[6 7] There is also some evidence that exposure to NSAIDs during an episode of an acute infection may result in an increased risk of adverse outcomes such as hospitalisation or longer duration of illness.[8–13] This association has also been observed in two trials, which found a longer duration of illness and higher rate of repeat consultation in patients who used NSAIDs.[14 15]

This evidence, however, derives from trials with small sample sizes or retrospective case–control studies. With complications from RTI and UTI generally occurring infrequently,[16 17] a large observational cohort is better suited to exploring whether there is an association between the exposure and outcome and whether the effect varies across age and comorbidity groups.

For most medicine prescribing, including antibiotic prescribing for RTIs, variations by practice are very large and cannot be fully explained by case mix.[18–20] Practice-level data, therefore, provide a useful 'natural experiment' and can provide a useful addition to individual-level analyses where it is more difficult to control fully for case mix.

This study, therefore, aimed to determine whether there is an association between NSAID prescribing and the rate of adverse outcomes including repeat consultation, hospital admission and death, in patients consulting primary care for RTI or UTI. We used both individual-level and practice-level data.

METHODS

Study design and population

We performed a retrospective cohort study in the CPRD GOLD,[21] an anonymised research database of records from participating general practices across the UK. CPRD is broadly representative of the UK population with approximately 4.7% of the UK general population and 4.6% of UK general practices contributing data.[21] For this study, we included those general practices in England eligible for linkage to Hospital Episodes Statistics (HES) for outcomes as well as individual patient-level deprivation data.[22] We sampled all patients who consulted with one or more RTI or UTI episodes between 1 April 2018 and 31 March 2019. Analysis included all consultations for RTI or UTI that these patients had over this timeframe. RTI and UTI consultations were identified using Read codes in CPRD clinical and referral records (see online supplemental appendix 1).[23]

The protocol for this study was approved by the CPRD Independent Scientific Advisory Committee (ISAC protocol 20_058R). This study is reported as per the Strengthening the Reporting of Observational Studies in Epidemiology guideline.[24]

Definition of the exposure

NSAID prescriptions were identified from product codes for NSAIDs listed in the British National Formulary (Chapter 10, section 1.1, online supplemental appendix 2). The exposure was classified into three groups: NSAID prescribed on the same day as an RTI/UTI consultation ('acute NSAID'); no NSAID prescribed on the day of the consultation; and repeat NSAID prescribing, where two or more prescriptions for an NSAID medication had been issued to the consulting patient in the 6 months prior to the RTI/UTI consultation.

Definition of the outcome

Adverse outcomes within 30 days of the original RTI or UTI consultation were defined as a binary outcome based on having one of (1) repeat consultation with the same illness, (2) hospital admission for any cause identified from linked HES data, or death.

Covariates

The analysis included covariates including: age; gender; ethnicity (categorised as Bangladeshi, Black African, Black Caribbean, Black Other, Chinese, Indian, Pakistani, Other Asian, White, Mixed, Other and Unknown); deprivation as measured by the Index of Multiple Deprivation 2015 corresponding to the patient's postcode in five categories from least deprived to most deprived; the seasonal influenza vaccination status in each year; the Elixhauser Comorbidity Index[25 26] in each year over the preceding 10 years; and whether an antibiotic was prescribed at the consultation. The Elixhauser Comorbidity Index is a measure of comorbidity based on 31 comorbidity categories identified in CPRD by Read codes.[27] Antibiotic prescriptions were identified based on the BNF produce codes in section 5.1, excluding methanamine and drugs for tuberculosis and leprosy as per a previous publication (see online supplemental appendix 3).[23] Multiple antibiotic prescriptions on the same day were considered as a single prescription.

Statistical analysis

Descriptive statistics were used to characterise the cohort. We evaluated the association between NSAID prescribing and adverse outcomes using mixed Poisson models with general practice as a random intercept and the person-time at risk as the exposure variable in Stata. Person time was calculated from the consultation date to the earlier of the end in cohort (death/end of registration/end of study period) or 30 days. Modelling allowing for the clustering of multiple consultations within patients. Covariates included in the model were age, sex, individual-level Index of Multiple Deprivation in five groups, ethnicity, influenza vaccination status, Elixhauser index and whether an antibiotic was prescribed at the initial consultation. Age and Elixhauser index were treated as continuous covariates; all other variables were treated as categorical. The analysis was of complete cases.

Practice-level analysis (see online supplemental appendix 4 for more detail). A linear regression model for controlled for the practice level values of the covariates listed in the individual level analyses.

Sensitivity and subgroup analyses

To explore the possibility that antibiotics may be more likely to modify the outcome in UTI than in RTI, we planned to conduct a sensitivity analysis where the exposure was categorised as 'no prescription/NSAID only/Antibiotic only/NSAID and Antibiotic'. On examination of the data, there was only a sufficient number of cases to allow this to be explored in the RTI data.

As the extremes of age and those with more comorbid conditions may be more vulnerable, we evaluated effect modification by age (<15 years, 16–64 years and 65 year

and over) and Elixhauser Index by testing the interactions with NSAID prescribing, and proceeding to evaluate subgroup effects if a significant interaction term was present at the 5% level.

All analyses were conducted in Stata V.16.0.

Patient and public involvement

We discussed the plans for this study with two members of the public who had experienced infections and used both antibiotics and self-management approaches in the past. They provided feedback on the proposed exposures, including the inclusion of a repeat NSAID user group, the appropriate outcomes to measure and the lay summary for the funding application. We incorporated this feedback as far as the available data allowed.

RESULTS

Cohort characteristics

The cohort included 142 925 patients from 87 general practices contributing 355 477 consultation episodes over the 1-year period. NSAID prescribing at RTI/UTI consultations was infrequent, with 2354 prescriptions representing 1.2% of RTI/UTI consultations. Of these 1.1% were for a single, acute NSAID prescription and 0.1% for repeated NSAID prescriptions.

Patients who received a single NSAID prescription were generally younger, with a higher proportion of children, more likely to be from a non-white ethnic group, in the most deprived quintile, and had less comorbidity. Repeated prescriptions tended to be issued in consultations with those who were women, older and had greater comorbidity (see table 1).

Repeat consultation within 30 days occurred in 66 080 (18.6%), hospital admission in 15 422 (4.3%) and death in 3922 (1.1%) of all RTI/UTI episodes. Repeat consultation

Table 1 Cohort characteristics by NSAID exposure at consultation

	Whole cohort (n=142 925)*	No NSAID (n=353 796)	Acute NSAID (n=1587)	Repeated NSAID (n=94)
Female	86 646 (60.6%)	219 549 (62.1%)	948 (59.7%)	59 (62.8%)
Mean age (SD)	39.3 (27.08)	38.6 (28.85)	19.5 (24.13)	58.75 (19.40)
Deprivation quintiles				
1 (least deprived)	39 993 (28.0%)	93, 472 (26.4%)	172 (10.8%)	18 (19.2%)
2	29 147 (20.4%)	71 151 (20.1%)	188 (11.9%)	16 (17.0%)
3	26 946 (18.9%)	66 512 (18.8%)	266 (16.8%)	19 (20.2%)
4	23 545 (16.5%)	60 008 (17.0%)	364 (22.9%)	19 (20.2%)
5 (most deprived)	23 254 (16.3%)	62 578 (17.7%)	597 (37.6%)	22 (23.4%)
Ethnicity†				
Bangladeshi	556 (0.4%)	1401 (0.4%)	18 (1.2%)	0
Black African	1598 (1.3%)	3295 (1.0%)	61 (4.2%)	0
Black Caribbean	755 (0.6%)	1560 (0.5%)	15 (1.0%)	2 (2.2%)
Black Other	522 (0.4%)	1199 (0.4%)	15 (1.0%)	0
Chinese	410 (0.3%)	850 (0.3%)	7 (0.5%)	0
Indian	2435 (2.0%)	6164 (1.9%)	38 (2.6%)	4 (4.4%)
Pakistani	1710 (1.4%)	4593 (1.4%)	54 (3.7%)	1 (1.1%)
Other Asian	1568 (1.3%)	3913 (1.2%)	31 (2.1%)	1 (1.1%)
White	106 689 (85.2%)	276 489 (86.2%)	1085 (73.9%)	82 (91.1%)
Mixed	2525 (2.0%)	6988 (2.2%)	58 (4.0%)	0
Other	2377 (1.9%)	5651 (1.8%)	51 (3.5%)	0
Unknown	4015 (3.2%)	8628 (2.7%)	36 (2.5%)	0
Mean Elixhauser Index (SD)	3.1 (5.89)	3.9 (6.68)	2.0 (5.36)	3.3 (6.25)
Repeat consultation within 30 days	N/A	65 782 (18.6%)	274 (17.3%)	24 (25.5%)
Hospital admission within 30 days	N/A	15 283 (4.3%)	106 (6.7%)	33 (35.1%)
Death within 30 days	N/A	3827 (1.1%)	69 (4.4%)	26 (27.7%)

*Figures for the whole cohort are as at 2018/2019. Figures for NSAID prescribing are over all consultations.
†Ethnicity only available for 125 160 patients.
NSAIDs, non-steroidal anti-inflammatory drugs.

Table 2 Unadjusted and adjusted rate ratios for the association of adverse outcome, repeat consultation and hospital admission/death within 30 days with NSAID prescribing exposure

	Repeat consultation within 30 days		Hospital admission or death within 30 days	
	Unadjusted rate ratio (95% CI)	Adjusted rate ratio* (95% CI)	Unadjusted rate ratio (95% CI)	Adjusted rate ratio* (95% CI)
RTI only				
No NSAID	REF	REF	REF	REF
Acute NSAID	1.03 (0.92 to 1.16)	0.99 (0.80 to 1.22)	1.38 (1.12 to 1.71)	2.73 (2.10 to 3.56)
Repeated NSAID	1.40 (0.94 to 2.09)	1.61 (1.09 to 2.41)	8.56 (5.98 to 12.27)	6.47 (4.46 to 9.39)
UTI only				
No NSAID	REF		REF	REF
Acute NSAID	0.95 (0.36 to 2.53)	1.12 (0.42 to 3.00)	2.26 (1.92 to 2.69)	3.03 (1.92 to 4.76)
Repeated NSAID	NA	NA	NA	NA

*Adjusted for age, sex, individual level Index of Multiple Deprivation, ethnicity, influenza vaccination status, Elixhauser index and antibiotic co-prescription.
NSAID, non-steroidal anti-inflammatory drug; RTI, respiratory tract infection; UTI, urinary tract infection.

occurred in 24 consultations (25.5%) for repeated NSAID prescriptions, 65 782 consultations (18.6%) for no NSAID prescription and 274 (17.3%) for an acute prescription. There were 33 consultations (35.1%) in the repeat NSAID group, leading to a hospital admission, 15 283 (4.3%) in the no NSAID group and 106 (6.7%) in the acute NSAID group. Twenty-six (27.7%) resulted in death within 30 days in the repeated NSAID group, 3827 (1.1%) in the no NSAID group and 69 (4.3%) in the acute NSAID group. Eighty-three per cent of deaths took place in hospitalised cases.

Risk of adverse event

There was an increased risk of repeat consultation with repeated NSAID prescribing for RTI. This was not estimable for UTI as there was no repeat consultation in patients with a repeat NSAID prescription. Although the number of events was small, there was evidence that hospital admission or death was higher for both acute and repeat NSAID prescriptions for both RTI and UTI (table 2).

There was an increased risk associated with NSAID prescribing alone or in combination with antibiotics, and a protective effect of antibiotics (table 3) for RTI patients for hospitalisation and death within 30 days. There was no effect on repeat consultations of NSAID prescriptions and a slightly elevated risk with antibiotic prescribing. It was not possible to estimate these models for UTI patients as there was only one repeat consultation for a patient with an NSAID prescription only.

Subgroup analyses

NSAID prescribing was very low for UTI in children. Only 1 child under 15 had a repeated NSAID prescription and 10 had an acute NSAID prescription at the time of a UTI consultation. There were no repeat consultations in those aged 65 and over for UTI with repeated NSAIDs.

There was no evidence for an interaction with age and acute NSAID prescribing in those aged 16–64 (interaction term:1.19, 95% CI 0.79 to 1.82 for acute NSAID prescription and 0.85; 95% CI 0.48 to 1.50 for repeat

Table 3 Unadjusted and adjusted rate ratios for the association of repeat consultation and hospital admission/death within 30 days with NSAID and antibiotic prescribing exposure for RTI patients

	Repeat consultation within 30 days		Hospital admission or death within 30 days	
	Unadjusted rate ratio (95% CI)	Adjusted rate ratio* (95% CI)	Unadjusted rate ratio (95% CI)	Adjusted rate ratio* (95% CI)
RTI only				
No prescription	REF	REF	REF	REF
NSAID only	1.15 (0.99 to 1.34)	1.04 (0.81 to 1.33)	2.07 (1.64 to 2.61)	3.19 (2.42 to 4.23)
Antibiotic only	0.91 (0.90 to 0.93)	1.03 (1.01 to 1.06)	0.77 (0.74 to 0.80)	0.89 (0.95 to 0.93)
NSAID+antibiotic	1.17 (0.98 to 1.40)	1.21 (0.91 to 1.62)	1.80 (1.34 to 2.41)	3.63 (2.59 to 5.09)

*Adjusted for age, sex, individual level Index of Multiple Deprivation, ethnicity, influenza vaccination status, Elixhauser index.
NSAID, non-steroidal anti-inflammatory drug; RTI, respiratory tract infection; UTI, urinary tract infection.

NSAID prescription) and 65+ years (interaction term: 1.18, 95% CI 0.73 to 1.90).

There was no statistically significant interaction with the Elixhauser Index (interaction terms 1.00, 95% CI 0.99 to 1.01 for acute NSAID prescription and 1.00, 95% CI 0.98 to 1.02 for repeated NSAID prescription).

Practice-level analyses (see online supplemental appendix 4 for fuller details)

The range in the percentage of patients experiencing hospital admission or death within 30 days was between 2.7% and 7.7% (median 4.7%, lower quartile 3.9%, upper quartile 5.2%). Higher NSAID prescribing rates and higher rates of hospital admission/death within 30 days were correlated (r=0.30). For each one percentage point increase in the percentage receiving an NSAID prescription, the percentage experiencing hospital admission/death within 30 days increased by 0.32 percentage points (95% CI 0.16, to 0.47).

DISCUSSION

Main findings

In this large cohort study of electronic health record data, NSAID prescribing for RTI or UTI was associated with an increased risk of hospital admission or death within 30 days in both practice and individual-level analyses. There was also a higher risk of repeat consultation within those with a repeated NSAID prescription, albeit in small numbers of patients. The lack of significant interactions with age and comorbidity suggests that the relationship is not modified by these factors.

Comparison with other studies

An individual patient data meta-analysis found that although the absolute excess risk was small, compared with placebo some NSAIDS (coxib and diclofenac) caused three major vascular events per 1000 patients per year, of which one event was fatal.[28] There is increased risk of acute kidney injury in those over 65 with NSAID use.[29] Our study is consistent with these findings, with a clear increase in all hospital admissions in this large routine data set. The point estimates of effect were larger than previously observed in the literature perhaps as they relate to a relatively small population prescribed NSAIDs over a 1-year period, even within this large cohort. There was no significant interaction with age over 65, however, suggesting that the risk may be present in younger adults as well.

In contrast to some trial evidence in both RTI[15 30] and UTI,[31] this study did not show an increased risk of repeat consultation except in those prescribed repeated NSAIDs. It is not clear why these results differ but it may be due to the different advice and/or patient behaviour in a trial context with respect to repeat consultation, the dilution of the signal due to over the counter use, smaller sample sizes or different patient populations.

Strengths and limitations

The strength of this study is that it is a large cohort conducted using CPRD and linked HES data, largely representative of UK general practice, and validated for the quality and accuracy of coding.

There may be some limitations in generalisability, however, as only the 87 general practices in England, which provide linked data were available for this analysis. Recent papers have suggested that in England, patient-level measures of deprivation and ethnicity were broadly similar to the general population.[32 33] However, the data included here were limited to general practices in England and different prescribing patterns and associations might be observed in a broader data set more representative of the UK population, especially as there are no prescription charges in devolved nations, which may encourage more patients to seek prescriptions for medications for self-management, such as NSAIDs, rather than purchasing them over the counter.

The individual-level analyses cannot control for all aspects of case mix, particularly the severity of the illness at the time of the initial consultation as measures of illness severity are not routinely coded by GPs. Patients prescribed NSAIDs may be at higher risk of hospital admission or death and there is potential that the results reflect residual confounding in respect of this and other unmeasured confounders. However, since case mix does not fully explain practice-level variation in prescribing for infections once overall population characteristics are controlled for the problem of confounding by indication due to case mix is less for practice-level analyses. Thus, the similarity of our findings in the practice-level analyses suggests that confounding by indication is not likely to completely explain the individual-level results.

There is potential for missing mild cases of UTI and RTI, since this study only includes those patients ill enough to consult a GP. Moreover, the analysis has used complete cases only with no allowance for missing data. GPs may possibly not code milder cases so this may somewhat limit the generalisability of these findings, but consultation with a GP for both RTI and UTI remains common, even in those with relatively mild symptoms, and, therefore, these results are likely to still be informative in clinical practice. In using this routine data, we may have included a small number of patients who could not be prescribed NSAIDs due to allergy or hypersensitivity as well as a small proportion who were coprescribed proton pump inhibitors or probiotics, which might have lessened any impact of NSAID prescribing. These small numbers are unlikely to have impacted on the inferences.

NSAID prescribing data can only be expected to detect a signal and not provide a full picture of the impact of NSAIDs since patients can access NSAIDs over-the-counter themselves. NSAID use is common with 50% of people with RTI and 20% of women with UTI reporting NSAID use during an episode of infection.[34 35] The prescribing rates observed in this study were considerably lower than this and it is likely that there is some misclassification, with a proportion of the 'no NSAID' group using NSAIDs. It is also possible that patients who are prescribed NSAIDs may not fill their prescriptions or may not take them.

Such misclassification would be more likely to render the signal undetectable and this suggests that the associations detected in our study may represent an underestimate.

Finally, this study was undertaken during a period of time prior to the COVID-19 pandemic. There is some evidence that the use of NSAIDs in those with COVID-19 infection does not lead to higher mortality or increased severity[36–39] and a clinical trial of ibuprofen use in COVID-19 is underway.[40] It has been hypothesised that this lack of association may be because the release of cytokines associated with more severe COVID-19 is moderated by NSAID treatment.[38 41 42] It has also been hypothesised that adverse events associated with NSAID use in RTI may be specific to bacterial infections.[37] Our findings, therefore cannot be generalised to the recent pandemic.

CONCLUSIONS AND IMPLICATIONS

The prescribing of NSAIDs during non-pandemic years may be associated with worse outcomes following acute infection. This routine data support other observational data and the limited trial data that prescribing of NSAIDs during non-pandemic years are likely to be associated with worse outcomes following acute infection, and they, therefore, should be prescribed with care.

Twitter Sam Wilding @GeogWilding

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval The CPRD holds over-arching Research Ethics Committee approval for observational studies using fully anonymised data. The study was based on analysis of fully anonymised data, and individual consent therefore not required.

Provenance and peer review Not commissioned; externally peer-reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Data cannot be shared publicly because they are analysed under licence. The data are available from the CPRD Independent Scientific Advisory Committee (contact viaisac@mhra.gov.uk) for researchers who meet the criteria for access to confidential data.The data underlying the results presented in the study are available from the Clinical Practice Research Datalink (cprdenquiries@mhra.gov.uk).

ORCID iDs
Beth Stuart http://orcid.org/0000-0001-5432-7437
Roderick Venekamp http://orcid.org/0000-0002-1446-9614
Hilda Hounkpatin http://orcid.org/0000-0002-1360-1791
Michael Moore http://orcid.org/0000-0002-5127-4509
Paul Little http://orcid.org/0000-0003-3664-1873
Martin C Gulliford http://orcid.org/0000-0003-1898-9075

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