

# A study of general practitioners' awareness of the National Institute for Health and Care Excellence guidelines regarding the use of non-steroidal anti-inflammatory drugs

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## ABSTRACT

### Background

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely prescribed for their analgesic, anti-pyretic and anti-inflammatory effects. There is no doubt regarding their benefits; however the importance of their side effects including gastrointestinal complications cannot be emphasized enough especially in high risk groups.

### Objectives

This study assessed the awareness of general practitioners (GPs) working within Maltese health centres of the National Institute for Health and Care Excellence (NICE) guidelines on the proper prescription of NSAIDs, especially the co-prescription of gastroprotective agents in high risk groups.

### Method

An online questionnaire based on the NICE guidelines on NSAID Prescribing Issues revised in July 2015 was distributed to doctors working within health centres across Malta.

### Results

Trauma was the most popular reason for NSAID prescription (75%), with the commonest patient age group being that below 45 years of age. Diclofenac was the most popular NSAID choice (55.4%) with COX-2 inhibitors being the preferred choice for 23.2%. Most doctors were aware of factors that need to be considered when initiating NSAIDs, being least aware of liver

comorbidities and fertility issues. The majority use licensed gastroprotective agents both in drug choice and in dose. More awareness is required on high risk patient groups especially patients with arthritis and patients on selective serotonin reuptake inhibitors (SSRIs).

### Conclusion

There is room for improvement in awareness on proper NSAID use and gastroprotection especially in identifying high risk groups, drug interactions and choice of gastroprotective agents. The importance of gastroprotection, side effect monitoring, prevention of unnecessary chronic NSAID use and promotion of coxib use over standard NSAIDs needs to be emphasized further especially in high risk groups.

### Keywords

General practitioners; awareness; protective agents; anti-inflammatory agents; proton pump inhibitors

## BACKGROUND

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely prescribed medications within general practice in the community for a multitude of medical conditions. They are mostly prescribed in view of their analgesic, anti-pyretic and in higher doses, their anti-inflammatory effects. NSAIDs demonstrate variable inhibition of both cyclooxygenase-1 and cyclooxygenase-2 isoenzymes, both involved in the formation of prostaglandins which play an active role in inflammatory processes (Neal, 2012).

Table 1: Table showing the main recommendations highlighted in the NICE guidelines NSAID Prescribing Issues last revised in July 2015

## NICE GUIDELINES NSAID PRESCRIBING ISSUES JULY 2015

Factors to consider when initiating NSAIDs	Licensed PPIs and their doses for gastroprotection
Contraindications	Lansoprazole 15-30mg daily.
Alternative treatment	Omeprazole 20mg daily
Patient already on NSAID?	Esomperazole 20mg daily
Lowest dose & shortest duration for effective treatment	Pantoprazole 20mg daily
Gastroprotection especially in high risk groups	
Side effect monitoring especially in high risk groups	
Drug interactions	
Absolute and Relative Contraindications	High risk patient groups - to consider PPI
Hypersensitivity	Patients on maximum recommended dose
Low eGFR	65 years +
Skin reactions and angioedema	History of GI bleeding/perforation
Asthma	Concomitant aspirin use
Heart Failure	Concomitant steroid use
Liver fibrosis and cirrhosis	Concomitant SSRI use
Acute liver failure and severe hepatic impairment (North Lewis, 2008)	Cardiovascular, hepatic, renal impairment
History of/current treatment for GI problems	Diabetics
IBD	Hypertensives
IHD, CVD, PAD	Osteoarthritis & Rheumatoid arthritis
Dehydration especially in diabetics	Chronic low back pain
HT	Heavy smoking or alcohol use
Women trying to conceive	H.pylori infection
Hepatitis and cholestasis	
Monitoring in high risk patient groups	Drug interactions in primary care
Blood pressure - especially within 1-2 weeks of starting/increasing dose	Low dose aspirin
Renal function - especially within 1-2 weeks of starting/increasing dose	ACE inhibitors
Features of heart failure including body weight	Ciclosporin
Enquire about GI bleeding and fluid retention in people with hepatic impairment	ARBs
	Thiazide type, potassium and loop diuretics
	Lithium
	Methotrexate
	Probenecid
	Quinolones
	Antidepressants
	Anticoagulants

NSAIDs can be classified as standard (such as diclofenac, ibuprofen and naproxen) or COX-2 inhibitors such as celecoxib and etoricoxib (NICE Guidelines NSAID Prescribing Issues, 2015). Whilst there is no doubt about the various benefits that can be derived from NSAID use, research done throughout the years on these drugs has highlighted the importance of being aware of possible adverse effects, such as the development of cardiovascular and gastrointestinal complications, the latter through mucosal injury and COX-1 derived prostaglandin inhibition. This should be taken into consideration in all patients but especially in high risk patient groups, most notably individuals with a past history of peptic ulcer disease, the elderly and concomitant aspirin use (Sostres et al., 2010). Guidelines have therefore been devised in order to emphasise the importance of both risk factor modification when possible and more importantly, in considering alternatives to NSAID therapy and ensuring the proper prescription of gastroprotective agents when such therapy is required.

The guidelines used in this study as a standard on which questions and results were based were the National Institute for Health and Care Excellence (NICE) guidelines on NSAID Prescribing Issues last revised in July 2015 (NICE Guidelines NSAID Prescribing Issues, 2015).

The NICE guidelines currently recommend addition of a proton pump inhibitor (PPI) with all NSAIDs including COX-2 inhibitors based on two papers reporting three randomised controlled trials (RCTs) by Scheiman et al. (2006) and Chan et al. (2007). Table 1 highlights the main recommendations in the NICE guidelines which this study aimed to explore.

## OBJECTIVES

This study was designed to assess awareness of NICE guidelines on NSAID Prescribing Issues among general practitioners on proper NSAID prescription. In light of these guidelines it specifically intended to address the following objectives:

- Assessment of the factors and medical issues considered by community doctors before initiating NSAIDs including knowledge of contraindications and drug interactions;
- To explore medical scenarios for which NSAIDs are used and patient age groups for which such medication is prescribed;

- To explore NSAID choices amongst general practitioners when NSAIDs are used;
- Assessment of NSAID side-effect monitoring within the community;
- Assessment of awareness amongst general practitioners (GPs) of which patients qualify as high risk;
- Assessment of co-prescription of gastroprotective agents by community doctors for high risk patient groups.

## METHODOLOGY

Permission to carry out this study was obtained from the administration of the Primary Health Care Department prior to distributing an online questionnaire in September 2016 to 139 doctors working in health centres across all regions in Malta. The data collected was then analysed in light of the NICE guidelines on NSAID prescribing issues last revised in July 2015.

Questions were aimed to assess awareness and practices amongst doctors working in the community and designed to address the objectives mentioned above.

## RESULTS

The questionnaire was distributed to a total of 139 doctors. Fifty-six doctors participated in the study – four foundation trainees, eleven GP trainees and forty-one general practitioners giving a response rate of 40.3%.

The most common reasons for which NSAIDs are usually prescribed in general practice resulted to be trauma (75%), followed by chronic back pain (12.5%) and osteoarthritis (10.7%). When questioned about patient age groups for which NSAIDs are usually prescribed, 76.8% (43 doctors) answered that they prescribe NSAIDs to patients less than 45 years of age whilst 23.2% (13 doctors) answered that they mostly prescribe NSAIDs to patients between 45 and 64 years of age. There were no doctors who chose the 65 years + patient age group as their most common patient group to which they prescribe NSAIDs.

The doctors were also asked what factors they usually consider when initiating a patient on NSAIDs in their practice. Contraindications and drug interactions were the two most common factors considered, with dose and side effect monitoring resulting to be the least popular responses. Figure 1 further demonstrates the results.

Figure 1: Factors considered by GPs when initiating a patient on NSAIDs

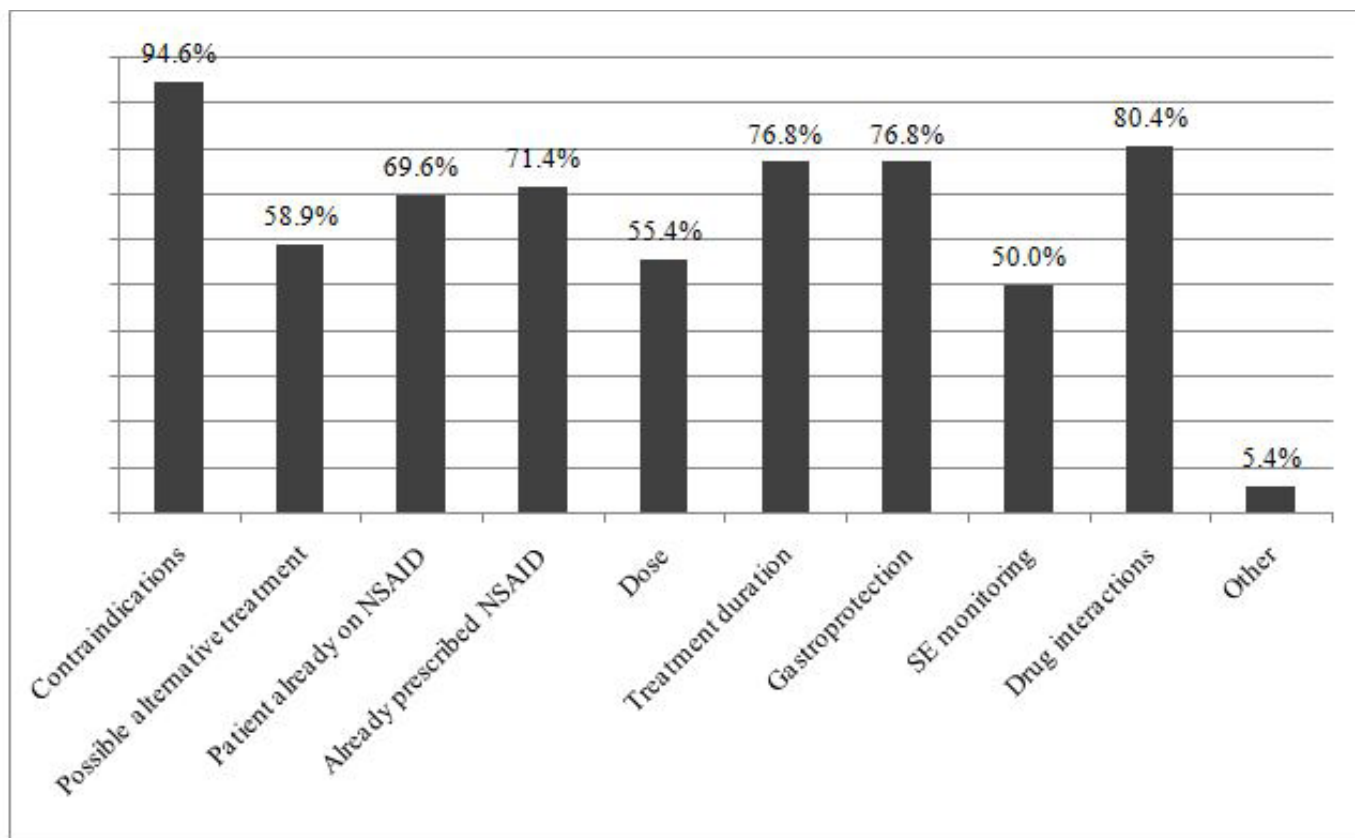
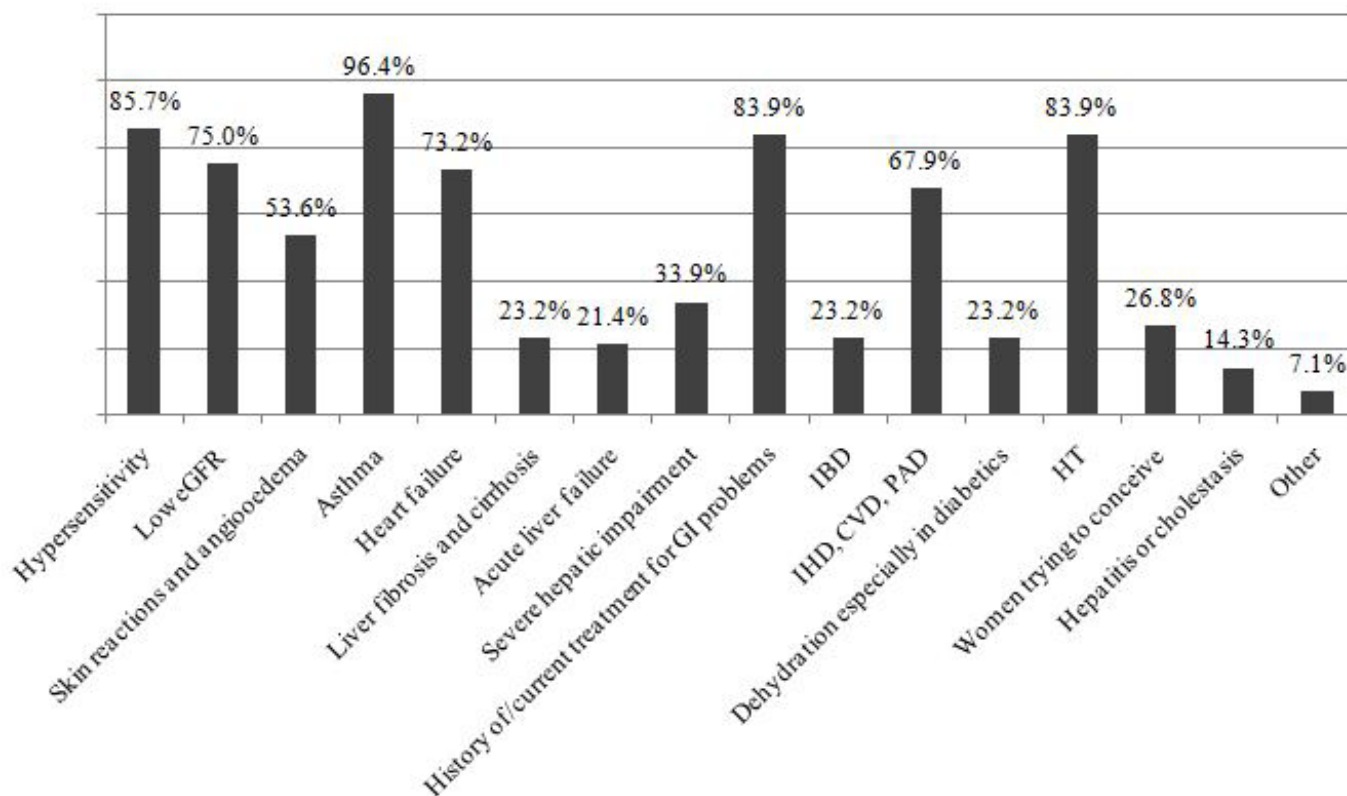


Figure 2: Patient medical issues looked out for by GPs when considering NSAID use



The most popular type of NSAID used resulted to be diclofenac (55.4%) followed by COX-2 inhibitors (23.2%), ibuprofen (14.3%) and naproxen (7.1%). This shows that standard NSAIDs are still the most popular choice at 76.8% versus COX-2 inhibitors at 23.2%.

Doctors were also asked whether they usually bring patients started on NSAIDs back for review of progress and to assess for continued need of NSAID use. 69.6% (39 doctors) replied that they review patients only in cases of no improvement or in cases of patients experiencing adverse events. 19.6% (11 doctors) responded that they do not review patients after NSAID initiation whilst 10.7% (6 doctors) replied that they always review patients started on such treatment.

Figure 2 demonstrates patient medical issues usually looked out for by general practitioners when considering NSAIDs. Hypersensitivity, asthma and history of GI problems were the three commonest medical issues looked out for by community doctors when considering NSAID use with liver problems, fertility and dehydration amongst the least popular responses.

GPs were also questioned on awareness regarding drugs commonly encountered in primary care and their interactions with NSAIDs. Anticoagulants were by far

the most popular choice at 87.5%, unlike drugs such as diuretics, ciclosporin and probenecid that were amongst the least popular choices. Figure 3 further demonstrates these results.

87.5% of respondents perform blood pressure monitoring within their practice when monitoring for NSAID adverse effects. This was closely followed by monitoring for heart failure features at 82.1%. Interesting to note was that only 5.4% include body weight assessment as part of their monitoring. Results are shown in Figure 4.

Figure 5 demonstrates data for scenarios in which doctors co-prescribe a gastroprotective agent when prescribing NSAIDs:

When asked regarding co-prescription of PPIs in high risk patients, 60.7% replied that they only co-prescribe a PPI when they use potent NSAIDs such as diclofenac. 28.6% always prescribe a PPI irrespective of NSAID choice. 7.1% replied that they usually co-prescribe a PPI when they use ibuprofen whilst 3.6% advise a PPI when prescribing COX-2 inhibitors.

Study participants were also asked about regimes they use in their practice for gastroprotection when prescribing NSAIDs and results of their responses are demonstrated in Figure 6.

Figure 3: Awareness amongst GPs on NSAID interactions with medications frequently used in the community

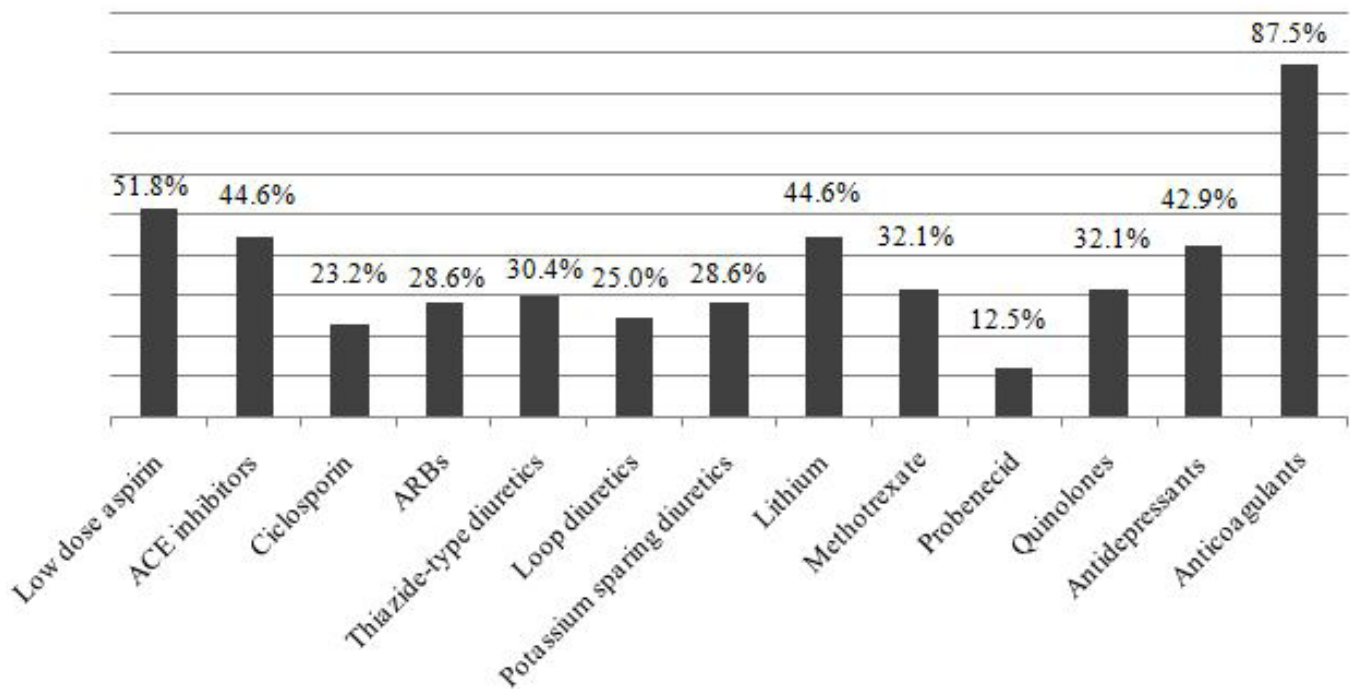


Figure 4: Parameters, investigations and examination findings used by GPs to assess for NSAID adverse events

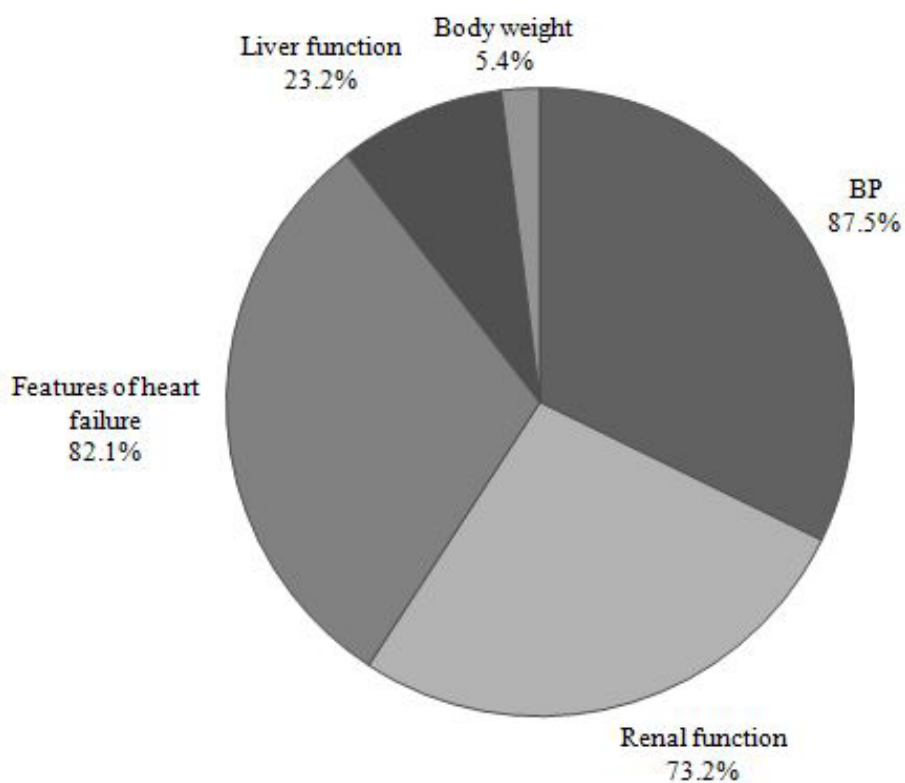


Figure 5: Scenarios in which doctors co-prescribe a gastroprotective agent with NSAIDs

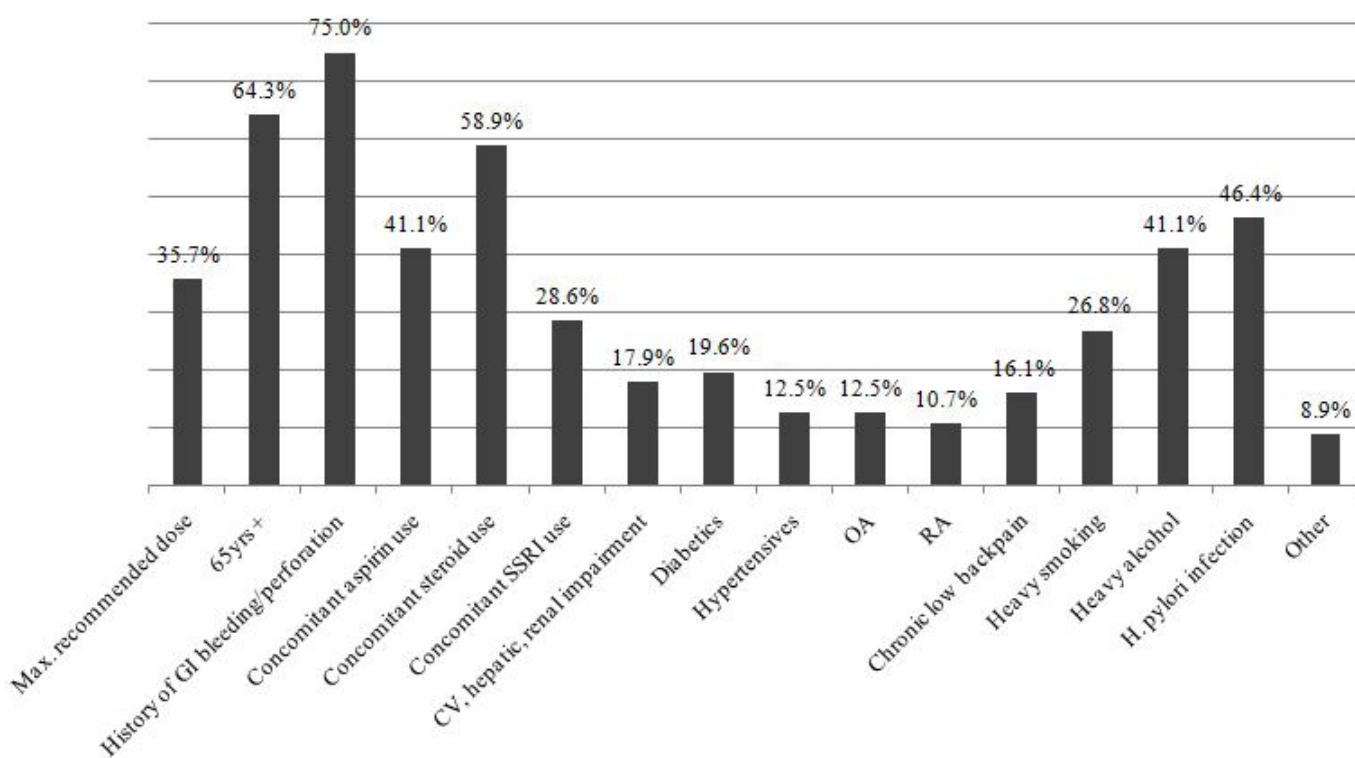
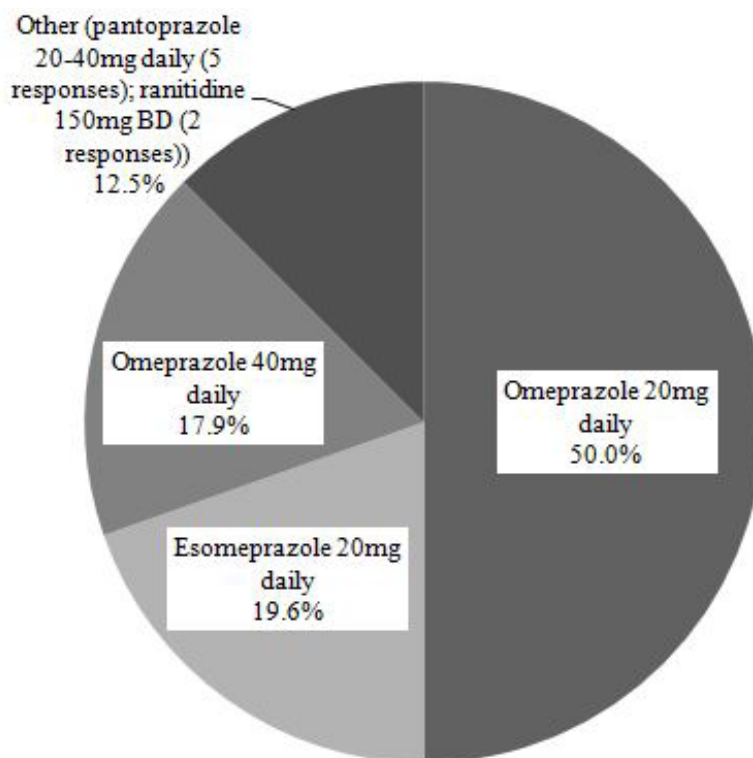




Figure 6: Regimes used by GPs for gastroprotection when prescribing NSAIDs



## DISCUSSION

The popularity of NSAID use within the community is undisputable as demonstrated by various studies performed throughout the years such as that by Bradbury in 2004 performed in Ireland, showing diclofenac, nimesulide and ibuprofen to make up 80% of total prescription issued by GPs (Bradbury, 2004). Similar to the current study, an Italian study by Motola et al. in 2004 showed that the main reasons for NSAID use within the community were osteoarticular pain (19%), unspecified pain (15%) and osteoarthritis (9%). Given the usual chronicity of such scenarios, this further emphasises the importance of correct NSAID prescription including the identification of high risk groups to avoid potential adverse effects. It is also of note that in this study, diclofenac resulted to be the most popular choice (55.4%) despite its various documented side effects, with COX-2 inhibitors being the preferred choice for only 23.2% of the GPs. This is in contrast to what seems to be the current situation within the UK as outlined by a clinical audit on NSAID safety performed across the UK in 2014 demonstrating the most frequently prescribed agents to be naproxen (59%), ibuprofen (19%) and diclofenac at 9% (NHS Specialist Pharmacy Services, 2014). Possible reasons for such a choice are many, including the fact that standard NSAIDs have been on the market for years

and therefore clinicians might feel more comfortable with their use. It might also result from the fact that from past clinical experience, community doctors have found diclofenac to result in the highest patient satisfaction.

The NICE guidelines recommend using NSAIDs with caution in the elderly in view of an increased risk of serious adverse effects such as gastrointestinal bleeding and perforation which may be fatal. In this study, patient age groups for which NSAIDs are preferably prescribed resulted to be 76.8% for patients less than 45 years of age and 23.2% for patients between 45 and 64 years of age. There were rightly no responses for patients older than 65 years of age, reflecting the fact that patients older than 65 years are the patient group most likely to have multiple co-morbidities and therefore increased likelihood of contraindications, drug interactions and side effects.

The majority of GPs were aware of most of the factors that should be considered when initiating NSAID treatment as outlined in the NICE guidelines, with contraindications to NSAID use being the most popular factor (94.6%). Of note is that only 76.8% currently consider the use of gastroprotection especially in high risk patients. Moreover, whilst 76.8% of doctors stated that they take into consideration treatment duration, only 55.4% of doctors highlighted the need to consider the actual dose

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used to address the medical problem in question. Possible reasons for this include that it might come as second nature to most GPs to start at the lowest possible dose when initiating treatment. It might also be due to the fact that community doctors might have their own preferred standard dose prescription which they have found most effective based on their past clinical experience.

It was also interesting to note that the least factor considered was side-effect monitoring, with only 50% of doctors highlighting the need to look out for possible medical reasons requiring closer monitoring for adverse effects. This fact was also brought out in other parts of the study namely when doctors were also asked whether they usually bring high risk patients started on NSAIDs back for review of progress and to assess for continued need of NSAID use. Whilst the majority of doctors (69.6%) replied that they usually review patients in cases of no improvement or in cases of patients experiencing adverse events, 19.6% responded that they do not review patients at all after NSAID initiation. This might reflect the fact that this study was distributed to community doctors working within government health centres which provides a walk-in service with duty allocation and thus makes such monitoring, patient review and follow up a challenge. This can encourage chronic NSAID use with a resulting increase in adverse side effects.

The majority of the GPs were able to mention most of the contraindications listed in the guidelines namely hypersensitivity (85.7%), asthma (96.4%), severe heart failure (73.2%), vascular disease including ischaemic heart disease, peripheral vascular disease, cerebrovascular disease at 67.9% and current treatment for gastrointestinal issues at 83.9%. However, a significant number of doctors failed to look out for severe skin reactions and angioedema (53.6%) which are listed as absolute contraindications within the guidelines, whilst the majority of GPs overlooked liver fibrosis and cirrhosis (23.2%), acute liver failure (21.4%) and severe hepatic impairment (33.9%). This might be due to the fact that, despite links between NSAID use and exacerbation of liver impairment being established, research is still ongoing on the subject, while acute symptomatic liver disease secondary to NSAID use is not a frequently encountered clinical problem when compared to respiratory and cardiovascular complications and therefore more awareness is required on the subject.

Although the level of risk of NSAIDs on conception is not yet known, the NICE guidelines recommend avoiding NSAID use based on advice from the Committee on Safety of Medicines (2006). In this study, only 26.8% of doctors

mentioned using caution in women trying to conceive and giving due consideration of possible impairment of female fertility. This might be due to the fact that whilst adverse renal, cardiovascular and gastrointestinal complications are well known, potential for NSAIDs to adversely affect ovulation has received much less attention overall, even though this potential complication has been described in the medical literature for multiple decades. Moreover the actual level of risk on conception is still unknown, as no large-scale, prospective controlled trials have yet proven a link between female infertility and NSAID or COX-2 inhibitor use.

The online questionnaire distributed also aimed to explore further knowledge amongst GPs with regards to key drug interactions with NSAIDs mentioned within the guidelines, in primary care. The majority of GPs (87.5%) rightfully mentioned concomitant anticoagulant use such as warfarin as being a key interaction. However, only 51.8% of GPs considered low-dose aspirin to be a key interaction. Of note is also the fact that the majority failed to mention looking out for possible interactions with anti-hypertensives (responses ranging between 44.6% for ACE inhibitors to 25% for loop diuretics) that might require dose adjustments of the anti-hypertensives or avoidance of concurrent use in certain cases (e.g. in cases of potassium-sparing diuretics). It also became evident that awareness on important interactions with drugs such as antidepressants, ciclosporin, methotrexate, quinolones and probenecid is also currently lacking. This emphasizes the importance of continued medical education and can be addressed in the form of evening medical updates outlining recently revised guidelines.

Whilst the majority of GPs successfully identified patients over 65 years of age and those with history of gastrointestinal (GI) problems as being patients at high risk of GI side effects thus requiring PPI prescription; the majority failed to identify hypertensives, people with chronic low back pain who are 45 years or older, patients with osteoarthritis or rheumatoid arthritis at any age and those with concomitant use of selective serotonin reuptake inhibitors (SSRIs). A study performed within GP practice in the UK by Hutchinson (2014) showed similar results. Moreover, awareness was also low for patients with cardiovascular, hepatic and renal impairment (17.9%), diabetics (19.6%), patients with concomitant aspirin and steroid use (41.1% and 58.9% respectively), patients with a history of heavy smoking or heavy alcohol use (26.8% and 41.1% respectively) and those with *Helicobacter pylori* infection (46.4%).



Doctors were also asked on the need for co-prescription of PPIs when prescribing different types of NSAIDs. The majority of GPs stated that they usually consider gastroprotection as an issue only when prescribing potent NSAIDs such as diclofenac (60.7%). Only 28.6% of GPs reported using gastroprotection with all kinds of NSAIDs used long term.

The NICE guidelines on NSAID prescription also describe specific licensed doses of proton pump inhibitors that should be used for gastroprotection for people who require continued NSAID treatment. Licensed PPIs and their doses mentioned in the guidelines include lansoprazole 15-30mg daily, omeprazole 20mg daily (the choice of 46.4% of GPs in this study), esomeprazole 20mg daily (used by 19.6% of GPs) and pantoprazole 20mg daily (used by 5.4% of GPs, though 3.6% reported also using a dose of 40mg of pantoprazole at occasions). Other responses in the study included use of omeprazole 40mg daily (19.6%) and of note was the fact that 3.6% of GPs chose ranitidine 150mg twice daily as their choice of gastroprotective agent, which is not licensed for gastroprotection during chronic NSAID use.

## LIMITATIONS

One limitation was the low response rate by GPs, the reasons for which could be various including lack of motivation and interest, the perception that participation may be time consuming and fear of lack of anonymity in the study with possible repercussions.

Results in this study were based on a questionnaire distributed amongst doctors working within the community and therefore only awareness of guidelines could be assessed. Data on actual implementation of such guidelines by GPs can only be gathered by assessing the actual practice records found within the various health centres for NSAID prescriptions. However, further addressing the objectives of this study by doing this was not possible in view of the high number and unpredictability of visits to the clinics, a lack of updated treatment records and furthermore, the lack of non-readily available lists of patient comorbidities within patient files. As a result, gathering information on treatment interactions and adverse effect monitoring was difficult. Participants' recall bias could have also occurred.

## CONCLUSION

This study showed that there is room for improvement in overall awareness on proper NSAID use and gastroprotection, identification of high risk patient

groups, drug interactions and choice and dose of gastroprotective agents. It is evident that there is need for further awareness on the importance of gastroprotection, need for more frequent monitoring of patients to prevent unnecessary chronic NSAID use and promoting coxib use over standard NSAIDs especially in high risk patients groups.

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## REFERENCES

- Bradybury, F., 2004. How important is the role of the physician in the correct use of a drug? An observational cohort study in general practice. *International Journal of Clinical Practice* [e-journal] 58, pp.27-32 Available through: Wiley Online Library [Accessed 5 December 2016].
- Chan, F., Suen, B., Wong, V., Wu, J. and Sung, J., 2007. Combination of a Cyclooxygenase (COX)-2 Selective NSAID and a Proton Pump Inhibitor for Prevention of Gastroduodenal Ulcers in Very High Risk Patients: A One-Year, Double-Blind, Randomized Trial. *Gastroenterology*, [e-journal] 134(4), p.A-19. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17499604> [Accessed 5 December 2016].
- Committee on Safety of Medicines, 2006. NSAIDs and infertility. *Current Problems in Pharmacovigilance*. [online] Available at: <https://assets.publishing.service.gov.uk/media/547307e5e5274a1301000030/con2023860.pdf> [Accessed 5 December 2016].
- Hutchinson S., 2014. An audit of the co-prescription of gastroprotective agents with non-steroidal anti-inflammatories in patients at high risk of gastrointestinal complications. *Warwick Medical School*. [online] Available at: [file:///C:/Users/user/Downloads/RCGP\\_Audit\\_NSAIDs%20\(2\).pdf](file:///C:/Users/user/Downloads/RCGP_Audit_NSAIDs%20(2).pdf) [Accessed 5 December 2016].
- Motola, D., Vaccheri, A., Silvani, M., Poluzzi, E., Bottoni, A., De Ponti, F. and Montanaro, N., 2004. Pattern of NSAID use in the Italian general population: a questionnaire-based survey. *European Journal of Clinical Pharmacology* [e-journal] 60(10), pp.731-738. Available through: PubMed Library <<https://www.ncbi.nlm.nih.gov/pubmed/15517225>> [Accessed 5 December 2016].
- Neal, M., 2012. *Medical Pharmacology at a Glance*. 1st ed. Chichester: Wiley-Blackwell Publishing.
- NHS Specialist Pharmacy Services, 2014. *Community pharmacy Non-Steroidal Anti-Inflammatory Drug Safety Audit 2014 National data from PharmOutcomes* [online]. Available at: [https://www.sps.nhs.uk/wp-content/uploads/2015/01/Community\\_pharmacy\\_Non-Steroidal\\_Anti-Inflammatory\\_Drug\\_safety\\_audit.pdf](https://www.sps.nhs.uk/wp-content/uploads/2015/01/Community_pharmacy_Non-Steroidal_Anti-Inflammatory_Drug_safety_audit.pdf) [Accessed 21 Mar 2017].
- NICE Guidelines NSAID Prescribing Issues, 2015. [online] Available at: <https://cks.nice.org.uk/nsaids-prescribing-issues> [Accessed 5 December 2016].
- North-Lewis, P., 2008. *Drugs and the liver*. London: Pharmaceutical Press
- Scheiman, J., Yeomans, N., Talley, N., Vakil, N., Chan, F., Tulassay, Z., Rainoldi, J., Szczepanski, L., Ung, K., Kleczkowski, D., Ahlbom, H., Naesdal, J. and Hawkey, C., 2006. Prevention of Ulcers by Esomeprazole in At-Risk Patients Using Non-Selective NSAIDs and COX-2 Inhibitors. *The American Journal of Gastroenterology* [online] 101(4), pp.701-710. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16494585> [Accessed 5 December 2016].
- Sostres, C., Gargallo, C., Arroyo, M. and Lanas, A. 2010. Adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs, aspirin and coxibs) on upper gastrointestinal tract. *Best Practice & Research Clinical Gastroenterology* [online] 24(2), pp.121-132. Available at: [http://www.bpgastro.com/article/S1521-6918\(09\)00158-9/fulltext](http://www.bpgastro.com/article/S1521-6918(09)00158-9/fulltext) [Accessed 5 December 2016].

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