

## **NSAIDs and Renal Impairment: Deprescribing Chronic NSAID use in General Practice**

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### **Abstract**

#### ***Aim***

NSAIDs are high-risk medicines that can commonly cause adverse renal effects. Recent evidence suggests a rise in the number of patients with acute and chronic renal disease. The aim of this audit is to determine our de-prescribing rate of chronic NSAID use in an Irish general practice.

#### ***Methods***

We reviewed NSAID-containing drug prescriptions that were issued over a three month period in 2018. A description analysis was performed to ascertain for the frequency and type of NSAIDs prescribed. An educational session was delivered to clinicians to encourage de-prescribing of NSAIDs if deemed clinically appropriate.

#### ***Results***

Fifty-one NSAID-containing prescriptions were identified. Thirty-six (71%) patients, who were prescribed a regular NSAID, were aged between 71-85 years. Meloxicam was used the most (31%), whilst the preferred NSAIDs (naproxen and ibuprofen) were used least (18%). A 37% improvement in de-prescribing of chronic NSAIDs was achieved upon re-auditing.

#### ***Conclusion***

NSAIDs are commonly implicated in inappropriate prescribing. Clinicians are encouraged to practice de-prescribing at every opportunity. Recent evidence suggests that pharmacy-led educational interventions can further assist de-prescribing of inappropriate medicines. Thus, a close collaboration between physicians and pharmacists is encouraged to further maximise quality of prescribing and patient care.

## Introduction

Inappropriate prescribing of high-risk medications remains prevalent in primary care. This represented 51% cases in 2015 compared with 45% in 2012<sup>1</sup>. Non-steroidal anti-inflammatory drugs (NSAIDs) are amongst the most frequent medications involved in high-risk prescribing<sup>2</sup> and their associated adverse drug reactions account for 30% of hospital admissions in the UK<sup>3</sup>.

Adverse renal effects are well-recognised complications of these medications and are often a reason for prescription error negligence claims<sup>4</sup>. Drug monitoring data from New Zealand<sup>5</sup> identified a large proportion (70%) of 119 reports of renal adverse reactions associated with NSAID use were considered serious adverse reactions, twelve of which were life-threatening and four cases were fatal, with the majority of these reports (74%) occurring in patients aged 50 years and over.

In Ireland<sup>6</sup>, chronic kidney disease (CKD) affects approximately 15% of adults in the Irish health system and, the numbers of patients developing renal failure have been increasing from 2,848 cases in 2005 to 4,440 in 2017, representing a growth of 56% in the number of patients requiring treatment. Recent research<sup>7</sup> has found a substantial rise in the cases of acute kidney injury (AKI), which may be responsible for the increase in cases of CKD. From 2005 to 2014, the overall rate of AKI was found to have increased by 126% (from 5.5% to 12.5%). Incidences increased across all healthcare settings and across all age groups, in particular in elderly patients. AKI stages 1, 2 and 3 occurred in 81.3%, 11.6% and 7.1% cases, respectively. Throughout the study period, stage 1 AKI was found to increase by 130% (from 4.4% to 10.1%) and stage 3 AKI by 76% (from 0.46% to 0.81%).

Exposure to NSAID use increases the risk of AKI by approximately 1.5-fold<sup>8</sup>. Furthermore, short-term use of these drugs appears to increase the risk of further developing end-stage renal disease (ESRD) requiring chronic dialysis treatment<sup>9</sup>. Patients with CKD and ESRD are at increased morbidity, in particular from cardiovascular disease and increased health care utilisation than in patients without renal failure<sup>10</sup>. Mortality rates are proportional with progressing stages of CKD. Adjusted all-cause mortality rates for Medicare patients aged 66 years and older by CKD stage in the United States revealed 79, 101, 182 deaths per 1,000 patient years for stages 1-2, stage 3 and stages 4-5, respectively in 2014<sup>11</sup>.

This prompts the need to review and to attempt minimise chronic NSAID prescribing in clinical practice, in particular in the elderly with evidence of renal impairment.

Currently, NICE guidance on non-steroid anti-inflammatory drugs recommends routinely reviewing the appropriateness of NSAID prescribing, especially in patients at high risk, and if necessary, ibuprofen or naproxen are the preferred NSAIDs to be used at the lowest dose and for the shortest duration of treatment necessary to control symptoms.

## Methods

We aim therefore to assess the frequency of chronic NSAID use, to determine the number of patients with CKD and on an NSAID and to perform de-prescribing of chronic use by reviewing our current repeat drug prescribing practices in patients 65 years and over.

Using Healthone medical software system, our first audit cycle aimed to obtain baseline data of patients aged 65 years and over from the 1<sup>st</sup> September 2018 to the 30<sup>th</sup> November 2018. The ATC M01 classification system code was used to identify these patients on non-steroidal anti-inflammatory drugs.

A descriptive data analysis was undertaken of the most up to date regular drug prescription during the study period to ascertain frequency and type of NSAIDs prescribed in Swan Park Surgery, a rural general practice in Monaghan with four doctors serving a population 9,395 patients, of whom 4,073 (43%) are public patients. Estimated GFR levels were obtained by reviewing the patients' latest laboratory results.

Results were subsequently disseminated to all prescribing clinicians at a practice meeting, aimed at increasing awareness of the adverse effects of long-term NSAID use. It was thus agreed upon to review the ongoing appropriateness of chronic NSAID use and to attempt de-prescribe if clinically deemed appropriate.

A re-audit of these patients' drug prescription was performed on the 19<sup>th</sup> April 2019, to identify the number of patients whose NSAID was subsequently discontinued or alternatively changed to a preferred NSAID.

## **Results**

Among patients aged 65 years and older, a total of 51 prescriptions containing an NSAID<sub>7</sub> were identified in this audit. Thirty two (63%) patients receiving an NSAID were female and 19 (37%) were male patients. The majority (71%) of patients, who were prescribed an NSAID, were aged between 71-85 years (table 1). Meloxicam (31%) and etoricoxib (20%) were prescribed the most (table 2). Naproxen was used in nine (18%) patients, whilst ibuprofen was not prescribed to any patients (table 2).

The majority (61%) of patients had mild stage 2 CKD (eGFR 60-89ml/min). Nine (18%) had moderate stage 3 CKD (eGFR 30-44ml/min), of whom three (33%) were in stage 3b CKD (eGFR 30-44ml/min). No NSAIDs were prescribed in stage 4 (eGFR 15-29ml/min) or 5 CKD (eGFR <15ml/min) (table 3).

Forty-eight of the 51 patients were re-issued their repeat prescription at the time of our re-audit, approximately three months later. Sixteen (33%) of these patients were no longer on a regular NSAID. Two patients had theirs changed to a preferred NSAID – naproxen. Of the 35 patients who had their NSAIDs continued, one (3%) had their NSAID subsequently deleted from their regular prescription list. This represents a 37% de-prescribing rate of NSAID use.

Of the nine patients with stage 3 CKD, five (56%) had their NSAIDs discontinued; two (33%) of the six patients with stage 3a CKD and two of the three (67%) patients with stage 3b CKD.

**Table 1:** Number of patients using NSAIDs by age group.

Age group	Number of patients
65-70 years	11 (22%)
71-85 years	36 (71%)
86-90 years	4 (8%)

**Table 2:** Frequency of NSAID use by NSAID drug type.

NSAID	Number of patients
Ibuprofen	0 (0%)
Ketoprofen	1 (2%)
Dexketoprofen	1 (2%)
Naproxen	9 (18%)
Meloxicam	16 (31%)
Diclofenac	6 (12%)
Aceclofenac	2 (4%)
Celecoxib	6 (12%)
Etoricoxib	10 (20%)

**Table 3:** Number of patients using NSAIDs by CKD stage.

CKD stage (GFR stage, ml/min)	Number of patients
1: >90	10 (20%)
2: 60-89	31 (61%)33%
3a: 45-59	6 (12%)
3b: 30-44	3 (6%)
4: 15-29	0 (0%)
5: <15	0 (0%)

## Discussion

NSAIDs are high-risk medicines, which are continued to be prescribed in elderly patients. Our audit shows that, of the 51 NSAID-containing prescriptions of patients aged  $\geq 65$  years, the majority of these were issued to those aged between 71 and 85 years (71%). Meloxicam was used the most (31%), whilst the preferred NSAIDs, naproxen and ibuprofen, were less frequently prescribed (18% and 0%, respectively). Upon completion of our audit, we achieved an improvement of 37% in de-prescribing of chronic NSAID use following a brief clinician-based educational intervention.

NSAIDs are one of the most frequently used medicines for pain and inflammation. Diclofenac, ibuprofen and etoricoxib are amongst the top 100 most frequently prescribed medicines in Ireland and public expenditure for these drugs has exceeded over 5 million euros in 2017<sup>12</sup>.

Current evidence shows trends towards decreased prescribing of these high-risk medications<sup>13-14</sup>, whose side effect profiles have been well established. These include an increased risk of renal impairment but also of adverse cardiovascular, gastric and bleeding risks<sup>15</sup>. These risks are further aggravated by co-prescriptions with other potentially interacting medications. Concomitant use of antiplatelets, anticoagulants, SSRIs, corticosteroids and aldosterone antagonists increase the risk of gastrointestinal<sup>16</sup> and intracranial bleeding<sup>17</sup>. Co-prescriptions with ACE inhibitors, ARBs, diuretics increase the risk of renal impairment<sup>18</sup>.

At-risk populations such as the elderly are particularly vulnerable to these adverse effects<sup>19</sup>. This is further compounded by the increasing prevalence of polypharmacy in these patients. Recent studies show an increase from 17.8% in 1997 to 60.4% in 2012 among Irish patients aged  $\geq 65$  years<sup>20</sup>, and from 12% in 1991 to 49% in 2011 among UK elderly patients<sup>21</sup>.

Potentially inappropriate prescribing (PIP) in older people is currently well recognised<sup>22</sup>. A TILDA study published in 2014 found an overall prevalence of up to 14.6% among Irish adults aged  $\geq 65$  years. NSAIDs were identified as one of the most common examples of PIP, accounting for 5.8% of all PIP identified<sup>23</sup>.

Optimising drug therapy in older patients continues to be challenging, both in primary and secondary care. This can be demonstrated in a recent Irish study in 2018, which found that, among patients who had at least one hospital admission in a year, the risk of having any potentially inappropriate prescription was increased by 72% after their admission<sup>1</sup>.

Despite these challenges, clinician should endeavour to practice de-prescribing at every patient contact. Drug utilisation review tools<sup>22</sup> such as the STOPP (Screening Tool of Older Person's Prescriptions) and BEER's criteria are amongst some of the strategies to help optimise de-prescribing for clinicians.

This audit achieved a de-prescribing rate of 37% of chronic NSAID use, following a physician-based educational intervention. However, recent evidence from a randomised controlled trial in Canada in 2018, involving community pharmacists, found that pharmacy-led educational interventions to both patients and physicians had significantly increased discontinuation rates of inappropriate medications; by 43% over a six month period, compared to 12% of patients receiving usual care. NSAID use in this study was reduced by 57.6% after intervention compared to 21.7% in their control group<sup>24</sup>.

Community pharmacists can thus additionally play a vital role in helping optimise potentially inappropriate drug prescribing. This may be achieved through a close collaboration of both physicians and pharmacists to help improve quality of prescribing and patient care.

**Declaration of Conflicts of Interest:**

No conflicts of interest declared.

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