Editorials

The dangers of NSAIDs:

look both ways

Non-steroidal anti-inflammatory drugs (NSAIDs) in a blister pack. The active ingredient is diclofenac diethylammonium. Collection: Medical Photographic Library. Credit: Julie Reza, Wellcome Images, 2007.

> *"... deaths from NSAIDs remain very high: more deaths than from road traffic accidents and twice as many deaths as from asthma or cervical cancer."*

Preventable adverse drug reactions (ADRs) are responsible for 10% of hospital admissions in older people at a cost of around £800 million annually. Non-steroidal anti-inflammatory drugs (NSAIDs) are responsible for 30% of hospital admissions for ADRs, mainly due to bleeding, heart attack, stroke, and renal damage.[1] In primary care 6% of patients prescribed NSAIDs reconsulted their GP with a potential ADR over the next 2 months. Most of these ADRs are avoidable because vulnerable groups and drug interactions can be predicted. Given that over 15 million NSAID prescriptions were dispensed in England in 2014, even a low rate of ADRs translates into a major cumulation of harm. Despite contraindications and guidance for the use of NSAIDs, their use in high-risk groups remains substantial and there has been no overall reduction in volume of NSAID prescribing. Safety is a system-wide attribute; what more should be done?

HARMS OF NSAIDS

From the first day of use, all NSAIDs increase the risk of gastrointestinal (GI) bleeding, myocardial infarction, and stroke. NSAIDs reduce prostaglandin synthesis, with differences in the extent of inhibition of the enzymes COX-1 and COX-2. All NSAIDs increase both bleeding and cardiovascular disease (CVD) risk but selective COX-2 inhibitors are more likely to cause cardiovascular events, whereas less selective NSAIDs are more likely to cause GI bleeds. The risk of bleeding and of cardiovascular events is considerably higher in older people, of whom many take medicines known to interact with NSAIDs.

NSAIDs affect the cardiovascular, GI, renal, and respiratory systems. NSAIDs reduce the antiplatelet effect of aspirin and have a thrombogenic effect on platelet function. NSAIDs increase systolic blood pressure by 5 mmHg and increase fluid retention. In patients taking coxibs, diclofenac, and higher-dose ibuprofen, these effects cause an excess risk of 7–9 non-fatal and 2 fatal cardiovascular events per 1000 patients per year.[2] All NSAIDs double the risk of hospitalisation due to heart failure.

NSAID use in patients aged >65 years more than doubles the risk of acute kidney injury in the next 30 days.[3]

NSAIDs can precipitate bronchospasm and 5–10% of adult patients with asthma will have an acute deterioration in symptoms after taking NSAIDs.[4] NSAIDs are also associated with a rise in HbA1c in type 2 diabetes.

Comorbidity and polypharmacy increase with age, as does the incidence of chronic musculoskeletal conditions such as osteoarthritis, for which NSAIDs are often prescribed. NSAIDs increase the risk of hospitalisation in older people, and multiple comorbidities and polypharmacy compound the risk of CVD and bleeding events.

Bleeding is the better-known consequence with all types of NSAID use. Non-selective NSAIDs increase the risk of a GI bleed 4-fold, whereas COX-2 inhibitors increase this risk 3-fold. Co-prescription of NSAIDs with corticosteroids increases bleeding risk 12-fold, spironolactone 11-fold, and selective serotonin reuptake inhibitors (SSRIs) 7-fold.[5] GI bleeds while taking NSAIDs are more likely to be fatal, with a mortality of 21%, whereas in patients not taking NSAIDs it is 7%.[6]

Older people have a higher baseline risk of cardiovascular events, GI bleeds, and impaired renal function, all of which are further increased by NSAIDs. NSAID prescribing is common in this older population, with 9% of patients aged >70 years receiving a prescription for >3 months. Self-medication is also extensive and 30% of a general population sample in the Netherlands reported NSAID use within the preceding 4 weeks.[7]

The National Institute for Health and Care Excellence (NICE) defines high-risk patients as: aged >65 years; interacting medications (including 20% of patients >75 years); patients with diabetes, hypertension, cardiovascular disease, renal or liver impairment; patients with a history of peptic ulcer or GI bleeding; and those taking long term NSAIDs or maximum doses.

WHAT SHOULD A GP DO INSTEAD?

What should a GP do for common musculoskeletal and osteoarthritis pains? The simplest and most effective way to reduce risk from NSAIDs is to avoid their use in older people and prescribe an alternative whenever possible. NICE recommends paracetamol or a topical NSAID as first line for pain relief in older patients or the use of opioid analgesics. Where an NSAID cannot be avoided, naproxen together with a proton pump inhibitor (PPI) is the least worst option. However, even with a PPI, patients will remain at increased risk of cardiovascular and renal harm from NSAIDs including naproxen.

Evidence for superiority of NSAIDs over paracetamol as analgesia for patients with osteoarthritis is poor, with small trial numbers and poor design. Many patients report neither of these drugs provide adequate pain relief. NICE recommends paracetamol at the lowest effective doses as the treatment of choice for osteoarthritis in older people, stepping up to a weak opioid if needed. NSAIDs may be slightly more effective than placebo for the treatment of low back pain but at the cost of significantly more side effects. Paracetamol has not

"Systematic quality improvement initiatives are long overdue."

been shown to be effective in low back pain. NICE also recommends topical NSAIDs, which may reduce acute musculoskeletal pain or pain in hand and knee osteoarthritis. However, most trials were small, enrolling an average of 50 patients, and of short duration. Four trials examined pain relief with topical NSAIDs for up to 12 weeks, and most benefit occurred in the first 4 weeks.[8]

IS THIS GOOD ENOUGH?

But is this good enough? Despite the well-advertised harms of NSAIDs, underpinned by Medicines and Healthcare products Regulatory Agency (MHRA) warnings and contraindications for diclofenac and COX-2 use in CVD,[9] deaths from NSAIDs remain very high: more deaths than from road traffic accidents and twice as many deaths as from asthma or cervical cancer.[10] Although there has been some decrease in diclofenac and COX-2 use, the total number of prescriptions has changed very little over the past 10 years. In the US the 'Choosing Wisely' campaign has shown that, without further systematic support, clinicians may not respond adequately to warnings and guidance.[11] There is thus an urgent need to consider NSAID use in the wider context of safety. Safety is a system-wide attribute that has received far less attention in primary care than in hospital settings. Further system-wide methods are needed to ensure safer prescribing, with review of existing NSAID use and decision support for clinicians to look both ways — bleeding and CVD events — before prescribing.

A feasibility study conducted over four general practices in Scotland to improve prescribing safety in primary care identified patients prescribed both NSAIDs and antiplatelets. When their medication was reviewed by a GP, the prescription could be changed in one-third of cases.[12] The PINCER study using pharmacists also showed the effectiveness of systematic procedures to identify and reduce inappropriate prescribing.[13]

NSAIDs are readily available over the counter and patient education forms an essential part of any risk-reduction strategy with co-prescription of a proton pump inhibitor to patients >65 years or at high risk of GI complications.

IT systems using 'trigger tools' are capable of systematically identifying patients at older ages at high risk of bleeding and CVD to allow clinical review. Systematic quality improvement initiatives are long overdue. These should engage local stakeholders, disseminate guidance and education, provide IT support, and develop identifiable peer audit including financial incentives. They need to include patients, community pharmacists, and dentists, and align improvement programmes across primary and secondary care. The use of NSAIDs is long overdue for system-wide attention.

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Provenance
Commissioned; not externally peer reviewed.

DOI: 10.3399/bjgp16X684433

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