

# Current trends in the prescription of non-steroidal anti-inflammatory drugs: A Pharmacoepidemiological Review

Godfrey B.S. Iyalomhe<sup>1\*</sup>, Sarah I. Iyalomhe<sup>2</sup>, Folasade O. Enahoro<sup>3</sup> and Okhemukhokho Okhiai<sup>4</sup>

<sup>1</sup>Department of Pharmacology and Therapeutics, College of Medicine, Ambrose Alli University, Ekpoma, Nigeria.

<sup>2</sup>Department of Public Health and Primary Healthcare, Central Hospital, Auchi, Nigeria.

<sup>3</sup>Department of Community Medicine, College of Medicine, Ambrose Alli University, Ekpoma, Nigeria.

<sup>4</sup>Department of Nursing Sciences, College of Medicine, Ambrose Alli University, Ekpoma, Nigeria.

There has been considerable confusion and concern among some practitioners and patients with regard to the prescription, abuse and adverse effects caused by non-steroidal anti-inflammatory drugs (NSAIDs), particularly gastrointestinal (GI) irritation and hemorrhage. The aim of this pharmacoepidemiological review therefore is to highlight the current prescription guidelines and prescribing precautions to prevent potential adverse effects. A manual literature and internet (Google, Medline, Embase, HINARI, Cochcrane Database) search showed that NSAIDs are commonly used but have risks associated with them, including significant upper GI bleeding. The elderly, patients with a history of peptic ulcer disease (PUD) and those on anticoagulants are at high risk. Although Aspirin is cardioprotective, other NSAIDs can aggravate congestive cardiac failure (CHF) and hypertension, and are associated with adverse cardiovascular (CV) events such as myocardial infaration (MI) and atrial fibrillation or flutter. Hepatic damage from NSAIDs is rare but these agents should not be used in patients with cirrhosis to avoid bleeding and renal failure. Caution should be exercised when prescribing NSAIDs for patients with platelet dysfunction, those taking anticoagulants and immediately before surgery. Potential central nervous system (CNS) effects include aseptic meningitis, psychosis and tinnitus. Asthma may be induced or exacerbated by NSAIDs. Though NSAIDs are likely safe in pregnancy, they should be avoided at the first trimester and in the last 6-8 weeks of pregnancy to prevent spontaneous abortion and prolonged gestation. Ibuprofen, Indometacin and Naproxen are safe in breast feeding women. Public enlightenment and patient education about correct dosing and NSAID overdose, are imperative.

**Keywords:** Current trends, prescription, non-steroidal anti-inflammatory drugs, review.

## INTRODUCTION

NSAIDs are widely used to treat inflammation, pain and fever because they decrease prostaglandin synthesis through blockage of the cyclo-oxygenase (COX) enzyme. These drugs possess different chemical and clinical profiles but essentially exert the same therapeutic properties and are associated with similar adverse

effects. GI injuries, which range from dyspepsia to frank hemorrhage (hematemesis or melena) or perforation, are among the most common adverse drug reactions (ADRs) associated with the use of NSAIDs (Helen-Salmivaara et al., 2007; Risser et al., 2009; Lapeyre-Mestre et al., 2011; Dhabali et al., 2012; Lanan et al., 2012). Other important ADRs include skin reactions, renal complications, allergic reactions, CV complications, alteration in hepatic enzyme levels and rarely hepatopathies. Epidemiological studies have reported the incidence of acute liver injury to be 1-9 cases per 100 000 NSAID users (Garcia et al., 1997;

Mandel, 1999).

According to current recommendations (National Institute for Health and Clinical Excellence (NICE), 2001; European Medicine Agency, 2009; Risser et al., 2009). NSAIDs should be prescribed at the lowest effective dose and for the shortest time necessary to control symptoms. Moreover, other factors such as the overall safety profile of each drug (e.g. potential GI injury and other concerns) and individual risk factors must be considered for improved patient management. However, in Nigeria and in many developing countries, virtually all NSAIDs can be obtained over the counter (OTC) without medical prescription. Some Medicine Vendors and Patent Medicine Dealers recommend 3 or more different NSAIDs sometimes with the addition of a corticosteroid in a single dosage to their unwary customers. This treatment option which can be repeated as often as needed even the same day, is popularly known as "selection" and it is adjudged to be very effective, in spite of its predisposition to dangerous adverse effects (Helin-Salmivaara, 2007; Risser et al., 2009).

Differences in safety profiles between NSAIDs are a key discriminator for choosing between one NSAID and another, for not all NSAIDs have the same level of risk for inducing GI ADRs. First generation NSAIDs (e.g. Aspirin, Indometacin, Diclofenac, Ibuprofen, Piroxicam, Naproxen) are non-selective blockers of the activity of both COX-1 and COX-2. Second generation agents, the COX-2 inhibitors (e.g. Celecoxib, Rofecoxib, Valdecoxib), were developed with the aim of reducing the incidence of GI adverse effects by sparing the gastroprotective functions of COX-1 while still inhibiting inflammation (Bennet and Tuvares, 2001; Deviere, 2002). However, it became clear soon after their commercialization that the use of these COX-2 inhibitors (i.e. Rofecoxib and Valdecoxib) was associated with an increase in CV risk, leading to their withdrawal from the market (Clark et al., 2004; Lapeyre-Mestre et al., 2011). Recently, Bavry et al. (2011) as well as Trelle et al. (2011) reported that chronic NSAID use among hypertensive patients with coronary artery disease (CAD) was associated with an increase in CV events including atrial fibrillation. Consequently, the foregoing events have led to revision of the overall safety profile of all NSAIDs, particularly in regard to their renal and CV risk profile. Furthermore, a number of studies evaluating the GI tolerability of COX-2 inhibitors did not demonstrate a lower risk of upper or lower GI events (Solomon et al., 2008; Risser et al., 2009).

Several factors predispose a patient to developing different ADRs while receiving NSAIDs. For example, elderly patients (they have decrease renal function with lower creatinine clearance; decrease in total body water; lean body mass, serum albumin and pharmacokinetic parameters with the tendency of drug accumulation) or those with CV disorders, chronic renal disease, rheumatoid arthritis or chronic obstructive pulmonary disease, are at greater risk of CV ADRs (Bavry et al.,

2011; Trelle et al., 2011). Risk factors for GI complications, according to the NICE London, include age over 65 years, the use of corticosteroids, Aspirin or anticoagulants, serious co-morbidity or a history of upper GI events (NICE, 2001).

To date, there is little evidence to support differences in effectiveness particularly for pain treatment when comparing all NSAIDs (Mandel, 1999; Dhabali et al., 2012). How then does a physician select a particular NSAID for a patient? This review is aimed at proffering solution to the above question because it provides current guidelines for prescribing NSAIDs to meet therapeutic needs.

## CURRENT CLINICAL RECOMMENDATIONS

For proper prescription of NSAIDs, the healthcare professional must adhere to the following current clinical recommendations:

- For persons who have had an NSAID-associated ulcer, but who must take NSAIDs, prescribe a proton pump inhibitor (PPI) e.g. Lansoprazole, double-dose H<sub>2</sub> histamine receptor antagonist e.g. Ranitidine or Famotidine, or use Misoprostol with the NSAIDs. Celecoxib can also be used by itself. Misoprostol should not be used in women who might be pregnant (Rostorn et al., 2002; Chou et al., 2006; Lanas et al., 2012).
- When possible, NSAIDs should be avoided in persons with pre-existing renal disease, CHF or cirrhosis to prevent acute renal failure (Riley and Smith, 1999; Patino et al., 2003).
- Serum creatinine levels should be monitored after initiation of NSAID therapy in persons at risk of renal failure, and in those taking angiotensin converting enzyme inhibitors (ACEIs) and angiotensin AT<sub>1</sub> receptor blockers (ARBs) (Patino et al., 2003).
- NSAIDs and Aspirin should be avoided in persons taking anticoagulants. If concurrent NSAID and anticoagulant use is necessary, there should be proper monitoring and anticoagulant dosage adjustment as well as initiation of GI prophylaxis (Chou et al., 2006).
- Aspirin should be used for primary and secondary prevention of CAD, stroke, and some colorectal cancers. All non-selective NSAIDs inhibit platelet aggregation through inhibition of COX-1 and the thromboxane A<sub>2</sub> (TXA<sub>2</sub>) pathway. Aspirin is unique in this regard because it binds covalently and irreversibly to the COX-1 enzyme responsible for mediating platelet aggregation, and its action lasts for the lifetime of the platelet (8-12 days) (Burke et al., 2006).
- Ibuprofen, Indometacin and Naproxen are safe to use in breast feeding women (American Academy of Pediatrics Committee on Drugs, 1994).

## Prescribing precautions to prevent adverse effects

NSAIDs are associated with morbidity related to different body systems: GI, CV, hepatic, renal, hematologic, CNS and respiratory. There are also special considerations for children and pregnant or lactating women. Adverse effects from NSAIDs can occur at anytime while taking them (Rosenfield and Loose, 2010). However, there is some evidence to support increased incidence of adverse effects with increased duration and dosing of selective and non-selective NSAIDs. Research has not shown whether strategies aimed at reducing risk such as intermittent dosing or drug holidays, are effective (Rostorn et al., 2002; Chou et al., 2006; Brunton and Parker, 2008; Harvey and Champe, 2009). However, when prescribing NSAIDs, healthcare providers should take precautions based on the peculiarity of the drug and the patient's risk.

### Gastrointestinal

The one-year risk of serious GI bleeding from chronic NSAID use ranges from 1 in 2 100 adults younger than 45 to 1 in 110 adults older than 75, and the risk of death ranges from 1 in 12 353 to 1 in 647 adults, respectively (Blower et al., 1997). Eradication of *Helicobacter pylori* appears to only minimally decrease the rate of peptic ulcer recurrence. Epidemiological studies suggest that in many patients who combine either non-selective NSAIDs or COX-2 inhibitors with cardioprotective low-dose Aspirin, the likelihood of GI adverse events increases significantly over either class of NSAID alone (Blower et al., 1997; Barkin, 1998; Chan et al., 2002; Chou et al., 2006; Brunton and Parker, 2008). Therefore, clinical recommendations should be followed carefully because taking Misoprostol with an NSAID has been shown to prevent ulcer related bleeding complications and concurrent treatment with NSAIDs and PPIs or double-dose histamine H<sub>2</sub>-receptor blockers have been shown to decrease endoscopically diagnosed ulcers (Rostorn et al., 2002).

### Cardiovascular

Since all NSAIDs are known to have the potential to aggravate hypertension, CHF, edema as well as increase incidence of cardiac ischemic events, they should be avoided in patients with CHF and used with caution in hypertensive patients (mean blood pressure increase with NSAID use is 5 mmHg) (Chou et al., 2006; Risser et al., 2009).

### Hepatic

Although clinically significant hepatotoxicity associated

with NSAID use is rare in the general population, these drugs, particularly Sulindac and Diclofenac, should be used with caution in patients with impaired hepatic function to avoid deleterious effects such as bleeding and renal failure especially in cirrhotic patients (Riley and Smith, 1998, 1999; Chou et al., 2006).

### Renal

The renal system relies on the vasodilatory effects of prostaglandins produced primarily by COX-2. This dependence is more marked in patients with renal disease, CHF or cirrhosis. Therefore, avoid NSAIDs in the above patients and use with caution when they are administered concomitantly with medications that potentially decrease renal function such as ACEIs and beta blockers (BBs) (Blower et al., 1997; Riley and Smith, 1999; Patino et al., 2003; Chou et al., 2006). In fact, because of renal complications 2% of patients stop taking NSAIDs (Patino et al., 2003).

### Hematologic

Since NSAIDs have antiplatelet effects, they should be avoided in patients with pre-existing platelet defects or thrombocytopenia. For high risk patients who have had a recent MI or recent placement of a cardiac stent, Aspirin should be continued before and after surgery. For other patients at risk of CV events, continuation of Aspirin should be considered and used in the pre-operative period. If Aspirin is to be stopped preoperatively, it should be stopped 7-10 days before surgery. Other NSAIDs are withheld pre-operatively for 5 elimination half-lives of the drug. For example, Ibuprofen is stopped 2 days before surgery, Naproxen 2-3 days and Piroxicam 10 days. Aspirin is associated with a slightly increased rate of hemorrhagic stroke and overall mortality but the survival benefits in patients at high risk of CV or neurovascular events outweigh the risks. However, Aspirin should be avoided in those at low risk (less than 3% annual risk) of CV disease (He et al., 1998). Avoid combining NSAIDs with anticoagulants as this increases the risk of GI bleeding 3-6 times (Chou et al., 2006).

### CNS

NSAID-associated CNS complications are rare but effects such as tinnitus, psychosis and cognitive changes, aseptic meningitis, depression, confusion and dizziness may occur (Hoppman et al., 1991).

### Respiratory

NSAIDs and Aspirin should be used with caution in

patients with asthma, especially in those with nasal polyps or recurrent sinusitis. Prevalence of Aspirin-exacerbated respiratory disease is 0.07% in general population and up to 21% in adults with asthma (Gollapudi et al., 2004; Chou et al., 2006). This phenomenon arises because in the presence of Aspirin or NSAID challenge, there is inhibition of COX-1 and the shunting of arachidonic acid down the leukotriene pathway (Jenkins et al., 2004; Knowles et al., 2007).

## Pregnancy and lactation

Although NSAIDs are not known to be teratogenic in humans, animal models indicate that NSAIDs can block blastocyst implantation; hence, women actively trying to conceive should avoid these medications (Ostensen, 1996). Nevertheless, NSAID use is generally considered safe in pregnancy as long as it is in low doses, is intermittent, and is discontinued 6-8 weeks before term (Nelson and Ostensen, 1997). Recently, however, Nakhair-Pour et al. (2011) who scrutinized medical records of 4 705 Canadian women, reported that gestational exposure to any type or dosage of non-Aspirin NSAIDs may increase the risk of spontaneous abortion and therefore advised that the drugs should be used with caution during pregnancy. Low-dose Aspirin (avoid large doses because of antiplatelet effects on mother and fetus) is generally considered safe for use throughout pregnancy (James et al., 2008).

## CONCLUSION

There has been considerable publicity in both lay and medical literature on the abuse and side effects caused by NSAIDs, a situation that begs the question "Which patients do we treat with NSAIDs and which do we not?" The answer lies on the NSAID risk versus benefit ratio which we can only demonstrate in an individual patient by trial and error. In other words, there is no best NSAID for all patients but 1 or 2 best NSAIDs for a specific patient (Furst et al., 2009). Used correctly and carefully, NSAIDs are among the most effective and least toxic drugs because most patients do excellently well on them with remote risk of serious ADRs. Public enlightenment on drug use and patient education on adherence and storage in childproof containers to prevent NSAID accidental overdosage (particularly among children) are imperative.

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