Epidemiology and **Public Health** Impact of **NSAID** Use

Authored by Koddus Ali

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a class of medications widely used for their analgesic, antipyretic, and anti-inflammatory properties. The primary mechanism through which NSAIDs exert their effects is the inhibition of cyclooxygenase (COX) enzymes, specifically COX-1 and COX-2. COX-1 is constitutively expressed in most tissues and is responsible for the production of prostaglandins that protect the gastric mucosa and maintain renal blood flow, while COX-2 is inducible and primarily involved in the inflammatory response (Sokołowska et al., 2022; Nunes et al., 2011). By inhibiting these enzymes, NSAIDs reduce the synthesis of prostaglandins, leading to decreased inflammation, pain relief, and fever reduction (Mizushima, 2010; Osafo et al., 2017).

The common uses of NSAIDs include the management of pain associated with conditions such as arthritis, menstrual cramps, and headaches, as well as the treatment of inflammatory disorders like rheumatoid arthritis and osteoarthritis (Meek et al., 2010; Kusunoki et al., 2008). Additionally, NSAIDs are often employed in the management of acute injuries and postoperative pain due to their effective analgesic properties (F et al., 2020; Miranda et al., 2019). Beyond their traditional uses, emerging research has explored the potential chemopreventive effects of NSAIDs in various cancers, particularly gastrointestinal cancers, due to their ability to modulate inflammatory pathways (Ayub & Islam, 2015; Ba et al., 2001).

Studying the epidemiology of NSAID use is significant for public health for several reasons. First, NSAIDs are among the most commonly used medications worldwide, with millions of prescriptions and over-the-counter (OTC) sales occurring annually (Duong et al., 2014). Understanding usage patterns can help identify populations at risk for adverse effects, such as gastrointestinal bleeding, cardiovascular events, and renal impairment, which are associated with prolonged NSAID use (Meek et al., 2010; Pereira-Leite et al., 2020). Furthermore, epidemiological studies can elucidate the relationship between NSAID use and chronic diseases, including their potential role in the prevention or exacerbation of conditions like Alzheimer's disease (Ba et al., 2001; Díaz-González et al., 1995).

Globally, the scope of NSAID usage varies significantly, influenced by factors such as healthcare access, cultural practices, and regulatory environments. In developed countries, NSAIDs are frequently available OTC, leading to widespread self-medication practices (Duong et al., 2014). Conversely, in developing regions, access to NSAIDs may be limited, resulting in underutilisation for pain management (Duong et al., 2014). Patterns of use also differ based on demographic factors, including age and sex, with older adults often being prescribed NSAIDs for chronic pain management (Meek et al., 2010).

The associated risks of NSAID use are a critical concern for public health. Long-term NSAID consumption has been linked to serious gastrointestinal complications, including ulcers and bleeding, particularly in individuals with pre-existing risk factors such as advanced age or concurrent use of anticoagulants (Sokołowska et al., 2022; Pereira-Leite et al., 2020). Additionally, certain NSAIDs, particularly COX-2 selective inhibitors, have been associated with an

increased risk of cardiovascular events, prompting regulatory scrutiny and recommendations for careful patient selection (Meek et al., 2010; F et al., 2020).

Public health implications of NSAID use extend beyond individual health risks; they encompass broader societal impacts, including healthcare costs associated with managing NSAID-related complications. The economic burden of treating adverse effects can be substantial, necessitating a careful balance between the benefits of pain relief and the potential for harm (Meek et al., 2010; Pereira-Leite et al., 2020). Furthermore, the promotion of safer prescribing practices and the development of alternative pain management strategies are essential to mitigate risks associated with NSAID use (Meek et al., 2010; Ayub & Islam, 2015).

Patterns and Prevalence of NSAID Use

NSAIDs such as ibuprofen, naproxen, and diclofenac, are commonly utilised for their analgesic and anti-inflammatory properties. A comprehensive understanding of NSAID usage patterns reveals substantial regional and demographic variations, influenced by factors such as healthcare access, cultural attitudes towards medication, and socioeconomic status.

In Germany, a study indicated that approximately 17% to 23% of the adult population reported using prescription and (OTC) analgesics, which prominently include NSAIDs (Sarganas et al., 2015). This aligns with findings from France, where national health insurance claims data revealed that about 20% of the population utilised OTC NSAIDs (Sarganas et al., 2015). Furthermore, a population-based study in the United States highlighted that NSAIDs are among the most frequently used medications, particularly among older adults

who often have chronic pain conditions (Davis et al., 2017). The demographic profile of NSAID users shows that older adults, especially women of reproductive age, are more likely to use these medications, often for managing conditions like osteoarthritis and menstrual pain (Davis et al., 2017; Jahangiri et al., 2022).

Regional variations in NSAID usage can also be attributed to differences in healthcare regulations and access. For example, in Egypt, NSAID use among chronic kidney disease patients ranged from 8.9% to 69.2%, reflecting the impact of local healthcare practices and regulations on medication availability (ElHafeez et al., 2019). In contrast, studies in Spain reported a significant association between higher education levels and increased NSAID consumption, suggesting that socioeconomic factors play a crucial role in medication usage patterns (Gómez-Acebo et al., 2018). This is further supported by research indicating that individuals with higher income levels tend to have greater access to healthcare resources, including prescription medications, which may lead to increased NSAID use (Gómez-Acebo et al., 2018).

The trends in NSAID usage have evolved over time, particularly with the rise of OTC medications. The widespread availability of NSAIDs without prescriptions has led to increased self-medication practices, which can pose risks due to a lack of awareness about potential adverse effects (Roshi et al., 2017; Biskupiak et al., 2006). For instance, a study in Thailand found that many patients perceived NSAIDs as safe, despite the known risks of gastrointestinal complications and renal issues associated with their use (Roshi et al., 2017; Phueanpinit et al., 2016). This perception of safety may contribute to the high prevalence of NSAID use among populations that self-treat pain without consulting healthcare professionals.

Concerns regarding the safety of NSAIDs have prompted discussions about the differences between OTC and prescription NSAID use. Prescription NSAIDs are often associated with more severe side effects and are typically prescribed for chronic conditions, whereas OTC NSAIDs are commonly used for acute pain relief (Duong et al., 2014; Biskupiak et al., 2006). A study comparing usage patterns in France found that individuals purchased significantly less NSAID medication than what is typically prescribed in clinical settings, indicating a potential gap in understanding appropriate dosing and usage (Duong et al., 2014). Furthermore, the concurrent use of multiple NSAIDs is a common practice among patients, which can exacerbate the risk of adverse drug reactions (Phueanpinit et al., 2016; Biskupiak et al., 2006).

Socioeconomic factors significantly influence NSAID usage patterns, with disparities evident in access to healthcare and medication. In many low- and middle-income countries, the lack of stringent regulations on NSAID sales can lead to higher rates of self-medication and misuse (ElHafeez et al., 2019; Veena et al., 2022). Conversely, in higher-income countries, the availability of prescription NSAIDs is often accompanied by better patient education regarding their risks and benefits, potentially leading to more responsible usage (Biskupiak et al., 2006; Rahme et al., 2001).

Over the years, the demographic profile of NSAID users has shifted, with an increasing number of younger individuals engaging in self-medication practices. This trend is particularly concerning given the potential for misuse and the associated health risks, such as gastrointestinal bleeding and acute kidney injury (Griffin et al., 2000; Biskupiak et al., 2006). The elderly population remains a significant demographic for NSAID use, primarily due to the prevalence of

chronic pain conditions associated with aging (Davis et al., 2017; Jahangiri et al., 2022; Griffin et al., 2000).

Risk Factors and Adverse Effects

The gastrointestinal adverse effects of NSAIDs are well-documented, with evidence indicating that these medications can increase the risk of serious complications such as ulcers, bleeding, and perforation. It has been reported that the risk of gastrointestinal adverse effects is approximately 2.5 times higher in patients taking NSAIDs compared to those receiving a placebo, with all NSAIDs, including COX-2 inhibitors, being implicated in gastrointestinal harms (Machado et al., 2017). Furthermore, chronic NSAID therapy is associated with significant upper gastrointestinal complications, with endoscopic ulcers detected in up to 30% of regular users (Chen et al., 2006). The mechanism of NSAID-induced mucosal injury involves both direct toxicity and the inhibition of protective prostaglandins, leading to erosions and ulcerations in the gastric lining (Al-Taie et al., 2021).

In addition to gastrointestinal complications, NSAIDs pose notable cardiovascular risks. The use of these drugs has been linked to an increased incidence of cardiovascular events, including myocardial infarction and stroke. A meta-analysis indicated that traditional NSAIDs and selective COX-2 inhibitors both carry a risk of atherothrombosis, with the risk being dose-dependent (Kearney et al., 2006). Furthermore, observational studies have shown that a significant proportion of cardiovascular patients using NSAIDs experience complications, with one study reporting that 13% of such patients developed cardiovascular issues while on these medications (Sharma et al., 2019). The cardiovascular risks associated with NSAIDs are believed to stem from their effects on renal function

and blood pressure regulation, as well as their impact on platelet aggregation and vascular health (Großer et al., 2017).

Renal complications are another critical concern associated with NSAID use. These drugs can lead to acute kidney injury (AKI), particularly in vulnerable populations such as the elderly and those with pre-existing renal conditions. A systematic review highlighted that NSAID use is a significant risk factor for AKI, with the incidence of renal adverse effects increasing in patients with diabetes, heart failure, and chronic kidney disease (CKD) (Zhang et al., 2017). The renal adverse effects of NSAIDs can manifest as electrolyte imbalances, reduced glomerular filtration rate, and even nephritic syndrome or chronic renal failure in severe cases (Harirforoosh & Jamali, 2009). The mechanisms underlying these renal complications include reduced renal blood flow and glomerular filtration due to the inhibition of renal prostaglandins, which are essential for maintaining renal perfusion (Bindu et al., 2020).

High-risk groups for NSAID-related complications include the elderly, individuals with a history of peptic ulcers, those with cardiovascular disease, and patients with renal impairment. The elderly are particularly susceptible due to age-related physiological changes, polypharmacy, and the presence of comorbidities (Chen et al., 2006). Additionally, patients with a history of gastrointestinal bleeding or ulcers are at increased risk for NSAID-induced gastropathy, necessitating careful monitoring and potential co-therapy with gastroprotective agents (Lanas, 2006). Furthermore, individuals with cardiovascular comorbidities must be cautious, as the use of NSAIDs can exacerbate hypertension and increase the risk of heart failure (Szeto et al., 2020).

The public health burden of NSAID misuse and complications is substantial, impacting healthcare systems significantly. The economic implications of NSAID-related gastrointestinal complications alone are staggering, with estimates suggesting that these adverse events lead to over 100,000 hospitalisations annually in the United States, costing approximately $1.6 billion (Spiegel et al., 2005). Furthermore, the mortality associated with NSAID-induced gastrointestinal complications is alarming, with around 17,000 deaths reported each year (Spiegel et al., 2005). The burden extends beyond direct healthcare costs, as NSAID misuse can lead to increased morbidity and decreased quality of life for affected individuals, necessitating further medical interventions and resources.

Regulatory and Prescribing Practices

Guidelines for NSAID use are often established by national health organisations and professional societies, which emphasise the importance of considering patient-specific factors such as age, comorbidities, and concurrent medications when prescribing these agents. For instance, the American College of Rheumatology and the European League Against Rheumatism provide recommendations that highlight the need for careful patient assessment prior to initiating NSAID therapy, particularly in populations at risk for adverse effects, such as the elderly and those with pre-existing cardiovascular or gastrointestinal conditions (Bloom et al., 2019; Plantinga et al., 2011).

In many healthcare systems, NSAIDs can be obtained both by prescription and OTC, which complicates the management of their use. The availability of NSAIDs without a prescription can lead to self-medication, where patients may not fully understand the risks associated with these medications. Studies have shown that self-

medication with NSAIDs is prevalent, particularly in populations experiencing acute pain, such as musculoskeletal complaints, where individuals often resort to OTC options without professional guidance (Nunes et al., 2016; Majumdar et al., 2020). This self-medication can result in adverse events, including gastrointestinal bleeding and renal impairment, particularly in vulnerable populations (Bedene et al., 2022; Alhouzani et al., 2020).

The challenges associated with OTC availability of NSAIDs are multifaceted. One significant issue is the lack of patient education regarding the potential side effects and contraindications of these medications. Research indicates that many patients perceive NSAIDs as safe due to their OTC status, which can lead to inappropriate use and increased risk of complications (Arain et al., 2019; Mehboob et al., 2022). Furthermore, the ease of access to these medications can result in higher consumption rates, particularly among adolescents and young adults, who may not be adequately informed about the risks involved (Barakat-Haddad & Siddiqua, 2017; Bahdailah, 2019).

Recent policy shifts have influenced prescribing patterns for NSAIDs, particularly in response to safety concerns raised by regulatory agencies. For example, following the withdrawal of rofecoxib (a COX-2 inhibitor) due to cardiovascular risks, there has been a notable shift towards prescribing non-selective NSAIDs, as evidenced by studies that track prescription trends over time (Dhananjay et al., 2013; Trelle et al., 2011). Additionally, guidelines have become more stringent regarding the use of NSAIDs in patients with chronic kidney disease, emphasising the need for healthcare providers to educate patients about the risks associated with NSAID use in this population (Plantinga et al., 2011).

Furthermore, the impact of media dissemination regarding the risks and benefits of NSAIDs has also shaped public perception and usage patterns. Awareness campaigns highlighting the potential for gastrointestinal bleeding and cardiovascular events have led to a decline in the inappropriate use of NSAIDs among certain populations (Zhou et al., 2013). However, despite these efforts, the prevalence of NSAID use remains high, particularly among individuals with chronic pain conditions, where self-management strategies often include OTC NSAIDs (Kovac et al., 2008; Zeinali et al., 2017).

Healthcare providers play a crucial role in mitigating the risks associated with NSAID use. By conducting thorough assessments and providing patient education, they can help ensure that NSAIDs are used safely and effectively. This includes discussing the importance of adhering to recommended dosages and recognising signs of adverse effects (Jang et al., 2019; Setiawan et al., 2022). Furthermore, the integration of pharmacists into the patient care team can enhance the management of NSAID therapy, as they can provide valuable counselling on the appropriate use of these medications and monitor for potential drug interactions (Calasan et al., 2011).

Gaps in Research and Future Directions

Despite the widespread use of NSAIDs for pain management and inflammatory conditions, significant knowledge gaps persist regarding their long-term effects on various populations. While gastrointestinal complications associated with NSAID use are well-documented, the long-term cardiovascular risks remain less understood. The withdrawal of COX-2 selective inhibitors like rofecoxib and valdecoxib highlighted the potential for serious

cardiovascular events; however, comprehensive long-term studies assessing the cumulative risks of both traditional and selective NSAIDs are still lacking (Conaghan, 2011; Sun et al., 2007).

Furthermore, regional data gaps exacerbate the issue of NSAID safety. The epidemiological data on NSAID-related adverse effects often stem from studies conducted in specific populations, primarily in high-income countries, which may not be generalisable to lower-income regions where different prescribing practices and patient demographics exist (Al-Saeed, 2011). For example, the prevalence of Helicobacter pylori infections, which can exacerbate NSAID-induced ulcers, varies significantly across regions, potentially influencing the risk profiles associated with NSAID use (Gisbert et al., 2001). Additionally, the interaction of NSAIDs with other medications, particularly in populations with high comorbidity rates, remains under-researched, leading to a lack of personalised guidelines for diverse patient groups (Bindu et al., 2020).

Emerging risks associated with NSAID use also warrant further investigation. Evidence suggests a potential link between NSAID use and neurodegenerative diseases, such as Alzheimer's disease, although the mechanisms remain poorly understood (Ba et al., 2001). Furthermore, the risk of myocardial infarction associated with NSAIDs, particularly in patients with pre-existing cardiovascular conditions, has been a topic of ongoing research, yet definitive conclusions are still elusive (Arfè et al., 2016; Chen & Ashcroft, 2007). The need for studies focusing on under-researched populations, such as the elderly and those with chronic illnesses, is critical to better understand the full spectrum of NSAID-related risks (Gargiulo et al., 2014).

In response to these challenges, innovations in the field of NSAID use are being developed, including advancements in personalised medicine and the exploration of safer alternatives. Personalised medicine approaches aim to adapt NSAID therapy based on individual patient profiles, including genetic predispositions to adverse drug reactions (Bindu et al., 2020). For instance, pharmacogenomic testing could help identify patients who are at a higher risk of experiencing severe gastrointestinal or cardiovascular events, allowing for more informed prescribing practices (Kearney et al., 2006).

Additionally, the development of safer alternatives to traditional NSAIDs is gaining traction. Research into novel analgesics that target specific pain pathways without the associated risks of NSAIDs is ongoing. For example, compounds that selectively inhibit COX-2 while sparing COX-1 are being explored to minimise gastrointestinal toxicity (Pepine & Gurbel, 2017). Furthermore, the use of adjunct therapies, such as proton pump inhibitors (PPIs) or misoprostol, in conjunction with NSAIDs has been shown to significantly reduce the risk of gastrointestinal complications (Howard et al., 2006; (Sun et al., 2007). These strategies highlight the importance of a multifaceted approach to managing pain while mitigating the risks associated with NSAID use.

Furthermore, the integration of digital health technologies into NSAID management is emerging as a promising avenue. Mobile health applications that track patient symptoms and medication adherence could provide valuable data to inform clinical decisions and enhance patient safety (Bindu et al., 2020). Such innovations could also facilitate the collection of real-time data on NSAID-

related adverse events, thereby addressing some of the regional data gaps that currently exist in NSAID epidemiology.

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