Non-opioid management of inflammation and musculoskeletal pain

Introduction
Pain is an emotional and debilitating experience for patients, regardless of whether it is caused by actual or potential damage to tissue nerves or joints. While acute pain may be seen as self-limiting, it is associated with tissue damage and resultant inflammation leading to peripheral sensitisation and central perception of pain.

Understanding the molecular mechanisms associated with inflammation and pain led to the development of non-steroidal anti-inflammatory drugs (NSAIDs). Newer concepts of inflammation are increasingly contributing to the development of novel anti-inflammatory and analgesic agents.

Over-prescription of opioids and awareness of their addictive properties and potential for abuse have resulted in a re-evaluation of pain management guidelines throughout the world. For example, tramadol, a weak opioid agonist with two mechanisms of action – binding to the µ-opioid receptor and inhibiting the reuptake of serotonin and norepinephrine – has been evaluated for addiction. Despite its weak opioid action which has made it a desirable analgesic, there is no evidence to support the concept that it is less addictive than any other opioid.1

Psychosocial factors are important contributors to both acute and chronic pain, and play a major role in how pain is experienced by individuals (Figure 1). This review explores the use and safety of NSAIDs in musculoskeletal conditions, with a specific focus on osteoarthritis and acute gout flare-ups.

KEY MESSAGES

- NSAIDs should be used at the lowest effective dose for the shortest time necessary to control symptoms, either intermittently or in longer cycles, rather than long term
- NSAIDs are known to pose a risk to the GI system, particularly non-selective NSAIDs (nsNSAIDs). Diclofenac has a lower risk of upper GI complications compared to naproxen and ibuprofen
- COX-2 inhibitor safety is similar to nsNSAIDs when the latter are used in combination with the gastroprotective proton pump inhibitors (PPIs) in respect of upper GI adverse events, GI symptoms and cardiovascular adverse events.

NSAIDs
Oral NSAIDs are universally recommended in international and national guidelines for patients presenting with moderate pain, pain of osteoarthritis or musculoskeletal pain, and those who are unresponsive to paracetamol.

It is important to note that international and local guidance recommend that in osteoporosis, osteoarthritis and musculoskeletal disease treatment, NSAIDs should be used at the lowest effective dose for the shortest time necessary to control symptoms, either intermittently or in longer cycles, rather than long term.

A recent update of the Cochrane review of 20112 provides, on the basis of systematic review, clinical guidance on the safety of nsNSAIDs (diclofenac, ibuprofen and naproxen) and the cyclooxygenase-2 (COX-2) inhibitors as a specific class of NSAIDs (celecoxib and rofecoxib).
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Mechanism of action of NSAIDs

These medications exert their anti-inflammatory and pain-relieving actions by inhibiting the COX enzymes, which are the first step in the conversion of arachidonic acid into various pro-inflammatory prostaglandins, thromboxanes and prosta
tacyclines. COX-1 and COX-2 are two iso
trans.

Figure 1. Pain explained

Painful stimuli or tissue damage activate specialised nerve cells (nociceptors), which in turn send pain signals to the spinal cord.

Figure 2. Actions of COX enzymes and mechanisms underlying drug-induced side effects of NSAIDs

NSAID side effects

<table>
<thead>
<tr>
<th>COX-1 inhibition</th>
<th>COX-2 &gt; COX-1 inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptic ulcers</td>
<td>Stroke</td>
</tr>
<tr>
<td>GI bleeding</td>
<td>Myocardial infarction</td>
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</table>

Pain signals enter the dorsal horn of the spinal cord, where some are increased or decreased by the interneuron before continuing up to the brain.

NSAIDs should be used at the lowest effective dose for the shortest time necessary to control symptoms, either intermittently or in longer cycles, rather than long term.

Thoughts, feelings and beliefs change the pain signals into individual’s experience of “pain.”

Certain parts of the brain generate signals that travel back down the spinal cord to reduce or increase pain signals at the interneuron.

Figure 2. Actions of COX enzymes and mechanisms underlying drug-induced side effects of NSAIDs

<table>
<thead>
<tr>
<th>Arachidonic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGE₂</td>
</tr>
<tr>
<td>GI mucosa</td>
</tr>
<tr>
<td>COX-1</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
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</tbody>
</table>

NSAIDs

- Peptic ulcers
- GI bleeding

COX inhibition

- Sodium & water retention
- Hypertension
- Haemodynamic acute kidney injury

COX-1 inhibition

- Vascular (COX-2: PGI₂)
- vasodilation
- inhibit platelet aggregation
- Platelet (COX-1: TXA₂)
- vasoconstriction

NSAId side effects

- Gastric protection
  - ↑ mucus secretion
  - ↑ bicarbonate
  - ↑ mucosal blood flow

COX-1 & 2

- Afferent arteriolar vasodilation (↑ GFR)
- ↑ Sodium & water excretion

COX-1 & 2

- Vascular (COX-2: PGI₂)
- vasodilation
- inhibit platelet aggregation
- Platelet (COX-1: TXA₂)
- vasoconstriction

- Peptic ulcers
- GI bleeding

COX-1 inhibition

- Vascular (COX-2: PGI₂)
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COX-1 & 2

- Vascular (COX-2: PGI₂)
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COX-1 & 2
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Safety of non-selective NSAIDs and COX-2 inhibitors

NSAIDs and risk of gastrointestinal adverse events

NSAIDs are known to pose a risk to the GI system, particularly non-selective NSAIDs. However, all NSAID regimens, including nsNSAIDs and COX-2 inhibitors, have been shown to increase upper GI complications (COX-2 inhibitors relative risk [RR]=1.81, 95% CI 1.17-2.81; p=0.0070; diclofenac’s RR=1.89, 95% CI 1.16-3.09; p=0.0106; ibuprofen’s RR=3.97, 95% CI 2.22-7.10; p<0.0001; and naproxen’s RR=4.22, 95% CI 2.71-6.56, p<0.0001). Diclofenac has a lower risk of upper GI complications compared to naproxen and ibuprofen.

A meta-analysis of six randomised clinical trials with a total of 6 219 patients has shown that COX-2 inhibitors safety is similar to nsNSAIDs when used in combination with the gastroprotective proton pump inhibitors (PPIs) in respect of upper GI adverse events, GI symptoms and cardiovascular adverse events. There was no difference in upper GI adverse events between COX-2 inhibitors and nsNSAIDs with concurrent use of PPIs (RR=0.61, 95% CI 0.34-1.09) (Figure 2). There was also no significant difference in GI symptoms (RR=1.10, 95% CI 0.88-1.39) and cardiovascular adverse events (RR=1.67, 95% CI 0.78-3.59) between the two groups, although there was some heterogeneity among the included studies (p=0.0003, I²=79%).

NSAIDs and risk of cardiovascular events

Cardiovascular risk exists for all nsNSAIDs and COX-2 inhibitors, in particular rofecoxib. Real-world use of oral NSAIDs has led to a clinical practice guideline for primary care practice (Table 1).

<table>
<thead>
<tr>
<th>Table 1. Practice points in the use of nsNSAIDs and COX-2 inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• All NSAIDs have the potential to induce adverse events through their actions on the COX-1 and COX-2 enzymes, including gastrointestinal ulcers and bleeding (COX-1), hypertension and kidney injury (COX-1 and COX-2), and cardiovascular events (myocardial infarction and stroke) (COX-2&gt;COX-1) (Figure 1)</td>
</tr>
<tr>
<td>• The rate of upper gastrointestinal complications (ulcers and bleeding) is increased with all NSAIDs; the upper gastrointestinal toxicity of nsNSAIDs may be reduced by concomitant use of PPIs to a level similar to that of COX-2-selective medications</td>
</tr>
<tr>
<td>• It would appear that cardiovascular risk may be drug specific and further research is needed to determine the extent of NSAID-induced cardiovascular adverse events for both the class and individual NSAIDs. Naproxen does not confer better cardiovascular outcomes than other NSAIDs</td>
</tr>
<tr>
<td>• In elderly patients with osteoarthritis taking analgesics, NSAIDs are associated with a lower risk of falls and fractures than opioids</td>
</tr>
<tr>
<td>• There is an increased risk of myocardial infarction with all NSAIDs, albeit small, which can occur within seven days of initiation of nsNSAIDs</td>
</tr>
<tr>
<td>• There is a higher risk of heart failure with all NSAIDs, probably as a result of sodium and water retention through inhibition of COX-driven prostaglandin synthesis</td>
</tr>
<tr>
<td>• There is an increased risk of stroke with certain nsNSAIDs that exhibit high COX-2 selectivity, namely diclofenac and meloxicam</td>
</tr>
<tr>
<td>• The risk of acute kidney injury is higher among NSAID users than the general population, and appears to be consistently high for all nsNSAIDs</td>
</tr>
</tbody>
</table>

Diclofenac has a lower risk of upper GI complications compared to naproxen and ibuprofen

In elderly patients with osteoarthritis taking analgesics, NSAIDs are associated with a lower risk of falls and fractures than opioids
Focus on gout

KEY MESSAGES

BEST CLINICAL PRACTICE

• Colchicine is a recommended option in acute gout if the attack began within the past 36 hours

• Select colchicine, NSAIDs or steroids on the basis of the patient’s profile (see guidelines from The American College of Rheumatology/European League Against Rheumatism (ACR/EULAR))

• Use combination therapy for intense pain and polyarticular presentation

• If the patient has been prescribed a urate-lowering therapy (ULT), e.g. allopurinol, ensure concomitant therapy with oral colchicine/low-dose NSAIDs as prophylaxis to prevent gout attacks during ULT therapy

• Patient education and adherence to medication are key to success.

What is gout?

Deposition of needle-like monosodium urate (MSU) crystals in the synovial space of joints causes an intense inflammatory response through activation of the innate immune system. It is the presence of these MSU crystals, detected by arthrocentesis and visualisation, which provides the definitive diagnosis.

How does gout present?

Gout has two clinical presentations: acute and chronic. Acute gout presents typically as monoarticular arthritis and is characterised by intense erythema, warmth, swelling and pain; with peak symptoms developing within 24 hours of onset. The most commonly affected joint is the big toe (metatarsophalangeal joint (MTP joint)), but other frequently affected joints include the insteps of the feet, heels, ankles and knees. Hips, shoulders and spine are almost never affected. Less commonly affected joints include the wrists, elbows and even small joints of the fingers. In between attacks, patients are asymptomatic.

Chronic gout is characterised by chronic arthritis with persistent low-grade inflammation, bone erosions and tophaceous deposits (tophi) in joints and soft tissue. This is a late feature and is associated with high levels of hyperuricaemia, as well as concomitant diuretic use or renal disease. From the time of the first attack, tophi generally take 10 years or more to develop, but can occur earlier in older patients with decreased creatinine clearance.

How to identify gout without joint aspiration or uric acid levels?

The ACR/EULAR classification is useful to identify gout reliably. It was initially developed to standardise enrolment of patients into clinical trials; and although not intended for use in the clinical setting, it provides a useful guide for practitioners who are unable to perform a joint aspiration (Table 2). Uric acid levels are also useful but are not definitive, as they may be normal in an acute attack or elevated in some individuals who do not present with gout.
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An online risk calculator can be accessed at https://www.mdcalc.com/acr-eular-gout-classification-criteria. A score of 8 or higher is definitive of gout.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Definitions/considerations</th>
<th>Score*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1 – Entry criteria</td>
<td>Must have ≥1 episode of swelling, pain or tenderness in a peripheral joint or bursa</td>
<td>Needed for entry into criteria</td>
</tr>
<tr>
<td>Step 2 – Sufficient for diagnosis</td>
<td>Tophus or MSU crystals present within symptomatic joint/bursa</td>
<td>Diagnostic of gout. If negative, use criteria below</td>
</tr>
<tr>
<td>Step 3 – Criteria with scoring (if sufficiency criterion above is not met)</td>
<td>Number of points</td>
<td></td>
</tr>
<tr>
<td>Pattern of joint/bursa involvement during episodes</td>
<td>Distribution of involvement</td>
<td>MTP1: 2 Ankle/midfoot without MTP1: 1 Any other joint: 0</td>
</tr>
<tr>
<td>Characteristics of symptomatic episodes</td>
<td>Presence of:</td>
<td>Three characteristics: 3 Two characteristics: 2 One characteristic: 1 No characteristics: 0</td>
</tr>
<tr>
<td>- Difficulty with walking or inability to use the joint</td>
<td></td>
<td></td>
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<tr>
<td>- Inability to bear touch/pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Erythema overlying the affected joint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time course</td>
<td>Typical episode with presence of &gt;2 of the following:</td>
<td>Recurrent typical episodes: 2 One typical episode: 1 No typical episodes: 0</td>
</tr>
<tr>
<td>- Time to maximal pain &lt;24h</td>
<td></td>
<td></td>
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<tr>
<td>- Resolution ≤14d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Complete resolution between episodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical evidence of tophus</td>
<td>Present or absent</td>
<td>Present: 4 Absent: 0</td>
</tr>
<tr>
<td>Serum urate cut-offs</td>
<td>&lt;4mg/dl</td>
<td>-4</td>
</tr>
<tr>
<td></td>
<td>4-6mg/dl</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>6-&lt;8mg/dl</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>8-&lt;10mg/dl</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>≥10mg/dl</td>
<td>4</td>
</tr>
<tr>
<td>Synovial fluid analysis</td>
<td>MSU negative or not performed (MSU positive is sufficient on its own)</td>
<td>Not performed: 0 MSU negative: -2</td>
</tr>
<tr>
<td>Imaging evidence of urate deposition</td>
<td>Ultrasound/dual energy computed tomography (DECT) - presence or absence</td>
<td>Present: 4 (either modality) Absent: 0</td>
</tr>
<tr>
<td></td>
<td>Gout-related erosions - presence or absence</td>
<td>Present: 4 Absent: 0</td>
</tr>
</tbody>
</table>

*A score of 8 or higher allows for gout classification.

An online risk calculator can be accessed at https://www.mdcalc.com/acr-eular-gout-classification-criteria. Synovial fluid positive for MSU crystals immediately classifies a patient as having gout.

**How to manage acute gout flares?**

Start treatment as soon as possible. Prompt treatment of acute gout flares works best. Consider the patient’s profile when treating gout flares (comorbidities, medication, contraindications) with colchicine, high-dosage NSAIDs, or with oral or intra-muscular corticosteroid treatment (Table 3). Intra-articular steroid injection, if feasible, is very effective if a single joint is affected. Combine lifestyle and dietary advice with the pharmacological treatment to ensure optimal gout management (Table 4).

Importantly the patient should be screened for comorbidities; hypertension, diabetes and dyslipidaemia should be considered. Chronic medication should be reviewed to ensure that there are no drugs that will cause hyperuricaemia.
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Table 3. Acute attack treatments

<table>
<thead>
<tr>
<th></th>
<th>Colchicine</th>
<th>NSAIDs</th>
<th>Oral/intramuscular corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>1mg; then 0.5mg as tolerated</td>
<td>e.g. diclofenac 100-150mg – take 2-3 tablets as divided dose (max 150mg); piroxicam 40mg/day for first two days, then 20mg daily</td>
<td>e.g. prednisolone 30-50mg daily; then taper</td>
<td></td>
</tr>
</tbody>
</table>

**Mechanism**
- Anti-crystallogenesis action
- Anti-inflammatory action
- Most effective within 36 hours of symptom onset
- Anti-inflammatory action
- Reduces activation of inflammatory cytokines

**Contraindications**
- Severe renal impairment
- Severe hepatic impairment
- Co-administration with a macrolide, except spiramycin
- Co-administration with pristinamycin
- Gastroesophageal pathology (active gastric and duodenal ulcer, peptic ulcer history or repeated haemorrhage)
- Bleeding history or digestive perforation with NSAIDs
- Anticoagulation/antiplatelet therapy
- Severe renal impairment
- Severe hepatic impairment
- Severe heart failure
- Pregnancy (>24 weeks of amenorrhoea)
- Known hypersensitivity
- Systemic fungal infections
- Avoid in diabetes
- Caution in hypertension, hypothyroidism and tuberculosis

**Preferred therapy**
- In patients with cardiovascular comorbidities
- In patients with moderate renal impairment
- In patients with renal disease

**Consider**
Combination therapy in more severe cases with intense pain and multiple joint presentation

**Common adverse events**
- Gastrointestinal effects: diarrhoea, nausea, vomiting
- Gastrointestinal effects: risk of severe digestive complications (bleeding, ulcers, perforation)
- Cardiovascular toxicity
- Cutaneous manifestations (rash, exfoliative dermatitis, Stevens-Johnson and Lyell syndromes)
- Increased appetite, weight gain, sudden mood swings, muscle weakness and blurred vision

**At initiation, provide gastrointestinal protection?**
No
Yes, in case of risk factors
No, only necessary for long-term high-dose steroid treatment
Start colchicine treatment as soon as possible. Prompt treatment of acute gout flares works best.

Table 4. Risk factors for gout and lifestyle modifications11

<table>
<thead>
<tr>
<th>Modifiable risk factors</th>
<th>Non-modifiable risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Obesity</td>
<td>• Men older than 30 years</td>
</tr>
<tr>
<td>• Diet</td>
<td>• Women older than 50 years</td>
</tr>
<tr>
<td>- Rich in purines (e.g. organ meats)</td>
<td>• History of urolithiasis</td>
</tr>
<tr>
<td>- Excessive alcohol intake (males: &gt;2 drinks/day; females: &gt;1 drink/day)</td>
<td>• Renal dysfunction</td>
</tr>
<tr>
<td>- Large intake of high-fructose corn syrup</td>
<td></td>
</tr>
<tr>
<td>• Comorbid conditions: diabetes, dyslipidaemia, hypertension, smoking</td>
<td></td>
</tr>
<tr>
<td>• Medications that can increase uric acid levels and risk of gout attack (e.g. loop diuretics, niacin, cyclosporine, tacrolimus)</td>
<td></td>
</tr>
</tbody>
</table>

Lifestyle modifications

| • Regular exercise to promote weight loss if applicable    |
| • Balanced diet                                           |
|   - Avoid large, fatty meals and diets rich in meat and seafood |
| • Avoid excessive alcohol intake                           |
| • Control of comorbid conditions                           |

Dosage instructions for colchicine in acute gout

Oral colchicine is as effective as NSAIDs, with low-dose colchicine showing a similar tolerability profile to placebo.12 The optimal colchicine regimen is 0.5-1.0mg spread over the day and not to exceed 1.0mg (one tablet) per administration. A loading dose of 1.0mg colchicine at the outset of therapy can then be followed 12 hours later with a prophylactic dosing of 0.5mg up to 2-3 times daily. Dosage should be adjusted according to tolerance and reduced in cases of diarrhoea (Figure 3).

Figure 3. Guidance for managing gout flares

- Intake of 0.5 to 1mg to be spread over the day, not exceeding 1mg colchicine (1 tablet) per administration
- Adjust the dosage according to efficacy and tolerance
- Always reduce the dosage in cases of diarrhoea

Maximum dosage of 3mg (1mg three times per day) possible during the first day of treatment only in case of late gout flares management (>36h).

Figure 3. Guidance for managing gout flares
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References

Click on reference to access the scientific article

1. Wardhan R, Chelly J. Recent advances in acute pain management: understanding the mechanisms of acute pain, the prescription of opioids, and the role of multimodal pain therapy. *Pain* 2017; 6: 2065. Published online 2017 Nov 29. DOI: 10.12688/11000research.12286.1

This CPD accredited programme was written for deNovo Medica by Julia Aalbers B.Sc (Hons) Pharmacology. Reviewed by Dr S Salduker (Durban Pain Clinic)

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