

# Non-steroidal Anti-inflammatory Agents – Benefits and New Developments for Cancer Pain

a report by

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Pain is one of the complications of cancer that patients most fear, and its multifactorial aetiology makes it one of the most challenging conditions to treat.<sup>1</sup> A systematic review of epidemiological studies on cancer pain published between 1982 and 2001 revealed cancer pain prevalence rates of at least 14%.<sup>2</sup> A more recent systematic review identified prevalence rates of cancer pain in as many as one-third of patients after curative treatment and two-thirds of patients undergoing treatment regardless of the stage of disease. The wide variation in published prevalence rates is due to heterogeneity of the populations studied, diverse settings, site of primary cancer and stage and methodology used to ascertain prevalence.<sup>1</sup>

A multimodal approach to the treatment of cancer pain that deploys both pharmacological and non-pharmacological methods may be beneficial, particularly in more challenging cases. However, pharmacological management is usually the first-line therapeutic approach. Non-steroidal anti-inflammatory agents (NSAIDs) have long been part of the analgesic pharmacopoeia for cancer patients in mild to moderate pain.<sup>3</sup> The World Health Organization's (WHO's) method for cancer pain relief is a widely disseminated and clinically useful tool for managing pain in patients with cancer. Several large case series have demonstrated that adequate analgesia is achievable in the majority of patients treated according to these guidelines. The use of NSAIDs is advocated for mild to moderate cancer pain or step 1 of the WHO analgesic ladder.<sup>4</sup> NSAIDs also provide additional analgesic benefit when combined with opioids for moderate to severe cancer pain (steps 2 and 3 of the analgesic ladder).<sup>5</sup> NSAIDs have also been recommended for cancer-related bone pain.<sup>6,7</sup>

This article surveys the current role of NSAIDs in the management of cancer pain and elucidates newly recognised mechanisms that may provide a foundation for the next generation of NSAIDs for analgesia for cancer patients.

## Mechanism of Analgesic Effects

NSAIDs are a structurally diverse group of compounds known to prevent the formation of prostanoids (prostaglandins and thromboxane) from arachidonic acid through the inhibition of the enzyme cyclo-oxygenase (COX; see *Table 1*). COX has two isoenzymes: COX-1 is found ubiquitously in most tissues and produces prostaglandins and thromboxane, while COX-2 is located in certain tissues (brain, blood vessels and so on) and its expression increases during inflammation or fever. Emerging studies initially suggested the existence of at least one additional isozyme, COX-3, but this was subsequently found to be a variant of the COX-1 isoenzyme.<sup>8</sup> Prostanoids mediate various functions in the gastrointestinal, renovascular, pulmonary, central nervous, reproductive and immune systems.<sup>9</sup> Other mechanisms through which NSAIDs can produce analgesia are the inhibition of inflammatory mediator release from neutrophils and a central neuromodulatory effect probably mediated by NMDA receptors.<sup>10</sup> Central NMDA receptors activate the nitric oxide system, which causes the release of prostaglandins.<sup>5</sup>

Due to the non-selective action of traditional NSAIDs in inhibiting both COX-1 and COX-2, their use is associated with several adverse effects. The most common of these unwanted side effects are bleeding complications due to platelet aggregation inhibition, NSAID gastropathy and renal toxicity. Judicious use of NSAIDs is warranted when treating at-risk populations such as the elderly or patients with existing renal dysfunction, blood dyscrasias, previous peptic ulcers and those on corticosteroids.<sup>5</sup> NSAID-induced gastric toxicity is one of the most common adverse effects and is directly related to COX-1 inhibition. Various NSAIDs have differing degrees of selectivity towards COX-1 and COX-2 (see *Figure 1*). NSAIDs that inhibit both COX isoenzymes have potent anti-inflammatory action and significant gastrointestinal toxicity. COX-2 selectivity is associated with cardiovascular complications (heart failure, hypertension, stroke and myocardial infarction).<sup>11</sup>

## Non-steroidal Anti-inflammatory Agents and Cancer Pain

Adequate analgesia may be achieved in approximately 65–100% of patients treated with NSAIDs alone for the treatment of mild pain or step 1 of the WHO analgesic ladder.<sup>4</sup> If the WHO method for the treatment of cancer pain is implemented appropriately and adequately, it is estimated that 70–90% of cancer patients will attain adequate analgesia.<sup>4,14</sup> A recent systematic review identifying studies



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validating the WHO’s analgesic ladder from 1982 to 2004 concluded that 45–100% of cancer patients will attain sufficient analgesia. Heterogeneity across studies in methodology and interventions used precluded performing a meta-analysis.<sup>4</sup> Despite these promising numbers, there is a lack of strong evidence-based data validating the specific sequence of steps in the WHO ladder for cancer pain management.<sup>4,14</sup> Eisenberg et al. have argued that the second step may not be optimal, particularly in patients with rapidly escalating pain that needs to be brought under control quickly with strong opioids. They also point out that the invasive analgesic therapies available in many developed countries for patients with moderate to severe pain can provide greatest benefit when started early.<sup>15</sup> The literature provides little guidance on the use of one particular NSAID versus another for cancer pain. NSAIDs as a group were found to be significantly more effective than placebo in the management of cancer pain.<sup>3,6,16</sup> A meta-analysis was not performed due to differences in methodology.<sup>6</sup> There is limited evidence on the efficacy and safety of NSAIDs for long-term use in cancer pain. However, clinical data prove the utility of NSAIDs for the treatment of mild cancer pain and its short-term management.<sup>3,4</sup>

NSAIDs may also be used as an adjuvant with opioids for the treatment of moderate to severe cancer pain. This approach decreases total opioid consumption and hence the unwanted adverse effects associated with opioid use. The opioid-sparing effect of NSAIDs has been shown in the cancer pain literature<sup>17</sup> as well as in other contexts such as acute post-operative pain. Potential limitations to this approach are the known ceiling effect upon analgesic efficacy with increasing dose and adverse effects associated with long-term NSAID use.<sup>18</sup>

Owing to the key role of prostaglandins in the inflammatory cascade, NSAIDs are also indicated for pain associated with inflammation. Cancer-related bone pain is partly due to increased prostaglandin production, although other mediators such as endothelin are now being recognised. Bone pain in cancer may present as chronic background pain (‘tonic’ component) or acute ‘incident’ pain related to movement (‘phasic’ component).<sup>7</sup> Although most clinicians advocate the use of NSAIDs for cancer-induced bone pain, there are limited robust clinical data for their use as monotherapy.<sup>7</sup> COX-2 inhibitors may potentially play a role in the treatment of cancer-induced bone pain. Lumiracoxib and valdecoxib were shown to decrease background and movement-induced pain in an animal model of cancer-induced bone pain.<sup>19</sup>

Therefore, NSAIDs and coxibs are promising agents to augment and possibly allow dose reduction of a sustained-release opioid such as morphine administered for background bone pain with an immediate-release fentanyl or morphine preparation to relieve movement-related pain.<sup>7</sup> Combining two classes of agent for both the tonic and phasic components of cancer-related bone pain may obviate the unwanted adverse effects associated with reliance on a single type of agent.

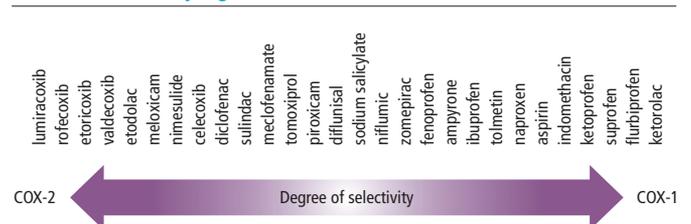
Apart from inflammation, cancer-induced bone pain also has nociceptive, neuropathic and ischaemic components. Therefore, the management of cancer-induced bone pain will continue to require several pharmacological modalities in the future, of which NSAIDs will remain important.<sup>7</sup>

**Table 1: Chemical Classification of Non-steroidal Anti-inflammatory Agents**

Para-aminophenol derivatives	Acetaminophen
Alkanones	Nabumetone
Salicyclic acid derivatives	Aspirin Sulfasalazine
Antranillic acids	Mefenamic acid Meclofenamic acid
Enolic acids	Oxicams (piroxicam, tenoxicam) Pyrazolidinediones (phenylbutazone, pxyphenanthrazone)
Indole and indene acetic acids	Indomethacin Sulindac Etodolac
Heteroaryl acetic acids	Tolmetin Diclofenac Ketorolac
Arylpropionic acids	Ibuprofen Naproxen Fluriprofen Ketoprofen Fenoprofen Oxaprozin
COX-2-selective inhibitors	Rofecoxib* Celecoxib Valdecoxib* Parecoxib Etoricoxib* Lumiracoxib*

\*Not available commercially.  
Adapted from Antman, 2005.<sup>12</sup>

**Figure 1: Relative Cyclo-oxygenase Selectivity of Non-steroidal Anti-inflammatory Agents**



Adapted from Warner, 2004.<sup>13</sup>

**Current Guidelines on the Use of Non-steroidal Anti-inflammatory Agents**

The American Heart Association (AHA) recently published a scientific statement on the use of NSAIDs for chronic pain. Cardiovascular risk during chronic therapy (in this case musculoskeletal disease) is minimised by using acetaminophen or aspirin at the lowest effective dose. The clinician must consider the risk–benefit balance when prescribing this class of drug. For patients with diminished hepatic glutathione content due to starvation or hepatic insufficiency from metastases, caution should be used when prescribing acetaminophen, since the toxic dose will be diminished.<sup>20</sup> For patients at a high risk of cardiovascular disease, selective COX-2 inhibitors must be used only as a last resort, using the lowest dose and shortest duration possible. More data are needed to resolve the issue of the cardiovascular safety of other types of NSAIDs.<sup>11</sup> Caution must be used when applying these guidelines to patients with cancer pain, in whom the nature of pain may be different.

The 2008 National Comprehensive Cancer Network (NCCN) Guidelines for Adult Cancer Pain advocate a therapeutic trial of NSAIDs for mild pain associated with inflammation and bone pain without oncological emergency. NSAIDs are to be used in caution in patients at high risk of renal, gastrointestinal or cardiac toxicities. Chemotherapeutic agents may aggravate the adverse effects associated with anti-inflammatory therapy.<sup>21</sup> The above guidelines emphasise an individualised therapeutic approach, with careful consideration of the patient's co-morbidities, concomitant medications and risk factors for NSAID-induced adverse events.

### **Future Targets/Novel Indications for Non-steroidal Anti-inflammatory Agents**

Advances in the understanding of pain pathways and mechanisms of actions of NSAIDs at the molecular level have opened new avenues for drug development. The following approaches are promising alternatives to the traditional NSAIDs.

#### **Nitric Oxide-releasing Non-steroidal Anti-inflammatory Agents**

The soluble gas neurotransmitter nitric oxide has also been found to play a role in the protection of the gastric mucosa. It increases mucus and bicarbonate production and decreases neutrophil adherence to

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the endothelium, both of which are key events in the pathogenesis of NSAID-induced gastropathy. Apart from decreasing the unwanted effects of NSAIDs in the gastrointestinal system, nitric oxide-releasing non-steroidal anti-inflammatory agents (NO-NSAIDs) have been found to potentiate the analgesic and anti-inflammatory effects of NSAIDs.<sup>22</sup> Nitric oxide has also been found to possess antineoplastic properties by stimulating cell necrosis and apoptosis and preventing angiogenesis. Pre-clinical studies have proved the utility of NO-NSAIDs as an analgesic and anticancer agent, and clinical trials on these indications are warranted.<sup>23</sup>

#### **Acid-sensing Ion Channel Blockers/VR1 Antagonists**

Tissue acidosis is a principal component in the pathophysiology of pain and inflammation. Nociceptive neurons express two main acid-sensing ion channels sensitive to extracellular pH changes: VR1 and the acid-sensing ion channel-3. NSAIDs have been found to prevent the inflammation-induced expression of acid-sensing ion channels. Detailed structure–activity analysis of such actions could potentially yield new targets for development of novel NSAIDs or other drugs.<sup>24,25</sup> This area of research could potentially be promising as the molecular mechanism of cancer-induced bone pain likely involves the release of protons, i.e. acidosis at the site of the tumour. Antagonists for these acid-sensitive channels are currently being studied.<sup>24</sup>

#### **Resolvins and Protectins**

Several local chemical mediators of inflammation are currently being investigated for their anti-inflammatory properties. Resolution-phase interaction products or 'resolvins' and protectins were recently discovered to possess anti-inflammatory, immunomodulatory and inflammation-resolving mechanisms.<sup>26</sup> These are lipid-derived families of chemical mediators. Resolvins and protectins both decrease the inflammatory response and injury induced by neutrophils.<sup>27</sup> The precise role for these novel agents in cancer pain is yet to be established.

#### **Nuclear Factor-kappa B Pathway**

Nuclear factor-kappa beta (NF- $\kappa$ b) is a group of transcription factors that are involved in the inflammatory response and apoptosis. There are several ways by which this group of proteins can be activated. The classic pathway results in the stimulation of the NF- $\kappa$ b essential modulators, I kinase alpha and I kinase beta, which are involved in inflammation and inhibition of apoptosis.

Pre-clinical studies have shown that NF may play a role in the pathophysiology of inflammatory hyperalgesia and neuropathic pain.<sup>28</sup> Several anti-inflammatory agents (aspirin, indomethacin, ibuprofen and sulindac) can inhibit NF stimulation. The concentration needed to block this pathway is beyond that needed to inhibit COX enzymes. Such blockade involves COX-independent mechanisms, although the specific pathway has not been fully elucidated.<sup>29</sup>

NF- $\kappa$ B may also play a role in cancer pathogenesis. This pro-inflammatory transcription factor is involved in cell proliferation, inflammation, cell metastases and angiogenesis – all aspects of tumorigenesis. Therefore, inhibition of this family of proteins is currently being investigated to modulate the inflammatory response in analgesia and its possible role in cancer pathogenesis.<sup>29</sup>

#### **KCNQ Channel Modulators**

Kv7 or the KCNQ channel modulators are a group of voltage gated K<sup>+</sup> channels that play a crucial role in neuronal hyperexcitability. The aetiology of neuropathic pain and epilepsy is attributable to neuronal hyperexcitability. Two anti-inflammatory agents (meclofenamic acid and diclofenac) have been found to activate the KCNQ2/Q3 K<sup>+</sup> currents causing hyperpolarisation of the resting membrane potential and delaying the outward K<sup>+</sup> current. Meclofenamic acid and diclofenac may have novel indications in the treatment of epilepsy and neuropathic pain.<sup>30,31</sup>

#### **Dual Inhibitors of Cyclo-oxygenase-2 and 5-lipo-oxygenase**

The enzymes COX-2 and 5-lipo-oxygenase are involved in the modification of arachidonic acid to produce pro-inflammatory molecules, prostanoids and leukotrienes. Drugs that could potentially inhibit both enzymes would possess more potent anti-inflammatory effects and spare the unwanted gastrointestinal adverse effects associated with selective COX-2 inhibition. These dual inhibitory compounds are promising alternatives to traditional NSAIDs.<sup>32,33</sup>

The dual inhibitor licofelone has successfully completed phase III clinical trials for osteoarthritis.<sup>34</sup> Studies on use of these agents for cancer pain are needed.

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## Possible Role of Non-steroidal Anti-inflammatory Agents in Cancer Prevention and Therapy

As well as their role as an analgesic, aspirin, COX-2 inhibitors and other NSAIDs have been explored as preventative therapy for cancer. It is well known that inflammation plays a role in cancer pathogenesis and, consequently, that NSAIDs may play a role in cancer prevention.

Non-steroidal anti-inflammatory drugs have been the mainstay of pharmacological management of mild cancer pain as adjuvants for moderate to severe cancer pain and bone pain.

Both observational and randomised interventional studies have shown that aspirin and other NSAIDs play a beneficial role in inhibiting the development of colorectal cancer from adenomatous polyps that overexpress COX-2 messenger RNA (mRNA).<sup>35-36</sup> The precise role of NSAIDs in the prevention of primary or recurrent gastric, oesophageal, breast and lung cancer is also being examined.<sup>35</sup> The exact dosage and duration of therapy are questions that remain to be answered.

In the US, the Agency for Healthcare Research and Quality and the American Cancer Society currently advise against the routine use of aspirin for the prevention of colorectal cancer in patients at an average risk of colorectal carcinoma due to the associated gastrointestinal side effects associated with its use. There are no clear guidelines on the use of aspirin for populations at a higher risk.<sup>37,38</sup>

## Conclusion

NSAIDs are a structurally diverse group of compounds with a shared mechanism of action: inhibition of the enzyme COX and consequent decrease in the formation of prostanoids and leukotrienes. NSAIDs have been the mainstay of pharmacological management of mild cancer pain as adjuvants for moderate to severe cancer pain and bone pain. The evidence on the long-term risks and benefits of NSAIDs in this context remains limited.<sup>3,6</sup> On the other hand, the opioid-sparing effect of NSAIDs is well-documented. Systematic reviews provide evidence to support the use of NSAIDs for short-term control of mild cancer pain.<sup>3,4,6</sup> The detrimental cardiovascular effects of COX-2 inhibitors have already been elucidated.<sup>11</sup> More research is needed on the efficacy and cardiovascular safety of traditional NSAIDs for cancer pain.

Advances in the knowledge of pain mechanisms and molecular pathways of mechanisms of actions of drugs have led to the discovery of promising analgesic agents that may, in time, come to replace NSAIDs. Such compounds may also have potential roles in cancer chemoprevention.<sup>35,36</sup>

The scientific community eagerly awaits the results of clinical trials. Currently, NSAIDs are an integral component of the multimodal management of cancer pain. NSAIDs have a direct effect on the inflammatory pathway and are inexpensive. The lowest possible dose needed to relieve the patient's pain is the appropriate dose to use. Frequent reassessment is essential for conscientious management of every patient. An individualised therapeutic approach to management of cancer pain is regarded as the standard of clinical practice. ■

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