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## PHARMACOLOGICAL MANAGEMENT OF PAIN IN PRIMARY CARE (1): NON-OPIOIDS

-  Pain is one of the commonest presenting symptoms in primary care
-  Inadequately controlled acute pain can lead to chronic pain syndromes
-  Pharmacotherapy should be individualised; combining opioid and non-opioid analgesics may provide greater pain relief and reduce the risk of adverse effects
-  Non-analgesic adjuvant therapies may be useful in the management of chronic pain

### INTRODUCTION

Pain may be defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"<sup>1</sup>. Pain is one of the commonest symptomatic reasons to seek a medical consultation. Chronic pain has been shown to be a major problem in the community; approximately 50% of patients self-reported chronic pain in a recent UK primary care survey<sup>2</sup>. Chronic pain is independently related to low self-rated health<sup>3</sup> - persons with persistent pain have been shown to be substantially more likely to have an anxiety or depressive disorder, compared with persons with no pain<sup>4</sup>. In addition, pain costs money. A US study estimated that > \$61 billion were lost each year either through absence or reduced performance in the workplace due to pain<sup>5</sup>, while the management of pain places a substantial economic burden on the state's healthcare system<sup>6</sup>. This is the first of 3 bulletins on pain reviewing the pharmacotherapy of pain in primary care. **This bulletin deals with the non-opioid treatment options (including adjuvant therapies) for the management of pain; subsequent bulletins will deal with use of opioids and the management of cancer pain.**

### PERCEPTION OF PAIN

Pain is perceived in the cerebral cortex. A painful stimulus, generated by an injury passes along several different types of sensory nerve fibres in the peripheral nervous system (PNS) to the spinal cord (so-called nociception) and from there to the cerebral cortex<sup>7</sup>. The initial painful stimulus is regarded as physiological as it warns the body of potential danger from the noxious stimulus, thus allowing it to remove itself from the area of the stimulus. With repeated stimulation, pain receptors become "sensitised" so that there can be a reduction in the threshold for activation, an increase in the response to a given stimulus or the appearance of spontaneous activity<sup>8</sup>.

The central nervous (CNS) pain sensory system is connected to all areas within the brain, including those that activate autonomic reflexes, emotional and motivational states and movement<sup>9</sup>. Endorphins, which are produced by the pituitary gland and hypothalamus, may also be released as a general response to physical stress, including pain. These factors are important in modulating sensory activity and producing an appropriate body response to the noxious stimulus. **Pharmacologic agents, used to treat pain, may act at peripheral level (e.g. non-steroidal anti-inflammatory drugs, NSAIDs) by inhibiting the production / release / activity of endogenous chemicals released at the site of tissue damage (such as histamine, kinins, prostaglandins, tumour necrosis factor) or may exert their action via an effect at CNS level (e.g. opioids).** Therefore it is possible to combine different therapies for optimum management.

It is important to remember that emotion may play an important role in the interpretation of pain signals and therefore in the perception of pain<sup>10</sup>. Huge variations (due to cultural, psychological or spiritual factors) may exist between responses to similar painful stimuli in different individuals. Moreover, one individual may exhibit different responses to the same stimulus, depending on these factors.

### CLASSIFICATION OF PAIN

Pain is a complex multidimensional symptom and appropriate management depends on the characteristics of the pain. Pain may be classified according to aetiology, duration or severity.

#### 1. Aetiology

Pain may be divided into **nociceptive** (perception of pain due to identifiable tissue damage) or **neuropathic** (pain initiated or caused by a primary lesion or dysfunction in either the PNS or CNS)<sup>11</sup>. **Table 1** outlines examples of each type of pain. Neuropathic pain is characterised by partial or complete somatosensory change in a specific innervation territory resulting in the paradoxical occurrence of pain and hypersensitivity phenomena within that zone<sup>12</sup>. The initiating factors for neuropathic pain are similar to those for chronic pain (see below) therefore the therapeutic approach may be similar.

**Table 1: Classification of pain by aetiology**<sup>10</sup>

Class	Type	Examples
Nociceptive	Somatic	skin lesions / tension headache
	Musculoskeletal	bone pain/arthritis
	Visceral	major organ pain (e.g. heart) colic
Neuropathic	Peripheral	diabetic peripheral neuropathy post-herpetic neuralgia
	Central	post-stroke pain multiple sclerosis pain

## 2. Duration

**Acute pain** may be defined as “the normal predicted physiological response to an adverse chemical, thermal or mechanical stimulus associated with surgery, trauma and acute illness”<sup>13</sup>. Acute pain is usually associated with an identifiable cause, and may be regarded as a symptom and not harmful in itself<sup>14</sup>. Acute pain typically lasts for hours - days and may be mild and even self-limiting. **However uncontrolled / inadequately controlled pain in the acute stages may eventually lead to chronic pain syndromes**<sup>15</sup>. Moreover, poorly controlled pain has been shown to modify recovery from surgery and other trauma, even in the unconscious patient<sup>10, 15</sup>.

**Chronic pain** may be defined as “continuous or intermittent pain or discomfort, which has persisted for at least 3 months and for which painkillers have been taken and treatment sought recently and frequently”<sup>3</sup>. **In practical terms this means pain that has persisted for longer than the time expected for healing**<sup>16</sup>. Several theories exist as to why patients develop chronic pain. These include: 1) sensitisation (as described above) occurring at both PNS and CNS levels, 2) demyelination resulting in interaction between bare neurons and 3) influences of one/more areas in the brain connected to the sensory system<sup>9</sup>. **Table 2** outlines the differences between acute and chronic pain.

**Table 2: Classification of pain by duration**<sup>14</sup>

Characteristic	Acute	Chronic
Duration	typically days	months +
Associated cause	present	commonly absent
Prognosis	predictable	unpredictable
Nerve conduction	rapid	slow
Associated problems	uncommon	depression, anxiety
Social sequelae	few / none	often profound
Treatment	primarily analgesics	usually multimodal required

## 3. Severity

Pain may be classified as **mild, moderate or severe**<sup>11</sup>; the severity of pain is important in terms of treatment options for the patient. However, the same stimulus may produce pain of differing severity in different individuals / the one individual; moreover, inadequately treated acute pain may result in a chronic pain syndrome, the severity of which cannot be linked to the degree of the original injury<sup>8,11</sup>.

# MANAGEMENT OF PAIN IN CLINICAL PRACTICE

Analgesics are the mainstay of treatment of acute pain; they may be accompanied by non-pharmacological measures (e.g. icepacks, heat, physiotherapy) depending on the cause and circumstance of the pain. It is not recommended to continue treatment without a diagnosis for the cause of the pain. The management of chronic pain may require the use of so-called adjuvant therapies in addition to / in place of analgesic agents. Non-pharmacological methods (physiotherapy, acupuncture and TENS (transcutaneous electronic nerve stimulation))<sup>17</sup> may also play a role on an individual basis.

The World Health Organisation devised an analgesic ladder for cancer pain<sup>18</sup>, which can be adapted for the management of pain in general. This recommends a stepwise approach from non-opioid to opioid therapies, titrated according to the individual patient needs (Figure 1). It recommends combining non-opioids with opioids of gradually increasing potency in order to achieve maximum pain relief, with the lowest possible opioid dose. Where combination therapy is indicated, the use of individual drugs rather than a combined formulation may be preferable as it enables separate titration of each drug<sup>19</sup>.

## ANALGESIC THERAPIES

**Paracetamol** is thought to exert its analgesic effect by blocking prostaglandin synthesis within the CNS; however it does not have any significant anti-inflammatory activity<sup>20</sup>. At doses of up to 4 g/day, given in divided doses, it is as effective as aspirin, with the same time-effect curve<sup>21</sup>. **It should be administered regularly in order to achieve its maximum benefit**; altering the dosage regimen (e.g. 1g in the morning, 500mg every 4 hours for 3 doses during the day and 1 g at bedtime) may improve pain control<sup>10</sup>. Although it does not have the gastrointestinal toxicity noted with NSAIDs, it can cause irreversible serious or fatal hepatic injury, following overdose, and should be used with caution (even at therapeutic dose levels) in patients with known hepatic dysfunction<sup>20</sup>.

**Use in acute pain:** the main uses of paracetamol are in the management of mild-moderate pain, such as acute soft tissue injury or osteoarthritis, toothache, headache, dysmenorrhoea or after minor surgery. **It is regarded as the analgesic of first choice for the young, the elderly and those on warfarin**<sup>19</sup>. It is also suitable for adjunctive treatment with other analgesics in the management of severe pain. Paracetamol is only minimally effective for visceral pain.

**Use in chronic pain:** paracetamol is recommended as the analgesic of first choice for ongoing management of mild-moderate joint pain in osteoarthritis (OA), either at full dose or on an "as required" basis, depending on the individual patient<sup>22</sup>. OA patients on chronic NSAID therapy may be transferred to paracetamol treatment with good results, both in terms of pain relief and patient satisfaction<sup>23</sup>. For other types of chronic pain, paracetamol may be used, either alone or in combination with an opioid, as part of the stepwise approach to pain management (**Figure 1**).

**Figure 1: World Health Organisation Analgesic Ladder**<sup>18</sup>

Step 1	Step 2	Step 3
Non-opioids (paracetamol / NSAIDs)	Weak opioids (e.g. codeine) in combination with non-opioids	Stronger opioids (e.g. morphine) in combination with non-opioids

**Non-steroidal anti-inflammatory drugs (NSAIDs)** are a group of drugs that includes aspirin, which inhibit prostaglandin synthesis by binding to the cyclo-oxygenase (COX-1 and COX-2) enzymes. This results in a reduction of pain-producing substances at the peripheral level of pain sensation. Although they also inhibit prostaglandins at CNS level, the impact of this on pain perception is not proven<sup>10</sup>.

**Pharmacology: NSAIDs have analgesic, antipyretic and anti-inflammatory properties.** They are effective in the management of acute pain of mild-moderate severity, especially nociceptive pain of somatic or musculoskeletal origin (**Table 1**). **NSAIDs may also be used in association with opioids to reduce the dosage requirement of opioids in severe pain**<sup>24</sup>. The analgesic effect of NSAIDs becomes apparent within a few hours / days but, depending on the NSAID, the full anti-inflammatory effect may take several weeks to develop<sup>15</sup>. NSAIDs can be administered orally or rectally, parenterally (IM) and topically. There has been debate about the usefulness of topical NSAIDs compared with other therapeutic alternatives<sup>19</sup>; however it is thought that they may provide relief of pain in some musculoskeletal conditions<sup>25</sup>. **All NSAIDs have a ceiling dose, above which the risk of adverse effects increases without an increase in analgesic effect**<sup>10</sup>.

**The use of NSAIDs is limited by toxicity**, the most significant of which is an increased risk of gastrointestinal (GI) toxicity, including peptic ulceration and GI haemorrhage. This is due to inhibition of the COX-1 isoenzyme and therefore, NSAIDs with selective COX-2 inhibitor properties were thought to be associated with a lower risk of serious upper GI toxicity, compared with non-selective NSAIDs<sup>26</sup>. However since these drugs have been shown to be associated with an increased risk of cardiovascular disease their usage has been restricted<sup>27</sup>: they are contraindicated in patients with existing cardiovascular disease, including heart failure. Moreover, the COX-2 inhibitors currently on the market in Ireland are not licensed as simple analgesics, but rather as anti-inflammatory agents. The risk of GI toxicity increases with increasing dosage and duration of use of NSAIDs - the risk of GI haemorrhage from a course of NSAIDs lasting less than 14 days is reported to be <0.5%<sup>10</sup>. The UK Committee on the Safety of Medicines has stated that **ibuprofen is associated with the lowest risk of GI toxicity among non-selective NSAIDs while naproxen, diclofenac, indometacin and ketoprofen are associated with intermediate risks**<sup>28</sup>. Topical NSAIDs are reported to be associated with a lower risk of GI toxicity<sup>19</sup>. The risk is increased in older people, smokers, patients with a history of peptic ulceration, or those taking medications such as warfarin, corticosteroids or aspirin<sup>25</sup>; **for at-risk patients, the use of concomitant proton pump inhibitors or misoprostol may be warranted**<sup>29</sup>. Because of their prostaglandin inhibition, NSAIDs can produce or exacerbate renal dysfunction and/or hypertension and/or heart failure. However a review of use of NSAIDs for postoperative pain relief showed small, temporary negative effects on healthy adult kidneys<sup>30</sup>. In addition, certain asthmatic patients are at risk of a hypersensitivity reaction with aspirin and other NSAIDs, resulting in severe bronchospasm<sup>30</sup>.

**Use in acute pain:** NSAIDs are especially suitable for mild-moderate musculoskeletal pain (i.e. originating from bone, joints or teeth, where the pain is mediated by prostaglandin) but may also be effective for headache and dysmenorrhoea. **It has been estimated that approximately 60% of individuals will respond to any NSAID and in those who fail to respond to one compound, another may be effective**<sup>25</sup>, therefore, the type of NSAID prescribed should be changed if it has not produced adequate relief of pain after a few days - one week's treatment. In cases of non-response to one NSAID, it may be reasonable to prescribe an NSAID from a different class, although individual response to any NSAID is not predictable<sup>31</sup>. **Table 3** outlines the most commonly prescribed NSAIDs on the GMS prescribing scheme in Ireland, according to class. A recent review showed that NSAIDs provided effective analgesia in acute renal colic, which was comparable to pethidine, but with a lower incidence of adverse events, especially vomiting<sup>32</sup>; however NSAIDs alone may not be sufficient to treat all types of acute visceral pain<sup>31</sup>. NSAIDs may be effectively combined with opioids to control severe pain; this combination therapy enables lower doses of each drug to be administered with improved patient safety<sup>24</sup>.

**Use in chronic pain:** NSAIDs are useful for painful exacerbations of chronic arthritic conditions (i.e. associated with inflammation<sup>22</sup>). However, the data to support use of oral NSAIDs for >6 weeks in the management of OA are lacking<sup>22,32</sup>. Moreover, topical NSAIDs have only been shown to be more effective than placebo for 2 weeks' treatment<sup>34</sup>. For other types of chronic pain, it is recommended that NSAIDs be tried initially as part of the stepwise approach to pain management (Figure 1). Since the Irish Medicines Board has recommended that all NSAIDs should be used at the lowest effective dose for the shortest time possible<sup>35</sup>, dosage regimens should be individually titrated and the drug discontinued if there is no relief of pain after a few weeks' treatment (i.e. when the maximum analgesic and anti-inflammatory effects have been achieved).

**Table 3: Chemical Classification of NSAIDs\*<sup>30</sup>**

Class	Drug Name	Oral Dosage Regimens	Cost (14 days)** Euro
Phenyl acetic acid	Diclofenac	100 - 150mg daily (divided doses)	6.44
Aryl Propionic acid	Ibuprofen	1.2 - 2.4 g daily (divided doses)	2.94
	Naproxen	0.5 - 1g daily (divided doses)	4.62
Sulfonanilide	Nimesulide	100mg twice daily	10.92
Anthranilic acid (fenamates)	Mefenamic acid	500mg three times daily	4.20
Oxicam	Meloxicam***	7.5 - 15mg daily	9.94
Coxibs	Celecoxib***	200 - 400mg daily (divided doses)	14.70
	Etoricoxib***	60 - 120mg daily	14.28

\*List includes the most commonly prescribed NSAIDs from the GMS database December 2005

\*\* Costs calculated, using defined / average daily doses, from the GMS database December 2005

\*\*\* not licensed as simple analgesics in Ireland

## ADJUVANT ANALGESIC THERAPIES

These are a diverse group of drugs, originally called "adjuvant" therapies because they were added on to opioid or other analgesic therapies for the management of pain<sup>36</sup>. Many were developed for other indications such as depression or epilepsy and although used, some are not licensed for analgesic indications. Characteristically these therapies do not provide immediate pain relief; rather their effects are noticeable only after days or weeks of therapy<sup>36</sup>. The main classes are anti-convulsants and anti-depressants.

**Anti-convulsants:** The group includes several chemically dissimilar drugs that are thought to exert their analgesic effects by interfering with various ion channels; this reduces neuronal firing and lessens pain sensation<sup>36</sup>.

**Use in Pain:** From the limited clinical data available in **acute pain**, there is no evidence of efficacy, hence their use is **not recommended**<sup>37,38</sup>. **Most of the data on their clinical use in chronic pain relates to neuropathic conditions** such as post-herpetic neuralgia, trigeminal neuralgia and painful diabetic neuropathy. Randomised controlled trials (RCTs) of 2-3 months'

duration have shown benefit in 35-50% of patients. However, these drugs have well documented toxicity profiles that may limit their usage, particularly in older people. Moreover, **none of these agents should be discontinued abruptly**, in case of rebound CNS effects, but rather they should be tapered off gradually, over a minimum of one week. In Ireland, carbamazepine, gabapentin and pregabalin are currently licensed for the management of various types of neuropathic pain. Other anti-convulsants such as phenytoin and lamotrigine have been used, but there are insufficient data to evaluate their potential role as adjuvant analgesic agents.

**Carbamazepine** is a benzodiazepine derivative, licensed for the symptomatic treatment of several neuropathic syndromes. It has been estimated that approximately one out of every two patients treated will achieve some relief of symptoms<sup>37</sup>, but almost one in four will experience toxicity. Adverse symptoms include somnolence, dizziness, ataxia and confusion, especially at higher doses in elderly patients. In addition, **carbamazepine is known to interact with many drugs because it is metabolised by the cytochrome P450 3A4 enzyme**, which metabolises many other drugs, such as verapamil, diltiazem, fluoxetine, and macrolide and azole anti-microbial agents<sup>39</sup>. The dosage should be titrated to the individual patient, starting at 100mg twice daily and gradually increasing to a usual dose of 200mg 3-4 times daily. Doses of up to 1600mg daily have been used.

**Gabapentin** is structurally related to the neurotransmitter gamma-aminobutyric acid (GABA) and is licensed for the treatment of neuropathic pain. A recent systematic review estimated that approximately one in four patients treated may achieve moderate or better improvement of pain, with as many experiencing minor adverse symptoms<sup>38</sup>. Studies have also shown improvements in mood, quality of life and interference with sleep<sup>40</sup>. Adverse effects reported include dizziness, somnolence, headache, GI symptoms and confusion. Drug-drug interactions do not pose a major practical problem with gabapentin. It is recommended to start dosing at 300mg on day 1, 300mg BD on day 2 and 300mg TDS on day 3; thereafter the dose may be increased up to a maximum of 3,600mg per day in three divided doses. **Gabapentin is excreted unchanged via the kidneys, therefore the dosage should be reduced in patients with impaired renal function**<sup>41</sup>.

**Pregabalin** is also structurally related to GABA, and is licensed for the treatment of peripheral neuropathic pain. Its efficacy and safety profiles appear to be similar to gabapentin<sup>42,43</sup>. The recommended starting dose is 150mg daily, taken in two or three divided doses. This may be increased incrementally every 3-7 days, according to patient response to a total daily dose of 600mg daily. **Pregabalin is also primarily excreted unchanged via the kidneys therefore the dosage should be reduced in patients with impaired renal function**<sup>42</sup>.

**Anti-depressants.** For many years anti-depressants have been used to manage **neuropathic pain**, often as treatment of first choice<sup>44</sup>. However, most of the drugs used are not licensed for such use.

**Pharmacology.** Data are available for tricyclic anti-depressants, primarily amitriptyline (currently not licensed in Ireland). The mechanism of action in the alleviation of neuropathic pain is unclear. However, it is known that the analgesia occurs earlier (usually within a few days) and at a lower dose than the onset of any anti-depressant effect, which may take up to 6 weeks to develop<sup>44</sup>. Doses of 10-25mg of amitriptyline, administered at night have been used, which may be increased to a total of 75mg daily, depending on patient response<sup>45</sup>. Studies have shown that approximately 50% of patients will achieve at least moderate pain relief while approximately one in four will experience at least moderate adverse effects<sup>43</sup>, including dizziness, tachycardia and anticholinergic effects<sup>46</sup>. Although the SSRIs have much better safety profiles compared with tricyclic agents in the management of depression, their efficacy in the management of chronic pain has not been adequately proven<sup>12</sup>.

**Duloxetine** (a combined serotonin and noradrenaline reuptake inhibitor) is licensed for the **management of diabetic peripheral neuropathic pain**. RCTs showed 50% pain reduction in 50% patients compared with 26% on placebo<sup>47</sup>. The recommended dose is 60mg daily but doses of up to 60mg twice daily have been used. Somnolence, nausea, headache and dizziness are the most commonly observed adverse reactions<sup>47</sup>.

**Practical advice on clinical use of adjuvant treatments.** There are insufficient direct comparative studies to determine which of the anti-convulsants should be considered as drug of first choice. Neither is it possible to determine if patients, failing treatment with one GABA analogue might respond to the other<sup>48</sup>. A systematic review of anti-depressants and anti-convulsants showed that both drug classes were equally effective in the management of diabetic neuropathy and post-herpetic neuralgia<sup>43</sup>. Therefore, the decision to use any of these agents, instead of or in association with other analgesic agents such as opioids, should be made according to the individual patient's circumstances and the expected toxicity profile of the drug. As the pathophysiology of neuropathic pain is dynamic, the earlier treatment is initiated, the greater the chance of success<sup>16</sup>. Therefore, it is recommended that treatment be initiated early on in the management of patients with neuropathic pain, such post-herpetic neuralgia.

## LOCALISED ANALGESIC THERAPIES

**Rubefacients**, such as capsaicin, act by counter-irritation. They may help to alleviate both superficial and deep-seated nociceptive and neuropathic pain by producing irritation of the overlying skin where they are rubbed<sup>25</sup>. However, many patients are unable to tolerate the associated burning sensation.

**Lignocaine 5% patches** have been tried with some success in patients with localised areas of neuropathic pain<sup>49</sup>. Patches are used for 12 hours on, with an "off" period of 12 hours. This results in minimal accumulation of drug, in patients with normal hepatic function. RCTs have shown significant improvements compared with placebo patches in patients with post herpetic neuralgia. These patches are currently not licensed in Ireland.

## SUMMARY

In recent years, great advances have been made in the understanding of the mechanisms that underlie pain, and in the need for individualised treatment of people who complain of pain<sup>1</sup>. It is recognised that individuals react differently to the same painful stimulus and therefore dosage should be individually titrated in the management of pain. The management of chronic pain syndromes should be tailored to the underlying condition, if known; treatment should involve a stepwise use of analgesic agents and/or adjunctive therapy as appropriate to the individual's needs and status. This should be combined with appropriate non-pharmacologic methods.

*References available on request.* Date prepared: May 2006

Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue. Prescribers are recommended to refer to the drug data sheet or summary of product characteristics (SPC), also available on [www.medicines.ie](http://www.medicines.ie) for specific information on drug use.

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