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REVIEW

# In search of an ideal analgesic for common acute pain☆

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**Summary** The choice of an oral analgesic is an important determinant in achieving effective pain relief. Properties of an 'ideal analgesic' required for the management of acute pain are discussed and current evidence for the suitability of available analgesics — acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) (such as ibuprofen), opioids and combination therapy — is reviewed. The hypothesis that an 'ideal analgesic' for acute pain should have a rapid onset of action, act over an extended period of time, reduce awareness of pain quickly and minimise interruption by pain, be well tolerated and produce analgesia over a wide range of pain types in different patient populations, is proposed herein. Currently available analgesics may fulfil only some of these characteristics and, because individual patient response also varies, the challenge is to define what constitutes an acceptable analgesic for a specific patient or pain type.

Various tools for measurement of each of these characteristics exist, but there is currently no single measure to determine the 'ideal analgesic' for a specific patient with a specific pain type that takes into account all the characteristics of an 'ideal analgesic' and provides an overall measure to quantify the quality of relief produced.


## Contents



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## 1. Introduction

Pain is 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage' [1]. Pain is subjective and its perception depends on the individual's psychological state [2—4]. Hence, anxiety [5] and depression [6] can elevate the perception of it. Pain has adverse effects on well-being and quality of life that may be far reaching, resulting in reduced physical and emotional function [7]. Pain interrupts, distracts and is difficult to disengage from and requires a coping strategy that rapidly and successfully moderates interruption by pain [8].

Chronic pain, associated with a chronic pathological process, is defined as pain that persists longer than the temporal course of natural healing and is associated with a particular type of injury or disease process [9]. Acute pain generally follows soft-tissue damage, infection and/or inflammation, and typically lasts less than 1-month—but in some instances it may last as long as 6 months. The duration of pain can also be much shorter, such as in the case of pain associated with dysmenorrhoea, common headache or migraine, sore throat or mild trauma, which typically lasts from a few hours to a few days; these are the most common types of acute pain seen in general practice, and account for the majority of analgesics prescribed [10—12]. Inadequate treatment of acute pain may lead to persistent and chronic pain [13], indicating the importance of managing acute pain quickly and effectively. Acute pain is generally managed with pharmacological agents. There are several therapeutic approaches to treating acute pain. Analgesics — including acetaminophen (paracetamol), non-steroidal anti-inflammatory drugs (NSAIDs), opioids and synthetic drugs with narcotic properties — target different components of the peripheral and central nervous system. Acetaminophen and NSAIDs are among the most widely prescribed analgesics. In 1995, there were 32 million prescriptions for non-opioid drugs (mainly acetaminophen and its combinations), 17 million for NSAIDs and 4 million for opioids in the UK [14].

Management of acute pain requires an analgesic that is effective and associated with few side effects. Appropriate therapy should offer a combination of efficacy and safety for each individual patient. The aim of this article is to discuss the properties of an 'ideal analgesic', required for the outpatient management of acute pain. It is hypothesised herein that an 'ideal analgesic' for acute pain should have rapid onset of action, act over an extended period of time, reduce awareness of pain quickly and minimise interruption by pain, be well tolerated, and produce analgesia over a wide range of pain types. Currently available analgesics are reviewed in light of their efficacy and safety data, and their suitability for the management of acute pain.

This review is not concerned by the issues of peri-operative relief of post-surgical pain using injectable analgesics; this is a highly specialised field, which is best addressed by anaesthesiologists, and where several promising approaches are being tested to reduce long-term opioid hyperalgesia. However, as soon as oral analgesia is possible, these products can again be considered. This paper also does not consider specific pain, such as migraine, that might benefit from specific drugs such as triptans. This review is not concerned either by the management of chronic pain, but only by the treatment of acute common pain as described above, that is usually alleviated by steps 1 or 2 analgesics according to the common WHO classification of analgesics.

## 2. Common analgesics for acute pain

### 2.1. Acetaminophen (paracetamol)

Acetaminophen is an analgesic and anti-pyretic that is commonly used for the relief of acute pain and fever. Its mode of action is not clear, but it has no known significant anti-inflammatory action [15,16]. Acetaminophen is thought to indirectly inhibit a variant of the cyclo-oxygenase (COX) enzyme; this is not COX-1 or -2 [16], and has been referred to as COX-3 [16,17], which is a centrally acting enzyme [17]. Although acetaminophen has been shown to

inhibit COX-3 in mice [18], but not in man [19], and an effect on COX-2 was demonstrated [20], the exact mechanism by which acetaminophen relieves pain remains uncertain [21].

Pharmacokinetic data show that acetaminophen is well absorbed orally, reaching peak concentrations within 1 h of oral administration [22]. Acetaminophen is well tolerated and effective in treating mild-to-moderate pain; however, intentional or accidental overdose with acetaminophen has been linked to severe hepatotoxicity, which can be fatal [23,24]. It is the primary cause of transplantations for acute liver failure in the United States [25].

A meta-analysis of 40 trials, including 4171 patients, demonstrated that acetaminophen 1000 mg had a number-needed-to-treat (NNT) of 4.6 for at least 50% pain relief compared with placebo [26]. The NNT with acetaminophen 600/650 mg was 5.3 [26]. In comparison with NSAIDs, acetaminophen is a slightly weaker analgesic, associated with <10 points on a 100-point visual analogue scale (VAS) [27,28]. A standard dose of 400 mg ibuprofen, the commonest over-the-counter (OTC) NSAID, was shown to be significantly more effective than the standard 1000 mg dose of acetaminophen in relieving acute dental pain [29,30].

## 2.2. NSAIDs

NSAIDs are commonly used for the control of acute and chronic pain, and are effective in patients with moderate-to-severe pain. They are inhibitors of the COX-1 and -2 enzymes, which catalyse the formation of the prostaglandins that mediate the process of inflammation. Evidence also suggests that they may have anti-nociceptive actions mediated through the endogenous opioid system [31—34]. The formation of prostaglandins in inflammation is mostly mediated by COX-2, which is inducible, whereas COX-1 is generally not thought to be inducible, and is associated with gastric resistance to aggression, the synthesis of thromboxane by platelets, and also to the transmission of painful stimuli, among many other actions.

NSAIDs are rapidly absorbed and metabolised by the liver. Ibuprofen was the first NSAID to be approved for OTC use. OTC doses of ibuprofen range from 200 to 1200 mg and up to 3600 mg for prescription doses. A review of ibuprofen pharmacokinetics shows that after a single oral dose of 400 mg of ibuprofen, the peak plasma concentration occurs within 1—2 h [35]. The safety profile of NSAIDs is related to the duration and intensity of COX (particularly COX-1) inhibition, i.e., pharmacological potency, pharmacokinetic parameters (such as elimination half-life) or tissue distribution, and therefore is dose- and duration-dependent [36].

NSAIDs are effective analgesics with no clinically important difference in efficacy among specific drugs [37]. NSAIDs have been shown to be more effective than acetaminophen for some types of pain and in many acute pain settings they provide analgesia equal to the usual starting doses of opioids [38]. Strong evidence supports the use of non-prescription NSAIDs for dysmenorrhoea and acute post-partum pain. In a meta-analysis of randomised controlled trials of analgesics for dysmenorrhoea, ibuprofen and naproxen were equally effective, and both were better than acetaminophen [39].

Of the NSAIDs, ibuprofen appeared to have the most favourable benefit—risk profile [39]. In patients undergoing oral surgery, ibuprofen 200 mg was comparable with naproxen 220 mg, and ibuprofen 400 mg was similar to ketoprofen 25 mg [40,41]. Furthermore, ibuprofen 400 mg has been shown to be as effective as aspirin 600 or 900 mg/day in models of moderate pain and more effective than aspirin or acetaminophen in more sensitive models such as dental pain [41].

Quantitative reviews of post-operative pain management have demonstrated that the NNT for one patient to achieve at least 50% pain relief is 2.7 for ibuprofen 400 mg and 4.6 for acetaminophen 1000 mg, both compared with placebo [42,43].

The duration of action of ibuprofen 400 mg is at least 6 h compared with 4—6 h for ibuprofen 200 mg or acetaminophen [29]. Time-effect curves have shown that ibuprofen 400 mg had a substantially greater peak effect and maintained this differential effect over acetaminophen 1000 mg from approximately 2 h following administration to the end of a 6-h observation period [29]. Moreover, in contrast to the sustained efficacy of ibuprofen at 6 h, acetaminophen was shown to be no more effective than placebo, suggesting that ibuprofen has a more prolonged duration of action [29]. Other comparative studies have demonstrated that ibuprofen 400 mg also provides greater pain relief than acetaminophen 1000 mg for different types of pain, including tension headache [44] and sore throat [45].

Aspirin is the prototype NSAID, which irreversibly acetylates COX-1 and COX-2 [46]. Aspirin is an effective analgesic for acute pain. A Cochrane review assessing 72 randomised clinical studies to assess the analgesic efficacy and adverse effects of a single dose of aspirin in acute pain (of moderate-to-severe intensity) found significant benefit with aspirin 600/650 mg, 1000 mg and 1200 mg, com-

pared with placebo [47]. However, aspirin was associated with significantly more drowsiness and gastric irritation than placebo [47].

Side effects tend to vary between the NSAIDs. Gastrointestinal (GI) side effects are encountered most frequently and present with considerable concern. Compared with non-use of NSAIDs, the adjusted relative risk for serious upper GI complications ranged from 3.13 for aspirin to 8.7 for piroxicam [48]. It is known that NSAIDs that have a short half-life and a rapid onset of action are usually considered to have a better safety profile, because they remain in the body for a limited period of time. Ibuprofen at low doses (800—1200 mg) was shown to be well tolerated, with a GI safety profile no different from placebo [49] and a lower risk of adverse events compared with other NSAIDs [50]. Even at prescribed and presumably equipotent doses, ibuprofen seems to be associated with a lower risk of GI complications compared with most other NSAIDs [36,48,51]. The adjusted relative risk of serious upper GI complications for ibuprofen was 2.22 [48]. Additionally, the incidence of GI adverse events associated with ibuprofen was shown to be similar to that of acetaminophen [52,53]. In a study by Moore et al., ibuprofen, 1200 mg/day, was shown to have an equivalent adverse event profile to acetaminophen 3 g/day and a better adverse event profile than aspirin 3 g/day [54]. Similar low-dose NSAIDs with short half-lives, such as diclofenac might have similar safety profiles [55].

The development of selective COX-2 inhibitors that inhibit COX-2 more than COX-1 by a factor of 7—40 [56] has shown favourable outcomes in terms of anti-inflammatory activity and less GI toxicity related to COX-1 inhibition, although concerns over cardiovascular (CV) risk continue to be addressed. Several studies have shown an association between selective COX-2 inhibition and increased risk of serious CV events [57—59], which led to the withdrawal of rofecoxib from the market. However, the relative risk of CV events with traditional NSAIDs has been shown to be low: 0.97, 1.06 and 1.07 for naproxen, piroxicam and ibuprofen, respectively [60]. The CV risk associated with traditional and selective NSAIDs seems to be related to dose and duration of use, and to the potency of COX-2 inhibition [61].

Selective inhibition of COX-2 may result in reduced analgesic efficacy because COX-1 is also involved in pain transmission [62—64]. This has resulted in higher dosages for analgesia than for anti-inflammatory effects. For example, the analgesic dose of rofecoxib was 50 mg, whereas the anti-inflammatory dose was only 25 mg. For celecoxib, the respective doses for inflammation and analgesia are 400 and 800 mg, respectively. This is in contrast to the non-selective NSAIDs, such as ibuprofen or diclofenac, where the analgesic dose is about half of the anti-inflammatory dose. The short-term use of low-dose NSAIDs for the management of acute pain is associated with only a very low risk of GI toxicity [54]. Because the main benefit of COX-2 selectivity is GI safety, these drugs have little advantage in the treatment of common pain—especially when considering price differences with traditional NSAIDs.

In addition, the situation of analgesia using COX-2-selective agents is currently obscured by the fact that several trials in this field seem to have been fraudulent, and the whole body of evidence needs to be re-examined [65].

## 2.3. Opioids

Opioids are used for the treatment of pain that is not responsive to other analgesics, including moderate-to-severe and neuropathic pain. They act through the spinal dorsla root ganglia and cerebral opioid receptor system. Drugs used orally for the treatment of mild-to-moderate pain include codeine, oxycodone, hydrocodone, There is little difference between these opioids in speed of onset and duration of effect; faster onset and longer effect may be achieved by changing the route of administration or formulation. Normal-release oral formulations take up to 1 hour to work, whereas sustained-release formulations may take 2—4 h [42]. The duration of action for these opioids is 4—6 h. Dextropropoxiphene, which had a longer half-life has recently been removed from the market.

The more powerful opiates (morphine, fentanyl, etc.) are used mostly in an anaesthetic context, or to treat chronic pain under strict supervision, because of a high potential for abuse and dependence.

The most commonly used opioid to treat common pain is codeine, which is a weak analgesic at the doses used. Codeine is effective against mild-to-moderate pain when combined with acetaminophen and NSAIDs [66,67]; however, on its own, it produces only a mild analgesic effect [68]. Another commonly used drug in the acute setting is tramadol, which has weak opioid activity and inhibits serotonine and noradrenaline reuptake. Tramadol appears to be less effective when compared with an acetaminophen/weak opiate combination or an NSAID.

In one meta-analysis, the administration of 60 mg of codeine produced only a 15% analgesic response in 1305 patients and this response did not differ from a placebo tablet (18% response

in >10,000 patients) [68]. In this same meta-analysis, tramadol produced dose-related analgesia at 50 mg (19% in 770 patients), 75 mg (32% of 563 patients), 100 mg (30% of 882 patients) and 150 mg (48% of 561 patients) [68]. In comparison, 200 mg of ibuprofen produced a 45% analgesic response in 1414 patients [68]. In another study, Turturro et al. compared oral tramadol (100 mg) with oral hydrocodone/acetaminophen (5/500 mg) for acute musculoskeletal pain secondary to minor trauma [69]. Sixty-two adult patients participated in the study. Tramadol provided inferior analgesia compared with the hydrocodone/acetaminophen combination, a difference that was clinically and statistically significant. Additional studies have shown that tramadol/acetaminophen combination tablets were similar in efficacy to other weak opiate/acetaminophen combinations and to NSAIDs [70]. High-end doses of tramadol (150 mg) were more efficacious than the other analgesic options but were also more likely to cause side effects (e.g., nausea, vomiting and dizziness) [71].

Opioid side effects are well known and include respiratory depression, nausea, sedation, euphoria or dysphoria, constipation and itching [72]. Although sedation and nausea tend to resolve over time as steady serum levels are obtained, such is not the case with constipation. As a rule, patients receiving chronic opioid therapy require continuous laxative therapy [72]. Addiction has been implicated with the use of opioids; however, the risk of addiction when treating pain with opioids appears very small. In a review by Porter and Jick, 11,882 patients without a prior history of addiction who were treated for pain with opioids were followed to determine how many developed addictive behaviour—only four did so [73]. A more recent study reviewed statistics on the medical use of opioids and the incidence of opioid abuse from 1990 to 1996 in the United States. It concluded that, ''the trend of increasing medical use of opioid analgesics to treat pain does not appear to contribute to increases in the health consequences of opioid analgesic abuse'' [74]. Short-acting opioids are useful for the treatment of acute pain. However, the short half-life also means frequent doses that can make compliance difficult, although compliance is generally not an issue during treatment of acute pain. Tolerance to side effects may occur with repeated dosage but is unlikely with use in the acute setting [66].

## 2.4. Combination therapy

Synergistic or at least additive effects of analgesic combinations may provide more effective analgesia than would a single agent alone [75]. These can provide faster onset and prolonged duration of action, and can combat pain at multiple sites of action [76]. Acetaminophen is a suitable basic analgesic, with a good tolerability profile; however, it is less effective than NSAIDs and, consequently, is preferable in combination with other analgesics [75]. Opioid and acetaminophen combination studies show that combination therapy is better than opioids or acetaminophen alone [77,78]. Interestingly, the efficacy of ibuprofen (400 mg) was similar to the combination of acetaminophen (600 mg), codeine (60 mg) and caffeine (15 mg) in patients with postpartum perineal pain. Ibuprofen was also associated with significantly fewer side effects [79].

NSAIDs, when combined with opioids, allow for a significant dose reduction of opioids and can be useful in minimising opioid side effects [80]. A meta-analysis of randomised clinical trials demonstrated that the combination of ibuprofen 400 mg and codeine 60 mg was more effective than ibuprofen 400 mg alone [81]. The combination of ibuprofen 400 mg with hydrocodone 15 mg was also shown to have a better analgesic effect than the combination of acetaminophen 600 mg with codeine 60 mg following third-molar extraction [82].

The combination of NSAIDs and acetaminophen is frequently used empirically, but there is little high-quality information from clinical trials [83]. Recent studies have found some benefit in the combination of ketoprofen with acetaminophen over either alone [84]. An ibuprofen—acetaminophen combination seemed as effective and better tolerated than an acetaminophen—codeine combination [85], but the addition of acetaminophen to 800 mg three-times-daily ibuprofen did not confer any benefit [86].

Clearly, this association might be considered reasonable, and it would appear preferable if pain does not respond to acetaminophen to add an NSAID such as ibuprofen rather than increase the dose of acetaminophen. However, this is not evidence-based, and more studies of the risks and benefits of acetaminophen—NSAIDs associations need to be performed.

The combination of ibuprofen and acetaminophen has also been tested for the treatment of fever in children, with little superiority of the combination over ibuprofen alone [87].

Therefore, when efficacy and side effects are balanced, evidence supports the use of acetaminophen or ibuprofen for the treatment of acute pain of mild-to-moderate intensity. Progression to the opioids or combination therapies with

acetaminophen or ibuprofen should be reserved for acute pain that is severe and resistant to single compounds [50].

## 3. The ideal analgesic

Inadequately treated acute pain often leads to chronic pain [13], which is more difficult to treat. Management of acute pain requires an analgesic with a rapid onset of action and long duration of analgesia. An analgesic might be considered ideal for acute pain if it had the following characteristics:

1. Rapid onset of action.
2. Prolonged duration of action.
3. Minimisation of interruption by pain.
4. Production of analgesia over a wide range of pain types.
5. Effectiveness in different patient populations.
6. Good tolerability profile.

Such a combination of characteristics is probably unattainable, and the challenge may simply be to define what constitutes an acceptable analgesic for a specific patient or pain type. As individual patient response varies, therapeutic failure with one analgesic does not preclude success with another. Although the currently available analgesics may not fit all of the criteria, preference of one analgesic over another depends on the type of pain, severity of pain, age of the patient and any underlying organ dysfunctions.

Various tools for measurement of each of these characteristics currently exist, generally used mostly in the context of clinical trials. However, there is no one measure that determines the ideal analgesic for a specific patient with a specific pain type, takes into account all the characteristics of an 'ideal analgesic' and provides an overall measure to quantify the quality of relief produced by an analgesic. An analgesic with enhanced quality of relief would encompass all the characteristics described above for a specific patient.

Long-acting analgesics — ideally drugs that can be dosed once or twice-daily — are thought to be a valuable choice for treating acute pain because they offer multiple advantages, including more consistent pain control, less frequent dosing, improved night-time pain control and decreased analgesic gaps (less pain interruption). However, the longer the half-life of the drug, the slower the onset of the effect is [88]. There is a risk of inadvertent overdosing associated with slower onset of analgesia. As a rule, agents with a short half-life have a rapid onset of action. Although the opiates are potent and may be effective in moderate-to-severe pain, the poor tolerability and risk of dependence means that the risks probably outweigh the benefits, at least as first-line drugs. Analgesics that do have a favourable benefit—risk profile include acetaminophen and the traditional NSAIDs. There is increasing evidence to support the use of NSAIDs or acetaminophen in acute pain as primary analgesics and the addition of an opioid to be reserved for situations when additional analgesia is required [76], or for the first dosing when severe acute pain is expected (e.g., molar or wisdom tooth extraction).

Acetaminophen [89,90] and short half-life NSAIDs such as ibuprofen or diclofenac act rapidly, attaining peak plasma levels within 2—4 h following administration [91]. The peak analgesic effect occurs around 1—2 h after administration [29,92,93]. Low doses, short half-life and short duration of use are also elements of good tolerability of NSAIDs in acute pain, in contrast to the risks associated with long-term high-dose use common in chronic rheumatic or inflammatory diseases.

In terms of minimal interruption by pain, ibuprofen has been shown to produce effective analgesia over extended periods compared with acetaminophen (up to 6 h) [29] and aspirin [92]. The rate of interruption of pain — as rated by the need for re-medication — is also lower with ibuprofen in comparison with acetaminophen or placebo [93]. Rescue medication was taken within 6 h by 73% of patients receiving aspirin 650 mg compared with only 59% of those receiving ibuprofen 400 mg [92]. This demonstrates that ibuprofen provides less interruption by pain and prolonged duration of analgesia than acetaminophen or aspirin, even though this still does not reach twice-daily dosing. Other low-dose NSAIDs such as diclofenac, naproxen or ketoprofen with similar characteristics are also available OTC. Choosing the one most appropriate for any individual patient depends on the patient's preference and experience, as well as previous medical history, concomitant medication and diseases, and risk factors.

The choice of analgesic is an important determinant in achieving effective pain relief. This review has identified a set of characteristics for an 'ideal analgesic'. Ideally, an analgesic has a rapid onset of action, prolonged maintenance phase, provides minimal interruption by pain, is effective over a wide range of pain types and in different patient populations, and has a favourable tolerability profile. Such properties allow the analgesic to provide good quality of pain relief. However, individual needs determine the suitability and choice of the most appropriate drug.

## Conflict of interest

This author has acted as consultant expert for Boots Healthcare and Reckitt Benckiser, the manufacturers of ibuprofen, and for other pharmaceutical companies that manufacture and/or sell various NSAIDs, such as diclofenac, ketoprofen, naproxen, nimesulide, celecoxib or rofecoxib. Medical writing support was provided courtesy of Reckitt Benckiser, under the total control of the author. The author has received no compensation or fee for this paper, whose initial idea, and direction were entirely his. The final content was not submitted to Reckitt Benckiser but is entirely the responsibility of the author.

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