A review of weak opioids used in combination with other analgesics to treat low back pain

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Abstract

Low back pain affects a large percentage of the population at some point in their lives. Most cases of acute low back pain settle within six weeks. The most commonly used medicines for acute low back pain are paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), skeletal muscle relaxants, and opioid analgesics.

Chronic low back pain may also respond to these medicines, but combination therapy is usually recommended when a single agent, such as paracetamol, fails to control chronic low back pain. Combinations used in this situation should follow the principles of multimodal analgesia, with demonstrated efficacy and safety. A brief discussion follows on the efficacy and safety of weak opioids, when used in combination with paracetamol or aspirin, for low back pain.

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Introduction

Low back pain affects 60-80% of the population at some time in their lives, and is often recurrent.1 The annual incidence in adults in developed countries is up to 45%, with those aged 35-55 years being affected most often.2 Although 90% of episodes of acute low back pain settle within six weeks, up to seven per cent of patients develop chronic pain.3 Acute back pain is generally regarded as lasting less than six weeks, subacute for six to 12 weeks, and chronic, longer than 12 weeks.1

Causes of low back pain

Low back pain has many causes, but muscle strains and ligament sprains are the most common.3 Strains and sprains may result from lifting, exercising, or moving in an unexpected way, such as when falling, or when in a car accident.3 Overall, only 1% of patients presenting with back pain in primary care have a neoplasm, 4% have fractures, and 1-3% have a prolapsed or herniated disc.3 Suspicion of an underlying complaint should be high when the patient is under 20 years of age or over 55, when pain is non-mechanical, or thoracic, and when systemic symptoms, a structural deformity, neurological signs, or human immunodeficiency virus (HIV) infection, are present.2

Medical treatment of acute and chronic low back pain

Medicines are the most frequently recommended intervention for low back pain.4 The most commonly used medicines are paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), skeletal muscle relaxants, and opioid analgesics.4 Benzodiazepines, systemic corticosteroids, antidepressants, and anti-epileptic medicines, are also prescribed.4

Over-the-counter medicines can be taken to relieve pain and reduce inflammation, if inflammation is contributing to the pain.2 Frequently used over-the-counter (OTC) medicines include paracetamol, aspirin, certain NSAIDs, and weak opioids, such as codeine, used in combination with paracetamol or aspirin.4 In most cases, paracetamol is recommended for pain relief, instead of a NSAID, while NSAIDs are preferred for back pain with an inflammatory component.3 Paracetamol also has a superior safety profile to the NSAIDs, especially when used over a longer term.

A challenge when choosing pharmacological therapy for low back pain is that each class of medicine is associated with a unique balance of risks and benefits. In addition, individual patients are likely to differ in how they weigh potential benefits, harms, and costs of various medications.4

The benefits of combination therapy

For several reasons, it may be difficult to achieve effective pain control using a single agent:3

• Most analgesics cannot be prescribed at unlimited doses, due to the ceiling of efficacy and safety and tolerability concerns, such as liver damage with paracetamol, gastrointestinal, and cardiovascular risks with NSAIDs and selective cyclo-oxygenase 2 inhibitors, or sedation and constipation from opioid analgesics.
Many patients experience pain due to multiple causes. For example, chronic moderate-to-severe pain often requires the effective control of pain, involving multiple pain pathways. It is unlikely that a single agent is able to target every pain mechanism in these patients.

Combining analgesics from different classes, i.e. multimodal analgesia, offers effective analgesia at individual agent doses, which may reduce the severity of dose-related effects. Furthermore, combining analgesics with different mechanisms of action offers increased efficacy due to additive or synergistic analgesic effects. The ideal combination would enhance analgesic efficacy and reduce side-effects, compared with either treatment alone. For example, paracetamol appears to act on COX-2 and via a central mechanism, while pure agonist opioids, such as codeine and tramadol, bind to opioid receptors in the central nervous system. Therefore, the combination of paracetamol, plus codeine or tramadol, fulfills the pharmacodynamic criteria for rational combination products in that their mechanisms of action do not overlap.

**Combination analgesia: weak opioids**

The combination of paracetamol, aspirin or a NSAID, with a weak opioid, is a well-established step in the treatment of pain, and is a recommended Step 2 approach on the World Health Organization (WHO) analgesic ladder. Although the WHO analgesic ladder was originally developed for the treatment of cancer pain, now it is also used extensively for the treatment of non-cancer pain.

Several such weak opioid combinations are available, including paracetamol plus codeine, paracetamol or aspirin plus dextro-proxyphephene (now discontinued) and paracetamol plus tramadol.

Paracetamol plus codeine is a traditionally popular analgesic option that offers a moderate improvement on the efficacy of paracetamol alone. Few studies have evaluated the efficacy of paracetamol and codeine in low back pain. However, the combination is preferred to analgesic preparations containing a multiplicity of ingredients. This is because many of the currently available polycocomponent analgesic preparations, which may be sourced OTC to treat low back pain, contain irrational combinations. Their analgesic efficacy is suspect, and their potential for toxicity is great. Nonetheless, codeine exhibits side-effects that are characteristic of opioids, namely somnolence, dizziness, and constipation. There is also some potential for abuse.

The paracetamol plus tramadol combination has demonstrated synergistic analgesic effects, and combines paracetamol's rapid onset of action with tramadol's prolonged analgesic effect. As a single-dose treatment for acute pain, the combination delivers rapid and sustained pain relief that is greater than either agent alone. There is also evidence of efficacy in the long-term management of chronic pain conditions, including low back pain, osteoarthritis and fibromyalgia.

Two three-month placebo-controlled trials have shown that tramadol plus paracetamol was effective in terms of providing pain relief to patients with moderate-to-severe low back pain. Tramadol plus paracetamol was shown to decrease pain and increase function at three months, compared with placebo.

The efficacy and tolerability of tramadol plus paracetamol, compared with tramadol alone, was compared in patients with subacute low back pain. The study showed that tramadol alone, and in combination with paracetamol, was effective in the treatment of patients with subacute low back pain. However, the tramadol plus paracetamol combination enabled a 25% reduction in the tramadol dose, which considerably reduced the incidence of adverse effects and improved tolerability.

A comparative trial has shown that paracetamol plus tramadol has comparable efficacy to paracetamol plus codeine, but with reduced somnolence and constipation, compared with the codeine combination.

A one-month comparator-controlled clinical trial showed that tramadol plus paracetamol was as effective as codeine/paracetamol in terms of analgesic efficacy in patients with chronic low back pain, osteoarthritis pain, or both. Although generally, the nature of treatment-emergent adverse effects associated with tramadol plus paracetamol are similar to that of codeine plus paracetamol, tramadol plus paracetamol patients have reported less constipation, vomiting and somnolence. Only rare cases of dependence and abuse have been reported.

**Conclusion**

Low back pain is an extremely common condition. Most cases resolve fairly quickly after the acute episode. However, a small, but significant, number of patients, develop chronic low back pain; a persistent disabling condition.

Paracetamol is frequently recommended as first-line therapy for acute low back pain. However, some patients with acute low back pain may require an oral opioid to control it. The opioid is often combined with a non-opioid because this permits an additive analgesic effect, and may also permit the use of lower doses of the opioid, thereby reducing the potential for adverse effects.

As with acute pain, several published articles support the use of combination analgesics or multimodal analgesia for chronic non-cancer pain. Although the use of opioids for chronic pain was considered ill-advised for many years, a number of pain-related organisations and experts have expressed support for the judicious use of opioids in patients with chronic non-cancer pain.

Paracetamol remains a first-line therapy for chronic low back pain, but when it fails to control chronic low back pain, patients and doctors are faced with choosing a NSAID, or an opioid. Studies show that paracetamol may be more effective when combined with a weak opioid in patients who are not obtaining adequate relief from paracetamol alone. The use of an opioid, together
with paracetamol, may also be recommended for short-term use in patients who are taking paracetamol for mild-to-moderate flare-ups of low back pain. The weak opioid/paracetamol combination is also more appropriate than a NSAID in patients with gastrointestinal and renal problems.

There are few published trials evaluating the efficacy of weak opioids, when used in combination with aspirin or paracetamol, for acute or chronic low back pain. Additional comparative and long-term studies are required to confirm the position of these combinations over other analgesics, e.g. paracetamol alone or the NSAIDs in the management of low back pain. A re-evaluation of the role of multimodal analgesia, using a weak opioid in combination with paracetamol or aspirin, may offer prescribers and patients a valuable alternative to NSAIDs in the treatment of acute and chronic moderate-to-severe pain.

References