Chapter

# Multimodal Pharmacological Analgesia in Pain Management

*Antonella Paladini and Giustino Varrassi*

## Abstract

The knowledge of the pathophysiology of pain has gradually evolved in recent years, allowing the development of new management strategies, more specifically addressing single pain types and patient profiles. Despite these advancements, pain management still remains an open issue, given the limitations of single agent therapies, the potential abuse/misuse of opioids and the risk of adverse events. The advent of multimodal analgesic strategies paves the way for major improvements in pain management, combining increased efficacy with better tolerability and an opioid-sparing effect. The association of analgesics with different mechanisms of action represents a successful strategy for a wide range of pain conditions, minimizing side effects and taking advantage of the additive or synergistic actions of individual agents. Last but not least, the increasing availability of oral fixed-dose combinations of analgesics will offer further advantages over extemporaneous combinations, by increasing ease of administration and patient adherence to treatment.

**Keywords:** acute pain, chronic pain, analgesia, multimodal, drug combination, opioid, anti-inflammatory agents, nonsteroidal, acetaminophen

## 1. Introduction

Whatever its cause, pain, both acute and chronic, often emerges from multiple pathogenic pathways [1], which makes drug treatment particularly difficult [2]. In recent decades, the pharmacological arsenal against pain, in addition to traditional nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol, has been enriched, on the one hand with molecules operating on different pain mechanisms (as anticonvulsants and antidepressants), and on the other hand with opioids [3]. However, the single-agent approach to pain remains quite challenging, since a single drug, acting on a single pain component, is generally not successful to achieve a clinically meaningful pain reduction, whereas its use at high doses may cause significant side effects [2]. On the other hand, the increasing prescription of opioids for noncancer chronic pain, besides providing limited clinical advantage compared with non-opioid alternatives [4], has opened the door to problematic opioid use and addiction problems: up to 50% of patients on long-term opioid therapy develop physical dependence or tolerance, leading to problematic opioid use in 5–10% of patients and to addiction in 1–2% [5]. As a consequence, pain management is far from being optimal and patients are exposed to the risks associated with misuse of single agents [6, 7].

Considering the complexity of pain pathogenesis, which involves multiple pathways [1], and the difficulty to reach complete symptoms control, especially for chronic pain which still affects 25–35% of adults in Europe [8], multimodal pharmacological analgesia may represent a possible solution to the still unsolved problem of pain management, thanks to a number of potential advantages: first, a decrease of the administered doses of the individual components; second, the reduction of side effects; and third, a simultaneous action on different pain components [9]. Thanks to these features, multimodal pharmacological therapy gives clinicians the opportunity to make a further step forward to a fully individualized therapy of pain in its various components and clinical manifestations [3].

In this chapter, we will present the therapeutic strategies currently available to address the specific needs in the treatment of different painful conditions and the new possibilities for pain intervention according to the multimodal approach.

## 2. Pain management: unmet needs and future challenges

Despite the multiple treatment options available, pain remains a mostly unresolved topic in every day clinical practice. The analgesic efficacy of single drug treatment is often not sufficient to provide an adequate pain relief, since most analgesic drugs cannot be prescribed at unlimited doses due to the ceiling effect and safety concerns. Another limitation of single-agent analgesia is that it cannot address the multiple pathways underlying pain pathogenesis. Combining drugs from different classes, with different and complementary mechanisms of action, may provide a better opportunity for effective analgesia at reduced doses of individual agents, with a potential reduction of dose-related adverse events.

Based on these considerations, clinical practice is gradually moving from a traditional one-fits-all approach to a more tailored strategy. The traditional approach to pain management refers to the three-step World Health Organization (WHO) pain ladder, which recommends the following regimen, based on the intensity of the patient's pain [10]:

Step I: a non-opioid analgesic should be used for moderate pain, with co-analgesics if necessary.

Step II: if pain persists or increases, a weak opioid may be added.

Step III: if pain still persists, then a change should be made to a strong opioid.

By contrast, newer guidelines aim at treating pain according to the mechanism or mechanisms involved, i.e., neuropathic, nociceptive, or a combination of both [11]. Clinicians should seek to identify the basic pain mechanisms and treat the patient, accordingly, choosing the drug with the most appropriate mechanism of action [6].

Pain is a complex construct with sophisticated transmission pathways in the nervous system, which can be altered physiologically or pharmacologically [2]. Modulation of the transmission of pain can be divided into three approaches:

1. Modulating the upward transmission

2. Altering perception centrally

3. Modulating descending inhibitory pathways

Intervening in all three areas with multiple drugs is more effective than single drug treatment, and it allows to reduce the total dose of any one drug, thereby limiting unwanted effects [9].

Different drugs act at different areas:

i. Peripherally acting drugs:
   - Local anesthetics
   - NSAIDS

ii. Drugs acting in the spinal cord:
   - Opiates
   - NSAIDS
   - N-methyl-D-aspartate (NMDA) receptor antagonists
   - Gabapentinoids

iii. Drugs acting centrally:
   - Opiates
   - Paracetamol

iv. Drugs acting on descending pathways:
   - Tramadol
   - Clonidine
   - 5HT3 antagonists

The principle of multimedia analgesia is the use of a number of drugs (analgesic or adjuvant) in combination to achieve the best pain relief in acute or chronic pain. Combining analgesics that act by different mechanisms of action allows modulating multiple transmission pathways and enables individual agents to act with potentially additive or synergistic effects [12].

Multimodal analgesia is widely acknowledged to be superior to a single drug approach, having demonstrated improved pain relief, with the fewest side effects [2]. This concept was pharmacologically studied in the 1960s by Houde et al. [13], then clinically suggested (especially in postoperative pain) in the 1980s [14], and a few years later diffused by Kehlet and Dahl [9], who first introduced the term "multimodal" or "blended" analgesia. Since then, multimodal analgesia has been deeply studied, demonstrating a broader spectrum of action, greater efficacy, better patient compliance, and an improved efficacy/safety ratio compared with monotherapy [12]. As a result, analgesic combinations are recommended by the WHO, American Pain Society (APS), and American College of Rheumatology (ACR) [15–17] and are commonly used in clinical practice. As regards the ease of use, fixed-dose combinations (FDCs) may offer additional advantages, including ease of administration, reduction of pill burden, and improved adherence [18].

## 3. Analgesic drug combinations

The pharmacological therapeutic approach of multimodal analgesia includes all the frontline drugs available, used alone or in combination according to the specific needs of the patient [19].

Drugs for pain control fall into four main categories [20]:

1. weak analgesics (paracetamol and metamizole)
2. NSAIDs (ibuprofen, diclofenac, ketoprofen, and dexketoprofen)
3. opioids (morphine, hydromorphone, and oxycodone)
4. adjuvant drugs (antidepressant, antiepileptic medications, corticosteroids, colchicine, neurotrophine, and biologic drugs)

The choice of the most appropriate drug combination should consider the pathogenic mechanisms of pain and satisfy the following criteria:

- The drugs to be combined should have different mechanisms of action and preferably act at different sites;
- The drugs to be combined should not interfere with the preexisting comorbidities of the patient; and
- FDCs should be preferred, if available, aiming at improving patient adherence to therapy.

| Drug | Mechanism of action |
|---|---|
| Paracetamol | Inhibits prostaglandin synthesis in the central nervous system. |
| NSAIDs | Inhibit prostaglandin production by blocking cyclooxygenase both peripherally and centrally. |
| Opioids | Have multiple sites of action:<br>○ In the brain, they activate descending pain inhibitors.<br>○ In the periphery, they work by reducing inflammation.<br>○ In the spine, they decrease presynaptic calcium and sodium influx, production and release of excitatory amino acids, such as substance P, and postsynaptic excitability. |
| Anticonvulsants | Inhibit high-frequency neuronal firing by blocking sodium channels and reducing neuron hyperexcitability. |
| NMDA-receptor antagonists (ketamine) | Bind to the NMDA receptor, thereby inhibiting glutamate activation. Glutamate is an excitatory amino acid found in laminae I, II, and III of the dorsal horn of the spinal cord, where it activates primary afferent neurons. |
| Alpha-2 adrenergic agonists | Act on the descending pain pathways supra-spinally, activating receptors to stimulate acetylcholine release, and on the ascending pain pathways, by inhibiting substance P release from the primary afferent neurons, thus reducing transmission of pain. |
| Antidepressants | Alter neurotransmitters that affect pain pathways by inhibiting presynaptic neuronal reuptake of serotonin and norepinephrine at the descending pain pathway, resulting in improved inhibition of pain. |

**Table 1.**
*Mechanism of action of different analgesics (elaborated from text in Ref. [3]).*

Different drugs with different mechanism(s) of action may be combined for enhanced efficacy [20]. Analgesics relieve pain through a variety of mechanisms of action along multiple sites of the nociceptive pathway (**Table 1**) [3].

Analgesic combinations are currently recommended by several guidelines and are used in clinical practice [21]. In patients with moderate-to-severe pain, the general recommendation is the combination of opioid and non-opioid analgesics [22]:

1. Among the possible combinations, paracetamol has been associated with weak (e.g., codeine or tramadol) or strong (e.g., morphine or oxycodone) opioids. Besides being less effective than NSAIDs [23, 24], paracetamol may cause gastrointestinal (GI), cardiovascular (CV), and hepatic adverse effects [25, 26].

2. NSAID/opioid combinations have the advantage of anti-inflammatory and additive analgesic effect, along with a well-demonstrated opioid-sparing activity [27]. Currently available NSAID/opioid FDCs include:

    - Hydrocodone/ibuprofen (7.5/400 mg) and oxycodone/ibuprofen (5/400 mg) are two oral, fixed-dose combination formulations, approved for the short-term management of acute, moderate-to-severe pain. A single tablet provided better analgesia than low-dose hydrocodone/oxycodone or ibuprofen administered alone, in most trials, and appeared to be more effective than a single dose of some other fixed-dose combination analgesics [28–31].

    - An FDC of the fast-acting NSAID, dexketoprofen trometamol, and the long-acting opioid, tramadol hydrochloride, have been recently developed to generate multimodal analgesia at lower and better tolerated doses than those of the single agents used alone. The different modes and sites of action of the two components, together with their complementary pharmacokinetic profiles, and the lower incidence of the typical side effects of each class [32–35] provides physicians with an effective and safe analgesic for the treatment of moderate-to-severe acute pain [36]. This FDC provides a comprehensive multimodal approach for moderate-to-severe acute pain, thanks to the central analgesic effect, peripheral analgesic action, and anti-inflammatory activity [21].

## 4. Multimodal analgesia: different combinations for different types of pain

Thanks to the possibility to minimize drug dosages optimizing efficacy, multimodal therapy is useful in various medical field, from acute pain management to post-trauma or postsurgical pain treatment, besides control of chronic pain and its exacerbations or reduction of pain associated with post-immobilization rehabilitation [19]. Each type of pain requires a specific analgesic therapy, which should also be personalized according to the patient's profile. The main applications of multimodal therapy to different pain conditions are the following.

### 4.1 Musculoskeletal pain (MP)

Given the multiplicity of mechanisms responsible for MP, the combination of analgesics with different mechanisms of action for the relief of acute and chronic skeletal muscle pain is often recommended, with the possible advantage of pharmacokinetic synergy and improved patient adherence.

The main pharmacological associations currently available for the treatment of MP are [19]:

- codeine 30 mg + paracetamol 500 mg,
- ibuprofen 150 mg + paracetamol 500 mg,
- codeine 30 mg + ibuprofen 400 mg,
- tramadol 37.5 mg + paracetamol 325 mg,
- tramadol 75 mg + dexketoprofen 25 mg, and
- oxycodone 5 mg (10 and 20 mg) + paracetamol 325 mg.

For all these combinations, careful monitoring must be performed in order to assess whether continuation of therapy, suspension, or transition to a strong opioid is necessary [19].

### 4.2 Osteoarthritis (OA) pain

Pain associated with rheumatologic conditions has a strong peripheral nociceptive component, although recent data also suggest a central sensitization [37]. Ideal treatment of rheumatic pain should be through a multimodal approach, integrating non-pharmacologic and pharmacologic treatments [38]. In the context of rheumatological painful conditions, the association of dexketoprofen and tramadol may represent an attractive medication for acute exacerbations of OA pain, due to its pharmacological profile: the combination of dexketoprofen and tramadol, targeting different sites of action, is suitable for OA type of pain, arising from different body structures (joints, muscles, ligaments, etc.) [21]. The rapid onset of analgesic effect of dexketoprofen, with its anti-inflammatory activity, associated to the sustained action of tramadol, makes their combination a valuable tool to achieve multimodal analgesia in OA patients [21].

### 4.3 Back pain

Back problems are the third reason for seeking medical help, with about 90% of people suffering from them at some point in their lives [39, 40]. Most episodes of back pain are short lasting with little or no consequence, but recurrent episodes are common and back pain is increasingly understood as a long-lasting condition with a variable course rather than episodes of unrelated occurrences [41]. The complexity of chronic back pain management highlights the need for early intervention in patients with acute back pain in order to prevent progression to chronic back pain [42]. Chronic low back pain has been shown to be secondary to both neuropathic and nociceptive pain mechanisms [43]: a multimodal approach is therefore appropriate. The pain treatment armamentarium for both acute and chronic back pain includes NSAIDs, opioids, steroids, topical medicines, and adjuvants: the choice of medication depends on a number of factors, including the duration of symptoms, severity of symptoms, expected benefits, prior response to medications, adverse effect profile, presence of comorbidities, costs, and degree of supporting evidence [44]. Most guidelines endorse (NSAIDs) and weak opioids for short periods when there is contraindication or lack of improvement with NSAIDs [45].

### 4.4 Fibromyalgia

Fibromyalgia is mainly a centralized pain disorder, accompanied by fatigue, sleep disturbance, and memory and mood difficulties [43]. Effective drugs combinations for this condition include tramadol + paracetamol [46], cyclobenzaprine + fluoxetine [47], pregabalin added to either quetiapine or trazodone [48], and fluoxetine + amitriptyline [49].

### 4.5 Postsurgical pain

Surgical pain may be nociceptive, neuropathic, mixed, psychogenic, or idiopathic, depending on the surgical procedure. The value of balanced analgesia in treating postoperative pain was recognized by Kehlet and Dahl [9] over two decades ago. Non-opioid analgesics are the cornerstone of postsurgical pain multimodal management: in addition to their opioid-sparing effects, many of these agents are highly effective in reducing postoperative pain and allowing for faster mobilization [50].

- Many current multimodal protocols include paracetamol [51–53], based on its opioid-sparing effects, despite the risk of GI, CV, and hepatic adverse events [25, 26].

- NSAIDs represent another class of medication that is highly effective for perioperative pain management: despite concerns about the increased risk of postoperative bleeding with NSAIDs, a meta-analysis revealed that ketorolac does not increase the risk of perioperative bleeding [54]. Nevertheless, this drug has shown several other side effects. Preoperative COX inhibitors (primarily selective COX-2 inhibitors) [55] and postoperative nonselective and selective NSAIDs [56] have been associated with reduced postoperative opioid consumption [57]. The combination of NSAIDs with opioids represents another tool to limit opioid use: in particular, the combination dexketoprofen/tramadol was shown to be superior vs. single components in terms of control of moderate-to-severe acute pain after abdominal hysterectomy [58] and total hip arthroplasty [59], with a safety profile fully in line with that previously known for the single agents in monotherapy. Recently, the analgesic efficacy of dexketoprofen/tramadol was compared in a head-to-head study (DAVID study) to that of tramadol/paracetamol combination in moderate-to-severe pain following surgical removal of impacted lower third molar, showing the greatest sustained analgesia during the 6-hour post dose period [60].

- Another class of analgesics commonly used in multimodal analgesic protocols is the gabapentinoids, which include gabapentin and pregabalin. Meta-analyses have demonstrated that gabapentin [61] and pregabalin [62] improve postoperative pain when part of a multimodal regimen but are associated with sedation, particularly in elderly patients.

- Other agents to consider in multimodal protocols include NMDA antagonists, such as ketamine. Ketamine has a clear opioid-sparing effect in the perioperative period [63] and may reduce long-term opioid consumption in opioid-tolerant patients [64] as well as persistent postsurgical pain when used intravenously [65].

- Multimodal and preemptive analgesia as part of an ERAS (Enhanced Recovery after Surgery) protocol facilitates early mobility and early return of bowel function and decreases postoperative morbidity [66].

### 4.6 Neuropathic pain

The International Association for the Study of Pain defines neuropathic pain as "Pain caused by a lesion or disease of the somatosensory system." This includes central disorders (e.g., spinal cord injury pain, multiple sclerosis pain, and post-stroke thalamic pain) as well as peripheral disorders (e.g., diabetic neuropathy and postherpetic neuralgia) [43].

Both tricyclic antidepressants and gabapentinoids are proposed as firstline agents for neuropathic pain [67]. These medications have completely different mechanisms of actions:

- gabapentinoids are alpha-2-delta calcium channel modulators;
- tricyclic antidepressants have multiple mechanisms of action, including norepinephrine and serotonin reuptake inhibition, and so are logical candidates for combination therapy.

Opioids and gabapentinoids were also studied for neuropathic pain and the combination was found to be positive [68–70]. However, given the limited trial size and the short duration of the studies conducted so far, it is not possible to make recommendations for any specific combination for neuropathic pain [43].

## 5. Conclusions

As illustrated above, in recent years, the WHO ladder approach has gradually been replaced with the multimodal approach, customized from patient to patient taking into account the characteristics of pain (based on pain generator, its cause, type, and intensity) and patient comorbidity. This allows to control not only chronic pain but also its exacerbations, through the association to long-term analgesic therapy of additional drugs for acute pain as needed. In this respect, multimodal therapy represents a useful tool, not only for specialists but for general practitioners as well to personalize analgesic treatment according to the patient's characteristics and needs [71].

The availability of FDCs of most recommended combinations may help in the implementation of multimodal analgesia in clinical practice, improving patient adherence to treatment and contributing to the optimization of pain management.

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## Conflict of interest

The authors do not have any potential conflict of interest related to this chapter.

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