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Original article

Pain Management Among Different Pharmacological Methods: A Continuously Challenging Debate

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Abstract
Pain is not a purely physical event. It is shaped by psychological state, social circumstances, and the body's own injury signals working together. Clinicians draw on several pharmacological tools to manage it: non-opioid analgesics for mild to moderate pain, opioids for moderate to severe pain, adjuvant agents such as antidepressants and anticonvulsants, and corticosteroids for pain driven by inflammation. Each carries its own trade-offs. Opioids relieve severe pain effectively but bring constipation, sedation, respiratory depression, and a real risk of dependence and addiction with extended use. This review set out to examine the pharmacological approaches currently used in pain management. We searched PubMed, Scopus, and Google Scholar and drew on original studies, review articles, clinical guidelines, and randomized controlled trials. Across this literature, opioids, NSAIDs, anticonvulsants, and antidepressants emerged as the medications used most often. Opioids performed well for short courses of severe pain, but tolerance, dependence, and addiction became concerns the longer they were used. NSAIDs helped with inflammatory pain, though gastrointestinal bleeding and kidney injury limited how freely they could be prescribed.
Keywords. Pain, Opioids, Pharmacology, Analgesia.

Introduction

Pain rarely has a single cause. Illness, injury, inflammation, and nerve damage can all trigger it, and how a person experiences it depends as much on their psychological state and social circumstances as on the tissue damage itself. Pain that persists can quietly erode a person's capacity to work, care for a household, or stay connected to family and friends [1]. At the biological level, the pathway from injury to conscious pain is a relay: sensory neurons fire, chemical and electrical signals travel through the spinal cord and brainstem, and higher brain regions interpret what those signals mean [2]. Several overlapping systems drive this process.

Nociceptors, the sensory neurons tuned to detect harmful stimuli, sit at the front line. They carry ion channels such as acid-sensing ion channels (ASICs) and transient receptor potential vanilloid 1 (TRPV1) that open in response to heat, acidity, or other noxious triggers [1,3]. Once these channels open and the neuron depolarizes, it releases excitatory neurotransmitters, chiefly glutamate and substance P, which excite neighboring neurons and send the signal climbing toward the spinal cord, partly along the spinothalamic tract [4]. From there, secondary neurons in the spinal cord relay the signal onward to the brain. How strongly a person feels that signal depends on the intensity and duration of the stimulus, their emotional state at the time, and even the setting in which the pain occurs [3,5]. The nervous system also modulates pain from the top down; descending pathways originating in higher brain centers release endorphins and enkephalins that dampen the transmission of pain signals at the spinal cord [6]. Tissue inflammation or injury sensitizes nociceptors, which leads to hyperalgesia, an exaggerated response to noxious stimuli. Consequently, this state can also induce allodynia, causing pain from stimuli that are typically innocuous. Given how many pathways and signaling molecules are involved, understanding this system matters directly for designing treatments that work [1,3,7].

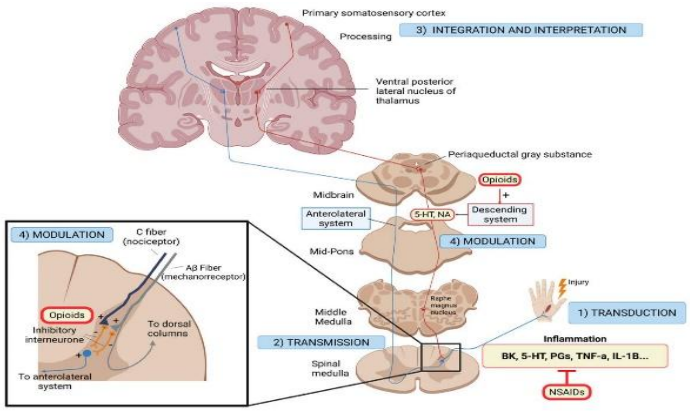

Figure 1. Pain processing mechanisms [1].

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Pain is one of the most common reasons people seek medical care, and its reach extends well beyond the individual patient to healthcare systems and society at large [4,6]. Improving how it is managed remains a persistent priority in medicine, and doing so effectively usually calls for a combination of pharmacological and non-pharmacological approaches rather than either alone [3,5,8]. This review aims to evaluate the pharmacological methods currently used in pain management. We conducted this work as a narrative review, searching PubMed, Scopus, and Google Scholar for relevant literature. Eligible sources included original research articles, reviews, clinical practice guidelines, and randomized controlled trials.

Pain Management: A Global Concern

Clinicians managing pain pharmacologically draw on four broad categories mapped directly to the four-step analgesic ladder: non-opioid analgesics, weak opioids, strong opioids, and interventional or adjuvant modalities. As illustrated in Figure 2, treatment progresses through distinct stages: Step 1 utilizes non-opioid analgesics (such as NSAIDs) with or without adjuvants for mild pain; Step 2 introduces weak opioids for persistent or escalating pain; Step 3 employs strong opioids (like morphine or its equivalent) for moderate to severe cases [3,9], and Step 4 incorporates advanced interventions such as nerve blocks, epidurals, and neuromodulation techniques. While opioids provide significant strength, they come at a cost; constipation, sedation, and respiratory depression are common side effects, and dependence or addiction is a genuine risk with continued use. [10] Adjuvant analgesics, a category that includes antidepressants and anticonvulsants, are added alongside other agents to sharpen pain relief. [11] Corticosteroids, meanwhile, target inflammation directly and are commonly prescribed for conditions such as low back pain and rheumatoid arthritis. Newer neuromodulation techniques, including spinal cord stimulation, deep brain stimulation, and transcutaneous electrical nerve stimulation, offer another route: rather than a drug acting on receptors, an electrical or device-based intervention alters nervous system activity directly to reduce chronic pain. [9,11] Choosing the right drug and dose is rarely a one-size-fits-all decision. The type and severity of a patient's pain shape which medication makes sense in the first place [12], and coexisting conditions matter just as much. A patient with liver or kidney disease, cardiovascular problems, or gastrointestinal issues often needs a different dose, or a different drug altogether, to avoid compounding those problems or triggering unwanted interactions. [13].

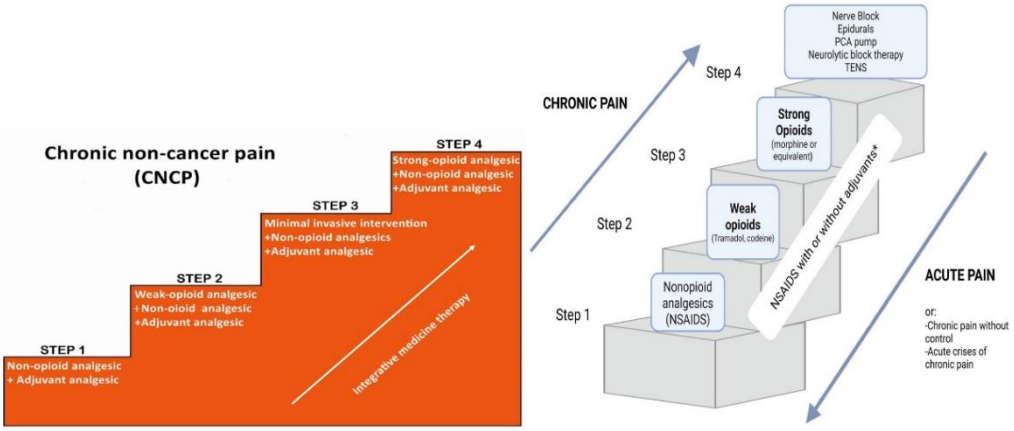

Figure 2. The WHO analgesic ladder, shown as a four-step process. Acute pain typically follows a step-down approach, starting with stronger interventions and tapering, while chronic pain follows a step-up approach that escalates through the steps. Adjuvants such as anticonvulsants and antidepressants can be added at any level [1]

Age adds another layer of complexity. Older patients often process and respond to drugs differently, which makes them more vulnerable to adverse effects and often means lower doses or better-tolerated alternatives are warranted [10,13]. A careful review of a patient's full medication list also matters, since other drugs can blunt an analgesic's effect or raise the risk of harm through interaction [11,12]. Getting pain management right, as part of a broader, patient-specific plan, is what allows people with acute or chronic pain to actually get back to their lives with the fewest side effects possible [9,10,13].

Non-Opioid Analgesics

Non-opioid analgesics are the standard first-line choice for mild to moderate pain. Aspirin, acetaminophen, and NSAIDs such as ibuprofen and naproxen fall into this group, and most are available over the counter with little risk of dependence [14]. The category splits naturally into three types: NSAIDs, acetaminophen, and topical agents. NSAIDs are used more than any other non-opioid analgesic. They work by blocking prostaglandin synthesis, since prostaglandins drive both pain and inflammation, and they fall into two categories: nonselective agents such as aspirin, ibuprofen, and naproxen, which inhibit both COX-1 and COX-2 enzymes, and selective agents such as celecoxib, which target COX-2 specifically [15,16,17]. Acetaminophen works differently, suppressing prostaglandin production in the central nervous system rather than at the site of injury. It does not reduce inflammation the way NSAIDs do, but it controls mild to moderate pain reliably, carries a low side effect burden, and is often reached for when NSAIDs are not a good option [14,17]. Topical formulations such as diclofenac gel and capsaicin cream are a newer addition to this category. Applied directly to the skin, they interrupt pain signaling locally rather than acting on the whole body [14,15,18].

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Beyond pain relief, NSAIDs bring additional pharmacological effects worth noting. By suppressing cytokines and other inflammatory mediators, they reduce inflammation; by blocking the prostaglandins that regulate body temperature, they lower fever; and they also produce a measurable antiplatelet effect [15,19,20]. None of these drugs are free of risk. NSAIDs can cause dyspepsia, nausea, vomiting, and peptic ulcers, and they carry a real risk of acute or chronic kidney injury, which is why they call for caution in patients with kidney disease, heart failure, or a history of gastrointestinal bleeding [16,17]. Acetaminophen is generally well tolerated, but overdose can cause serious liver damage. Topical agents mostly cause local irritation, itching, or a burning sensation at the application site, though enough systemic absorption can still produce gastrointestinal upset, headache, or dizziness [14,18,20].

Opioid Analgesics

Opioids remain the most potent analgesics available. Beyond pain relief, they produce sedation, respiratory suppression, and euphoria, and with long-term use, they raise the risk of respiratory depression, gastrointestinal problems, hormonal disruption, tolerance, and dependence [21]. That risk profile is exactly why patients on opioid therapy need close monitoring. Morphine, oxycodone, hydrocodone, fentanyl, and codeine are the drugs most often used in this class, all prescription-only given their abuse potential [22]. They fall into three families based on origin: natural opioids such as morphine, codeine, and thebaine, extracted from the opium poppy; synthetic opioids such as fentanyl, methadone, and tramadol, built entirely in the lab; and semi-synthetic opioids such as buprenorphine, oxycodone, and hydrocodone, which start from a natural compound and are chemically modified [21,23]. Mechanistically, opioids bind to receptors distributed across the nervous system, triggering G-protein activation and suppressing neurotransmitter release, a cascade that dulls pain signaling at multiple points [24]. Three receptor subtypes matter most. Mu receptors drive analgesia. Delta and kappa receptors contribute more to sedation and anxiety reduction. Opioids also suppress cough, slow gut motility, and constrict the pupils, effects that show up as side effects in some contexts and therapeutic uses in others [25].

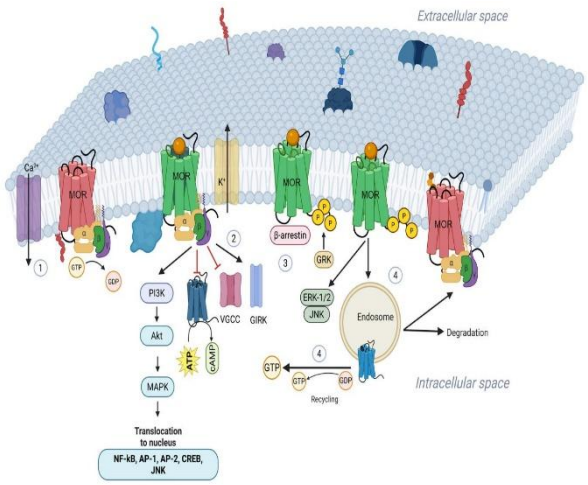

Figure 3. Opioid mechanism of action [1]

The side effect profile is what limits opioid use in practice. Central nervous system effects, sedation, dizziness, confusion, and respiratory depression, are the most common and the most dangerous, since respiratory depression can be fatal and demands vigilant monitoring [22,26]. Gastrointestinal effects such as nausea, vomiting, and constipation are near universal, and opioids can also cause urinary retention, a particular concern for men with benign prostatic hyperplasia [23,24]. Hormonally, chronic use tends to lower testosterone and raise prolactin [24,26], and with time, the body adapts. Tolerance builds, so higher doses are needed for the same relief; dependence sets in, and stopping abruptly can trigger withdrawal, anxiety, restlessness, and flu-like symptoms among them [22,23,25].

Adjuvant Analgesics

Adjuvant analgesics are not painkillers in the classic sense. They are a mixed group of drugs added alongside primary analgesics to boost pain relief or to target pain types that don't respond well to conventional agents [5,13,20], generally by acting on neurotransmitter activity and ion channels in the central and peripheral nervous systems. The category spans antidepressants, benzodiazepines, anticonvulsants, and corticosteroids, each suited to different pain presentations [9,10,18,24].

Antidepressants

Antidepressants that act on serotonin and noradrenaline signaling have a genuine role in pain management, largely because they strengthen the brainstem-to-spinal cord pathways that dampen pain [27]. SSRIs such as fluoxetine and paroxetine help with chronic conditions including fibromyalgia, chronic low back pain, and neuropathic pain [28]. Tricyclic antidepressants, amitriptyline and nortriptyline in particular, are used even more often, with demonstrated benefit for diabetic neuropathy,

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postherpetic neuralgia, and chronic low back pain, though dry mouth, drowsiness, and cognitive slowing are common trade-offs [27,29].

Anticonvulsants

Gabapentin and pregabalin, both anticonvulsants, are a mainstay of neuropathic pain treatment. They act on voltage-gated calcium channels in the central nervous system, reducing the release of excitatory neurotransmitters and calming the neuronal hyperactivity that sustains chronic pain [28,30]. Beyond analgesia, they tend to improve sleep and ease the anxiety and depression that often accompany chronic pain [31]. Clinical evidence supports their use in diabetic neuropathy, postherpetic neuralgia, and spinal cord injury pain, though sedation, dizziness, and cognitive dulling are recognized downsides [30,31].

Local Anesthetics

Local anesthetics such as lidocaine and bupivacaine have a place in chronic pain management too. They block voltage-gated sodium channels in nerve fibers, preventing the sodium influx that action potentials depend on and numbing sensation in the treated region, useful for conditions such as neuropathic pain or postherpetic neuralgia [32]. How well they work depends on the specific drug, the route of delivery, and the tissue being treated [28,33]. Delivery methods vary: infiltration and nerve block for localized numbing, epidural injection into the epidural space, and intrathecal injection directly into the cerebrospinal fluid for more extensive coverage [32,34]. Onset is fast, which contributes to its appeal, but they are not risk-free. Systemic toxicity can occur if a dose is given intravascularly by accident or exceeds a drug's narrow therapeutic window, producing central nervous system depression, cardiovascular collapse, or respiratory failure [33,34]. Lipid emulsion therapy is the standard rescue treatment for this complication. Allergic reactions and nerve injury are also possible, and patients with liver or kidney impairment need particular care in drug selection and dosing [28,33,34].

Corticosteroids

Corticosteroids such as prednisone and dexamethasone bring strong anti-inflammatory and analgesic effects by suppressing prostaglandins, leukotrienes, and cytokines, the same compounds that drive inflammatory pain [9,35]. Their immunosuppressive action also makes them useful for autoimmune-related pain, rheumatoid arthritis in particular, alongside osteoarthritis and both acute and chronic pain more broadly [28,36]. The tradeoff comes with sustained use. Weight gain, fluid retention, hypertension, mood changes, and gastrointestinal ulceration are established risks, and long-term therapy adds osteoporosis, muscle weakness, and higher infection risk to that list [35,36].

Emerging Therapies

Neuromodulation offers a different route into chronic pain that has not responded to conventional drug therapy, using electrical or chemical stimuli to change how the nervous system functions rather than acting through a receptor [37]. Spinal cord stimulation implants a small device near the spinal cord to deliver electrical impulses that interfere with pain transmission. Deep brain stimulation places electrodes in specific brain regions to correct the abnormal neural activity associated with pain [38]. Transcutaneous electrical nerve stimulation is far less invasive: a handheld device delivers low-voltage signals near the painful area to block or reduce pain signaling. Intrathecal drug delivery takes a different approach again, using an implanted pump to deliver analgesic medication directly into the spinal fluid. Taken together, these techniques act on the neural pathways underlying pain perception itself, offering an alternative for patients whose pain has not responded to drugs alone [37,39].

Non-Pharmacological Interventions

Not every effective pain treatment comes in a pill or an injection. Non-pharmacological approaches lean on physical, psychological, and complementary strategies instead [2]. Physical therapy, built around exercise, stretching, and hands-on techniques such as massage, heat and cold therapy, ultrasound, and Transcutaneous Electrical Nerve Stimulation (TENS), improves mobility, strength, and flexibility, and is used widely for musculoskeletal pain, injury recovery, and post-surgical rehabilitation [5]. Psychological approaches, cognitive behavioral therapy foremost among them, work by reshaping the thoughts, emotions, and behaviors tied to pain.

Cognitive Behavioral Therapy (CBT) gives patients coping strategies, relaxation techniques, and stress management skills that improve both how pain is perceived and how well patients function day to day, with particular value for fibromyalgia and chronic low back pain [40]. Complementary and alternative approaches round out the picture: acupuncture, which places fine needles at specific points to encourage pain relief, alongside mind-body practices like mindfulness meditation and yoga that build relaxation and body awareness as tools for managing pain [2,5,41]. How well this works varies from person to person, but many patients do find real benefit. Combined with pharmacological treatment rather than used in isolation, and tailored to what an individual patient actually needs, these interventions round out a more complete approach to pain care [42].

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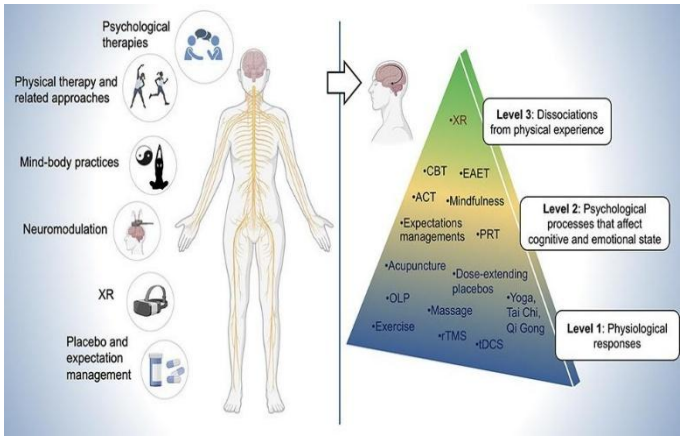

Figure 4. Non-pharmacological options for pain relief [2]

Conclusion and Recommendations

Taken together, this review points to opioids, NSAIDs, anticonvulsants, and antidepressants as the medications clinicians reach for most often. Opioids remain the most effective option for short-term severe pain, but tolerance, dependence, and addiction become real concerns the longer treatment continues. NSAIDs work well against inflammatory pain, though gastrointestinal bleeding and kidney injury cap how widely they can be used. Anticonvulsants and antidepressants have carved out a clearer role in neuropathic pain, where they reduce pain intensity and improve function, but they too carry side effects that call for careful patient selection and dose titration. The field seems to be heading toward more targeted therapy: new drug targets aimed at specific receptors, ion channels, or signaling pathways involved in pain transmission, paired with better drug delivery systems that could make relief more effective and individualized. None of this changes the core principle. Pharmacological pain management still works best when it is applied carefully and matched to what each patient actually needs rather than following a fixed protocol.

Conflicts of interest

The authors affirm that they have no conflicts of interest.

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