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Role of Painkiller on Human Body

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ABSTRACT: An analgesic drug, also called simply an analgesic, pain reliever, or painkiller, is any member of the group of drugs used for pain management. Analgesics are conceptually distinct from anesthetics, which temporarily reduce, and in some instances eliminate, sensation, although analgesia and anesthesia are neurophysiologically overlapping and thus various drugs have both analgesic and anesthetic effects.

KEYWORDS-analgesic, pain, killer, sensation, neurophysiologically, anesthetic

I. INTRODUCTION

Analgesic choice is also determined by the type of pain: For neuropathic pain, recent research has suggested that classes of drugs that are not normally considered analgesics, such as tricyclic [1,2,3] antidepressants and anticonvulsants may be considered as an alternative.[1]

Various analgesics, such as many NSAIDs, are available over the counter in most countries, whereas various others are prescription drugs owing to the substantial risks and high chances of overdose, misuse, and addiction in the absence of medical supervision.

Classification[edit]

Analgesics are typically classified based on their mechanism of action.[5]

Paracetamol (acetaminophen)

Paracetamol, also known as acetaminophen or APAP, is a medication used to treat pain and fever.[6] It is typically used for mild to moderate pain.[6] In combination with opioid pain medication, paracetamol is now used for more severe pain such as cancer pain and after surgery.[7] It is typically used either by mouth or rectally but is also available intravenously.[6][8] Effects last between two and four hours.[8] Paracetamol is classified as a mild analgesic.[8] Paracetamol is generally safe at recommended doses.[9]

NSAIDs

Nonsteroidal anti-inflammatory drugs (usually abbreviated to NSAIDs), are a drug class that groups together drugs that decrease pain[10] and lower fever, and, in higher doses, decrease inflammation.[11] The most prominent members of this group of drugs, aspirin, ibuprofen and naproxen, are all available over the counter in most countries.[12]

COX-2 inhibitors

These drugs have been derived from NSAIDs. The cyclooxygenase enzyme inhibited by NSAIDs was discovered to have at least two different versions: COX1 and COX2. Research suggested most of the adverse effects of NSAIDs to be mediated by blocking the COX1 (constitutive) enzyme, with the analgesic effects being mediated by the COX2 (inducible) enzyme. Thus, the COX2 inhibitors were developed to inhibit only the COX2 enzyme (traditional NSAIDs block both versions in general). These drugs (such as rofecoxib, celecoxib, and etoricoxib) are equally effective analgesics when compared with NSAIDs, but cause less gastrointestinal hemorrhage in particular.[13]

After widespread adoption of the COX-2 inhibitors, it was discovered that most of the drugs in this class increase the risk of cardiovascular events by 40% on average. This led to the withdrawal of rofecoxib and valdecoxib, and warnings on others. Etoricoxib seems relatively safe, with the risk of thrombotic events similar to that of non-coxib NSAID diclofenac.[13]

Opioids

Morphine, the archetypal opioid, and other opioids [4,5,6] (e.g., codeine, oxycodone, hydrocodone, dihydromorphine, pethidine) all exert a similar influence on the cerebral opioid receptor system. Buprenorphine is a partial agonist of the μ-opioid receptor, and tramadol is a

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serotonin norepinephrine reuptake inhibitor (SNRI) with weak μ-opioid receptor agonist properties.[14] Tramadol is structurally closer to venlafaxine than to codeine and delivers analgesia by not only delivering "opioid-like" effects (through mild agonism of the mu receptor) but also by acting as a weak but fast-acting serotonin releasing agent and norepinephrine reuptake inhibitor.[15][16][17][18] Tapentadol, with some structural similarities to tramadol, presents what is believed to be a novel drug working through two (and possibly three) different modes of action in the fashion of both a traditional opioid and as an SNRI. The effects of serotonin and norepinephrine on pain, while not completely understood, have had causal links established and drugs in the SNRI class are commonly used in conjunction with opioids (especially tapentadol and tramadol) with greater success in pain relief.

Dosing of all opioids may be limited by opioid toxicity (confusion, respiratory depression, myoclonic jerks and pinpoint pupils), seizures (tramadol), but opioid-tolerant individuals usually have higher dose ceilings than patients without tolerance.[19] Opioids, while very effective analgesics, may have some unpleasant side-effects. Patients starting morphine may experience nausea and vomiting (generally relieved by a short course of antiemetics such as phenergan). Pruritus (itching) may require switching to a different opioid. Constipation occurs in almost all patients on opioids, and laxatives (lactulose, macrogol-containing or co-danthramer) are typically co-prescribed.[20]

When used appropriately, opioids and other central analgesics are safe and effective; however, risks such as addiction and the body's becoming used to the drug (tolerance) can occur. The effect of tolerance means that frequent use of the drug may result in its diminished effect. When safe to do so, the dosage may need to be increased to maintain effectiveness against tolerance, which may be of particular concern regarding patients with chronic pain and requiring an analgesic over long periods. Opioid tolerance is often addressed with opioid rotation therapy in which a patient is routinely switched between two or more non-cross-tolerant opioid medications in order to prevent exceeding safe dosages in the attempt to achieve an adequate analgesic effect.

Opioid tolerance should not be confused with opioid-induced hyperalgesia. The symptoms of these two conditions can appear very similar but the mechanism of action is different. Opioid-induced hyperalgesia is when exposure to opioids increases the sensation of pain (hyperalgesia) and can even make non-painful stimuli painful (allodynia).[21]

Alcohol

Alcohol has biological, mental, and social effects which influence the consequences of using alcohol for pain.[22] Moderate use of alcohol can lessen certain types of pain in certain circumstances.[22]

The majority of its analgesic effects come from antagonizing NMDA receptors, similarly to ketamine, thus decreasing the activity of the primary excitatory (signal boosting) neurotransmitter, glutamate. It also functions as an analgesic to a lesser degree by increasing the activity of the primary inhibitory (signal reducing) neurotransmitter, GABA.[23]

Attempting to use alcohol to treat pain has also been observed to lead to negative outcomes including excessive drinking and alcohol use disorder.[22]

Cannabis

Medical cannabis, or medical marijuana, refers to cannabis or its cannabinoids used to treat disease or improve symptoms.[24][25] There is evidence suggesting that cannabis can be used to treat chronic pain and muscle spasms, with some trials indicating improved relief of neuropathic pain over opioids.[26][27][28]

Combinations

Analgesics are frequently used in combination, such as the paracetamol and codeine preparations found in many non-prescription pain relievers. They can also be found in combination with vasoconstrictor drugs such as pseudoephedrine for sinus-related preparations, or with antihistamine drugs for people with allergies.

While the use of paracetamol, aspirin, ibuprofen, naproxen, and other NSAIDS concurrently with weak to mid-range opiates (up to about the hydrocodone level) has been said to show beneficial synergistic effects by combating pain at multiple sites of action,[29][30] several combination analgesic products have been shown to have few efficacy benefits when compared to similar doses of their individual components. Moreover, these combination analgesics can often result in significant adverse events, including accidental overdoses, most often due to confusion that arises from the multiple (and often non-acting) components of these combinations.[31]

Alternative medicine

There is some evidence that some treatments using alternative medicine can relieve some types of pain more effectively than placebo.[32] The available research concludes that more research would be necessary to better understand the use of alternative medicine.[32]

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Other drugs

Nefopam—a monoamine reuptake inhibitor, and calcium and sodium channel modulator—is also approved for the treatment of moderate to severe pain in some countries.[33]

Flupirtine is a centrally acting K^+ channel opener with weak NMDA antagonist properties.[34] It was used in Europe for moderate to strong pain, as well as its migraine-treating and muscle-relaxant properties. It has no significant anticholinergic properties, and is believed to be devoid of any activity on dopamine, serotonin, or histamine receptors. It is not addictive, and tolerance usually does not develop.[35] However, tolerance may develop in some cases.[36]

Ziconotide, a blocker of potent N-type voltage-gated calcium channels, is administered intrathecally for the relief of severe, usually cancer-related pain.[37]

Adjuvants[7,8,9]

Certain drugs that have been introduced for uses other than analgesics are also used in pain management. Both first-generation (such as amitriptyline) and newer antidepressants (such as duloxetine) are used alongside NSAIDs and opioids for pain involving nerve damage and similar problems. Other agents directly potentiate the effects of analgesics, such as using hydroxyzine, promethazine, carisoprodol, or tripelennamine to increase the pain-killing ability of a given dose of opioid analgesic.

Adjuvant analgesics, also called atypical analgesics, include orphenadrine, mexiletine, pregabalin, gabapentin, cyclobenzaprine, hyoscine (scopolamine), and other drugs possessing anticonvulsant, anticholinergic, and/or antispasmodic properties, as well as many other drugs with CNS actions. These drugs are used along with analgesics to modulate and/or modify the action of opioids when used against pain, especially of neuropathic origin.

Dextromethorphan has been noted to slow the development of and reverse tolerance to opioids, as well as to exert additional analgesia by acting upon NMDA receptors, as does ketamine.[38] Some analgesics such as methadone and ketobemidone and perhaps piritramide have intrinsic NMDA action.[39]

High-alcohol liquor, two forms of which were found in the US Pharmacopoeia up until 1916 and in common use by physicians well into the 1930s, has been used in the past as an agent for dulling pain, due to the CNS depressant effects of ethyl alcohol, a notable example being the American Civil War.[40][However, the ability of alcohol to relieve severe pain is likely inferior to many analgesics used today (e.g., morphine, codeine). As such, in general, the idea of alcohol for analgesia is considered a primitive practice in virtually all industrialized countries today.

The anticonvulsant carbamazepine is used to treat neuropathic pain. Similarly, the gabapentinoids gabapentin and pregabalin are prescribed for neuropathic pain, and phenibut is available without prescription. Gabapentinoids work as $\alpha_2\delta$-subunit blockers of voltage-gated calcium channels, and tend to have other mechanisms of action as well. Gabapentinoids are all anticonvulsants, which are most commonly used for neuropathic pain, as their mechanism of action tends to inhibit pain sensation originating from the nervous system.[41]

Other uses

Topical analgesia is generally recommended to avoid systemic side-effects. Painful joints, for example, may be treated with an ibuprofen- or diclofenac-containing gel (The labeling for topical diclofenac has been updated to warn about drug-induced hepatotoxicity.[42]); capsaicin also is used topically. Lidocaine, an anesthetic, and steroids may be injected into joints for longer-term pain relief. Lidocaine is also used for painful mouth sores and to numb areas for dental work and minor medical procedures. In February 2007 the FDA notified consumers and healthcare professionals of the potential hazards of topical anesthetics entering the bloodstream when applied in large doses to the skin without medical supervision. These topical anesthetics contain anesthetic drugs such as lidocaine, tetracaine, benzocaine, and prilocaine in a cream, ointment, or gel.[43]

Uses

Topical nonsteroidal anti-inflammatory drugs provide pain relief in common conditions such as muscle sprains and overuse injuries. Since the side effects are also lesser, topical preparations could be preferred over oral medications in these conditions.[44]

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Research[10,11,12]

Some novel and investigational analgesics include subtype-selective voltage-gated sodium channel blockers such as funapide and raxatrigine, as well as multimodal agents such as ralfinamide.[129]

II. DISCUSSION

Pain management is an aspect of medicine and health care involving relief of pain (pain relief, analgesia, pain control) in various dimensions, from acute and simple to chronic and challenging. Most physicians and other health professionals provide some pain control in the normal course of their practice, and for the more complex instances of pain, they also call on additional help from a specific medical specialty devoted to pain, which is called pain medicine.

Pain management often uses a multidisciplinary approach for easing the suffering and improving the quality of life of anyone experiencing pain,[2] whether acute pain or chronic pain. Relief of pain in general (analgesia) is often an acute affair, whereas managing chronic pain requires additional dimensions.

A typical multidisciplinary pain management team may include: medical practitioners, pharmacists, clinical psychologists, physiotherapists, occupational therapists, recreational therapists, physician assistants, nurses, and dentists.[3] The team may also include other mental health specialists and massage therapists. Pain sometimes resolves quickly once the underlying trauma or pathology has healed, and is treated by one practitioner, with drugs such as pain relievers (analgesics) and occasionally also anxiolytics.[13,14,15]

Effective management of chronic (long-term) pain, however, frequently requires the coordinated efforts of the pain management team.[4] Effective pain management does not always mean total eradication of all pain. Rather, it often means achieving adequate quality of life in the presence of pain, through any combination of lessening the pain and/or better understanding it and being able to live happily despite it. Medicine treats injuries and diseases to support and speed healing. It treats distressing symptoms such as pain and discomfort to reduce any suffering during treatment, healing, and dying.

The task of medicine is to relieve suffering under three circumstances. The first is when a painful injury or pathology is resistant to treatment and persists. The second is when pain persists after the injury or pathology has healed. Finally, the third circumstance is when medical science cannot identify the cause of pain. Treatment approaches to chronic pain include pharmacological measures, such as analgesics (pain killer drugs), antidepressants, and anticonvulsants; interventional procedures, physical therapy, physical exercise, application of ice or heat; and psychological measures, such as biofeedback and cognitive behavioral therapy.

Defining pain

In the nursing profession, one common definition of pain is any problem that is "whatever the experiencing person says it is, existing whenever the experiencing person says it does".[5]

Pain management includes patient and communication about the pain problem.[6] To define the pain problem, a health care provider will likely ask questions such as:[6]

- How intense is the pain?
- How does the pain feel?
- Where is the pain?
- What, if anything, makes the pain lessen?
- What, if anything, makes the pain increase?
- When did the pain start?

After asking such questions, the health care provider will have a description of the pain.[6] Pain management will then be used to address that pain.[6]

Adverse effects[16,17,18]

There are many types of pain management. Each have their own benefits, drawbacks, and limits.[6]

A common challenge in pain management is communication between the health care provider and the person experiencing pain.[6] People experiencing pain may have difficulty recognizing or describing what they feel and how

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intense it is.[6] Health care providers and patients may have difficulty communicating with each other about how pain responds to treatments.[6] There is a risk in many types of pain management for the patient to take treatment that is less effective than needed or which causes other difficulties and side effects.[6] Some treatments for pain can be harmful if overused.[6] A goal of pain management for the patient and their health care provider is to identify the amount of treatment needed to address the pain without going beyond that limit.[6]

Another problem with pain management is that pain is the body's natural way of communicating a problem.[6] Pain is supposed to resolve as the body heals itself with time and pain management.[6] Sometimes pain management covers a problem, and the patient might be less aware that they need treatment for a deeper problem.[6]

Physical approach

Physical medicine and rehabilitation

Physical medicine and rehabilitation uses a range of physical techniques such as heat and electrotherapy, as well as therapeutic exercises and behavioral therapy. These techniques are usually part of an interdisciplinary or multidisciplinary program that might also include pharmaceutical medicines.[7] Spa therapy has showed positive effects in reducing pain among patients with chronic low back pain. However, there are limited studies looking at this approach.[8] Studies have shown that kinesiotape could be used on individuals with chronic low back pain to reduce pain.[9] The Center for Disease Control recommends that physical therapy and exercise can be prescribed as a positive alternative to opioids for decreasing one's pain in multiple injuries, illnesses, or diseases.[10] This can include chronic low back pain, osteoarthritis of the hip and knee,[19,20,21] or fibromyalgia.[10] Exercise alone or with other rehabilitation disciplines (such as psychologically based approaches) can have a positive effect on reducing pain.[10] In addition to improving pain, exercise also can improve one's well-being and general health.[10]

Manipulative and mobilization therapy are safe interventions that likely reduce pain for patients with chronic low back pain. However, manipulation produces a larger effect than mobilization.[11]

Specifically in chronic low back pain, education about the way the brain processes pain in conjunction with routine physiotherapy interventions may provide short term relief of disability and pain.[12]

Exercise interventions

Physical activity interventions, such as tai chi, yoga and Pilates, promote harmony of the mind and body through total body awareness. These practices incorporate breathing techniques, meditation and a wide variety of movements, while training the body to perform functionally by increasing strength, flexibility, and range of motion.[13] Physical activity and exercise may improve chronic pain (pain lasting more than 12 weeks),[14] and overall quality of life, while minimizing the need for pain medications.[13] More specifically, walking has been effective in improving pain management in chronic low back pain.[15]

TENS

Transcutaneous electrical nerve stimulation (TENS) is a self-operated portable device intended to help regulate and control chronic pain via electrical impulses.[16] Limited research has explored the effectiveness of TENS in relation to pain management of multiple sclerosis (MS). MS is a chronic autoimmune neurological disorder, which consists of the demyelination of the nerve axons and disruption of nerve conduction velocity and efficiency.[16] In one study, electrodes were placed over the lumbar spine and participants received treatment twice a day and at any time when they experienced a painful episode.[16] This study found that TENS would be beneficial to MS patients who reported localized or limited symptoms to one limb.[16] The research is mixed with whether or not TENS helps manage pain in MS patients.

Transcutaneous electrical nerve stimulation has been found to be ineffective for lower back pain. However, it might help with diabetic neuropathy[17] as well as other illnesses.[22,23,24]

tDCS

Transcranial direct current stimulation (tDCS) is a non-invasive technique of brain stimulation that can modulate activity in specific brain cortex regions, and it involves the application of low-intensity (up to 2 mA) constant direct current to the scalp through electrodes in order to modulate excitability of large cortical areas.[18] tDCS may have a role in pain assessment by contributing to efforts in distinguishing between somatic and affective aspects of pain experience.[18] Zaghi and colleagues (2011) found that the motor cortex, when stimulated with tDCS, increases the threshold for both the perception of non-painful and painful stimuli.[18] Although there is a greater need for research examining the mechanism of electrical stimulation in relation to pain treatment, one theory suggests that the changes in thalamic activity may be due the influence of motor cortex stimulation on the decrease in pain sensations.[18]

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In relation to MS, a study found that after daily tDCS sessions resulted in an individual's subjective report of pain to decrease when compared to a sham condition.[16] In addition, the study found a similar improvement at 1 to 3 days before and after each tDCS session.[16]

Fibromyalgia is a disorder in which an individual experiences dysfunctional brain activity, musculoskeletal pain, fatigue, and tenderness in localized areas.[19] Research examining tDCS for pain treatment in fibromyalgia has found initial evidence for pain decreases.[19] Specifically, the stimulation of the primary motor cortex resulted in significantly greater pain improvement in comparison to the control group (e.g., sham stimulation, stimulation of the DLPFC).[19] However, this effect decreased after treatment ended, but remained significant for three weeks following the extinction of treatment.[19]

Acupuncture

Acupuncture involves the insertion and manipulation of needles into specific points on the body to relieve pain or for therapeutic purposes. An analysis of the 13 highest quality studies of pain treatment with acupuncture, published in January 2009 in the British Medical Journal, was unable to quantify the difference in the effect on pain of real, sham and no acupuncture.[20] A systematic review in 2019 reported that acupuncture injection therapy was an effective treatment for patients with nonspecific chronic low back pain, and is widely used in Southeast Asian countries.[21]

Light therapy[25,26,27]

Research has found evidence that light therapy such as low level laser therapy is an effective therapy for relieving low back pain.[22][23] Instead of being thermal, where reactant energy is originated through heat, LLLT utilizes photochemical reactions.[24] Photochemical reactions need light in order to function. Photons, energy created from light, provide the reactants with energy. [25] Acute and chronic conditions can be helped through the use of lower level laser therapy.[24]

Sound therapy

Audioanalgesia and music therapy are both examples of using auditory stimuli to manage pain or other distress. They are generally viewed as insufficient when used alone, but also as helpful adjuncts to other forms of therapy.

Interventional procedures

Interventional radiology procedures for pain control, typically used for chronic back pain, include epidural steroid injections, facet joint injections, neurolytic blocks, spinal cord stimulators and intrathecal drug delivery system implants.

Pulsed radiofrequency, neuromodulation, direct introduction of medication and nerve ablation may be used to target either the tissue structures and organ/systems responsible for persistent nociception or the nociceptors from the structures implicated as the source of chronic pain. Radiofrequency treatment has been seen to improve pain in patients for facet joint low back pain. However, continuous radiofrequency is more effective in managing pain than pulsed radiofrequency.[31]

An intrathecal pump used to deliver very small quantities of medications directly to the spinal fluid. This is similar to epidural infusions used in labour and postoperatively. The major differences are that it is much more common for the drug to be delivered into the spinal fluid (intrathecal) rather than epidurally, and the pump can be fully implanted under the skin.

A spinal cord stimulator is an implantable medical device that creates electric impulses and applies them near the dorsal surface of the spinal cord provides a paresthesia ("tingling") sensation that alters the perception of pain by the patient.

Intra-articular ozone therapy

Intra-articular ozone therapy has been seen to efficiently alleviate chronic pain in patients with knee osteoarthritis.[32]

Psychological approach

Acceptance and commitment therapy [28,29]

Acceptance and Commitment Therapy (ACT) is a form of cognitive behavioral therapy that focuses on behavior change rather than symptom change, includes methods designed to alter the context around psychological experiences rather than to alter the makeup of the experiences, and emphasizes the use of experiential behavior change methods.[33] The central process in ACT revolves around psychological flexibility, which in turn includes processes of acceptance, awareness, a present-oriented quality in interacting with experiences, an ability to persist or change

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behavior, and an ability to be guided by one's values.[33] ACT has an increased evidence base for range of health and behavior problems, including chronic pain.[33] ACT influences patients to adopt a tandem process to acceptance and change, which allows for a greater flexibility in the focus of treatment.[33]

Recent research has applied ACT successfully to chronic pain in older adults due to in part of its direction from individual values and being highly customizable to any stage of life.[33] In line with the therapeutic model of ACT, significant increases in process variables, pain acceptance, and mindfulness were also observed in a study applying ACT to chronic pain in older adults.[33] In addition, these primary results suggested that an ACT based treatment may significantly improve levels of physical disability, psychosocial disability, and depression post-treatment and at a three-month follow-up for older adults with chronic pain.[33]

Cognitive behavioral therapy

Cognitive behavioral therapy (CBT) helps patients with pain to understand the relationship between their pain, thoughts, emotions, and behaviors. A main goal in treatment is cognitive (thinking, reasoning or remembering) restructuring to encourage helpful thought patterns.[34] This will target healthy activities such as regular exercise and pacing. Lifestyle changes are also trained to improve sleep patterns and to develop better coping skills for pain and other stressors using various techniques (e.g., relaxation, diaphragmatic breathing, and even biofeedback).

Studies have demonstrated the usefulness of cognitive behavioral therapy in the management of chronic low back pain, producing significant decreases in physical and psychosocial disability.[35] CBT is significantly more effective than standard care in treatment of people with body-wide pain, like fibromyalgia. Evidence for the usefulness of CBT in the management of adult chronic pain is generally poorly understood, due partly to the proliferation of techniques of doubtful quality, and the poor quality of reporting in clinical trials.[citation needed] The crucial content of individual interventions has not been isolated and the important contextual elements, such as therapist training and development of treatment manuals, have not been determined. The widely varying nature of the resulting data makes useful systematic review and meta-analysis within the field very difficult.[36]

In 2020, a systematic review of randomized controlled trials (RCTs) evaluated the clinical effectiveness of psychological therapies for the management of adult chronic pain (excluding headaches). There is no evidence that behaviour therapy (BT) is effective for reducing this type of pain, however BT may be useful for improving a person's mood immediately after treatment. This improvement appears to be small, and is short term in duration.[37] CBT may have a small positive short-term effect on pain immediately following treatment. CBT may also have a small effect on reducing disability and potential catastrophizing that may be associated with adult chronic pain. These benefits do not appear to last very long following the therapy.[37] CBT may contribute towards improving the mood of an adult who experiences chronic pain, which could possibility be maintained for longer periods of time.[37]

For children and adolescents, a review of RCTs evaluating the effectiveness of psychological therapy for the management of chronic and recurrent pain found that psychological treatments are effective in reducing pain when people under 18 years old have headaches.[38] This beneficial effect may be maintained for at least three months following the therapy.[39] Psychological treatments may also improve pain control for children or adolescents who experience pain not related to headaches. It is not known if psychological therapy improves a child or adolescents mood and the potential for disability related to their chronic pain.[39]

Hypnosis

A 2007 review of 13 studies found evidence for the efficacy of hypnosis in the reduction of pain in some conditions. However the studies had some limitations like small study sizes, bringing up issues of power to detect group differences, and lacking credible controls for placebo or expectation. The authors concluded that "although the findings provide support for the general applicability of hypnosis in the treatment of chronic pain, considerably more research will be needed to fully determine the effects of hypnosis for different chronic-pain conditions."[40]:283

Hypnosis has reduced the pain of some harmful medical procedures in children and adolescents.[41] In clinical trials addressing other patient groups, it has significantly reduced pain compared to no treatment or some other non-hypnotic interventions.[42] The effects of self hypnosis on chronic pain are roughly comparable to those of progressive muscle relaxation.[43]

Hypnosis with analgesic (painkiller) has been seen to relieve chronic pain for most people and may be a safe and effective alternative to medications. However, high quality clinical data is needed to generalize to the whole chronic pain population.[44]

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Mindfulness meditation

A 2013 meta-analysis of studies that used techniques centered around the concept of mindfulness, concluded, "that MBIs [mindfulness-based interventions] decrease the intensity of pain for chronic pain patients."[45] A 2019 review of studies of brief mindfulness-based interventions (BMBI) concluded that BMBI are not recommended as a first-line treatment and could not confirm their efficacy in managing chronic or acute pain.[46]

Mindfulness-based pain management[21,22,23]

Mindfulness-based pain management (MBPM) is a mindfulness-based intervention (MBI) providing specific applications for people living with chronic pain and illness.[47][48] Adapting the core concepts and practices of mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy (MBCT), MBPM includes a distinctive emphasis on the practice of 'loving-kindness', and has been seen as sensitive to concerns about removing mindfulness teaching from its original ethical framework within Buddhism.[47][49] It was developed by Vidyamala Burch and is delivered through the programs of Breathworks.[47][48] It has been subject to a range of clinical studies demonstrating its effectiveness.

Medications

The World Health Organization (WHO) recommends a pain ladder for managing pain relief with pharmaceutical medicine. It was first described for use in cancer pain. However it can be used by medical professionals as a general principle when managing any type of pain.[57][58] In the treatment of chronic pain, the three-step WHO Analgesic Ladder provides guidelines for selecting the appropriate medicine. The exact medications recommended will vary by country and the individual treatment center, but the following gives an example of the WHO approach to treating chronic pain with medications. If, at any point, treatment fails to provide adequate pain relief, then the doctor and patient move onto the next step.

Common types of pain and typical drug management		
Pain type	typical initial drug treatment	comments
headache	paracetamol/acetaminophen, NSAIDs[59]	doctor consultation is appropriate if headaches are severe, persistent, accompanied by fever, vomiting, or speech or balance problems;[59] self-medication should be limited to two weeks[59]
migraine	paracetamol, NSAIDs[59]	triptans are used when the others do not work, or when migraines are frequent or severe[59]
menstrual cramps	NSAIDs[59]	some NSAIDs are marketed for cramps, but any NSAID would work[59]
minor trauma, such as a bruise, abrasions, sprain	paracetamol, NSAIDs[59]	opioids not recommended[59]
severe trauma, such as a wound, burn, bone fracture, or severe sprain	opioids[59]	more than two weeks of pain requiring opioid treatment is unusual[59]
strain or pulled muscle	NSAIDs, muscle relaxants[59]	if inflammation is involved, NSAIDs may work better; short-term use only[59]
minor pain after surgery	paracetamol, NSAIDs[59]	opioids rarely needed[59]
severe pain after surgery	opioids[59]	combinations of opioids may be prescribed if pain is severe[59]
muscle ache	paracetamol, NSAIDs[59]	if inflammation involved, NSAIDs

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Common types of pain and typical drug management		
Pain type	typical initial drug treatment	comments
		may work better.[59]
toothache or pain from dental procedures	paracetamol, NSAIDs[59]	this should be short term use; opioids may be necessary for severe pain[59]
kidney stone pain	paracetamol, NSAIDs, opioids[59]	opioids usually needed if pain is severe.[59]
pain due to heartburn or gastroesophageal reflux disease	antacid, H2 antagonist, proton-pump inhibitor[59]	heartburn lasting more than a week requires medical attention; aspirin and NSAIDs should be avoided[59]
chronic back pain	paracetamol, NSAIDs[59]	opioids may be necessary if other drugs do not control pain and pain is persistent[59]
osteoarthritis pain	paracetamol, NSAIDs[59]	medical attention is recommended if pain persists.[59]
fibromyalgia	antidepressant, anticonvulsant[59]	evidence suggests that opioids are not effective in treating fibromyalgia[59]

Mild pain

Paracetamol (acetaminophen), or a nonsteroidal anti-inflammatory drug (NSAID) such as ibuprofen will relieve mild pain.[60][

Mild to moderate pain

Paracetamol, an NSAID or paracetamol in a combination product with a weak opioid such as tramadol, may provide greater relief than their separate use. A combination of opioid with acetaminophen can be frequently used such as Percocet, Vicodin, or Norco.

Moderate to severe pain

When treating moderate to severe pain, the type of the pain, acute or chronic, needs to be considered. The type of pain can result in different medications being prescribed. Certain medications may work better for acute pain, others for chronic pain, and some may work equally well on both. Acute pain medication is for rapid onset of pain such as from an inflicted trauma or to treat post-operative pain. Chronic pain medication is for alleviating long-lasting, ongoing pain.

Morphine is the gold standard to which all narcotics are compared. Semi-synthetic derivatives of morphine such as hydromorphone (Dilaudid), oxymorphone (Numorphan, Opana), nicomorphine (Vilan), hydromorphinol and others vary in such ways as duration of action, side effect profile and milligramme potency. Fentanyl has the benefit of less histamine release and thus fewer side effects. It can also be administered via transdermal patch which is convenient for chronic pain management. In addition to the intrathecal patch and injectable fentanyl formulations, the FDA (Food and Drug Administration) has approved various immediate release fentanyl products for breakthrough cancer pain (Actiq/OTFC/Fentora/Onsolis/Subsys/Lazanda/Abstral). Oxycodone is used across the Americas and Europe for relief of serious chronic pain. Its main slow-release formula is known as OxyContin. Short-acting tablets, capsules, syrups and ampules which contain oxycodone are available making it suitable for acute intractable pain or breakthrough pain. Diamorphine, and methadone are used less frequently.[citation needed] Clinical studies have shown that transdermal buprenorphine is effective at reducing chronic pain.[61] Pethidine, known in North America as meperidine, is not recommended for pain management due to its low potency, short duration of action, and toxicity associated with repeated use.[citation needed] Pentazocine, dextromoramide and dipipanone are also not recommended in new patients except for acute pain where other analgesics are not tolerated or are inappropriate, for pharmacological and misuse-related reasons. In some countries potent synthetics such as piritramide and ketobemidone are used for severe pain. Tapentadol is a newer agent introduced in the last decade.

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For moderate pain, tramadol, codeine, dihydrocodeine, and hydrocodone are used, with nicocodeine, ethylmorphine and propoxyphene or dextropropoxyphene (less commonly).[23,24]

Drugs of other types can be used to help opioids combat certain types of pain. Amitriptyline is prescribed for chronic muscular pain in the arms, legs, neck and lower back with an opiate, or sometimes without it or with an NSAID.

While opiates are often used in the management of chronic pain, high doses are associated with an increased risk of opioid overdose.[62]

Opioids

In 2009, the Food and Drug Administration stated: "According to the National Institutes of Health, studies have shown that properly managed medical use of opioid analgesic compounds (taken exactly as prescribed) is safe, can manage pain effectively, and rarely causes addiction."[63] In 2013, the FDA stated that "abuse and misuse of these products have created a serious and growing public health problem".[64]

Opioid medications can provide short, intermediate or long acting analgesia depending upon the specific properties of the medication and whether it is formulated as an extended release drug. Opioid medications may be administered orally, by injection, via nasal mucosa or oral mucosa, rectally, transdermally, intravenously, epidurally and intrathecally. In chronic pain conditions that are opioid responsive, a combination of a long-acting (OxyContin, MS Contin, Opana ER, Exalgo and Methadone) or extended release medication is often prescribed along with a shorter-acting medication (oxycodone, morphine or hydromorphone) for breakthrough pain, or exacerbations.

Most opioid treatment used by patients outside of healthcare settings is oral (tablet, capsule or liquid), but suppositories and skin patches can be prescribed. An opioid injection is rarely needed for patients with chronic pain.

Although opioids are strong analgesics, they do not provide complete analgesia regardless of whether the pain is acute or chronic in origin. Opioids are effective analgesics in chronic malignant pain and modestly effective in nonmalignant pain management.[65] However, there are associated adverse effects, especially during the commencement or change in dose. When opioids are used for prolonged periods drug tolerance will occur. Other risks can include chemical dependency, diversion and addiction.[66][67]

Clinical guidelines for prescribing opioids for chronic pain have been issued by the American Pain Society and the American Academy of Pain Medicine. Included in these guidelines is the importance of assessing the patient for the risk of substance abuse, misuse, or addiction. Factors correlated with an elevated risk of opioid misuse include a history of substance use disorder, younger age, major depression, and the use of psychotropic medications.[68] Physicians who prescribe opioids should integrate this treatment with any psychotherapeutic intervention the patient may be receiving. The guidelines also recommend monitoring not only the pain but also the level of functioning and the achievement of therapeutic goals. The prescribing physician should be suspicious of abuse when a patient reports a reduction in pain but has no accompanying improvement in function or progress in achieving identified goals.[69]

The list below consists of commonly used opioid analgesics which have long-acting formulations. Common brand names for the extended release formulation are in parentheses.[27]

- Oxycodone (OxyContin)
- Hydromorphone (Exalgo, Hydromorph Contin)
- Morphine (M-Eslon, MS Contin)
- Oxymorphone (Opana ER)
- Fentanyl, transdermal (Duragesic)
- Buprenorphine*, transdermal (Butrans)
- Tramadol (Ultram ER)
- Tapentadol (Nucynta ER)
- Methadone* (Metadol, Methadose)
- Hydrocodone bitartrate (Hysingla ER) and bicarbonate (Zohydro ER)

*Methadone and buprenorphine are each used both for the treatment of opioid addiction and as analgesics

Nonsteroidal anti-inflammatory drugs

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The other major group of analgesics are nonsteroidal anti-inflammatory drugs (NSAID). They work by inhibiting the release of prostaglandins, which cause inflammatory pain. Acetaminophen/paracetamol is not always included in this class of medications. However, acetaminophen may be administered as a single medication or in combination with other analgesics (both NSAIDs and opioids). The alternatively prescribed NSAIDs such as ketoprofen and piroxicam have limited benefit in chronic pain disorders and with long-term use are associated with significant adverse effects. The use of selective NSAIDs designated as selective COX-2 inhibitors have significant cardiovascular and cerebrovascular risks which have limited their utilization.[70][71] Common NSAIDs include aspirin, ibuprofen, and naproxen. There are many NSAIDs such as parecoxib (selective COX-2 inhibitor) with proven effectiveness after different surgical procedures. Wide use of non-opioid analgesics can reduce opioid-induced side-effects.[72]

Antidepressants and antiepileptic drugs

Some antidepressant and antiepileptic drugs are used in chronic pain management and act primarily within the pain pathways of the central nervous system, though peripheral mechanisms have been attributed as well. They are generally used to treat nerve brain that results from injury to the nervous system. Neuropathy can be due to chronic high blood sugar levels (diabetic neuropathy). These drugs also reduce pain from viruses such as shingles, phantom limb pain and post-stroke pain.[73] These mechanisms vary and in general are more effective in neuropathic pain disorders as well as complex regional pain syndrome.[74] A common anti-epileptic drug is gabapentin, and an example of an antidepressant would be amitriptyline.

Cannabinoids

Evidence of medical marijuana's effect on reducing pain is generally conclusive. Detailed in a 1999 report by the Institute of Medicine, "the available evidence from animal and human studies indicates that cannabinoids can have a substantial analgesic effect".[75] In a 2013 review study published in Fundamental & Clinical Pharmacology, various studies were cited in demonstrating that cannabinoids exhibit comparable effectiveness to opioids in models of acute pain and even greater effectiveness in models of chronic pain.[76] It is mainly the THC strain of medical marijuana that provide analgesic benefits, as opposed to the CBD strain[28]

Ketamine

Low-dose ketamine is sometimes used as an alternative to opioids for the treatment of acute pain in hospital emergency departments.[77][78] Ketamine probably? reduces pain more than opioids and with less nausea and vomiting.[79]

Other analgesics

Other drugs which can potentiate conventional analgesics or have analgesic properties in certain circumstances are called analgesic adjuvant medications.[80] Gabapentin, an anticonvulsant, can reduce neuropathic pain itself and can also potentiate opiates.[81] Drugs with anticholinergic activity, such as orphenadrine and cyclobenzaprine, are given in conjunction with opioids for neuropathic pain. Orphenadrine and cyclobenzaprine are also muscle relaxants, and are useful in painful musculoskeletal conditions. Clonidine, an alpha-2 receptor agonist, is another drug that has found use as an analgesic adjuvant.[80] In 2021, researchers described a novel type of pain therapy — a CRISPR-dCas9 epigenome editing method for repressing $Na_v1.7$ gene expression which showed therapeutic potential in three mouse models of chronic pain.[82][83]

Self-management

Self-management of chronic pain has been described as the individual's ability to manage various aspects of their chronic pain.[84] Self-management can include building self-efficacy, monitoring one's own symptoms, goal setting and action planning. It also includes patient-physician shared decision-making, among others.[84] The benefits of self-management vary depending on self-management techniques used. They only have marginal benefits in management of chronic musculoskeletal pain.[85] Some research has shown that self-management of pain can use different approaches. Those approaches can range from different therapies such as yoga, acupuncture,exercise and other relaxation techniques. Patients could also take a more natural approach by taking different minerals, vitamins or herbs. However, research has shown there is a difference between rural patients and non-rural patients having more access to different self-management approaches. Physicians in these areas may be readily prescribing more pain medication in these rural cities due to being less experienced with pain management. Simply put, it is sometimes easier for rural patients to get a prescription that insurance pays for instead of natural approaches that cost more money than they can afford to spend on their pain management. Self-management may be a more expensive alternative.[86]

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Society and culture

The medical treatment of pain as practiced in Greece and Turkey is called algology (from the Greek άλγος, algos, "pain"). The Hellenic Society of Algology[87] and the Turkish Algology-Pain Society[88] are the relevant local bodies affiliated to the International Association for the Study of Pain (IASP).[89]

Undertreatment

Undertreatment of pain is the absence of pain management therapy for a person in pain when treatment is indicated.

Consensus in evidence-based medicine and the recommendations of medical specialty organizations establish guidelines to determine the treatment for pain which health care providers ought to offer.[90] For various social reasons, persons in pain may not seek or may not be able to access treatment for their pain.[90] Health care providers may not provide the treatment which authorities recommend.[90] Some studies about gender biases have concluded that female pain recipients are often overlooked when it comes to the perception of their pain. Whether they appeared to be in high levels of pain didn't make a difference for their observers. The women participants in the studies were still perceived to be in less pain than they actually were. Men participants on the other hand were offered pain relief while their self reporting indicated that their pain levels didn't necessarily warrant treatment. Biases exist when it comes to gender. Prescribers have been seen over and under prescribing treatment to individuals based on them being male or female [91].There are other prevalent reasons that undertreatment of pain occurs. Gender is a factor as well as race. When it comes to prescribers treating patients racial disparities has become a real factor. Research has shown that non-white individuals pain perception has affected their pain treatment. The African-American community has been shown to suffer significantly when it comes to trusting the medical community to treat them. Oftentimes medication although available to be prescribed is dispensed in less quantities due to their pain being perceived on a smaller scale. The black community could be undermined by physicians thinking they are not in as much pain as they are reporting. Another occurrence may be physicians simply making the choice not to treat the patient accordingly in spite of the self-reported pain level. Racial disparity is definitely a real issue in the world of pain management.[92]

In children

Acute pain is common in children and adolescents as a result of injury, illness, or necessary medical procedures.[93] Chronic pain is present in approximately 15–25% of children and adolescents. It may be caused by an underlying disease, such as sickle cell anemia, cystic fibrosis, rheumatoid arthritis. Cancer or functional disorders such as migraines, fibromyalgia, and complex regional pain could also cause chronic pain in children.[94]

Pain assessment in children is often challenging due to limitations in developmental level, cognitive ability, or their previous pain experiences. Clinicians must observe physiological and behavioral cues exhibited by the child to make an assessment. Self-report, if possible, is the most accurate measure of pain. Self-report pain scales involve younger kids matching their pain intensity to photographs of other children's faces, such as the Oucher Scale, pointing to schematics of faces showing different pain levels, or pointing out the location of pain on a body outline.[95] Questionnaires for older children and adolescents include the Varni-Thompson Pediatric Pain Questionnaire (PPQ) and the Children's Comprehensive Pain Questionnaire. They are often utilized for individuals with chronic or persistent pain.[95]

Acetaminophen, nonsteroidal anti-inflammatory agents, and opioid analgesics are commonly used to treat acute or chronic pain symptoms in children and adolescents. However a pediatrician should be consulted before administering any medication.[95]

Caregivers may provide nonpharmacological treatment for children and adolescents because it carries minimal risk and is cost effective compared to pharmacological treatment. Nonpharmacologic interventions vary by age and developmental factors. Physical interventions to ease pain in infants include swaddling, rocking, or sucrose via a pacifier. For children and adolescents physical interventions include hot or cold application, massage, or acupuncture.[96] Cognitive behavioral therapy (CBT) aims to reduce the emotional distress and improve the daily functioning of school-aged children and adolescents with pain by changing the relationship between their thoughts and emotions. In addition this therapy teaches them adaptive coping strategies. Integrated interventions in CBT include relaxation technique, mindfulness, biofeedback, and acceptance (in the case of chronic pain).[97] Many therapists will hold sessions for caregivers to provide them with effective management strategies.[94]

Professional certification

Pain management practitioners come from all fields of medicine. In addition to medical practitioners, a pain management team may often benefit from the input of pharmacists, physiotherapists, clinical

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psychologists and occupational therapists, among others. Together the multidisciplinary team can help create a package of care suitable to the patient.

Pain medicine in the United States

Pain physicians are often fellowship-trained board-certified anesthesiologists, neurologists, physiatrists, emergency physicians, or psychiatrists. Palliative care doctors are also specialists in pain management. The American Society of Interventional Pain Physicians, the American Board of Anesthesiology, the American Osteopathic Board of Anesthesiology (recognized by the AOABOS), the American Board of Physical Medicine and Rehabilitation, the American Board of Emergency Medicine and the American Board of Psychiatry and Neurology[98] each provide certification for a subspecialty in pain management following fellowship training. The fellowship training is recognized by the American Board of Medical Specialties (ABMS) or the American Osteopathic Association Bureau of Osteopathic Specialists (AOABOS). As the field of pain medicine has grown rapidly, many practitioners have entered the field, some non-ACGME board-certified[28]

III. RESULTS

Paracetamol (acetaminophen[a] or para-hydroxyacetanilide) is a non-opioid analgesic and antipyretic agent used to treat fever and mild to moderate pain.[13][14][15] It is a widely used over the counter medication. Common brand names include Tylenol and Panadol.

At a standard dose, paracetamol only slightly decreases body temperature;[14][16][17] it is inferior to ibuprofen in that respect,[18] and the benefits of its use for fever are unclear, particularly in the context of fever of viral origins.[14][19][20] Paracetamol may relieve pain in acute mild migraine but only slightly in episodic tension headache.[21][22] However, the aspirin/paracetamol/caffeine combination helps with both conditions where the pain is mild and is recommended as a first-line treatment for them.[23][24] Paracetamol is effective for post-surgical pain, but it is inferior to ibuprofen.[25] The paracetamol/ibuprofen combination provides further increase in potency and is superior to either drug alone.[25][26] The pain relief paracetamol provides in osteoarthritis is small and clinically insignificant.[15][27][28] The evidence in its favor for the use in low back pain, cancer pain, and neuropathic pain is insufficient.[15][29][27][30][31][32]

In the short term, paracetamol is safe and effective when used as directed.[33] Short term adverse effects are uncommon and similar to ibuprofen,[34] but paracetamol is typically safer than non-steroidal anti-inflammatory drugs (NSAID) for long term use.[35] Paracetamol is also often used in patients who cannot tolerate NSAIDs like ibuprofen.[36][37] Chronic consumption of paracetamol may result in a drop in hemoglobin level, indicating possible gastrointestinal bleeding,[38] and abnormal liver function tests. Some epidemiological studies have linked paracetamol to cardiovascular, renal, and gastrointestinal diseases, but are largely due to confounding biases and of insignificant relevance with short-term use of paracetamol.[39][40][38][37][41] Paracetamol may slightly increase systolic blood pressure in hypertensive patients at a dose of 4 grams a day.[42][43] Elevated frequency of asthma and developmental and reproductive disorders is observed in the offspring of women with prolonged use of paracetamol during pregnancy, although whether paracetamol is the true cause of this increase is unclear.[42] Some studies suggest that there is evidence for an association between paracetamol during pregnancy and autism spectrum disorder and attention deficit hyperactivity disorder, while making clear further research is required to establish any causal link,[44][45] which has prompted some calls to limit its use in pregnancy to the lowest effective dosage for the shortest possible time.[42][46][47]

The recommended maximum daily dose for an adult is three to four grams.[48][49][27] Higher doses may lead to toxicity, including liver failure.[50] Paracetamol poisoning is the foremost cause of acute liver failure in the Western world, and accounts for most drug overdoses in the United States, the United Kingdom, Australia, and New Zealand.[51][52][53]

Paracetamol was first made in 1878 by Harmon Northrop Morse or possibly 1852 by Charles Frédéric Gerhardt.[54][55][56] It is the most commonly used medication for pain and fever in both the United States and Europe.[57] It is on the World Health Organization's List of Essential Medicines.[58] Paracetamol is available as a generic medication, with brand names including Tylenol and Panadol among others.[59] In 2021, it was the 113th most commonly prescribed medication in the United States, with more than 5 million prescriptions.[60][61]

Etymology

The word "acetaminophen" is a shortened form of N-acetyl aminophenol, and was coined and first marketed by McNeil Laboratories in 1955.[62]

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The word "paracetamol" is a shortened form of para-acetyl-amino-phenol,[63] and was coined by Frederick Stearns & Co in 1956.[64]

Medical uses

Fever

Paracetamol is a drug of choice for reducing fever. However, there has been a lack of research on its antipyretic properties, particularly in adults.[14] The most recent review on paracetamol and management of fever in the general practice (2008) argued that its benefits are unclear.[14] In addition, when used for the common cold, paracetamol may relieve a stuffed or runny nose, but not other cold symptoms such as a sore throat, malaise, sneezing, or cough; however, these data are of poor quality.[65]

For patients in critical care, paracetamol decreased body temperature by only 0.2–0.3 °C more than control interventions; there was no difference in mortality.[16] It did not change the outcome in febrile patients with stroke.[66] The results are contradictory for paracetamol use in sepsis: higher mortality, lower mortality, and no change in mortality were all reported.[16] Paracetamol offered no benefit in the treatment of dengue fever and was accompanied by a higher rate of liver enzyme elevation: a sign of a potential liver damage.[67] Overall, there is no support for a routine administration of antipyretic drugs, including paracetamol, to hospitalized patients with fever and infection.[20]

The efficacy of paracetamol in children with fever is unclear.[68] Paracetamol should not be used solely with the aim of reducing body temperature; however, it may be considered for children with fever who appear distressed.[69] It does not prevent febrile seizures and should not be used for that purpose.[69][70] It appears that 0.2 °C decrease of the body temperature in children after a standard dose of paracetamol is of questionable value, particularly in emergency situations.[14] Based on this, some physicians advocate using higher doses that may decrease the temperature by as much as 0.7 °C.[17] Meta-analyses showed that paracetamol is less effective than ibuprofen in children (marginally less effective, according to another analysis[71]), including children younger than 2 years old,[72] with equivalent safety.[18] Exacerbation of asthma occurs with similar frequency for both medications.[73] Giving paracetamol and ibuprofen together at the same time to children under 5 is not recommended, however doses may be alternated if required.[69]

Pain

Paracetamol is used for the relief of mild to moderate pain such as headache, muscle aches, minor arthritis pain, toothache as well as pain caused by cold, flu, sprains, and dysmenorrhea.[74] It is recommended, in particular, for acute mild to moderate pain, since the evidence for the treatment of chronic pain is insufficient.[15]

Musculoskeletal pain

The benefits of paracetamol in musculoskeletal conditions, such as osteoarthritis and backache, are uncertain.[15]

It appears to provide only small and not clinically important benefits in osteoarthritis.[15][27] American College of Rheumatology and Arthritis Foundation guideline for the management of osteoarthritis notes that the effect size in clinical trials of paracetamol has been very small, which suggests that for most individuals it is ineffective.[28] The guideline conditionally recommends paracetamol for short-term and episodic use to those who do not tolerate nonsteroidal anti-inflammatory drugs. For people taking it regularly, monitoring for liver toxicity is required.[28] Essentially the same recommendation was issued by EULAR for hand osteoarthritis.[75] Similarly, the ESCEO algorithm for the treatment of knee osteoarthritis recommends limiting the use of paracetamol to short-term rescue analgesia only.[76]

Paracetamol is ineffective for acute low back pain.[15][29] No randomized clinical trials evaluated its use for chronic or radicular back pain, and the evidence in favor of paracetamol is lacking.[27][30][29]

Headaches

Paracetamol is effective for acute migraine:[21] 39% of people experience pain relief at one hour compared with 20% in the control group.[77] The aspirin/paracetamol/caffeine combination also "has strong evidence of effectiveness and can be used as a first-line treatment for migraine".[23] Paracetamol on its own only slightly alleviates episodic tension headache in those who have them frequently.[22] However, the aspirin/paracetamol/caffeine combination is superior to both paracetamol alone and placebo and offers meaningful relief of tension headache: 2 hours after administering the medication, 29% of those who took the combination were pain-free as compared with 21% on paracetamol and 18% on placebo.[78] The German, Austrian, and Swiss headache societies and the German Society of Neurology recommend this combination as a "highlighted" one for self-medication of tension headache, with paracetamol/caffeine combination being a "remedy of first choice", and paracetamol a "remedy of second choice".[24]

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Dental and other post-surgical pain

Pain after a dental surgery provides a reliable model for the action of analgesics on other kinds of acute pain.[79] For the relief of such pain, paracetamol is inferior to ibuprofen.[25] Full therapeutic doses of non-steroidal anti-inflammatory drugs (NSAIDs) ibuprofen, naproxen or diclofenac are clearly more efficacious than the paracetamol/codeine combination which is frequently prescribed for dental pain.[80] The combinations of paracetamol and NSAIDs ibuprofen or diclofenac are promising, possibly offering better pain control than either paracetamol or the NSAID alone.[25][26][81][82] Additionally, the paracetamol/ibuprofen combination may be superior to paracetamol/codeine and ibuprofen/codeine combinations.[26]

A meta-analysis of general post-surgical pain, which included dental and other surgery, showed the paracetamol/codeine combination to be more effective than paracetamol alone: it provided significant pain relief to as much as 53% of the participants, while the placebo helped only 7%.[83]

Other pain

Paracetamol fails to relieve procedural pain in newborn babies.[84][85] For perineal pain postpartum paracetamol appears to be less effective than non-steroidal anti-inflammatory drugs (NSAIDs).[86]

The studies to support or refute the use of paracetamol for cancer pain and for neuropathic pain are lacking.[31][32] There is limited evidence in favor of the use of the intravenous form of paracetamol for acute pain control in the emergency department.[87] The combination of paracetamol with caffeine is superior to paracetamol alone for the treatment of acute pain.[88]

Patent ductus arteriosus

Paracetamol helps ductal closure in patent ductus arteriosus. It is as effective for this purpose as ibuprofen or indomethacin, but results in less frequent gastrointestinal bleeding than ibuprofen.[89] Its use for extremely low birth weight and gestational age infants however requires further study.[89]

Adverse effects

Gastrointestinal adverse effects such as nausea and abdominal pain are common, and their frequency is similar to that of ibuprofen.[37] Increase in risk-taking behavior is possible.[90] According to the US Food and Drug Administration, the drug may cause rare and possibly fatal skin reactions such as Stevens–Johnson syndrome and toxic epidermal necrolysis,[91] Rechallenge tests and an analysis of American but not French pharmacovigilance databases indicated a risk of these reactions.[91][92]

In clinical trials for osteoarthritis, the number of participants reporting adverse effects was similar for those on paracetamol and on placebo. However, the abnormal liver function tests (meaning there was some inflammation or damage to the liver) were almost four times more likely in those on paracetamol, although the clinical importance of this effect is uncertain.[40] After 13 weeks of paracetamol therapy for knee pain, a drop in hemoglobin level indicating gastrointestinal bleeding was observed in 20% of participants, this rate being similar to ibuprofen group.[38]

Due to the absence of controlled studies, most of the information about the long-term safety of paracetamol comes from observational studies.[37] These indicate a consistent pattern of increased mortality as well as cardiovascular (stroke, myocardial infarction), gastrointestinal (ulcers, bleeding) and renal adverse effects with increased dose of paracetamol.[38][37][41] Use of paracetamol is associated with 1.9 times higher risk of peptic ulcer.[37] Those who take it regularly at a higher dose (more than 2–3 g daily) are at much higher risk (3.6–3.7 times) of gastrointestinal bleeding and other bleeding events.[42] Meta-analyses suggest that paracetamol may increase the risk of kidney impairment by 23%[93] and kidney cancer by 28%.[41] Paracetamol is particularly dangerous to the liver in overdose, but even without overdose those who take this drug may develop acute liver failure requiring liver transplantation more frequently than the users of nonsteroidal anti-inflammatory drugs.[36] Paracetamol slightly but significantly increases blood pressure and heart rate.[37] The majority of observational studies suggests that, used chronically, it may increase the risk of developing hypertension, as confirmed in a prospective randomized confirmed trial.[43] The risk is higher with the higher dose.[42]

The association between paracetamol use and asthma in children has been a matter of controversy.[94] However, the most recent research suggests that there is no association,[95] and that the frequency of asthma exacerbations in children after paracetamol is the same as after another frequently used pain killer ibuprofen.[73]

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Use in pregnancy

Paracetamol safety in pregnancy has been under increased scrutiny. There appears to be no link between paracetamol use in the first trimester and adverse pregnancy outcomes or birth defects. However, indications exist of a possible increase of asthma and developmental and reproductive disorders in the offspring of women with prolonged use of paracetamol during pregnancy.[42]

Paracetamol use by the mother during pregnancy is associated with an increased risk of childhood asthma,[96][97] but so are the maternal infections for which paracetamol may be used, and separating these influences is difficult.[42] Paracetamol, in a small scale meta-analysis was also associated with 20–30% increase in autism spectrum disorder, attention deficit hyperactivity disorder, hyperactivity symptoms, and conduct disorder, with the association being lower in a meta-analysis where a larger demographic was used, but it is unclear whether this is a causal relationship and there was potential bias in the findings.[42][98][99] There is also an argument that the large number, consistency, and the robust designs of the studies provide a strong evidence in favor of paracetamol causing the increased risk of these neurodevelopmental disorders.[44][45] In animal experiments, paracetamol disrupts fetal testosterone production, and several epidemiological studies linked cryptorchidism with mother's paracetamol use for more than two weeks in the second trimester. On the other hand, several studies did not find any association.[42]

The consensus recommendation appears to be to avoid prolonged use of paracetamol in pregnancy and use it only when necessary, at the lowest effective dosage and for the shortest time.[42][46][47]

Overdose

Overdose of paracetamol is caused by taking more than the recommended maximum daily dose of paracetamol for healthy adults (three or four grams),[48][49] and can cause potentially fatal liver damage.[100][101] A single dose should not exceed 1000 mg, and doses should be taken no sooner than four hours apart.[48] While a majority of adult overdoses are linked to suicide attempts, many cases are accidental, often due to the use of more than one paracetamol-containing product over an extended period.[102]

Paracetamol toxicity is the foremost cause of acute liver failure in the Western world, and accounts for most drug overdoses in the United States, the United Kingdom, Australia, and New Zealand.[51][103][52][53] Paracetamol overdose results in more calls to poison control centers in the US than overdose of any other pharmacological substance.[104] According to the FDA, in the United States, "56,000 emergency room visits, 26,000 hospitalizations, and 458 deaths per year [were] related to acetaminophen-associated overdoses during the 1990s. Within these estimates, unintentional acetaminophen overdose accounted for nearly 25% of the emergency department visits, 10% of the hospitalizations, and 25% of the deaths."[105]

Overdoses are frequently related to high-dose recreational use of prescription opioids, as these opioids are most often combined with paracetamol.[106] The overdose risk may be heightened by frequent consumption of alcohol.[107]

Untreated paracetamol overdose results in a lengthy, painful illness. Signs and symptoms of paracetamol toxicity may initially be absent or non-specific symptoms. The first symptoms of overdose usually begin several hours after ingestion, with nausea, vomiting, sweating, and pain as acute liver failure starts.[108] People who take overdoses of paracetamol do not fall asleep or lose consciousness, although most people who attempt suicide with paracetamol wrongly believe that they will be rendered unconscious by the drug.[109][110]

Treatment is aimed at removing the paracetamol from the body and replenishing glutathione.[110] Activated charcoal can be used to decrease absorption of paracetamol if the person comes to the hospital soon after the overdose. While the antidote, acetylcysteine (also called N-acetylcysteine or NAC), acts as a precursor for glutathione, helping the body regenerate enough to prevent or at least decrease the possible damage to the liver; a liver transplant is often required if damage to the liver becomes severe.[51][111]

NAC was usually given following a treatment nomogram (one for people with risk factors, and one for those without), but the use of the nomogram is no longer recommended as evidence to support the use of risk factors was poor and inconsistent, and many of the risk factors are imprecise and difficult to determine with sufficient certainty in clinical practice.[112][113] Toxicity of paracetamol is due to its quinone metabolite NAPQI and NAC also helps in neutralizing it.[110] Kidney failure is also a possible side effect.[107]

Interactions

Prokinetic agents such as metoclopramide accelerate gastric emptying, shorten time (t_{max}) to paracetamol peak blood plasma concentration (C_{max}), and increase C_{max}. Medications slowing gastric emptying such

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as propantheline and morphine lengthen t_{max} and decrease C_{max}.[114][115] The interaction with morphine may result in patients failing to achieve the therapeutic concentration of paracetamol; the clinical significance of interactions with metoclopramide and propantheline is unclear.[115]

There have been suspicions that cytochrome inducers may enhance the toxic pathway of paracetamol metabolism to NAPQI (see Paracetamol#Pharmacokinetics). By and large, these suspicions have not been confirmed.[115] Out of the inducers studied, the evidence of potentially increased liver toxicity in paracetamol overdose exists for phenobarbital, primidone, isoniazid, and possibly St John's wort.[116] On the other hand, the anti-tuberculosis drug isoniazid cuts the formation of NAPQI by 70%.[115]

Ranitidine increased paracetamol area under the curve (AUC) 1.6-fold. AUC increases are also observed with nizatidine and cisapride. The effect is explained by these drugs inhibiting glucuronidation of paracetamol.[115]

Paracetamol raises plasma concentrations of ethinylestradiol by 22% by inhibiting its sulfation.[115] Paracetamol increases INR during warfarin therapy and should be limited to no more than 2 g per week.[117][118][119]

Pharmacology

Pharmacodynamics

Paracetamol appears to exert its effects through two mechanisms: the inhibition of cyclooxygenase and actions of its metabolite N-arachidonoylphenolamine (AM404).[120]

Supporting the first mechanism, pharmacologically and in its side effects, paracetamol is close to classical nonsteroidal anti-inflammatory drugs (NSAIDs) that act by inhibiting COX-1 and COX-2 enzymes and especially similar to selective COX-2 inhibitors.[121] Paracetamol inhibits prostaglandin synthesis by reducing the active form of COX-1 and COX-2 enzymes. This occurs only when the concentration of arachidonic acid and peroxides is low. Under these conditions, COX-2 is the predominant form of cyclooxygenase, which explains the apparent COX-2 selectivity of paracetamol. Under the conditions of inflammation, the concentration of peroxides is high, which counteracts the reducing effect of paracetamol. Accordingly, the anti-inflammatory action of paracetamol is slight.[120][121] The anti-inflammatory action of paracetamol (via COX inhibition) has also been found to primarily target the central nervous system and not peripheral areas of the body, explaining the lack of side effects associated with conventional NSAIDs such as gastric bleeding.

The second mechanism centers on the paracetamol metabolite AM404. This metabolite has been detected in the brains of animals and cerebrospinal fluid of humans taking paracetamol.[120][122] It is formed in the brain from another paracetamol metabolite 4-aminophenol by action of fatty acid amide hydrolase.[120] AM404 is a weak agonist of cannabinoid receptors CB1 and CB2, an inhibitor of endocannabinoid transporter, and a potent activator of TRPV1 receptor.[120] This and other research indicate that cannabinoid system and TRPV1 may play an important role in the analgesic effect of paracetamol.[120][123]

In 2018, Suemaru et al. found that, in mice, paracetamol exerts anticonvulsant effect by activation of TRPV1 receptors[124] and decrease in neuronal excitability by hyperpolarization of neurons.[125] The exact mechanism of the anticonvulsant effect of acetaminophen is not clear. According to Suemaru et al., acetaminophen and its active metabolite AM404 show a dose-dependent anticonvulsant activity against pentylenetetrazol-induced seizures in mice.[124]

Pharmacokinetics

After being taken by mouth, paracetamol is rapidly absorbed from the small intestine, while absorption from the stomach is negligible. Thus, the rate of absorption depends on stomach emptying. Food slows the stomach emptying and absorption, but the total amount absorbed stays the same.[126] In the same subjects, the peak plasma concentration of paracetamol was reached after 20 minutes when fasting versus 90 minutes when fed. High carbohydrate (but not high protein or high fat) food decreases paracetamol peak plasma concentration by four times. Even in the fasting state, the rate of absorption of paracetamol is variable and depends on the formulation, with maximum plasma concentration being reached after 20 minutes to 1.5 hours.[6]

Paracetamol's bioavailability is dose-dependent: it increases from 63% for 500 mg dose to 89% for 1000 mg dose.[6] Its plasma terminal elimination half-life is 1.9–2.5 hours,[6] and volume of distribution is roughly 50 L.[127] Protein binding is negligible, except under the conditions of overdose, when it may reach 15–21%.[6] The concentration in serum after a typical dose of paracetamol usually peaks below 30 µg/mL (200 µmol/L).[128] After 4 hours, the concentration is usually less than 10 µg/mL (66 µmol/L).[128]

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Paracetamol is metabolized primarily in the liver, mainly by glucuronidation and sulfation, and the products are then eliminated in the urine (see the Scheme on the right). Only 2–5% of the drug is excreted unchanged in the urine.[6] Glucuronidation by UGT1A1 and UGT1A6 accounts for 50–70% of the drug metabolism. Additional 25–35% of paracetamol is converted to sulfate by sulfation enzymes SULT1A1, SULT1A3, and SULT1E1.[129]

A minor metabolic pathway (5–15%) of oxidation by cytochrome P450 enzymes, mainly by CYP2E1, forms a toxic metabolite known as NAPQI (N-acetyl-p-benzoquinone imine).[129] NAPQI is responsible for the liver toxicity of paracetamol. At usual doses of paracetamol, NAPQI is quickly detoxified by conjugation with glutathione. The non-toxic conjugate APAP-GSH is taken up in the bile and further degraded to mercapturic and cysteine conjugates that are excreted in the urine. In overdose, glutathione is depleted by the large amount of formed NAPQI, and NAPQI binds to mitochondria proteins of the liver cells causing oxidative stress and toxicity.[129]

Yet another minor but important direction of metabolism is deacetylation of 1–2% of paracetamol to form p-aminophenol. p-Aminophenol is then converted in the brain by fatty acid amide hydrolase into AM404, a compound that may be partially responsible for the analgesic action of paracetamol.[127]

Synthesis

Classical methods

The classical methods for the production of paracetamol involve the acetylation of 4-aminophenol with acetic anhydride as the last step. They differ in how 4-aminophenol is prepared. In one method, nitration of phenol with nitric acid affords 4-nitrophenol, which is reduced to 4-aminophenol by hydrogenation over Raney nickel. In another method, nitrobenzene is reduced electrolytically giving 4-aminophenol directly. Additionally, 4-nitrophenol can be selectively reduced by Tin(II) Chloride in absolute ethanol or ethyl acetate to produce a 91% yield of 4-aminophenol.[130][131][132]

Celanese synthesis

An alternative industrial synthesis developed at Celanese involves firstly direct acylation of phenol with acetic anhydride in the presence of hydrogen fluoride to a ketone, then the conversion of the ketone with hydroxylamine to a ketoxime, and finally the acid-catalyzed Beckmann rearrangement of the cetoxime to the para-acetylaminophenol product.[130][133]

Reactions

4-Aminophenol may be obtained by the amide hydrolysis of paracetamol. This reaction is also used to determine paracetamol in urine samples: After hydrolysis with hydrochloric acid, 4-aminophenol reacts in ammonia solution with a phenol derivate, e.g. salicylic acid, to form an indophenol dye under oxidization by air.[134]

Acetanilide was the first aniline derivative serendipitously found to possess analgesic as well as antipyretic properties, and was quickly introduced into medical practice under the name of Antifebrin by Cahn & Hepp in 1886.[135] But its unacceptable toxic effects—the most alarming being cyanosis due to methemoglobinemia, an increase of hemoglobin in its ferric [Fe^{3+}] state, called methemoglobin, which cannot bind oxygen, and thus decreases overall carriage of oxygen to tissue—prompted the search for less toxic aniline derivatives.[136] Some reports state that Cahn & Hepp or a French chemist called Charles Gerhardt first synthesized paracetamol in 1852.[55][56]

Harmon Northrop Morse synthesized paracetamol at Johns Hopkins University via the reduction of p-nitrophenol with tin in glacial acetic acid in 1877,[137][138] but it was not until 1887 that clinical pharmacologist Joseph von Mering tried paracetamol on humans.[136] In 1893, von Mering published a paper reporting on the clinical results of paracetamol with phenacetin, another aniline derivative.[139] Von Mering claimed that, unlike phenacetin, paracetamol had a slight tendency to produce methemoglobinemia. Paracetamol was then quickly discarded in favor of phenacetin. The sales of phenacetin established Bayer as a leading pharmaceutical company.[140]

Von Mering's claims remained essentially unchallenged for half a century, until two teams of researchers from the United States analyzed the metabolism of acetanilide and phenacetin.[140] In 1947, David Lester and Leon Greenberg found strong evidence that paracetamol was a major metabolite of acetanilide in human blood, and in a subsequent study they reported that large doses of paracetamol given to albino rats did not cause methemoglobinemia.[141] In 1948, Bernard Brodie, Julius Axelrod and Frederick Flinn confirmed that paracetamol was the major metabolite of acetanilide in humans, and established that it was just as efficacious an analgesic as its precursor.[142][143][144] They also suggested that methemoglobinemia is produced in humans mainly by another metabolite, phenylhydroxylamine. A follow-up paper by Brodie and Axelrod in 1949 established that phenacetin was also metabolized to paracetamol.[145] This led to a "rediscovery" of paracetamol.[136]

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Paracetamol was first marketed in the United States in 1950 under the name Triagesic, a combination of paracetamol, aspirin, and caffeine.[138] Reports in 1951 of three users stricken with the blood disease agranulocytosis led to its removal from the marketplace, and it took several years until it became clear that the disease was unconnected.[138] The following year, 1952, paracetamol returned to the US market as a prescription drug.[146] In the United Kingdom, marketing of paracetamol began in 1956 by Sterling-Winthrop Co. as Panadol, available only by prescription, and promoted as preferable to aspirin since it was safe for children and people with ulcers.[147][148] In 1963, paracetamol was added to the British Pharmacopoeia, and has gained popularity since then as an analgesic agent with few side-effects and little interaction with other pharmaceutical agents.[147][138]

Concerns about paracetamol's safety delayed its widespread acceptance until the 1970s, but in the 1980s paracetamol sales exceeded those of aspirin in many countries, including the United Kingdom. This was accompanied by the commercial demise of phenacetin, blamed as the cause of analgesic nephropathy and hematological toxicity.[136] Available in the US without a prescription since 1955[146] (1960, according to another source[149]) paracetamol has become a common household drug.[150] In 1988, Sterling Winthrop was acquired by Eastman Kodak which sold the over the counter drug rights to SmithKline Beecham in 1994.[151]

In June 2009, an FDA advisory committee recommended that new restrictions be placed on paracetamol use in the United States to help protect people from the potential toxic effects. The maximum single adult dosage would be decreased from 1000 mg to 650 mg, while combinations of paracetamol and other products would be prohibited. Committee members were particularly concerned by the fact that the then-present maximum dosages of paracetamol had been shown to produce alterations in liver function.[152]

In January 2011, the FDA asked manufacturers of prescription combination products containing paracetamol to limit its amount to no more than 325 mg per tablet or capsule and began requiring manufacturers to update the labels of all prescription combination paracetamol products to warn of the potential risk of severe liver damage.[153][154][155][156][157] Manufacturers had three years to limit the amount of paracetamol in their prescription drug products to 325 mg per dosage unit.[154][156]

In November 2011, the Medicines and Healthcare products Regulatory Agency revised UK dosing of liquid paracetamol for children.[158]

In September 2013, "Use Only as Directed", an episode of the radio program This American Life[159] highlighted deaths from paracetamol overdose. This report was followed by two reports by ProPublica alleging that the "FDA has long been aware of studies showing the risks of acetaminophen. So has the maker of Tylenol, McNeil Consumer Healthcare, a division of Johnson & Johnson"[160] and "McNeil, the maker of Tylenol, ... has repeatedly opposed safety warnings, dosage restrictions and other measures meant to safeguard users of the drug."[161]

During the COVID-19 pandemic it was considered by some in the scientific community that it was an effective analgesic medication to treat symptoms of COVID-19, but this was found to be unsubstantiated.[162][163][164][165]

Society and culture

Naming

Paracetamol is the Australian Approved Name[166] and British Approved Name[167] as well as the international nonproprietary name used by the WHO and in many other countries; acetaminophen is the United States Adopted Name[167] and Japanese Accepted Name and also the name generally used in Canada,[167] Venezuela, Colombia, and Iran.[167][168] Both paracetamol and acetaminophen are contractions of para-acetylaminophenol, a chemical name for the compound. The initialism APAP used by dispensing pharmacists in the United States comes from the alternative chemical name [N-]acetyl-para-aminophenol.[169]

Available forms

Paracetamol is available in oral, suppository, and intravenous forms.[170] Intravenous paracetamol is sold under the brand name Ofirmev in the United States.[171]

In some formulations, paracetamol is combined with the opiate codeine, sometimes referred to as co-codamol (BAN) and Panadeine in Australia. In the US, this combination is available only by prescription.[172] As of 1 February 2018, medications containing codeine also became prescription-only in Australia.[173] Paracetamol is also combined with other opioids such as dihydrocodeine,[174] referred to as co-dydramol (British Approved Name (BAN)), oxycodone[175] or hydrocodone.[176] Another very commonly used analgesic combination includes paracetamol in combination with propoxyphene napsylate.[177] A combination of paracetamol, codeine, and the doxylamine succinate is also available.[178]

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Paracetamol is sometimes combined with phenylephrine hydrochloride.[179] Sometimes a third active ingredient, such as ascorbic acid,[179][180] caffeine,[181][182] chlorpheniramine maleate,[183] or guaifenesin[184][185][186] is added to this combination.

Veterinary use

Cats

Paracetamol is extremely toxic to cats, which lack the necessary UGT1A6 enzyme to detoxify it. Initial symptoms include vomiting, salivation, and discoloration of the tongue and gums. Unlike an overdose in humans, liver damage is rarely the cause of death; instead, methemoglobin formation and the production of Heinz bodies in red blood cells inhibit oxygen transport by the blood, causing asphyxiation (methemoglobinemia and hemolytic anemia).[187] Treatment of the toxicosis with N-acetylcysteine is recommended.[188]

Dogs

Paracetamol has been reported to be as effective as aspirin in the treatment of musculoskeletal pain in dogs.[189] A paracetamol–codeine product (brand name Pardale-V)[190] licensed for use in dogs is available for purchase under supervision of a vet, pharmacist or other qualified person.[190] It should be administered to dogs only on veterinary advice and with extreme caution.[190]

The main effect of toxicity in dogs is liver damage, and GI ulceration has been reported.[188][191][192][193] N-acetylcysteine treatment is efficacious in dogs when administered within two hours of paracetamol ingestion.[188][189]

Snakes

Paracetamol is lethal to snakes[194] and has been suggested as a chemical control program for the invasive brown tree snake (Boiga irregularis) in Guam.[195][196] Doses of 80 mg are inserted into dead mice that are scattered by helicopter[197] as lethal bait to be consumed by the snakes.[25]

IV. CONCLUSION

Historically, the dominant therapeutic modalities for managing chronic pain have been oral analgesics. However, various treatment approaches, pharmacologic and non-pharmacologic, are available to manage chronic pain.

Non-steroidal anti-inflammatory drugs (NSAIDs) have powerful analgesic, anti-inflammatory, and antipyretic effects. NSAIDs work by inhibiting cyclooxygenase (COX) enzymes COX-1 and COX-2, which impairs the synthesis of prostanoids (12). While NSAIDs are generally safe and well-tolerated, their side-effect profiles limit their use, particularly when used long-term or when high doses are required to control pain (13). The side effects include gastrointestinal ulceration and bleeding, renal insufficiency, coronary heart disease, and thrombotic cardiovascular events (14, 15).

Opioids are commonly prescribed for chronic pain management and produce their pharmacological actions, including analgesia, by activating opioid receptors on nerve cells (16). Although opioids are effective for moderate to severe acute pain, evidence of their long-term efficacy is limited and controversial (17). The interpretation of studies assessing the utilization of opioids for managing chronic pain is limited due to high patient drop-out rates, largely secondary to adverse events or insufficient pain relief (18). However, the use of opioids rarely provides long-term pain relief for patients with CNCP as their side-effect profile limits significant dosage adjustments (19). Common side-effects and risks associated with the use of opioids include sedation, dizziness, respiratory depression, constipation, nausea, vomiting, tolerance, physical dependence, hyperalgesia, and addiction, leading to opioid use disorder (OUD) (20, 21). Compared to full agonists such as morphine, oxycodone, and fentanyl, buprenorphine, an opioid partial agonist used in the treatment of both pain and OUD, has a lower likelihood of producing serious side effects (22). However, it remains underutilized due to misconceptions regarding its use and structural obstacles in the healthcare system.

Topical and transdermal analgesic agents, including NSAIDs, opioids, rubefacients, capsaicin, clonidine, and lidocaine, are attractive treatment options and alternatives to oral analgesic agents for chronic pain (23). While topical drugs exert analgesic effects by penetrating the skin via passive diffusion, transdermal delivery is achieved through percutaneous

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absorption and relies on systemic distribution (24). Topical and transdermal analgesic agents offer the advantage of reducing systemic adverse effects. However, they are associated with application-site reactions, including irritation, burning, erythema, and discoloration (25). Although a recent Cochrane review found that topical salicylate, low-concentration capsaicin, clonidine, and lidocaine are not well supported by evidence, there may be beneficial outcomes for certain patients (24).

Gabapentinoids (gabapentin, pregabalin, and mirogabalin), originally developed as anticonvulsant drugs, are commonly utilized to manage various chronic pain conditions (26-29). They exert their analgesic effects by binding to the α-2-δ subunit of voltage-dependent calcium channels. Gabapentinoids may cause sedation, respiratory depression, and altered cognition, and they possess the potential for abuse (30-35).

Tricyclic antidepressants (TCAs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) are classes of antidepressants that have been shown to exhibit analgesic properties and be effective in the management of a variety of neuropathic conditions (36, 37). TCAs and SNRIs provide analgesia by increasing the activity of the serotonergic and noradrenergic descending pathways in the brainstem and midbrain (36, 38). Notably, the analgesic effects of antidepressants occur at lower doses than those required for the treatment of depression and are effective even in patients who are not clinically depressed (39). However, treatment with antidepressants may be limited due to their varying side-effect profiles, including dry mouth, dizziness, sedation, constipation, urinary retention, orthostatic hypotension, hypertension, and cardiac conduction abnormalities (38).

Interventional procedures vary by complexity and invasiveness, including trigger point injections, epidural steroid injections, sympathetic nerve blocks, radiofrequency ablation, cryoneuroablation, intrathecal drug delivery systems, and spinal cord stimulators, and deep brain stimulation (40-46). Although interventional therapies have associated risks, such as infection, dural puncture, spinal cord trauma, or nerve injury, the significant improvement in quality of life for certain patients makes them attractive treatment options, particularly in those who do not respond well to topical or oral analgesic agents (47-53).

Transcutaneous electrical nerve stimulation (TENS) is a surface-applied unit that delivers low voltage electrical current through the skin to produce analgesia. Although TENS may provide effective analgesia for some patients, insufficient evidence supports its efficacy in chronic pain management (54).

Psychosocial treatment modalities, which include cognitive behavioral therapy, mind-body therapy, and physical and occupational therapy, can improve the overall pain experience by addressing the psychological and social factors that influence and account for the variability in the experience of pain (55, 56).

Conolidine has unique qualities that can be beneficial for the management of chronic pain. Conolidine is found in the bark of the flowering shrub T. divaricata, otherwise known as the pinwheel flower or crepe jasmine, and is used in traditional Chinese, Ayurvedic, and Thai medicine to treat pain and fever (57). The compound makes up .00014% of T. divaricata bark. Tabernaemontana divaricatea contains several alkaloid compounds with a carbon-based framework resembling opioids (57). It is plausible that conolidine induced analgesia may lack complications associated with classic opioid medications (58). It is now being investigated for its effects on the atypical chemokine receptor (ACK3), an opioid scavenger of the dynorphin, enkephalin, and nociceptin families (59, 60). The ACK3 receptor has been found to regulate the availability of these opiates to classical opiate receptors. It is found in high concentrations in several important opiate-related centers of the brain (59). It was demonstrated that this novel receptor does not trigger the G protein cascade signaling pathway, and peptides specific to this receptor block the downregulatory effect it has on endogenous opiate levels, resulting in increased availability of opiate peptides for other classical opioid receptors (58). Modulation of this receptor has been postulated as an alternative opiate system target, and evaluations by Szpakowska et al. found it to be highly responsive to conolidine (58). Conolidine is a potent non-opioid analgesic and has been found to lack the typical complications associated with opiate analgesics like nausea, vomiting, respiratory depression, constipation, tolerance, and physical dependence (60).

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Elucidating the precise pharmacological mechanism of action (MOA) of naturally occurring compounds can be challenging. Although Tarselli et al. (60) developed the first de novo synthetic pathway to conolidine and showcased that this naturally occurring compound effectively suppresses responses to both chemically induced and inflammation-derived pain, the pharmacologic target responsible for its antinociceptive action remained elusive. Given the difficulties associated with standard pharmacological and physiological approaches, Mendis et al. utilized cultured neuronal networks grown on multi-electrode array (MEA) technology coupled with pattern matching response profiles to provide a potential MOA of conolidine (61). A comparison of drug effects in the MEA cultures of central nervous system active compounds identified that the response profile of conolidine was most similar to that of ω-conotoxin CVIE, a $Ca_v2.2$ calcium channel blocker (61). More recently, conolidine has been identified to target the highly expressed atypical chemokine receptor ACKR3, which functions as a scavenger that prevents endogenous opioid peptides from binding to the classical opioid receptors (MOR, DOR, KOR, and NOP) (58, 59). As a modulator of ACKR3, conolidine increases the availability of endogenous opioid peptides, thereby inducing analgesia. Notably, ACKR3 is not modulated by prescription opioids and does not trigger classical G protein signaling but rather mainly relies on β-arrestin recruitment (59). Although recent studies have paved a pathway for conolidine as a potential novel analgesic agent in managing chronic pain, further studies are necessary to elucidate its precise MOA or numerous biologic targets.

Conolidine and cannabidiol are natural compounds with anti-nociceptive properties that may advance the future of chronic pain management (61). The shared mechanisms between the two may explain shared action regarding analgesia. The two compounds were compared using numerous firing parameters via multi-electrode arrays (61). The values were extracted from neuronal networks cultured and subjected to specific pattern recognition to similar compounds (61). Currently, the identification of novel compounds requires multiple functional screening assays incorporating isolated biological agents (61). These comparisons are made in a static environment, whereas ion gated channels operate in a specialized and interactive domain (61). Cultured networks create similar and realistic substrates to test CNS compounds (61). The drawback of the cultured network method is extracting and analyzing signature patterns for a given compound used for similar indexes (61). Multi-electrode arrays rely on single parameters for identifying differences in drug actions (61). During multi electrode array, conolidine and cannabidiol blocked Ca 2.2 channels (61).

Ca 2.2 channel blockade is important because Ca channels play key roles in pain perception by modulating calcium entry through neuron depolarization (61). Compounds that interact with the presynaptic Ca pathway are potential pain modulators due to Ca-dependent vesicle fusion effects (61). Secondarily, w-Conotoxin through Ca inhibits nociceptive signaling and reverses allodynia in animal models (61). Based on past research, Ca 2.2 channels are upregulated in sciatic nerve models of neuropathic pain (61). Knockout of the Ca 2.2 gene has been shown to reduce inflammation and neuropathic pain (61). Multidimensional scaling analysis has demonstrated the conolidine effect towards T-type calcium channel Ni whom Cannabidiol is known to inhibit (61). The inhibition of T type calcium channel could be caused by Ca 2.2 and Ca 3 inhibition (61). The model suggests Ca 2.2 and Ca 3 channels play an important role in conolidine's mechanism of action (61).

2.4. Clinical Studies Summary

Research on conolidine is limited, but the few studies currently available show that the drug holds promise as a possible opiate-like therapeutic for chronic pain. Conolidine was first synthesized in 2011 as part of a study by Tarselli et al. (60) The first de novo pathway to synthetic production found that their synthesized form served as effective analgesics against chronic, persistent pain in an in-vivo model (60). A biphasic pain model was utilized, in which formalin solution is injected into a rodent's paw. This results in a primary pain response immediately following injection and a secondary pain response 20 - 40 minutes after injection (62). The second pain phase is due to an inflammatory response, while the primary response is acute injury to the nerve fibers. Conolidine injection was found to suppress both the phase 1 and 2 pain response (60). This suggests conolidine effectively suppresses both chemically or inflammatory pain of both an acute and persistent nature. Further evaluation by Tarselli et al. found conolidine to have no affinity for the mu-opioid receptor, suggesting a different mode of action from traditional opiate analgesics. Furthermore, this study revealed that the drug does not alter locomotor activity in mice subjects, suggesting a lack of side effects like sedation or addiction found in other dopamine-promoting substances (60).

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In another study completed by Arita et al., a related derivative of conolidine, known as DS39201083, was discovered (63). It was found to be even more potent than conolidine while also showing no mu-opioid receptor activity. Several other groups have also been successful in synthesizing derivatives of conolidine (64, 65). This study aimed to produce conolidine derivatives with an even greater analgesic effect and oral bioavailability. Using various synthesis techniques, derivatives were produced and tested for effect, ultimately resulting in the selection of compound 17a, which exhibited a more potent analgesic efficacy of 92% (63). This compound was also tested for mu-opioid receptor activity, and like conolidine, was found to have no activity at the site. Utilizing the same paw injection test, several alternatives with greater efficacy were found that inhibited the initial pain response, indicating opiate-like activity. Given the different mechanisms of these conolidine derivatives, it was also suspected that they would provide this analgesic effect without mimicking opiate side effects (63). The same group synthesized additional conolidine derivatives, finding an additional compound known as 15a that had similar properties and did not bind the mu-opioid receptor (66).

Most recently, it has been identified that conolidine and the above derivatives act on the atypical chemokine receptor 3 (ACKR3. Expressed in similar areas as classical opioid receptors, it binds to a wide array of endogenous opioids. Unlike most opioid receptors, this receptor acts as a scavenger and does not activate a second messenger system (59). As discussed by Meyrath et al., this also indicated a possible link between these receptors and the endogenous opiate system (59). This study ultimately determined that the ACKR3 receptor did not produce any G protein signal response by measuring and finding no mini G protein interactions, unlike classical opiate receptors, which recruit these proteins for signaling. Importantly, these receptors were found to have been activated by a wide range of endogenous opioids at a concentration similar to that observed for activation and signaling of classical opiate receptors. In turn, these receptors were found to have scavenging activity, binding to and decreasing endogenous levels of opiates available for binding to opiate receptors (59). This scavenging activity was found to offer promise as a negative regulator of opiate function and as an alternative manner of control to the classical opiate signaling pathway.

Szpakowska et al. also studied conolidone and its action on the ACKR3 receptor, which helps to explain its previously unknown mechanism of action in both acute and chronic pain control (58). It was found that receptor levels of ACKR3 were as high or even higher as those of the endogenous opiate system and were correlated to similar areas of the CNS. This receptor was also not modulated by classic opiate agonists, including morphine, fentanyl, buprenorphine, or antagonists like naloxone. In a rat model, it was found that a competitor molecule binding to ACKR3 resulted in inhibition of ACKR3's inhibitory activity, causing an overall increase in opiate receptor activity. While the opiate receptor relies on G protein coupling for signal transduction, this receptor was found to utilize arrestin activation for internalization of the receptor. Otherwise, the receptor promoted no other signaling cascades (59) Modifications of conolidine have resulted in variable improvement in binding efficacy. This binding ultimately increased endogenous opioid peptide concentrations, increasing binding to opiate receptors and the associated pain relief.

While it is unknown whether other unknown interactions are occurring at the receptor that contribute to its effects, the receptor plays a role as a negative down regulator of endogenous opiate levels via scavenging activity. This drug-receptor interaction offers an alternative to manipulation of the classical opiate pathway. It may provide many of the same benefits of pain relief without the pitfalls of opiate use. Future facets of study could revolve around molecular analogs to conolidine, including percine, apparicine, and stemmadenine (58).

CNCP is a multifactorial process. Biological, psychological, and social factors influence and account for the variability in the experience of pain. Despite advances in research and the discovery of novel agents to manage CNCP, it remains a significant and life-altering problem. An array of pain management techniques, pharmacologic and nonpharmacologic, are available, each with notable limitations and therapeutic profiles that minimize their use in certain patients. However, opioids, despite the lack of evidence supporting their efficacy in managing CNCP and substantial liabilities associated with their use, have become one of the most utilized therapeutic modalities. In light of the current opioid epidemic, there is an urgent need to identify novel agents and mechanisms with improved safety profiles to treat CNCP. Researchers have recently identified and succeeded in synthesizing conolidine, a natural compound that shows promise as a potent analgesic agent with a more favorable safety profile. Although the exact mechanism of action remains elusive, it is currently postulated that conolidine may have numerous biologic targets. Presently, conolidine has been shown to inhibit $Ca_v2.2$ calcium channels and increase the availability of endogenous

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opioid peptides by binding to a recently identified opioid scavenger ACKR3. Although the identification of conolidine as a potential novel analgesic agent provides an additional avenue to address the opioid crisis and manage CNCP, further studies are necessary to understand its mechanism of action and utility and efficacy in managing CNCP.[28]

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