Update and review on the basics of pain management

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ABSTRACT

يستعرض هذا المقال نتائج الأبحاث التي سلطت الضوء على أنواع العقاقير المستخدمة في علاج الآلام المزمنة والحادة. ويقوم هذا المقال أيضاً بعمل مقارنة بين سلبيات وإيجابيات مجموعة من العقاقير الرئيسية المستخدمة للتحكم بالألم (مثل الأفيونات، ومضادات الالتهاب الخالية من الستيرويد)، والعقاقير الثانوية التي تُستخدم في تخفيف الألم (مثل المرخيات العضلية، ومضادات الاكتئاب، ومضادات الاختلاج)، بالإضافة إلى تحديد دواعي استعمالها. تهدف هذه الدراسة إلى استعراض البيانات المستجدة والدقيقة حول أنواع العقاقير المسكنة والخيارات المتاحة في استخدامها.

This article reviews the major findings of research related to pharmacological pain therapies used in treating acute and chronic pain, it compares advantages and disadvantages of certain drugs used mainly in pain management (for example, opioids and non steroidal anti-inflammatory drugs), and others that have a secondary use in pain management (for example, skeletal muscle relaxants, antidepressants, and anticonvulsants) and their intended indications. Our goal is to present accurate up-to-date applicable data on these pharmacological choices.

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There are numerous different definitions for pain. The most widely accepted definition of pain is the one used by The International Association for the Study of Pain (IASP). It defines pain as: "An unpleasant sensory and emotional experience arising from actual or potential tissue damage or described in terms of such damage."[1] Margo McCaffrey gave the definition of pain that is most appropriate for use in clinical practice in 1968. Defining pain as "whatever the experiencing person says it is, existing whenever he says it does."[2] Many, if not most, illnesses cause pain.[3] Therefore, pain differs from other sensations in that it is a warning signal of noxious stimuli causing or threatening to cause tissue damage, pain motivates us to withdraw from potentially damaging situations, protect a damaged body part while it heals, and avoid those situations in the future.[4] However, pain is almost invariably an unpleasant sensation that despite its protective function; may hinder one's daily activity, general functioning, and alters emotions.[3] Indeed, depending upon the severity of pain, the quality of life may be reduced. Furthermore, every individual has his own limits of coping with pain; once the limits are exceeded life is rendered intolerable.[5] Alas, pain is a common reason for a physician consultation, since many ailments are the cause of pain.[6] Therefore, easing the suffering and improving the quality of life of those living with pain is an important issue in medicine. While pain usually subsides instantly with the removal of the inciting stimulus or pathology, and healing of the damaged tissue ensues, pain may persist, even if the tissue has completely recovered and the stimulus completely removed.[7] Furthermore, it may arise in the absence of any detectable stimulus, damage, or pathology.[7] Restoration of normal function and alleviation of pain is the aim of any therapeutic approach towards pain. The pharmacological management of pain constitutes an important branch in medicine; therefore, a comprehensive review regarding the basics and the latest updates of this management line is our main purpose.

The basic physiology of pain. Somatogenically there are 2 main types of pain, nociceptive, and neuropathic.[8] A nociceptor is a sensory receptor that detects noxious stimuli; these stimuli may be mechanical, thermal, or chemical.[5,9,10] Activated nociceptors transmit a signal through the spinal cord, brain stem, thalamus, to the brain; this signal is interpreted as pain.[5,9] Nociception, therefore, is defined as "the neural processes of encoding and processing noxious stimuli."[11] Physiologically, nociception is modulated centrally, namely, within the

CNS, or peripherally, namely, within the peripheral nervous system by the use of several different types of opioid receptors both central and peripheral.[5,9] There are 3 areas within the CNS that are involved in modulating nociception: the periaquaductal grey matter, the nucleus raphe magnus, and the nociception inhibitory neurons within the dorsal horns of the spinal cord.[5,9] These 3 areas are controlled by the brain and function as an endogenous analgesic system.[5,9] Enkephalin is a major neurotransmitter depicted in this system.[5,9] Peripheral modulation of nociceptors occurs at the site of injury.[9] In the periphery, immune cells due to inflammation produce many opioid peptides.[9] These endogenous opioids act on different opioid receptors on the afferent nerve fibers to reduce the pain that would otherwise be felt.[9] Neuropathic pain is the pain caused by a lesion in the somatosensory nerves when they are structurally or functionally damaged.[12] It is called central pain if the lesion is in the CNS,[12] or called peripheral neuropathic pain if the lesion is in the peripheral nervous system,[12] and called mixed neuropathic pain if it has both central and peripheral components.[12] In addition to the pain modulating mechanisms described above, reducing the pain signals that are being transmitted can modulate neuropathic pain.[5,9,13]

Classification of pain. Pain can be classified in many ways, for example, based on etiology, anatomical region, system affected, temporal characteristics, severity, and duration; it is the later, the duration, which we emphasized upon in this paper due to the simplicity of the classification and the features of each type of pain.[7]

Acute versus chronic pain. Pain is usually transient, and once the noxious stimulus is removed, pathology corrected, and damage healed; pain resolves.[7] However, pain may be persistent even after the removal of the cause.[7] Furthermore, pain maybe idiopathic.[7] In all instances pain is classified into acute pain and chronic pain.[7] The distinction between acute and chronic can be dependent upon an arbitrary interval of time from onset; the most commonly used indicators are 3 and 6 months since the onset of pain.[14] An alternative definition of chronic pain, involving no duration is "pain that extends beyond the expected period of healing."[14,15] But, perhaps, the best definitions of acute and chronic pain are; acute pain is defined as "pain of recent onset and probable limited duration. It usually has an identifiable temporal and causal relationship to injury or disease."[16,17] While chronic pain is defined as "pain that commonly persists beyond the time of healing of an injury and frequently there may not be a clearly identifiable cause."[17] Rather than distinct entities, acute and chronic pain are believed to represent a continuum. Indeed, untreated or insufficiently treated acute pain can become chronic.

Treatment of pain. Pain is the most important and most common reason people seek medical attention.[6] In addition to being an unpleasant sensation that reduces the quality of life, pain prompts an immediate intervention, because pain is a sign of damage or impending damage that must be dealt with instantly.[3,4] Since pain is a subjective experience an extensive protocol for assessing pain, and monitoring treatment is necessary.[18,19] There is a wide array of treatments available for pain ranging from simple drug intervention to major surgeries. Treatment differs from person to person depending on duration, type, and severity of pain.[18,19] The pharmacological management is presented in this review.

Diagnosis and assessment of pain. Diagnosing pain depends on diagnosing the underlying cause of the pain, by good history taking, physical examination, and investigations (CT, MRI, discography, myelograms, EMG, bone scans, ultrasound), and by focusing on the patient's health behavior.[20] Assessing the patient's pain is a crucial step for deciding the course of the treatment, a patient's self-report of his/her pain provides the most valid measurement of the experience.[21] We need the help of certain tools to qualify and quantify the pain. The McGill pain questionnaire is one of the most commonly used tools for assessment of pain, and for children, the Faces Pain Scales is a very useful tool.[22,23]

Management of acute and chronic pain. Acute pain is often associated with an identifiable injury or trauma as a known antecedent, mostly acute pain serves a purpose: pointing towards a problem that needs to be addressed.[24,25] Acute pain, therefore, is mainly associated with a help seeking behavior.[25] Physiologic responses to acute pain are that of sympathetic nervous system activation, which includes tachycardia, tachypnea, and sweating.[25] Therefore, depending on severity, acute pain may easily be recognized. Chronic pain is different from acute pain. Mostly it does not serve a biological purpose.[25] While the suffering engendered may be as great as is that in acute pain, it is subjectively experienced and objectively displayed in a very different way.[25] Chronic pain is associated with signs of depression, which may include: physical and mental withdrawal, anorexia, anhedonia, lethargy, loss of libido, and sleep disturbances.[25] Thus, chronic pain is difficult to identify, constituting a barrier in successful treatment.[25]

Pharmacological management. Based on the characteristics of either acute or chronic, the management differs. The management of acute and chronic pain mainly involves the use of opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and Acetaminophen (Paracetamol). Capsaicin and inhaled nitrous oxide are beneficial in some acute situations. Some antidepressant and anticonvulsant drugs are used in chronic pain management. Skeletal muscle relaxants

are also beneficial in alleviating pain caused by muscle spasm. Local anesthetics provide analgesia and are beneficial especially in the treatment of neuropathic pain.

Opioids. In 1803, Friedrich Sertürner a German pharmacist was the first to isolate Morphine, the prototypical opioid agonist.[26] The source of this alkaloid was the opium poppy (*Papaver somniferum* and *Papaver album*).[26] The term opioid includes: natural opiates, semisynthetic opioids, synthetic opioids, and endogenous opioid peptides. There are 3 classical opioid receptors designated by the Greek alphabets mu (μ), kappa (κ) and delta (δ).[27] Each opioid receptor has a different function and exhibits a different specificity for the drug(s) it binds.[27] Opioids are classified on the basis of their interaction with their respective receptors to agonists, mixed agonist-antagonists, and antagonists.[28] Opioid agonists produce their effect by binding to the specific G protein-coupled opioid receptors to inhibit adenylyl cyclase activity,[29] activate the receptor-operated potassium currents and suppress the voltage-gated calcium currents.[30] All these lead to hyperpolarization of neuronal cell membranes involved in pain signal transmission and subsequently suppression of neurotransmitter release, thus, analgesia ensues.[31] Opioids that are mixed agonist-antagonists exert their action by activating one opioid receptor subtype and blocking another subtype.

Clinical uses/adverse effects of opioids. Opioid receptors are widely distributed throughout the body, so they have a wide array of clinical applications, but by the same token they have many adverse effects.[32] Other than analgesia, opioids are used for dyspnea due to pulmonary edema. Their proposed mechanism of action is by reducing anxiety and lowering pre-/after-load.[32] They can also be used as antitussives by depressing the cough reflex directly through their effect on the cough center in the medulla.[32] Opioids are thought to reduce peristalsis; thus, their use as antidiarrheals.[32] They can also reduce shivering by blocking subtypes of α_2 adrenoceptors.[32]

Despite the many benefits of opioids there are some severe adverse effects that limit the use of opioids. The most feared of the side effects is respiratory depression, which is considered to be the most common cause of death associated with opioid use. Opioids cause respiratory depression by decreasing the responsiveness to PCO_2 and also decreasing electrical stimulation in the respiratory centers in the brain stem. These effects are modulated by opioid receptors in the brain stem. The risk of respiratory depression is heightened in patients with pulmonary pathology and is dose-dependent, the higher the opioid dose, the higher the risk. In addition, sleep could precipitate the depressive effect of opioids on respiratory function. Furthermore, respiratory depression increases PCO_2, which causes vasodilation with the resultant increase in intracranial pressure. Therefore, it is contraindicated in head injuries.[32] Another side effect commonly linked with opioids is tolerance. The mechanism of opioid tolerance may involve "receptor uncoupling," which means loss of agonist signaling to the effector system. Cross-tolerance also develops owing to the similarity between various opioids. However, cross-tolerance is not complete and this clinical observation has led to the concept of "opioid rotation," which is mainly used in cancer patients because they require long-term use of opioids.[33] N-methyl d-aspartate antagonists (NMDA), for example, ketamine have been found in vivo to block opioid tolerance.[34] In addition, δ-receptor antagonists with μ-receptor agonists are emerging as a strategy to avoid the development of tolerance.[35] A feared side effect of chronic use is physical dependence. On abrupt discontinuance, physical dependence is revealed as an abstinence syndrome that is characterized by rhinorrhea, lacrimation, yawning, chills, gooseflesh, muscle aches, vomiting, diarrhea, hyperthermia, hyperventilation, mydriasis, anxiety, and hostility. A more intense state of precipitated withdrawal lasting for around one hour is observed when an opioid antagonist is administered to a physically dependent individual. There is a proportionate relationship between opioid dependence and opioid tolerance. As tolerance increases the dependence increases due to the proportionate increase in dosage.[36] The euphoria produced by opioids promotes their compulsive use, which in time causes psychological dependence. In addition, the addict experiences a pleasurable feeling that is likened to an intense sexual orgasm.[35] Major side effects of opioids are summarized in **Table 1**.

Table 1 - Adverse effects of opioids versus non-steroidal anti-inflammatory drugs (NSAIDs).[35,62]

Opioids	NSAIDs
Respiratory depression	Gastrointestinal irritation
Tolerance	Gastrointestinal ulceration
Physical and psychological dependence	Gastrointestinal bleeding
	Renal papillary necrosis
Nausea and vomiting	Hepatotoxicity
Constipation	Respiratory depression
Dry mouth	Respiratory acidosis
Confusion	Bronchospasm
Hallucinations	Hypersensitivity reactions
Delirium	Thrombocytopenia
Hypothermia	Myocardial infarction
Change in heart rate	Stroke
Dizziness	Diarrhea
Headache	Aplastic anemia
Urinary retention	Headache
Muscle rigidity	Dizziness

Clinically used opioids. Morphine, is the standard strong opioid analgesic and the first opioid discovered.[37] It is a natural opioid with pure μ-receptor agonist activity.[37] It is indicated for severe acute pain or moderate to severe chronic pain.[37] Morphine is given orally, rectally, or as an injectable formulation.[37] In an acute situation, morphine is administered intravenously whereas it is given chronically as an extended release tablet.[37] Morphine is very well distributed in the body, and it enters all body tissues.[37] Approximately 70% of morphine undergoes conjugation in the liver and emerges as morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G).[38] Both M6G and M3G still retain the μ-receptor agonist activity of morphine.[38] They are excreted with the unmetabolized morphine by the kidneys.[38] Hepatic and renal disease may significantly prolong the effect of morphine and its metabolites.[39]

Hydromorphone, is a semisynthetic hydrogenated ketone of morphine. Like morphine, it acts primarily on μ-receptors and to a lesser degree on δ-receptors.[40] Hydromorphone is much more potent than morphine with a relative potency of 8:1.[41] It has the same application of morphine except, it is preferred over morphine for patients with renal failure.[41] It is administered as tablets, solution, and powder.[41] Hydromorphone is distributed in all body spaces.[41] The liver metabolizes hydromorphone extensively rendering only 40% of the drug bioavailable.[41] Hydromorphone-3-glucuronide (H3G) is the resultant metabolite.[41] The H3G although similar in structure to M3G, is devoid of the agonistic activity.[41] Unlike morphine, both the liver, and the kidneys are responsible for excretion of hydromorphone and its metabolites.[41]

Oxycodone is a semisynthetic derivative of morphine.[42] It is used orally for moderate to severe pain mainly in an acute setting.[43] It is also used in postoperative, post exertion, and post partum pain.[42] In recent years, extended release preparations have been extensively used for chronic malignant and non-malignant pain.[42] Oxycodone is distributed in all body spaces.[42] The bioavailability of oxycodone is high in oral dosage.[44] However, it undergoes extensive hepatic conjugation and oxidative degradation to noroxycodone and oxymorphone, which have no analgesic effect and are excreted in urine.[44]

Fentanyl is the oldest synthetic piperidine opioid agonist.[46] It interacts primarily with μ-receptors.[45] Parenteral fentanyl is used as a first line treatment of acute pain.[46] Epidural fentanyl is used for postoperative analgesia.[45] A transmucosal preparation is used in the treatment of cancer patients with long standing severe pain.[45] Fentanyl is metabolized by CYP3A4 to hydroxyfentanyl and norfentanyl, which are inactive and non-toxic metabolites excreted by the kidneys.[46]

Methadone is a synthetic μ-receptor agonist that has an approximately equal potency to morphine.[47] However, it induces less euphoria and has a somewhat longer duration of action.[47] In addition to its opioid receptor activity, it is an antagonist of NMDA receptors.[48] The L isomer of methadone also inhibits the reuptake of serotonin and norepinephrine.[48] Methadone is increasingly used in the setting of cancer and chronic pain because it is an effective long-acting and relatively cheap opioid.[48] However, because of its long and highly variable half-life it is less useful and potentially dangerous when used in the treatment of acute pain.[48] Methadone is also used in controlled withdrawal of dependent abusers from heroin and morphine.[49] The administration of methadone is orally.[47] Methadone has a complex and variable half-life; it is metabolized in the liver by CYP3A4 mainly and the intestines and is excreted almost exclusively in feces.[50,51]

Codeine is suggested as the drug of choice in weak analgesia.[52] It exerts its pharmacological action through its transformation to morphine.[52] Its analgesic potency is approximately 50% of morphine because not all the administered codeine is transformed to morphine.[53] However, codeine has a higher oral effectiveness.[53] Codeine, in addition, is used as an antitussive.[53] The metabolism of codeine (a pro-drug) involves its activation by the hepatic microsomal enzyme CYP2D6 to morphine.[52] This enzyme is defective in approximately 10% of the population due to a genetic polymorphism this results in ineffectiveness of the enzyme.[53] Codeine is also metabolized by glucuronidation to codeine-6-glucuronide (C6G).[53]

Meperidine, is a synthetic opioid structurally unrelated to morphine.[54] It is a relatively weak opioid μ-receptor agonist with approximately 10% the effectiveness of morphine with significant anticholinergic and local anesthetic properties.[54] It is administered orally and parenterally.[54] It is used primarily to relive acute pain.[54] Meperidine is metabolized in the liver to normeperidine, which has a half-life of 15-30 hours as well as significant neurotoxic properties.[54] It causes CNS stimulation and seizures.[54] Excretion is by the kidneys.[54]

Pentazocine is a semisynthetic benzomorphan; it is a κ receptor agonist and a μ receptor antagonist or partial agonist.[55] It is administered orally, or through IV injection.[55] It is usually used to relieve moderate pain.[55] Pentazocine is metabolized almost exclusively in the liver to inactive glucuronides.[55]

Buprenorphine is a semisynthetic opioid derived from Thebaine, which is a natural opiate.[56] It is highly lipophilic and 25-50 times more potent than morphine.[56] Buprenorphine is a partial μ receptor agonist.[56] In naïve patients it acts like morphine,

however, it can precipitate withdrawal in morphine users.[56] Therefore, a major use of buprenorphine is in opiate detoxification.[56] Buprenorphine is relatively absorbed from most routes; therefore, it is available orally, sublingually, and parenterally.[57] The tablets are indicated for the treatment of opioid dependence, the injectable form is indicated for the relief of moderate to severe pain.[57] The liver metabolizes it and the resultant N-dealkylated and conjugated metabolites are detected in the urine, however most of the drug is excreted in the bile unchanged in the feces.[57]

Nonsteroidal anti-inflammatory Drugs (NSAIDs). A Scottish physician, Thomas John McLogan, launched salicin, extracted from the willow tree, in 1876,[58] which was later refined to salicylic acid by Charles Frederic Gerhardt in 1853 and was a breakthrough drug in the treatment of fever.[59] Nowadays, we know it has additional anti-inflammatory and analgesic effects. Its capacity to suppress inflammation makes it most useful in the management of disorders in which pain is related to the intensity of the inflammatory process.[60] Since aspirin the prototypic NSAID has a number of adverse effects, many other NSAIDs have been developed with better efficacy and less toxicity.[60] The NSAIDs act primarily by inhibiting both cyclooxygenase 1 (COX-1) and COX-2 enzymes. The (COX) enzymes catalyze the first step in prostaglandin synthesis. This leads to a decrease in prostaglandins with both beneficial and deleterious effects.[60]

Clinical uses/adverse effects of NSAIDs. Inflammation is a response to cell injury.[61] It is a complex process involving the immune system with activation of many mediators that produce many effects including fever and pain.[61] The nature of the pain produced due to inflammation could be acute or chronic.[61] The NSAIDs are mainly used as anti-inflammatory, anti-pyretic, and analgesic drugs.[61] In addition, they can also be used in more specific situations, such as patent ductus arteriosus in premature infants, dysmenorrhea, and aspirin is used as an anti-platelet aggregate.[61] The NSAIDs are the drugs most often reported as being responsible for adverse effects because of the large variety of side effects and their widespread use. Their usage can be associated with significant morbidity and mortality. The most common side effects and the side effects commonly associated with NSAIDs are the gastrointestinal effects. These are due to inhibition of prostaglandin synthesis, which leads to impairment of mucosal defensive factors, such as mucus, bicarbonate secretions, and mucosal blood flow. In addition NSAIDs have a direct toxic effect on the mucosa of the gastrointestinal tract. The adverse reactions range from superficial damage, to duodenal and gastric ulceration or fatal bleeding and perforation.[62] The NSAIDs can also cause renal impairment due to inhibition of prostaglandin synthesis in the kidney. It can be severe enough to cause non-oliguric renal failure.[63] Hepatotoxicity from NSAIDs ranges from mild hepatic dysfunction to Reye's syndrome from aspirin and hepatic necrosis from acetaminophen.[64] Aspirin, given its anti-platelet effect can also cause an increased risk of bleeding.[65] Large doses of salicylates carry a risk of respiratory depression and metabolic acidosis.[65] The NSAIDs can cause hypersensitivity reactions in susceptible individuals, which include urticaria and angioedema.[65] Major side effects of NSAIDs are summarized in **Table 1**.

Clinically used NSAIDs. Aspirin, the traditional NSAID, is a weak organic acid (acetylsalicylic acid) that is unique among NSAIDs, in that it irreversibly inactivates the cyclooxygenases.[66] Aspirin is the most widely used analgesic, anti-pyretic, and anti-inflammatory agent. It is still the standard for the comparison and evaluation of other NSAIDs.[66] Aspirin is administered orally. Fifty-eighty percent of aspirin in the blood is bound to plasma proteins (mainly albumin), while the rest remains in the active ionized state, protein binding is concentration dependent.[67] The salicylates are rapidly absorbed from the stomach and small intestine yielding a peak plasma level in 1-2 hours.[67] After that aspirin is rapidly hydrolyzed to acetic acid and salicylates by esterases in tissue, liver, and blood.[68] Excretion of aspirin is through the kidneys.[68] The COX-2 specific inhibitors (for example, Celecoxib, Meloxicam), produce less adverse effects than non-specific COX inhibitors, in addition they have no impact on platelet aggregation, however, they do not offer the cardioprotective effects of traditional NSAIDs, but they cause the same renal toxicities.[69,70] Ibuprofen is derived from phenylpropionic acid and is a non-selective COX inhibitor.[71] At lower doses (200mg) it acts only as an analgesic and anti-pyretic and is available without a prescription, but at higher doses it acts as an anti-inflammatory and requires a prescription.[71] Ibuprofen is rapidly absorbed after oral administration and peak plasma concentration levels are reached within 15-30 minutes.[71] In acute situations it is given intravenously.[71] It can also be applied topically as a cream preparation where it penetrates the fascia and muscle.[71] Ninety nine percent of ibuprofen is bound to plasma proteins; it passes slowly into the synovial spaces. In addition, it readily crosses the placenta.[71]

Indomethacin, a methylated indole derivative, was first introduced in 1963 as an anti-inflammatory for the treatment of rheumatoid arthritis; it was a widely used drug although it's toxicity limits the use of the drug nowadays.[72] Indomethacin has an anti-inflammatory, anti-pyretic, and analgesic effects.[72] It is a potent nonselective COX inhibitor and may also inhibit phospholipase A and C, which in turn causes a reduction

in neutrophil migration.[73] Indomethacin is indicated for use in gout and ankylosing spondylitis as well as other rheumatic conditions, but is now commonly replaced with an acetaminophen/prednisolone combination, which has similar efficacy but with less side effects.[74] The gastrointestinal tract rapidly absorbs indomethacin after oral ingestion, with a peak concentration occurring 1-2 hours after ingestion.[74] Indomethacin is ninety percent bound to plasma proteins and also extensively bound to tissues with increased concentrations in synovial fluids.[74] Indomethacin is metabolized in the liver by conjugation and N-deacylation to inactive metabolites, which are excreted in the urine, bile, and feces.[74]

Acetaminophen, also known as Paracetamol, is a widely used analgesic and antipyretic.[75] It was originally synthesized by Morse in 1878 but was first used clinically in 1887 by von Mering.[76] However, back then it was quickly discarded in favor of phenacetin.[76] Phenacetin is a prodrug that is metabolized to acetaminophen.[77] It is more toxic than its active metabolite.[77] The studies of Brodie and Axelrod[78] led to the "rediscovery" and marketing of acetaminophen in the 1950s in the United States as an analgesic replacement for phenacetin, which was "condemned" for its nephrotoxicity. Currently, acetaminophen is the only drug that belongs to the class of drugs known as "aniline analgesics" in use today.[79] Acetaminophen easily crosses the blood brain barrier and acts by inhibiting prostaglandin synthesis in the CNS.[80] It is a weak COX-1 and COX-2 inhibitor, but recent research indicates the presence of a different variant of the COX enzymes; COX-3 enzymes, which are present mainly in the CNS.[80] This might explain acetaminophen's selective inhibition of the COX enzymes in the CNS.[80] While it has analgesic and antipyretic properties comparable to those of aspirin or other NSAIDs, it cannot be classified as NSAIDs because it lacks the anti-inflammatory effect.[80] Acetaminophen is indicated as a replacement for aspirin and other NSAIDs, in those situations in which aspirin is contraindicated or anti-inflammation is not required.[80] Because of its selectivity for COX-3, it does not significantly inhibit the production of the pro-clotting thromboxanes.[80] Unlike opioids, acetaminophen is used for mild to moderate pain acutely and chronically.[81] The administration of acetaminophen is mainly orally although other less common routes are available.[82] Acetaminophen is metabolized by the liver microsomal enzymes in 3 pathways (Glucuronidation, Sulfation and N-hydroxylation) to inactive metabolites.[83] The major side effects of acetaminophen include liver and/or kidney toxicities that range in severity from mild elevation of liver enzymes to fatal hepatic failure, and acute renal tubular necrosis depending on the dose.[84] The kidneys excrete acetaminophen and its metabolites.[83,85]

Centrally acting analgesics. The pharmaceutical company Grünenthal GmbH developed Tramadol in the late 1970s.[86] It is an atypical analgesic that is synthetically derived from codeine, but is often not regarded as an opioid, because in addition to its centrally acting opioid μ-receptor agonistic activity, it primarily acts by inhibiting serotonin reuptake.[87] Tramadol has also been found to block the norepinephrine transporter.[87] Within the CNS, the increase of serotonin, and norepinephrine is associated with analgesia through the modulation of the physiological analgesic system.[87] Its actions make it ideal to use for moderate to moderately severe pain both in acute and chronic settings.[88] In addition, Tramadol is also used for fibromyalgia and other chronic musculoskeletal pains.[88] Oral and injectable forms of Tramadol are available.[89] The liver metabolizes Tramadol by O-demethylation and N-demethylation to 5 different metabolites of which O-desmethyltramadol is the most important.[90] There are 2 enantiomers of O-desmethyltramadol: (+)-O-desmethyltramadol and (-)-O-desmethyltramadol, both of which are inactive as serotonin reuptake inhibitors.[90] However, (+)-O-desmethyltramadol is more potent as a μ-receptor agonist and (-)-O-desmethyltramadol retains activity as a noradrenaline reuptake inhibitor.[90] Therefore, the mix of both the parent compound and metabolites produced contributes significantly to the complex pharmacological profile of Tramadol.[87] Tramadol and its metabolites have many adverse effects that mimic the adverse effects of opioids, and in addition it produces seizures, however, they produce less respiratory depression and less constipation.[91] The excretion of Tramadol and its metabolites are through the kidneys.[90]

Other drugs used in analgesia. Capsaicinoids. Capsaicin is the active component of chili pepper.[92] It was extracted from the genus *Capsicum*, which was native to the Americas.[92] In various parts of the world, the leaves and fruits of Capsicum are reported to have application in the treatment of painful menses, toothaches, and muscle pain.[93-99] Capsaicin causes its analgesic effect by acting on the transient receptor potential channel, vanilloid type 1 (TRPV1). The nonselective ligand gated ion channel vanilloid receptor is expressed centrally and peripherally in primary sensory neurons (nociceptors). Activation of these receptors selectively activates sensory neurons that convey information on noxious stimuli to the CNS. Persistently high intracellular calcium levels subsequently desensitize the primary sensory neurons causing degeneration of pain signaling.[100-102] Topical creams containing capsaicin are used to treat pain from post-therapeutic neuralgia, diabetic neuropathy, osteoarthritis, and rheumatoid arthritis, pruritus, psoriasis, mastectomy, and cluster headaches.[103]

Skeletal muscle relaxants. Spasmolytic drugs are used in the treatment of pain associated with muscle spasticity or spasm.[104] They can reduce muscle tone and the associated pain by one of 2 mechanisms: either by modifying the stretch reflex arc or by interfering directly with the skeletal muscle (namely, excitation-contraction coupling).[104] The drug of choice is probably baclofen, which acts directly on the muscle.[105] Baclofen is a derivative of the inhibitory neurotransmitter γ-aminobutyric acid GABA and appears to be an agonist at the $GABA_B$ receptor inducing muscle relaxation.[105] A drug that modifies the stretch reflex arc, is diazepam, it acts by facilitating the action of GABA at the central $GABA_A$ receptors and thereby reducing muscle tone.[105] Spasmolytics are used in both acute and chronic settings.[104]

Antidepressants. Persistent chronic pain is accompanied frequently by anxiety and depression.[106] Thus, it is not surprising that the use of antidepressants is a standard part of chronic pain management especially in depressed patients or patients suffering insomnia.[106] There is evidence that some of these drugs have some direct analgesic properties.[107] The tricyclic anti-depressants are frequently used for the treatment of chronic lumbar and neuropathic pains by inhibiting the reuptake of 5HT and/or noradrenalin in neurons in the brain and spinal cord, eventually causing a decrease in neurotransmitter release in synapses of nerves responsible for the conduction of pain.[107,108]

Anticonvulsants. The usefulness of anticonvulsants in neuropathic pain is well established. Phenytoin was first reported as a successful treatment for trigeminal neuralgia in 1942.[109] There are several classes in use today, which can be broadly classified as sodium channel blockers (carbamazepine, phenytoin), glutamate inhibitors (lamotrigine, gabapentin), GABA potentiators (sodium valproate, tiagabine), or with more than one effect (topiramate).[110] Many anticonvulsants block the activity of use-dependent sodium channels.[111] They stabilize the presynaptic neuronal membrane preventing the release of excitatory neurotransmitters and decrease the spontaneous firing rate in damaged and regenerating nociceptive fibers.[111] Conditions that may respond to anticonvulsants include, trigeminal neuralgia, glossopharyngeal neuralgia, and various neuropathies.[112]

Ketamine. Ketamine is a short-acting intravenous drug with a verity of actions, it can produce profound analgesia with stimulation of the central sympathetic system, which, in turn causes an increase in blood pressure and cardiac output.[113] Ketamine is used mainly in induction and maintenance of general anesthesia, and outside the medical world it is also used as a hallucinogenic recreational drug. Ketamine achieves its analgesic effect by acting as a NMDA receptor antagonist and as a weak opioid receptor agonist.[113]

Local anesthetics. Blockade of the voltage-gated sodium channels results in blockage of the pain impulses traveling in the afferent nerve fibers peripherally and centrally with diminished pain sensation.[114] The use of some local anesthetics (for example, lidocaine) can provide analgesia mainly in painful acute settings.[115] In addition, oral formulations of some local anesthetics (for example, mexiletine and tocainide) are used to relive neuropathic pain.[116]

In conclusion, a great degree of overlap in the agents used to treat acute and chronic pain is observed when viewing the pharmacological treatment of pain. This overlap is due to the mechanisms of action of the various agents applied. Therefore, many agents are useful in both acute and chronic settings. However, there are some that are useful in an acute application mainly, or a chronic application mainly. Agents that are useful mainly in acute pain are: oxycodone, fentanyl, meperidine, ibuprofen, capsaicin, lidocaine, and ketamine. Whereas, agents that are beneficial mainly in managing chronic pain are: methadone, tricyclic anti-depressants, and anticonvulsants.

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