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Chronic pain, a narrative review for the internist in 2024

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Abstract. Chronic pain is a complex and pervasive condition that profoundly affects individuals physically, emotionally, and socially. This narrative review aims to provide internists and healthcare professionals with a comprehensive overview of chronic pain, its various types, pathophysiology, epidemiology, clinical presentation, evaluation tools, and the burden it imposes on patients. We discuss the importance of recognizing chronic pain as a legitimate condition and the need for a compassionate, individualized approach to management. The review highlights the role of both pharmacological and non-pharmacological interventions in treating chronic pain, emphasizing the value of reducing pain, improving function, enhancing quality of life, and minimizing medication dependence. Additionally, we touch upon the promising future of pain treatment, including advancements in technology and personalized medicine. While not a comprehensive systematic review, this article serves as a valuable resource for healthcare providers seeking to understand, manage, and treat chronic pain effectively in their daily practice.



Fig. 1. "Chronic pain, a trip over troubled waters" by OpenAI. (2023). DALL-E [AI model]. https://openai.com/dall-e for "Chronic pain, a narrative review for the internist in 2024"

Keywords: chronic pain, management, treatment, evaluation tools.

What is new? What is important?

We acknowledge the organic mechanisms of chronic pain, the role of sensitization and its genetic and psychosocial components.
We stress the critical role of fostering resilience, recognizing its impact on patients' ability to cope with chronic pain.
Reuptake Inhibitors (SSRIs) and Tricyclic Antidepressants (TCAs) have an essential place in the pharmacological treatments for chronic pain.
We underscore the emerging role of video games and Virtual Reality (VR) as innovative tools in pain management.
We reinforce the essential role of non-pharmacological strategies that improve patient quality of life and reduce dependency on medications in chronic pain.

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INTRODUCTION

"Life is pain". This powerful statement, borrowed from the movie "The Princess Bride", captures the universal nature of human suffering. Our capacity to experience and respond to pain is often considered as one of the pillars of the definition of what it means to be human. As stoicism sees it, we need to accept and have a rational response to life's challenges, including pain, that should be embraced as an inherent part of existence.

Usually, pain represents the body's response to harmful or potentially harmful stimuli, manifesting as an unpleasant sensation. However, pain can also be present in the absence of any identifiable tissue damage. Pain that persists beyond the normal time of healing and recovery is called chronic pain.

Regardless of its subtype, recognizing pain, particularly chronic pain as a disruptive force that profoundly alters a patient's reality requires that physicians carefully balance empathy and objectivity. While medical training often emphasizes objectivity, the ability to empathize with and show compassion towards patients is an invaluable asset that internists develop throughout their careers. This narrative review aims to provide internists with a synthesis of objective and subjective insights that could help navigate – and alleviate – their patients' pain, with a specific focus on chronic pain. To achieve this, we will provide an overview of some pathophysiological and epidemiological aspects, the main classifications and mechanisms tied to chronic pain, and its burden. We will subsequently discuss the workup of the patient experiencing pain, the different approaches to pain management, the main pharmacological and non-pharmacological treatment options, the benefits, and limitations of treating pain, and conclude with some key points as a takeaway message.

TYPES OF CHRONIC PAIN, PHYSIOPATHOLOGY, AND EPIDEMIOLOGY

Medical professionals are trained to objectively assess pain as a sensation localized in time and space to a specific part of the body. However, the body part where pain is felt is merely the site of pain perception. Sometimes, the mechanisms underlying the origin of pain – the place where the painful stimuli truly act to generate the painful response – are far more complex.

DEFINITION OF CHRONIC PAIN

According to the International Association for the Study of Pain (IASP), pain is classified as either acute or chronic. Chronic pain is a type of pain that typically lasts for more than three months, beyond the usual healing time for tissue injury. Because of its duration, it is often seen as a pathological condition in itself.

CLASSIFICATION

The IASP classifies chronic pain as either primary or secondary. Primary chronic pain is a condition where the pain itself is the main problem, arising without any evident cause. Secondary chronic pain stems from a recognizable etiology but it persists beyond the typical healing time of a specific tissue. It can result from a consistent cause that induces tissue damage, such as an injury, cancer, disease, or medical treatment. Chronic pain is classified as either somatic (or visceral), neuropathic pain or nociplastic (or functional). While somatic pain originates from either the body's surface or deep tissues, neuropathic pain results from damage to the nervous system. Nociplastic pain, a more recent third category, is an abnormal interpretation of normal sensory input by the nervous system, a process considered to involve central or peripheral sensitization [1].

These categories, included in the International Classification of Diseases 11th Revision (ICD-11), are not mutually exclusive. They may coexist in the same patient.

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Chronic pain is believed to involve a complex interplay of various pathways that contribute to the persistence of pain perception. The initial step in these pathways is nociception which results from tissue damage or inflammation. This is a well-studied and accepted mechanism. Following nociceptor activation, several processes may come into play.

One important mechanism is sensitization, which can occur in both the peripheral and central nervous systems. Peripheral sensitization involves increased responsiveness of nociceptors to stimuli, resulting from the release of various inflammatory mediators and chemicals in the injured or inflamed tissues. This heightened sensitivity lowers the pain threshold, making individuals more susceptible to pain [2].

Central sensitization involves changes in the spinal cord and brain that amplify pain signals. Persistent periphery-initiated nociceptive input leads to an increase in the excitability of neurons in the spinal cord and brain, altering their response to subsequent stimuli. This process involves neuroplasticity, which includes changes in synaptic connections, receptor expression, and neurotransmitter release. The pathological circuits thus created perpetuate the painful sensation [3].

Persistent inflammation may account for part of the sensitization mechanism. After the initial injury or insult has resolved, there can be ongoing release of inflammatory substances, such as cytokines and chemokines, that sustain a local inflammatory response. It further contributes to the sensitization of nociceptors that in turn promotes the activation and recruitment of immune cells perpetuating the mechanism [4].

Collectively, the interaction between nociception, sensitization, and persistent inflammation appears to lead to the prolonged perception of pain in chronic pain conditions [5].

In all forms, chronic pain is estimated to affect 10 to 25% of adults during their lifetime. Twin studies underline that about 1/3 of susceptibility is heritable [6], and in part, there is a direct genetic origin [7]. Polymorphisms in genes related to serotonin receptors, opioid receptor Mu1, sodium channels, and catechol O-methyltransferase have been associated with increased susceptibility to chronic pain and higher pain sensitivity. Additionally, genetic variants in components of the inflammasome, such as regulation components of interleukins (IL-1, IL-6, TNF) expression and NF-kB activation have been linked to chronic pain [8].

Chronic pain is also tied to a series of social factors. Pain perception is altered by the menstrual cycle and women tend to seek help more often because of chronic pain conditions. Older age is tied to depression and slower healing, cognitive alterations and reduced physical activity that increase pain perception but also to higher resilience. Lower socioeconomic status, as well as geographical (like climate and pollutant exposure) and cultural factors also influence chronic pain [9]. A history of abuse, regardless of an actual physical injury is associated with a greater probability of chronic pain (10). Post-traumatic stress disorder is both a probable cause and a consequence of chronic pain.

In addition to these genetic, social, and environmental factors, it is important to acknowledge the role of acute nonspecific triggers that can initiate the chronic pain process, particularly in susceptible individuals. These triggers, distinct from background factors, may include recent infections, physical trauma, surgeries, or other significant events [11]. Psychological and emotional factors can interact with triggers, amplifying the pain experience and contributing to the development of chronic pain. Stress, anxiety, and trauma can sensitize the nervous system and influence pain perception [12]. In animal models, chronic stress can induce changes in the central nervous system equivalent to central sensitization. They contribute to the development of chronic pain [13]. The Fear-Avoidance Model of chronic pain illustrates how an individual's beliefs and responses to pain can influence its progression, where negative interpretations of pain can lead to fear, avoidance behaviours, disuse, disability, and ultimately chronic pain [14]. It's worth noting that the identification of the triggers for chronic pain is sometimes challenging due to this complex and interacting nature.

CLINICAL PRESENTATION, WORKUP AND BURDEN OF THE DISEASE

Naturally, the principal reason for a clinical consultation in the context of chronic pain is most often the pain itself. As chronic pain is a multifaceted syndrome, factors such as pain topography, temporal pattern, and precipitating causes can greatly vary. Table 1 provides some characteristics of chronic pain – may it be primary or secondary.

The onset of chronic pain can sometimes be insidious, as seen in fibromyalgia and neuropathy, gradual or progressive as often observed in cancer-related pain, or intermittent, as in cases of migraine or irritable bowel syndrome (IBS). A sudden onset is more characteristic of secondary chronic pain, where the initial injury or lesion can be identified. Occasionally, a delayed onset can be observed, with pain reappearing after a symptom-free period at the site of a previous injury. Chronic pain can persist, accentuate, or dissipate independently of the triggering event.

Its localisation varies, as does its origin. Both the musculoskeletal system and viscera can cause chronic pain. It can be persistent or recurrent with a regular pattern or occasional flare-ups.

Table 1

Chronic pain classification (ICD11) and clinical features

	Chronic Pain Syndrome type (ICD-11)	**Examples**	**Mechanisms of Production and Triggers**	**Common Symptoms**
Primary Chronic Pain	Nociplastic	Fibromyalgia, Chronic pelvic pain syndrome, Tension-type headache Complex regional pain syndrome	Altered nociception with central sensitization	Widespread pain, fatigue, sleep disturbances, cognitive difficulties
	Chronic Primary Headache and Orofacial Pain	Migraine, Chronic tension headache, Burning mouth syndrome, Chronic primary temporomandibular disorder	Altered nociception, possible central sensitization	Severe headache, facial pain, jaw pain
	Chronic Primary Musculoskeletal Pain	Myofascial pain syndrome, Chronic low back pain	Altered nociception, possible central sensitization	Localized muscle pain, trigger points, reduced range of motion
	Chronic Primary Visceral Pain	Chronic primary chest pain syndrome, Chronic pelvic pain syndrome, Chronic primary epigastric pain syndrome, Chronic primary painful bladder syndrome and interstitial cystitis, Chronic primary abdominal pain syndrome, irritable bowel syndrome	Altered nociception, visceral hypersensitivity/peripheral sensitization	Persistent or recurring pain in the chest, abdomen, or pelvis
Secondary Chronic Pain	Neuropathic	Diabetic neuropathy, Postherpetic neuralgia	Peripheral and central sensitization	Shooting or burning pain, numbness, tingling
	Post-Traumatic Neuropathy	Traumatic nerve injury, Amputation	Peripheral and central sensitization, nerve damage	Chronic pain at the site of injury or amputation
	Post-Stroke Pain	Pain after ischemic or hemorrhagic stroke	Central sensitization, brain damage	Pain in the affected areas, changes in sensation
	Nociceptive	Osteoarthritis, Rheumatoid arthritis, Chronic Pancreatitis, Chronic Pelvic Inflammatory Disease, Chronic Prostatitis, Chronic Proctitis (list not extensive),	Peripheral sensitization, ongoing activation of nociceptors	Localized joint or organ pain, inflammation

PAIN EVALUATION TOOLS

To objectively assess and quantify pain, we professional seek to associate the perceived severity of pain with categorical values that will transform vague sensations into numbers. These scales allow us to gauge pain intensity and to estimate its impact on patients' lives. Table 2 provides an overview of some widely used pain evaluation tools, including the Visual Analog Scale (VAS), Numeric Rating Scale (NRS), Faces Pain Scale – Revised (FPS-R), Brief Pain Inventory (BPI), McGill Pain Questionnaire, and others. Some tools have advantages depending on the patients' age, cognitive abilities, and preferences and may be adapted for persons that cannot communicate their suffering.

Additionally, pain topography charts allow easy identification and follow up of painful sites.

Table 2

Pain evaluation tools

Pain Evaluation Tool	Description	Target Population
Visual Analog Scale (VAS)	A simple, one-dimensional scale where individuals rate their pain intensity by marking a point on a line between "no pain" and "worst pain imaginable."	Adolescents and adults capable of understanding and using the scale.
Numeric Rating Scale (NRS)	Like VAS, but instead of a line, it uses a numerical scale (usually from 0 to 10) where individuals rate their pain intensity by selecting a number.	Adolescents and adults capable of understanding numbers and using the scale.
Faces Pain Scale - Revised (FPS-R)	Consists of a series of faces representing different levels of pain intensity, ranging from a smiling face (no pain) to a crying face (worst pain). Individuals choose the face that best represents their pain.	Children (ages 4 and older), individuals with cognitive impairment, or those who have difficulty using numerical or verbal scales.
Brief Pain Inventory (BPI)	A multidimensional pain assessment tool that measures pain intensity and its impact on daily functioning. It assesses pain severity, pain interference with daily activities, and the location of pain. It also evaluates the effectiveness of pain management interventions.	Adults with chronic pain conditions, such as cancer pain or neuropathic pain.
McGill Pain Questionnaire	A comprehensive tool that assesses multiple dimensions of pain, including sensory, affective, and evaluative aspects. It uses a list of words to describe pain qualities, and individuals select the words that best describe their pain experience.	Adults with chronic pain conditions who can comprehend and articulate pain descriptors.
PainDetect Questionnaire	A screening tool used to differentiate neuropathic pain from non-neuropathic pain. It consists of nine items assessing pain descriptors, spatial and temporal characteristics, and sensory symptoms associated with neuropathic pain.	Adults with chronic pain suspected to have neuropathic components.
Oswestry Disability Index (ODI)	Although not specifically a pain assessment tool, ODI is commonly used to evaluate pain-related disability in individuals with low back pain. It assesses the impact of pain on various activities of daily living, such as walking, standing, and lifting.	Individuals with low back pain or spinal disorders.
Verbal Descriptor Scale (VDS)	A simple set of descriptors on a 4 or 5 point scale with pain description varying from absent to very severe.	Individuals who may have difficulty using numerical or visual scales, or those who prefer verbal communication.
Nonverbal Pain Scale (NVPS) – Algoplus, Doloplus	An observational tool that assesses pain in individuals who are unable to communicate verbally. Use direct or indirect indicators of pain, such as facial expressions, body movements, vital signs, and vocalizations.	Infants, individuals with severe cognitive impairments, or those who cannot communicate verbally.

RED FLAGS OF CHRONIC PAIN

While chronic pain is frequent and most of the time the underlying pathogen is no longer present, sometimes it may require urgent evaluation and treatment. The presence of certain clinical signs and symptoms – red flags – should raise suspicion for a more severe and persistent disease. While the "red flag" list found in Table 3 is not complete, it should provide a good indicator of most conditions that warrant a rapid workup.

IMPACT AND COMPLICATIONS OF CHRONIC PAIN

Chronic pain extends beyond physical discomfort, affecting patients' psychological well-being, social interactions, daily functioning, and overall quality of life [15]. It can lead to increased stress, anxiety, depression, disrupted sleep patterns, and diminished self-esteem. Socially, chronic pain can result in isolation, loneliness, and a reduced support network, compounding mental health issues. Physical functioning and engagement in work or meaningful activities may be impaired, potentially leading to disability. Dependence on pain medications and their associated side effects further impacts one's well-being. The financial burden of managing chronic pain, including healthcare costs and potential loss of income, adds additional stress [16].

Table 3

Red flags of chronic pain

• Sudden onset of severe pain not attributable to an injury or activity.
• Age of onset over 50 years or before 20 years of age.
• History of drug abuse.
• Recent surgery or head trauma.
• Recent pregnancy.
• Recent bacterial infections.
• Constant, progressive pain that is not relieved by rest or analgesia.
• Pain associated with systemic symptoms such as fever, weight loss, malaise, iron deficiency anaemia, or dysphagia.
• Focal neurological symptoms such as weakness, numbness, bowel or bladder dysfunction.
• Pain that is disproportionate to the physical findings, such as a thunderclap headache.
• Pain in individuals with a personal or familial history of cancer, particularly if the pain is persistent and localized.
• Pain in individuals with known or suspected immunocompromise.
• Night pain or pain that wakes the patient from sleep

TREATMENT OF CHRONIC PAIN

The first step in the management of a disease should be to establish a clear diagnosis and identify treatable components. This allows us to prioritize interventions according to specific needs and mechanisms. Since pain is seen rather as a symptom than a disease, we tend to start treatment at the same time as we try to obtain an etiologic diagnosis. When treating pain, one should have in mind a balance between both physician objectively established and patient-centered goals [17] that take into consideration their preferences and wishes. This equilibrium can be achieved through a combination of pharmacological and non-pharmacological interventions.

PAIN REDUCTION

The primary objective for both patients and physicians is to decrease pain levels, as even partial pain reduction can greatly improve a patient's quality of life [18]. Pharmacological interventions are often effective in achieving short-term pain reduction, although they may not eliminate it entirely.

IMPROVING FUNCTION

Simply reducing pain through pharmacological intervention may not be sufficient, especially if both pain itself and its treatment hinder the individual's ability to engage in daily activities. Therefore, enhancing functional abilities is another crucial goal. Non-pharmacological interventions, such as physical therapy, exercise, and occupational therapy, play a significant role in improving physical function and restoring mobility.

ENHANCING QUALITY OF LIFE

Sleep, mood, and overall well-being are components of a patient's quality of life. Chronic pain often leads to depression and anxiety, necessitating psychological management. Non-pharmacological interventions, including psychotherapy, mindfulness, and relaxation techniques, specifically target these aspects improving the overall quality of life. Building resilience is of particular importance in enhancing quality of life and is based on social support and the development of coping mechanisms [19].

REDUCING DEPENDENCE ON MEDICATIONS

Managing pain requires particular attention when medication with addictive potential or serious side effects – such as opioids – are used. An algorithmic (Image 2) approach that emphasizes non-pharmacological and adjunctive interventions aiding medication sparing may reduce long-term use and minimize the risk of dependence.

When considering adapting the dosing of medication, one should consider a particular aspect of chronic pain. Patients may desire complete elimination of pain and strive to achieve it. Physicians understand that this may not always be possible [17]. Therefore, both patients' and physicians' expectations should be set to a level that will allow patients to function as normally as possible and embrace a resilient attitude. This delicate balance requires clear communication between patients and healthcare providers.

To achieve these goals, we will propose both nonpharmacological and pharmacological therapies.

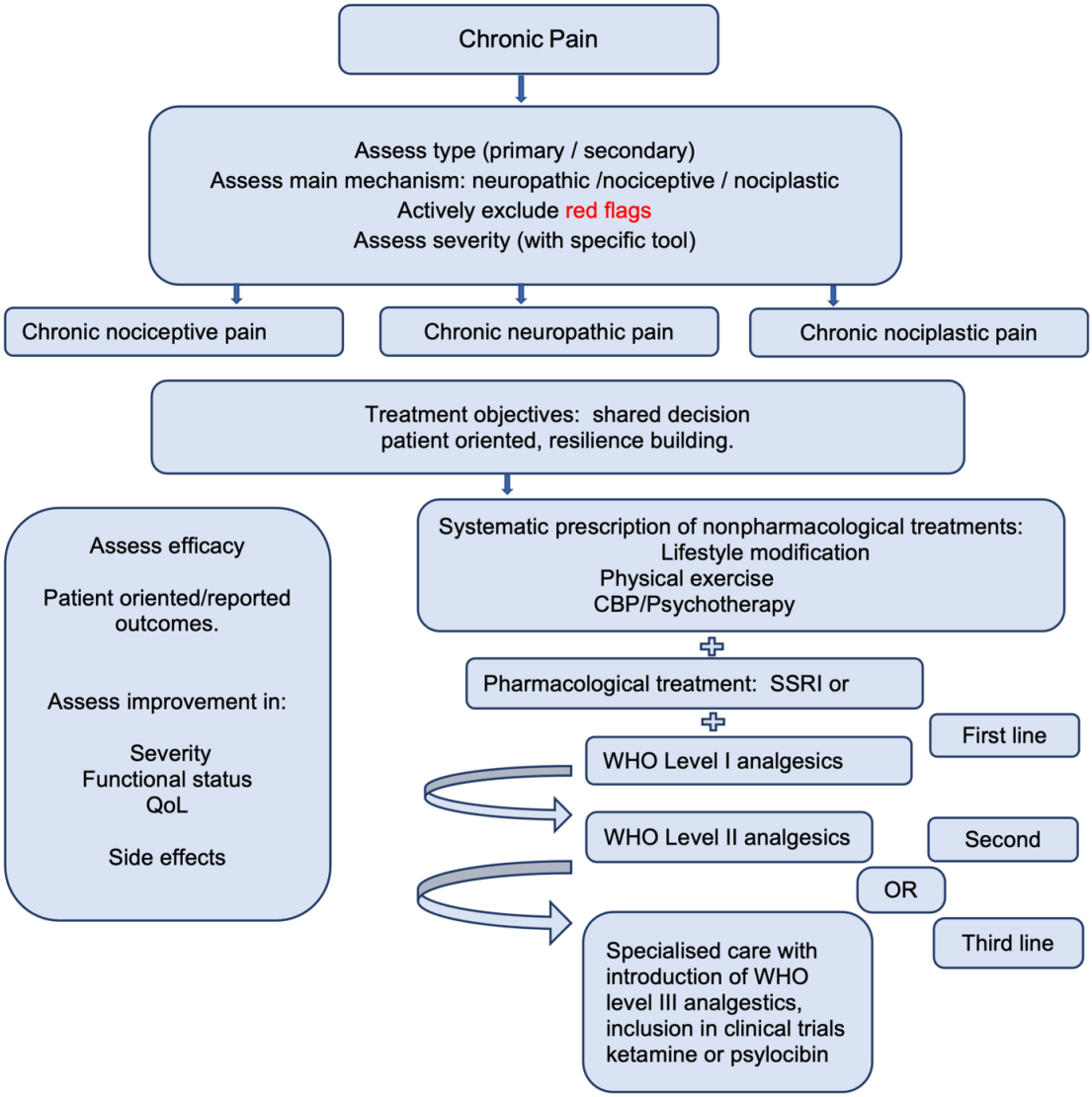


Fig 2. Chronic pain treatment algorithm.

NON-PHARMACOLOGICAL TREATMENT

Non-pharmacological interventions play a significant role in chronic pain management.

Physical therapy or exercise Physical activity can be beneficial in managing chronic pain even if the quality of evidence is low due to small sample studies [20]. Yoga has moderate quality evidence of efficacy in improving physical function and reduce pain in individuals with chronic low back pain. It can enhance physical flexibility, improve posture, and reduce muscle tension, all of which can help alleviate chronic pain. It seems it can also be proposed to elderly, selected, patients [21]. Physical resilience can contribute to better pain management outcomes.

Heat or cold therapy: Applying heat can help soothe stiff joints and relax muscles, while cold can help numb an area and reduce inflammation. The effectiveness of heat and cold

therapy may depend on the type of pain and personal preference. The level of evidence is low, but it's used is common practice [22].

Massage or other manual therapies can help relieve muscle tension, improve circulation, and promote relaxation, thereby alleviating pain. They fail to ameliorate function and the effect is only of short duration. It can be proposed in lower back pain and neck based on low quality evidence but with an excellent safety profile [23].

Transcutaneous electrical nerve stimulation (TENS): TENS is a form of neuromodulation that delivers small electrical impulses to the skin, which can help block pain signals from reaching the brain and stimulate the production of endorphins, the body's natural painkillers. Some moderate quality evidence supports the use of TENS to transiently lower pain intensity in lower back pain and neuropathic pain [24], but it's use is still off label.

Acupuncture can be effective in managing certain types of chronic pain, including low back pain and osteoarthritis. With a low certainty evidence, acupuncture does not alleviate pain but seems to improve function and has generally minor side effects [24] in lower back pain.

Spinal cord stimulation involves the placement of a device that delivers electrical impulses to the spinal cord to disrupt pain signals. It should probably be proposed only as part of a clinical trial [25].

Gaming and Virtual Reality present a supplementary approach to pain management by offering an alternative virtual environment that can divert the brain from receiving painful sensory input. Immersive and non-immersive technologies enable patients either to experience a heightened sense of presence within the virtual realm or adopt an external observer perspective. These methods operate by engaging the individual's cognitive resources, redirecting their attention away from real-world painful stimuli [26].

Occasionally, *invasive techniques* like nerve blocks or surgical denervation may be required in the management of severe chronic pain. These specific techniques are often performed in specialized clinics after a long duration follow-up [27].

Psychotherapy. The role of psychotherapy in the management of chronic pain is ample. Chronic pain often entails significant psychological and emotional challenges. Resilience is probably the mainstay of psychological therapy. It can help individuals build a positive mindset, enhance their coping strategies, and navigate the emotional roller coaster associated with chronic pain. Empowering individuals with chronic pain to develop self-management skills can enhance their ability to cope with pain and improve their quality-of-life. This may include education about pain management strategies, setting realistic goals, pacing activities, practicing relaxation techniques, and engaging in self-care activities that promote physical and emotional well-being [28]. Resilience can be bolstered through the support of others. Support networks can provide emotional validation, practical assistance, a sense of belonging, a space for sharing experiences. Resilience involves adapting to challenges and finding effective solutions. Helping individuals with chronic pain develop adaptive thinking skills and problem-solving abilities can enhance their resilience [29].

PHARMACOLOGICAL TREATMENT

Pharmacological interventions often serve as the first-line treatment for many types of pain. However, in the case of chronic pain, they may not eliminate it completely and can have side effects. Furthermore, these medications may address stress, but they do not address the psychological aspects often associated with chronic pain. An exhaustive list of medicines, their usual dose and mechanism of action, and their eventual place in the World Health Organisation 1986 analgesic ladder is detailed in Table 4.

The combined pharmacological and non-pharmacological approach to treatment acknowledges the unique needs and circumstances of individuals and provides long-term benefits in the management of chronic pain [30]. It enables us to effectively reduce pain, improve function, enhance quality of life and empower patients to actively engage in their self-care and well-being while minimizing reliance on medications. One idea that we hope to convey is the fact that chronic pain might fluctuate in intensity throughout its evolution and resolve event without or with minimal interventions. This might allow both patient and physician to concentrate their efforts to use evidence based and clinically relevant therapeutics. By approaching chronic pain through a step-by-step algorithm of treatment we should be able to adapt intervention to the current situation. We propose such an algorithm in Image 2.

Table 4

Main analgesic medicines, including the World Health Organization ladder classification

Class	Medications	Mechanism of action	Usual Dosage, rout	Side Effects	Duration of Treatment	Level of evidence on chronic pain
WHO Level I Analgesic	Acetaminophen	Inhibition of prostaglandin synthesis in the CNS	10 to 16mg/kg every 4-6 hours, up to 4000 mg/day, orally or IV	Chronic transaminase level increase, acute liver failure in overdose	Short-term or as needed	No or little efficacy with limited clinical relevance [32].
	Metamizole (dipyrone)	The exact mechanism not fully understood (NSAID like)	500-1000 mg every 6-8 hours, orally or IV	Allergic reactions, very rare severe agranulocytosis, and infections	Short-term or as needed	Evidence of efficacy in human trials of cancer related pain. [33].
	Nefopam	The exact mechanism not fully understood	20-40 mg every 6-8 hours, IV or off label oral	Dry mouth, dizziness, nausea, urine retention	Short-term or as needed	Low certainty evidence of efficacy [34].
NSAIDs	Ibuprofen	Inhibits COX, reducing inflammation	200-400 mg every 4-6 hours, up to 1200 mg/day	Gi bleed, colitis, hypertension	Short-term or as needed	For chronic LBP, we found low-certainty evidence that NSAIDs may provide a small effect on pain. Diclofenac – moderate efficacity in chronic cancer pain [35]
	Naproxen	Inhibits COX, reducing inflammation	250-500 mg twice daily, orally	Gi bleed, colitis, hypertension	Short-term or as needed	
	Diclofenac	Inhibits COX, reducing inflammation	50 mg 2–3 times per day, orally	Gi bleed, colitis, hypertension	Short-term	
	Celecoxib	Inhibits COX2 enzyme, reduces inflammation	100-200 mg twice daily, orally	Cardiovascular events	Short-term or as needed	
WHO Level II Analgesic	Tramadol	Binds to mu-opioid receptors and inhibits serotonin reuptake	25-100 mg every 4-6 hours, up to 400 mg/day, orally or IV	Nausea, dizziness, constipation, sedation	Short-term or as needed	Very low quality evidence [36].
	Codeine	Binds to mu-opioid receptors and acts as a weak opioid agonist	15-60 mg every 4-6 hours, up to 360 mg/day	Nausea, drowsiness, constipation, dependence	Short-term or as needed	Very low evidence on chronic pain [37].
WHO Level III Analgesic	Morphine	Binds to mu-opioid receptors and blocks receptor activity	10-30 mg every 4 hours, up to 360 mg/day	Respiratory depression, constipation, sedation	Short-term or as needed	Low- to moderate-quality evidence suggested similar improvements in pain and physical functioning compared with nonsteroidal anti-inflammatory drugs [38].
	Oxycodone	Binds to mu-opioid receptors and inhibits serotonin and norepinephrine reuptake	Varies depending on specific formulation	Nausea, constipation, drowsiness, sedation	Short-term or as needed	
	Fentanyl	Binds to mu-opioid receptors and blocks receptor activity	Varies depending on specific formulation	Respiratory depression, constipation, sedation	Short-term or as needed	

Table 4 (continued)

Class	Medications	Mechanism of action	Usual Dosage, rout	Side Effects	Duration of Treatment	Level of evidence on chronic pain
Antidepressants	Amitriptyline	Blocks the reuptake of norepinephrine and serotonin in the CNS	25-150 mg at bedtime	Dry mouth, drowsiness, constipation	Long-term,	Moderate to high quality evidence, efficacy in fibromyalgia, IBS [39-41].
	Duloxetine (other IRS/IRSS are less studied)	Inhibits the reuptake of norepinephrine and serotonin in the CNS	30-60 mg once daily	Nausea, headache, insomnia	Long-term	Adequate amounts of moderate quality evidence for overall chronic pain [42].
Anticonvulsants	Gabapentin	Binds to voltage-gated calcium channels and modulates neurotransmitter release	300mg-900mg 3 times daily	Dizziness, drowsiness, peripheral oedema	Long-term	Efficacy in postherpetic neuralgia, painful diabetic neuralgia, and mixed or unclassified post-traumatic neuropathic pain, and absence of efficacy in HIV neuropathy; evidence of efficacy in central neuropathic pain is inadequate. [43-44].
	Pregabalin	Binds to voltage-gated calcium channels and modulates neurotransmitter release	50mg to 300mg up to 3 times a day	Dizziness, drowsiness, peripheral oedema	Long-term	
Benzodiazepines Muscle Relaxants	Diazepam	Enhances the inhibitory effects of gamma-aminobutyric acid (GABA) in the CNS	2 mg to 10 mg 1 to 4 times daily.	Drowsiness, sedation, dependency 20-100% after 1-month, limited efficacy	Short-term or as needed, to be avoided, second line treatment	Benefit for burning mouth syndrome and stiff person syndrome. No conclusions for other pain conditions [45].
	Lorazepam	Enhances the inhibitory effects of gamma-aminobutyric acid in the CNS	10 to 30 mg, up to 3 or 4 times daily.	Drowsiness, sedation, dependency, limited efficacy	Short-term or as needed. Off label	No evidence
	Oxazepam	Enhances the inhibitory effects of gamma-aminobutyric acid (GABA) in the CNS	0.5 mg to 2 mg, up to 3 times daily.	Drowsiness, sedation, dependency, limited efficacy	Short-term or as needed. Off label	Very week evidence in some conditions.
	Baclofen	Activates GABA-B receptors, inhibiting neurotransmitter release	starting dose is 5 mg taken orally three times a day, maximum dosage of 80 mg per day	Drowsiness, dizziness, weakness	Short-term or as needed	Low level evidence in spasticity associated chronic pain but not in other chronic pain conditions [46].
	Tizanidine	Acts as an alpha-2 adrenergic agonist, reducing muscle spasticity	Varies depending on condition and response	Dry mouth, drowsiness, low blood pressure, CNS depressant	Short-term or as needed	Very low level evidence in spasticity and chronic back pain [47].

Table 4 (continued)

Class	Medications	Mechanism of action	Usual Dosage, rout	Side Effects	Duration of Treatment	Level of evidence on chronic pain
NMDA Receptor agonist	Ketamine	Blocks the N Methyl D aspartate (NMDA) glutamate receptor and increases synaptic plasticity.	Infusion or oral medication, dose range from 10-50 mg 3-4 times a day.	hallucinations, confusion, increased heart rate and blood pressure, abuse potential, dependency	short-term or periodic treatments	Significant short-term analgesic benefit in patients with refractory chronic pain, dose-response relationship. Low level evidence [48].
Cannabinoids	THC (tetrahydrocannabinol)	Binds to G protein coupled cannabinoid receptors in the CNS	.5-5 mg of THC, taken orally, 1-2 times a day	dizziness, dry mouth, psychoactive effects potential for dependency	long-term under medical supervision	Fragile risk-benefit balance, moderate quality evidence [49].
TRVP1 desensitizers	Capsaicin	Topical, Activates and then desensitizes TRPV1 receptors on nociceptive fibers on a temporary or definitive pattern	Ointments or patches, 0.025% to 5%	Local reactions	Long term for the low dose, punctual for the high doses	Effect on postherpetic neuralgia, HIV-neuropathy, and painful diabetic neuropathy - moderate to substantial levels of pain relief with moderate to very low quality of evidence [50].
Local anaesthetics	Lidocaine	Temporary blocking of nerve signals in the affected area	Ointments, creams or patches (2 to 10%)			Low quality evidence of substantial efficacy in neuropathic pain of diabetic and post surgical polyneuropathy.

EVALUATING SUCCESS, OR UNSUCCESS

Success is evaluated by how well these goals are met, especially how the pain is felt by the patient but also through the way he experiences life.

Pharmacological management of chronic pain involves a cautious approach, initiating, titrating, tapering, or discontinuing medications one at a time. This allows for a more accurate assessment of the individual's response and potential adverse effects. The goal is to find the lowest effective dose that provides reasonable symptom control while minimizing side effects. If a medication does not demonstrate clear benefit within 6 to 12 weeks, it should be considered for discontinuation.

Regular evaluation through direct interactions, clear communication, and shared decision-making adjustment of treatment plans are necessary to ensure optimal pain management. Thus, it is essential to maintain a strong patient-provider relationship for the effective management of chronic pain.

FUTURE OF PAIN TREATMENT

The future of pain treatment holds promise. Advances in technology and pharmacological approach (such as psylocibin, ketamine and neuromodulation techniques like spinal cord stimulation and targeted drug delivery systems by nanotechnology) [31], offer potential breakthroughs in pain management. Personalization of medicine will tailor treatment plans based on individual characteristics, genetics, and responses to therapies.

LIMITS OF THE REVIEW

Our review is neither systematic nor comprehensive. It is meant to aid the internist in his daily practice and may overemphasize the role of nonpharmacological and non-opioid treatment.

CONCLUSION

Chronic pain is a multifaceted condition that significantly impacts individuals physically,

psychologically, and socially. Despite the concept of multimodal pain management and specialized pain care, specialized clinics respond to the needs of only 2% of patients. This highlights the significant, real-life, ongoing and future role of internists, general practitioners, and other subspecialties in providing care for individuals with chronic pain.

It is essential to recognize chronic pain as a legitimate condition and provide compassionate care. It requires a comprehensive and individualized approach to management. By promoting resilience, implementing self-management strategies, fostering social support networks, and addressing physical and emotional well-being, healthcare providers can help patients with chronic pain lead more fulfilling lives and limit overuse of medicines.

Durerea cronică reprezintă o afecțiune complexă care afectează mulți oameni. Ea poate fi cauzată de diferiți factori, atât personali și externi și are un impact semnificativ asupra sănătății fizice și emoționale. Este important ca personalul medical să înțeleagă diferitele tipuri și mecanisme ale durerii cronice, precum și experiențele și nevoile individuale ale pacienților. Terapia durerii cronice asociază atât principii farmacologice cât și strategii non-medicamentoase. Dezvoltarea rezilienței, promovarea abilităților de autogestionare și oferirea de sprijin social sunt esențiale pentru a ajuta persoanele să facă față durerii cronice și pentru a-și îmbunătăți starea generală de bine.

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