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ANTIDEPRESSANTS IN CHRONIC PAIN MANAGEMENT IN CHILDREN AND ADOLESCENTS: A CRITICAL REVIEW OF THE LITERATURE

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ANTIDEPRESSANTS IN CHRONIC PAIN MANAGEMENT IN CHILDREN AND ADOLESCENTS: A CRITICAL REVIEW OF THE LITERATURE

ANTIDEPRESSIVOS NA GESTÃO DA DOR CRÓNICA EM CRIANÇAS E ADOLESCENTES: UMA REVISÃO CRÍTICA DA LITERATURA

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List of Abbreviations

TCAs: Tricyclic antidepressants
SNRIs: Serotonin and Noradrenaline Reuptake Inhibitors
SSRIs: Selective Serotonin Reuptake Inhibitors
RCTs: Randomised Controlled Trials
ICD-11: The 11th Revision of the International Classification of Diseases
CNCP: Chronic Non-cancer Pain
CNS: Central Nervous System
NMDA: N-methyl-D-aspartate
CRPS 1: Complex Regional Pain Syndrome Type 1
JFM: Juvenile Fibromyalgia
IBS: Irritable Bowel Syndrome
FAP: Functional Abdominal Pain
BPI: Brief Pain Inventory
PedIMMPACT: The Pediatric Initiative on Methods, Measurement and Pain Assessment in Clinical Trials
NICE: National Institute for Health and Care Excellence
WHO: World Health Organization

Abstract

Chronic pain, defined as pain persisting or recurring for longer than three months, represents a significant clinical and public health challenge, estimated to impact 20% to 35% of youth worldwide. This condition severely compromises the quality of life and social and academic development of children and adolescents, as well as their families and caregivers. Moreover, chronic pain is often associated with stigmatization and mental health disorders. Despite this negative impact and long-term consequences, chronic pain in children and adolescents remains undertreated. Current treatment approaches, including both non-pharmacological and pharmacological strategies, are often inadequately supported by evidence. In adult populations, antidepressant drugs, mainly SNRIs and TCAs, are the first-line pharmacotherapy choice for several chronic pain conditions. However, their efficacy and safety in paediatric populations is still controversial and understudied. Traditionally, pain treatment has focused primarily on the nociceptive component of pain, however, this paper takes a more biopsychosocial perspective, reviewing the interplay of biological, psychological, and social factors in the development of chronic pain. This narrative review synthesizes evidence from diverse research methodologies to explore the mechanisms of action of antidepressants in chronic pain and assess their potential efficacy in the paediatric context. Antidepressants exhibit unique analgesic properties, independent of their effects on mood. These drugs modulate pain by enhancing the availability of key neurotransmitters, notably noradrenaline, within descending pain pathways, a mechanism central to their action in chronic pain. Furthermore, antidepressants are shown to promote neuroplasticity, potentially reversing the maladaptive changes associated with chronic pain. This literature review aims to critically evaluate the existing body of knowledge regarding the efficacy and safety of antidepressants for paediatric chronic pain and explore current research gaps.

Keywords: Antidepressants**,** Chronic Pain, Chronic Pain Management, Children and Adolescents

Resumo

A dor crónica, definida como dor persistente ou recorrente por mais de três meses, representa um importante desafio clínico e problema de saúde pública, estimando-se que afete 20% a 35% dos jovens em todo o mundo. Esta doença compromete gravemente a qualidade de vida e o desenvolvimento social e académico das crianças e adolescentes, bem como das suas famílias e cuidadores. Além disso, a dor crónica está frequentemente associada à estigmatização e perturbações da saúde mental. Apesar deste impacto negativo e consequências a longo prazo, o tratamento da dor crónica em crianças e adolescentes continua a ser subótimo. As abordagens atuais na gestão da dor crónica, incluindo estratégias farmacológicas e não farmacológicas, são raramente baseadas na evidência. Nos adultos, os antidepressivos, principalmente os SNRIs e os TCAs, são os fármacos de primeira linha para vários tipos de dor crónica. No entanto, a sua eficácia e segurança na população pediátrica é ainda controversa e pouco estudada. O tratamento da dor tem-se centrado principalmente na sua componente nociceptiva, no entanto, este artigo adota uma perspetiva biopsicossocial, analisando a interação de fatores biológicos, psicológicos e sociais no desenvolvimento da dor crónica. Esta revisão narrativa sintetiza a evidência de diversas metodologias de investigação, para explorar os mecanismos de ação dos antidepressivos na dor crónica e avaliar a sua potencial eficácia no contexto pediátrico. Estes fármacos têm uma ação analgésica, independente dos seus efeitos no humor, modulando a dor através do aumento da disponibilidade de certos neurotransmissores, em especial a noradrenalina, nas vias descendentes da dor. Além disso, os antidepressivos parecem promover a neuroplasticidade, demonstrando o seu potencial para reverter alterações mal-adaptativas associadas à dor crónica. Esta revisão tem como objetivo fazer uma avaliação crítica da literatura quanto à segurança e eficácia dos antidepressivos na dor crónica pediátrica e identificar eventuais lacunas na investigação atual.

Palavras-chave: Antidepressivos**,** Dor Crónica, Gestão da Dor Crónica, Crianças e Adolescentes

Introduction

Pain is defined as an unpleasant sensory and emotional experience or resembling that associated with actual or potential tissue damage.[1] Acute pain is known to have a survival value, alerting us to injury or disease,[2] chronic pain however persists beyond the expected period of healing,[2,3] commonly referred to as pain that persists or recurs for longer than three months.[4] It seems to serve no adaptive purpose and is associated with a variety of conditions in both paediatric patients and adults.[2] Chronic pain can be either primary, which is considered a health condition in its own right, or secondary to a clear underlying cause.[5,6] Regardless of its origin, pain is one of the most frequent reasons for patients to seek medical care worldwide[6] and a leading source of human suffering and disability.[78] Despite this, chronic pain remains largely misunderstood and is often underdiagnosed and undertreated,[8,9] particularly in younger people.[3,10,11] Although the experience of pain is universal, each person's experience is subjective.[8] This subjectivity becomes particularly complex when considering chronic pain, especially in younger populations, where a multitude of physical and psychosocial factors interact to varying degrees, each playing a role in shaping the individual's experience of pain.

Estimates of the number of children and adolescents affected by chronic pain vary widely, due to differences in study populations, namely age, sample size, the definition of pain used and how pain is measured, making it difficult to determine its prevalence.[5,12] However, conservative estimates point towards 20% to 35% of young people affected by chronic pain worldwide.[10,13] Although existing studies on the Portuguese paediatric population are limited, research has shown that chronic pain is highly prevalent, ranging from 29.1% to 75.9%, depending on pain location.[14] The aetiology, type, and location of chronic pain seem to vary according to sex and the age group considered.[15] In the paediatric population, it is usually more expressive in adolescence, affecting seemingly more females than males worldwide.[15,16]

The uncertainty regarding the number of children and adolescents impacted by chronic pain may limit the appropriate allocation of clinical services for this population.[5] This is highly concerning given it is a significant public health problem,[17] with a profound impact[18] on the patient's quality of life and long-lasting consequences into adulthood.[7] Chronic pain compromises school attendance, academic success and social engagement.[16,19,20] There is also a strong association between chronic pain and mental health disorders, such as depression and anxiety,[2] which further complicates the condition.[5] Adolescents with chronic pain and depression are at elevated risk for suicidal ideation and suicide attempts.[10,21] Patients with chronic pain often face stigma and emotional distress,[18,22] leading to further isolation and exacerbation of mental health problems.[10] Long-term consequences include persistence of pain into adulthood,[23] reduced income, higher unemployment rates, risk of opioid misuse and psychiatric disorders.[10,12] Economically, the impact of chronic pain is significant and can be felt in various ways.[5,12,24] A cost-of-illness study in the United Kingdom found the overall annual cost to a household containing a child living with idiopathic chronic pain was three times higher than average.[25]

Effective management of chronic pain in youth is therefore crucial to mitigate these consequences.[18] Current recommendations include both non-pharmacological and pharmacological approaches, within interdisciplinary treatment programs.[5,26–29] Yet, effective management remains a challenge.[18] A growing body of evidence suggests that numerous medications commonly prescribed for chronic pain may in fact inflict more harm than good.[26] For example, this concern is underscored by the opioid epidemic,[30] a public health crisis with well-documented adverse effects, including in children and adolescents.[31] While opioids undeniably hold value in the management of both acute and chronic pain, healthcare professionals must recognize appropriate indications and carefully monitor their use.[31]

The complexity of treating paediatric chronic pain is exacerbated by the lack of high-quality research on effective interventions. Concomitant pain and mental health disorders often complicate pharmacological management,[21] yet the prevalence of comorbidity between depression and chronic pain presents as an opportunity for antidepressants to treat both conditions concomitantly.[32] While primarily prescribed for depression, antidepressants have increasingly been recognized for their analgesic properties.[33,34] The dual efficacy of antidepressants in alleviating both pain and associated mental health conditions[35] underscores their value in addressing both sensory and emotional aspects of chronic pain, improving overall patient quality of life.[30,31]

Antidepressants are often the first-line pharmacological treatment in adults with chronic pain[26], as reflected in prescribing trends, particularly among the elderly, where chronic pain is a more frequent reason for antidepressant prescriptions than depression itself.[36] In Portugal, 12% of people with back pain reported the use of an antidepressant to manage their condition.[37] Yet little is known about the evidence surrounding their use in children and adolescents. Children and adolescents suffering from chronic pain are often treated using a trial-and-error method that does not consider the particular characteristics of the individual or approaches based on guidelines mostly developed and tested in adults.[37]

Hence the relevance of this review. Chronic pain is often overlooked, especially in children and adolescents. Research in this area is limited, and there is a lack of comprehensive national policies and clinical practice guidelines for chronic pain management. With the recognition of pain management as a fundamental human right, it is crucial to look for better ways to manage paediatric chronic pain, aiming to improve patient outcomes and mitigate the societal impacts of inadequately managed pain in children and adolescents.

The primary objective of this literature review is to critically assess the current body of knowledge regarding the efficacy, safety and tolerability of antidepressants for the treatment of chronic pain in children and adolescents. Additionally, this review seeks to determine the underlying mechanisms by which antidepressants may alleviate chronic pain, and how various factors (biological, psychological and social) influence and perpetuate the experience of pain, based on a biopsychosocial model. This review aims to contribute to a better understanding of the potential role of antidepressants in paediatric

chronic pain, identify research gaps in the current literature and advise on future directions by offering a critical analysis of the literature.

Methods

This literature review adopts a narrative approach to examine the use of antidepressants for managing chronic pain in children and adolescents. Literature searches were run in PubMed, using natural language terms, keywords and MeSH Subject Headings, including “antidepressants”, “chronic pain”, “pain management”, “children” and “adolescents” combining them with the Boolean operators “AND” and “OR”. Keywords related to specific topics (tricyclic antidepressants, serotonin and noradrenaline reuptake inhibitors, treatment efficacy and safety, mechanisms of action, pain modulation, interdisciplinary treatment biopsychosocial model and paediatrics) were cross-referenced with the initial search terms using the identified databases.

Inclusion criteria: Initially articles in both English and Portuguese and studies published in the last ten years (between 2013 and 2023) were included. However, the temporal scope was later extended back to 2008, in order to encompass a wider range of studies.

Eligibility criteria: Systematic reviews, meta-analyses, clinical trials, case series and clinical practice guidelines. Studies with unclear or mixed interventions, lacking comparators, or terminated early were excluded.

The gathered abstracts were stratified according to their relevance to the topic, and the full texts of relevant articles were retrieved for in-depth analysis. To find additional related literature, the search was completed by manually reviewing the reference lists of selected articles.

Background

Classification of Chronic Pain

According to the ICD-11, chronic pain is broadly categorized into two main types: chronic primary pain and chronic secondary pain.[38] Chronic primary pain is defined as pain that occurs in one or more anatomical regions that persist or recurs for longer than three months and cannot be better accounted for by another chronic pain condition. All forms of pain can cause emotional distress and functional disability, but these features are particularly prominent in chronic primary pain.[39] This is a relatively new definition, that considers chronic pain as a health condition in its own right, rearranging previously known conditions that now fall into this category, like fibromyalgia, which is a type of chronic widespread pain.[6,26] Other types of chronic primary pain are complex regional pain syndrome, chronic primary headache and orofacial pain (e.g., chronic migraine or temporomandibular disorder), chronic primary visceral pain (e.g., IBS) and chronic primary musculoskeletal pain.[26,38]

Chronic primary pain is known for its disproportionate impact relative to any observable injury or disease,[2] making the underlying mechanisms of this disease not fully understood yet, hence meaning these classifications are subjected to change over time. The definition of chronic primary pain reflects a growing understanding that some forms of pain are significant clinical challenges, requiring nuanced approaches to treatment and management due to their debilitating nature, association of comorbidities and the absence of clear underlying conditions.

On the other hand, secondary pain has a clear underlying etiology such as a disease, injury or lesion, or their treatment.[2,39] Under these circumstances, pain initially serves as a symptom of an underlying disease.[6] In many cases, pain continues beyond successful treatment of the initial cause and in such cases, the pain diagnosis remains, even after the diagnosis of the underlying disease is no longer relevant.[40] Chronic secondary pain seems to have no direct correlation between the severity of the pain and the severity of the disease.[6] This category includes chronic cancer-related pain, which is notably prevalent[40] and arises directly from cancer or its treatment. Other forms of chronic secondary pain include postsurgical or posttraumatic pain, chronic secondary musculoskeletal pain, chronic secondary visceral pain, chronic neuropathic pain, and chronic secondary headache or orofacial pain,[5] which serve as differential diagnoses to their chronic primary pain counterparts.[1,6] Chronic postsurgical or posttraumatic pain is divided based on whether the cause is surgical or nonsurgical trauma, emphasizing the importance of prevention and management in rehabilitation.[6] Neuropathic pain requires evidence of nervous system injury for its diagnosis and is classified into chronic peripheral or central types.[41] Treatment of such complex conditions often requires an interdisciplinary team, reflecting the challenge of treating pain that is secondary to another medical issue.[38]

Chronic pain is therefore a complex and challenging condition to manage. Although the mechanisms behind it are not well understood, recognising the difference between primary and secondary pain can

help healthcare professionals develop comprehensive and targeted interventions, that address both the physical and psychological components of pain. As the medical community's understanding of chronic pain deepens, so too will its management.

Neuroscience of Chronic Pain

Through the years various theories have emerged to try and explain the science behind chronic pain. The Gate Control Theory of Pain was the first to introduce the effects of emotion and cognition into the experience of pain.[42] It marked a significant shift towards understanding the complex multidimensional nature of pain beyond the direct result of tissue damage or injury.[43] This theory proposed that the dorsal horn of the spinal cord acted as a gate that modulated sensory transmissions controlled by pain and touch fibres before reaching higher-level brain areas for perception.[42,43] This theory was a major advancement in the field of pain research and management by aiming at a more comprehensive explanation and prompting further research.[42,43]

Building from the Gate Control Theory, the Neuromatrix Theory of Pain[43] proposes that the experience of pain is like the output of a brain neural network called the "body-self neuromatrix",[44] involving the activation of different cortical and subcortical areas,[45] rather than a single brain area in direct response to sensory input following tissue injury or inflammation.[43] The term pain matrix refers to a network of brain regions activated by nociceptive stimuli. Numerous neuroimaging studies have since shown that brain regions activated by nociceptive stimuli can also be affected by various emotional and behavioural states.[21,43,45,46] Although different types of chronic pain can engage different parts of the brain and be perceived differently by individual patients, there is typically a shift away from regions involved in processing the sensory component of pain. Instead, there is a move towards regions that encode emotional and motivational responses and areas associated with processes like learning and memory.[45] This may explain some emotional and cognitive problems often seen in people with chronic pain, including anxiety and depression, impairments in emotional decision making and working memory.[45] This is relevant because it provides the neural mechanistic basis for a better understanding of how psychological factors affect pain.

For chronic pain in children and adolescents, the picture is further complicated by the immature state of their neural pain networks at birth, which undergo significant development. Peripheral and central nociception in the spinal cord and brain mature during infancy and childhood. This immaturity impacts their pain processing and coping mechanisms, creating a reduced ability to suppress incoming pain signals due to the relatively slower development of descending inhibitory systems from the brain to the spinal cord.[45] It has also been noted that in most cases, a correlation exists between specific brain changes and the duration and intensity of chronic pain.[45] This association suggests that long-term exposure to pain may cause central changes, however, recent studies have shown that effective treatment interventions may lead to normalization of brain structure and function, suggesting that brain plasticity can be bidirectional even in adulthood.[47,48]

The understanding of pain has therefore evolved from a simplistic, localized sensation to recognising it as an outcome of complex interactions within neural networks. This paradigm shift delineates pain not merely as a direct response to sensory stimuli but as a complex construct that integrates the sensory, cognitive and emotional dimensions of the human experience.

The Biopsychosocial Model of Chronic Pain

According to the biopsychosocial model of pain, pain is interpreted as a complex multidimensional process involving biological, psychological and social factors.[16,27] This model has been especially influential in the area of chronic pain.[43] The biopsychosocial model introduced the distinction between disease and illness, which is analogous to the distinction that can be made between pain and nociception.[43] Nociception is the biological process, designed to protect us from harm, which involves the stimulation of nerves that convey information to the brain about potential tissue damage. In contrast, pain is the subjective perception that results from the transduction, transmission and modulation of sensory information.[43]

Biological Factors

Pain is classified as to its mechanism into nociceptive, neuropathic or nociplastic.[16] Nociceptive pain is pain that arises from actual or threatened damage to non-neural tissue, due to the activation of nociceptors, which are sensory receptors responding to damaging stimuli, with the type of pain experienced depending on the nociceptor activated.[41] It is usually differentiated into somatic or visceral. This term is used to describe pain occurring within a normally functioning somatosensory nervous system, to contrast with the definition of neuropathic pain.[41] Neuropathic pain arises therefore as a consequence of an injury or disease of the somatosensory nervous system itself, and it can be subdivided into central and peripheral.[2,33,40] Nociplastic pain arises from altered nociception despite no clear evidence of tissue damage or somatosensory system lesion or disease causing the pain.[25,41] The mechanisms that underlie this type of pain are not well understood, but nociplastic pain is thought to be associated with primary chronic pain.[24,25]

When the nociceptive system is repeatedly or intensely exposed to harmful stimuli, it undergoes neurophysiological alterations,[2] including peripheral and central sensitization,[10] resulting in an increased sensitivity to pain,[29] known as primary and secondary hyperalgesia.[35,40] These changes are at the root of some chronic pain situations in which pain is no longer associated with the presence, intensity or duration of the peripheral nociceptive stimulus.[16,40] As a result, pain can outlast physical injury creating a vicious cycle in which the longer pain persists the more difficult it becomes to reverse, perpetuating the pain sensation even in the absence of initial stimuli.[49]

Psychological Factors

Psychological factors involve both emotion and cognition. Emotion is the more immediate reaction to nociception and is more midbrain-based.[43] Cognitions then attach meaning to the emotional experience[50] and can trigger additional emotional reactions and thereby amplify the experience of pain.[43] Historically, there has been a greater focus on the biological aspects of pain, but psychological factors, including personality traits such as resilience, coping mechanisms and the patient's beliefs about pain,[50] also have a significant impact on the experience of pain.[27,35] Building resilience, whether on an individual or interpersonal level, can help to reduce the impact of pain.[50] Examples of individual resilience resources are optimism, self-efficacy and cognitive flexibility, whereas positive relationships with peers, social engagement and the support of family and teachers are considered interpersonal resilience resources[16]. Conversely, catastrophizing and avoidance behaviours can exacerbate the experience of pain in children and adolescents.[10,51] Pain research suggests that children who are prone to negative thinking or catastrophizing may experience increased psychological distress and a greater need for medication.[50] Catastrophizing is associated with the anticipation of the worst possible outcomes,[52] representing a set of negative emotional and cognitive processes that include magnification, rumination, pessimism about pain sensations and feelings of helplessness when in pain.[10]

Certainly most, if not all, people seek to avoid pain.[10] Several behavioural models have been developed to explain how psychological factors contribute to the development of chronic pain. The fear-avoidance model is one of the most widely recognised ones, centring primarily on the emotion of fear.[52] Fear of pain and subsequent exacerbation of its effects is common in both children and adults.[10] The fear-avoidance model of pain states that interpreting pain as a threat leads to avoidance behaviours, creating a vicious cycle that may lead to loss of function, enhancing feelings of fear, incapacity and pain itself.[16] Diminishing the fear of pain strongly correlates with positive functional outcomes in children with primary pain disorders, suggesting an important therapeutic target for reducing pain-related disability.[10] This model of pain has therefore guided paediatric chronic pain research and clinical practice, providing the framework for a range of effective behavioural treatments, including cognitive-behavioural therapy, acceptance-based therapies and multidisciplinary pain rehabilitation.[21,53]

The experience of pain is also deeply influenced by the individual’s beliefs about the nature, cause, and consequences of pain, and whether it is understood and believed as real by clinicians.[50] Pain perceived as having little benefit or associated with potential disability or exacerbation of the underlying condition is likely to be less tolerated. For example, a child with a diagnosis of cancer may interpret pain as an indication of disease progression or relapse.[50] Addressing these beliefs and providing accurate pain education is essential for effective pain management.

Depression and Anxiety

Furthermore, comorbidity with mental health conditions, including anxiety and depression, is notably prevalent among adolescents with chronic pain.[2,10,54] The observations from functional imaging studies

suggest that this bidirectional relationship is due in part to shared neural mechanisms.[21,35,43] Although depression may be secondary to the physical illness or its treatment, the presence of a depressive disorder increases the risk of developing chronic pain conditions.[50] Pain often results in symptoms of anxiety, and anxiety may decrease the pain threshold and increase the sensation of pain. It is estimated that about 80% of adolescents with chronic pain have anxiety in some phase of the treatment. The consequences of anxiety, including somatization and avoidance behaviours, contribute to a vicious cycle that perpetuates and exacerbates pain. Space limitations preclude a thorough review of the relationship between chronic pain, anxiety and depression. Paediatricians should be particularly alert to suicide ideation or attempts in this at-risk population,[21,24] and they should ascertain the suicidality of depressed adolescents.[10,21,55] These comorbidities further complicate the clinical picture and call for a comprehensive approach to assessment and management, addressing both the pain and the associated psychological conditions.

Social Factors

Social, cultural and environmental factors also play a pivotal role in the expression of pain among children and adolescents.[5,22] Social functioning, school performance, and peer relationships can be negatively impacted, leading to isolation and victimisation, which can exacerbate the pain experience.[50] Accumulating evidence suggests that experiences of physical and social pain, namely social rejection, exclusion and bullying, share common neural pathways, underscoring the biopsychosocial nature of pain.[45] Theories of classical and operant conditioning offer insights into how pain behaviours are learned and reinforced within social settings.[27] Positive reinforcement of pain complaints, for example through increased attention or tangible rewards, inadvertently encourages the persistence of pain behaviours.[50] Thus, the child's experience of pain is significantly influenced by their social environment, particularly family dynamics.[27] Overprotective or overly attentive parenting styles can contribute to poorer functional outcomes by reinforcing pain behaviours.[27] In contrast, parents who demonstrate psychological flexibility and adopt supportive coping strategies can significantly improve their children's pain outcomes.[45]

Management of Chronic Pain in Children and Adolescents

Historically, pain has been treated simply as a biomedical problem. However, the understanding of chronic pain has evolved from a strictly biomedical approach to a holistic biopsychosocial perspective, recognizing the intricate interplay of physical, psychological, and social factors.[45,50] In particular, doctors need to determine the roles that each of these factors[50] and the physical illness itself play in the pain experience.[29,36] Pain is a subjective sensation, and it is important to believe the child's experience of pain[45] and try to avoid the dichotomy between primarily physical or psychological pain.[2,27] Treatment should be multidisciplinary and incorporate both pharmacological and non-pharmacological approaches.[29,56]

Non-pharmacological Management

An integrated non-pharmacological approach, including physical and occupational therapies, psychological interventions and complementary strategies, is essential for the treatment of paediatric chronic pain.[9,27,57] Physical therapies such as exercise, yoga and hydrotherapy enhance flexibility, mobility, and muscle relaxation, often complementing medical treatments.[26,29] Psychological therapies, notably Cognitive Behavioural Therapy, Acceptance and Commitment Therapy, and Mindfulness-Based Interventions,[50] target maladaptive cognitions and behaviours, fostering adaptive coping strategies and improved daily functioning.[21,47,48,58,59] Techniques like guided imagery, hypnosis and biofeedback[27] offer additional avenues for pain management,[27,50] emphasizing patient engagement and control over physiological responses.[17] The role of complementary therapies, including acupuncture[8] and music therapy, remains exploratory due to limited high-quality evidence.[29] Education for patients and families about pain management[23] and neuroscience is crucial, aiming to clear misconceptions and promote a comprehensive understanding of pain.[60] Family interventions target the promotion of supportive behaviours and the reduction of behaviours that reinforce pain, emphasizing the significance of a supportive environment for the child's coping and recovery.[16,50]

Pharmacological Management

Pharmacological treatments play a secondary role,[29] focusing on non-opioid analgesics like NSAIDs and paracetamol for mild pain.[40,50] Opioids are reserved for specific cases due to their associated risks.[40] The evidence for opioid effectiveness in children is particularly scarce, with harmful effects outweighing the benefits, leading to a consensus against their use for primary pain conditions.[26] Prescribers should be cognizant of their potential for the development of tolerance, dependence, and addiction.[31] Adjuvant therapy can enhance analgesic efficacy, treat coexistent symptoms or provide independent analgesic activity for specific types of pain.[26,40,61] Adjuvant analgesics, namely antidepressants and anticonvulsants, offer potential benefits in chronic pain management.[10,61] Gabapentin, for instance, is favoured for its lower side-effect profile and fewer drug interactions, making it a first-line option for neuropathic pain.[2829] However, the overall evidence supporting the use of antiepileptic drugs in paediatric chronic pain is inconclusive.[26]

In sum, a comprehensive, interdisciplinary approach that incorporates both pharmacological and non-pharmacological methods is recommended. The management of chronic pain in children and adolescents requires a careful, evidence-based approach that prioritizes safety and efficacy.

Antidepressants for Chronic Pain Management: Mechanisms of Action

Antidepressants are traditionally used to treat depression, through the modulation of certain neurotransmitters, like serotonin, noradrenaline or both. They work by targeting the reuptake of these neurotransmitters by the nerve terminals, thereby increasing their availability in the synaptic cleft. While a positive mood effect may help alleviate pain, their use over the years has led to the clinical impression that their pain-relieving effects are distinct from their effects on mood. On the one hand, pain can be

improved in euthymic patients, meaning analgesia is not dependent on mood elevation.[35,61,62] Furthermore, studies indicate that the dosages required for optimal pain relief are considerably lower than those prescribed for depression, and the onset of action is faster in analgesia.[32,33] More evidence for their independence is that there are differences in analgesic effectiveness between different classes.[25,54,62]

Despite their established clinical use, particularly in adults, the precise mechanisms by which antidepressants alleviate pain remain to be fully elucidated.[25] Pain pathways are complex, with several potential points for drug intervention.[50] This section aims to synthesize current understanding, drawing upon recent research to outline the potential pathways through which antidepressants mediate analgesic effects.

Neurotransmitter Modulation and Descending Pain Inhibitory Pathways

Pain modulation describes the process by which the body modifies a pain signal as it is transmitted along the pain pathway. This phenomenon explains the variability in individual responses to identical painful stimuli, underscoring the inconsistent relationship between the activation of nociceptive neurons and the sensory perception of pain. Most importantly, pain modulation elucidates the mechanisms of action underlying clinical analgesia.[63] Serotonin, noradrenaline, and to a lesser extent, dopamine, play important roles in both mood regulation and pain modulation.[27,63] Antidepressants, by increasing the levels of these neurotransmitters, can help modulate and alleviate pain.[35]

Inhibition of noradrenaline reuptake appears to be the most important mode of action.[25,61,64] Its increase, facilitated by antidepressants, directly inhibits pain via α_2-adrenergic receptors, which are important in allodynia and hyperalgesia, phenomenons commonly associated with chronic pain.[33] Furthermore, noradrenaline enhances the descending noradrenergic inhibitory system, which is essential for pain regulation.[33,63] Serotonin and dopamine further contribute to this analgesic effect, albeit in supporting roles, by modulating synaptic transmission and excitability.[35,63–67] Enhancement of the descending pain inhibitory pathways is another crucial mechanism.[27] These pathways, which extend from the brain to the spinal cord, play a vital role in modulating pain transmission. Their dysregulation is involved in the chronification of pain, suggesting that antidepressants may exert their analgesic effects by restoring balance to these systems.[46] This perspective highlights the potential of targeting neural circuits involved in pain modulation as a therapeutic strategy.

Other Actions

Antidepressants can also act as sodium channel blockers. Sodium channel blockers inhibit ectopic discharges occurring when there is nerve damage, thereby inhibiting neuropathic pain.[33] In addition, some antidepressants function as NMDA receptor antagonists.[8] Activation of these receptors is an important process in both the initiation and maintenance of central sensitization.[8,35]

Neuroplasticity

Chronic pain is associated with neuroplastic changes in the brain, characterized by alterations in neural structure and function.[8] Antidepressants promote neuroplasticity, potentially counteracting the maladaptive changes associated with chronic pain. [35] This suggests a role for antidepressants in addressing the underlying pathophysiology of chronic pain through the promotion of neural reorganization and the formation of new neural connections.

Effects on Mood

The interplay between chronic pain, anxiety, and depression is well-documented, with comorbid mood disorders often exacerbating the perception of pain.[35,66] Antidepressants, by addressing the underlying mood disorders, may indirectly contribute to pain relief. This underlines the importance of an integrated approach to managing chronic pain and associated mood disorders, aiming for therapies that target common neurobiological mechanisms.[21,68]

In summary, the analgesic effects of antidepressants in chronic pain management can be attributed to a multifaceted mechanism of action. These include the modulation of neurotransmitter activity, enhancement of descending pain inhibitory pathways, promotion of neuroplastic changes, and effects on ion channels and NMDA receptors. Despite the diversity in their mechanisms, the common thread across these actions is the potential for antidepressants to offer a holistic approach to chronic pain management, addressing both the sensory and affective dimensions of pain. Antidepressants that inhibit the reuptake of both noradrenaline and serotonin, such as TCAs and SNRIs, were reported to have the greatest therapeutic effect on chronic pain among adults, whereas SSRIs, which are frequently used to treat depression, don't seem to be effective against chronic pain. [64,69] Further research into these mechanisms holds promise for the development of more effective and targeted treatments, considering the complex and multifaceted nature of chronic pain.

Antidepressants for Chronic Pain Management: Evidence in Adults

Antidepressants are widely prescribed for adult chronic pain, often recommended as the first-line treatment option. The 2021 NICE Guidelines explicitly recommend against the use of other drugs apart from antidepressants to manage chronic primary pain in adults, citing their benefits for quality of life, sleep and psychological distress, even in the absence of a diagnosis of depression.[26,70] They highlight duloxetine for its long-term evidence of effectiveness, though they recommend choosing antidepressants based on a fully informed discussion with the patient, considering the risks and benefits.[26]

A recent Cochrane review, including 176 studies, aimed to assess the comparative efficacy and safety of antidepressants for adults with various types of chronic pain. [34] Once again, duloxetine emerged as the most effective antidepressant, particularly for fibromyalgia, musculoskeletal and neuropathic pain. Standard doses were proven as effective as higher doses, which are more likely to cause side effects. Milnacipran also showed efficacy but with lower certainty evidence.[34] Aside from duloxetine and milnacipran, there was insufficient evidence to draw robust conclusions about the efficacy and safety of any other antidepressant. Some questions remain unanswered, such as the long-term efficacy of these medications, their side effects, and the extent of their effects on mood and side effects.

Another overview of systematic reviews on 26 pain conditions revealed no high-certainty evidence for antidepressant efficacy, except for SNRIs, particularly duloxetine. Evidence for other conditions and antidepressant types, such as TCAs and SSRIs, varies greatly in quality and certainty, with some conditions showing low certainty evidence of efficacy and others showing no efficacy. However, further investigation by future trials is important. Caution is needed in interpreting these findings since there are potential biases due to industry ties. This is particularly relevant for the evidence on the efficacy of SNRIs, where 68% of trials were identified as having industry ties. Furthermore, recent studies suggest older trials may have overestimated treatment effects.[70]

There is currently no reliable evidence for the long-term efficacy of any antidepressant, and no reliable evidence for the safety of antidepressants for chronic pain at any time point.[69] The average length of studies was 10 weeks. The off-label prescription of antidepressants for pain management has significantly increased, raising concerns about their safety.[71] The relationship between dosage and side effects is crucial, as lower doses required for analgesic effects compared to mood improvement may result in fewer adverse outcomes.[32] Furthermore, most studies excluded people with mental health conditions, meaning that participants were already in the 'normal' ranges for anxiety and depression at the beginning of the studies.[34]

Notably, the literature highlights the variability in response among individuals, reminding us to be careful when extrapolating these findings, as treating younger populations based on evidence from adult studies can be inaccurate and potentially harmful.

Discussion

Antidepressants for Chronic Pain in Children and Adolescents

As stated previously, there is a significant gap in research, including systematic reviews, meta-analyses, and clinical trials. While a few systematic reviews have explored the use of pharmacological treatments for chronic pain in paediatric populations, only one was found that specifically focused on the use of antidepressants. Cooper et al. reviewed the use of antidepressants for various types of CNCP,[62] including data from four studies, three of which targeted amitriptyline and one citalopram, in participants aged from 6 to 18 years old. The analysed studies – Bahar 2008, Saps 2009, Roohafza 2014 and Brown 2016 – are included in Table 1. Although some of these studies showed promising results individually, collectively they contributed to a low level of certainty in the evidence derived from them. For example, the study comparing amitriptyline with placebo in adolescents with IBS reported a 15% improvement in quality of life in the treatment group compared to the control group.[6,72] However, the study had several limitations, namely a rather small sample size, limiting the quality of the findings. The study by Saps 2009 showed good and excellent therapeutic response with amitriptyline but when compared to placebo, at 4 weeks of treatment, there was no significant difference. When comparing amitriptyline to other pharmacological options (gabapentin) there were also no statistically significant differences between groups, in both pain reduction and sleep score. Overall, there were several limitations to the studies reviewed. No meta-analysis could be conducted due to insufficient data, leaving the authors unable to comment on the efficacy or safety of antidepressant therapies, nor make comparisons between different classes.[62]

More recently, Bruijn et al. reviewed the efficacy and safety of antidepressant agents in children and adolescents, focusing solely on functional abdominal pain disorders.[57] They highlighted the need for future research to enhance the certainty of findings in this area. In line with previously discussed results, the success rate of treating children and adolescents with antidepressants appears to be no greater than that of a placebo.[57] However, given that a placebo is not a common approach in clinical practice, future research should focus on direct comparisons between non-pharmacological treatments and antidepressants. Such research can offer valuable insights into the benefits and risks of either option, as well as the effectiveness of combination therapy versus monotherapy.[57]

A meta-analysis on the effectiveness of psychotropic medications in managing chronic pain in children and adolescents concluded they could be a viable treatment option.[25] This is particularly important as they can offer a safer alternative to opioids, especially in a population at high risk for tolerance, opioid-induced hyperalgesia and opioid use disorder.[25] This meta-analysis expanded upon previous findings by including a study comparing duloxetine with placebo in adolescents with juvenile fibromyalgia (Table 1). This study reported a significant decrease in pain severity over 30% and 50% post-intervention.[5,73]

Tabela 1. Study and Patient Characteristics of Included Studies

First Author, Year	Age Group (years), Population	Intervention vs. Comparator	Indication	Relevant Outcomes Assessed	Treatment and Follow-up Interval	Conclusions
Upadhyaya, 2019[73]	13 to 17 N = 184	DLX vs. PLC	JFM	1. Mean change in 24-hour BPI average pain severity 2. Treatment response; Functional disability; Depression; Anxiety	13 weeks	No statistically significant difference between DLX and PLC in mean change in 24-hour BPI average pain severity >30% and >50% reduction in pain severity with DLX compared to PLC
Roohafza, 2014[74]	6 to 18 N = 115	CIT vs. PLC	FAP	1. Pain intensity 2. Depression Anxiety; Somatization	4 weeks 12 weeks	In PP analysis, more reduction was observed in pain and global severity scores in the CIT group compared with the placebo group Such differences were not present in the ITT analysis
Brown, 2016[75]	7 to 18 N = 34	AMI vs. GBP	CRPS 1 NP	1. Pain intensity 2. Sleep quality	4 weeks 6 weeks	AMI and GBP significantly decreased pain intensity scores and improved sleep No statistically significant differences between groups
Saps, 2009[76]	8 to 17 N = 90	AMI vs. PLC	FAP FD IBS	1. Overall response to treatment (child's assessment of pain relief and sense of improvement) 2. Effect on psychosocial traits; Daily functioning	4 weeks 5 weeks	Both AMI and PLC were associated with excellent therapeutic response There was no significant difference between AMI and PLC after 4 weeks of treatment
Bahar, 2008[72]	12 to 18 N = 33	AMI vs. PLC	IBS	1. Quality of life 2. Pain intensity and frequency	7 weeks 13 weeks	15% improvement in overall quality of life score with AMI, at 10 and 13 weeks of treatment

Legenda: DLX: duloxetine; PLC: placebo; CIT: citalopram, AMI: amitriptyline; GBP: gabapentin; JFM: juvenile fibromyalgia; FAP: functional abdominal pain; CRPS 1: Complex Regional Pain Syndrome Type 1; NP: neuropathic pain; IBS: Irritable Bowel Syndrome; FD: functional dyspepsia; BPI: Brief Pain Inventory; PP: per-protocol; ITT: intention-to-treat.

Despite some limitations regarding sample size and generalizability of the findings, the study did showcase methodological improvements and a broader scope of outcomes assessed compared to preceding studies, hopefully indicating a trajectory towards enhanced quality in research concerning chronic pain conditions in children and adolescents. In addition, it suggests that a treatment period of 12 to 13 weeks is necessary to observe significant analgesic effects.[25] This explains why studies with shorter durations may have reported limited efficacy, potentially contributing to the methodological limitations observed in prior research.

As for secondary outcomes, the Cochrane reviews (Cooper et al. and Bruijn et al.) included a broad range of outcome measures, such as Carer Global Impression of Change, sleep quality, acceptability of treatment, quality of life and any adverse events or withdrawals due to adverse events, based on the PedIMMPACT guidelines.[57,62] Regrettably, for most of these secondary outcomes, the quality of the evidence was very low across all studies. This was due to various factors, namely the lack of data, the small number of events and the high heterogeneity of reported outcomes.[57,62] Overall, no significant effects were observed on functional disability, anxiety and depression, activity participation and patient satisfaction.[5,62] More adverse events related to treatment groups than controls were reported, though not statistically significant.[5]

Concerning safety, it remains unclear whether antidepressants account for more withdrawals due to adverse events compared to placebo groups, due to insufficient data across all studies.[57] One study noted more treatment-related adverse effects in the group receiving duloxetine compared to placebo, but these findings were similar to that reported previously in duloxetine paediatric trials of other indications and no new safety concerns emerged.[73] Adverse events across all studies, both in the intervention and comparator groups, were mild reactions such as nausea, dizziness, drowsiness, tiredness and abdominal discomfort (very low-quality evidence), and no serious adverse events were reported.[62] Notably, the included RCTs were generally small, which means they may not have had sufficient power to detect statistically significant differences in the incidence of less common adverse events.[5]

A critical appraisal of the literature

There are two main problems regarding the evidence on this topic, limiting the drawing of conclusions: (1) the small number of trials and lack of overall research in paediatric populations and (2) the various limitations of the few existing studies. The lack of paediatric-specific research is a significant barrier to advancing evidence-based pharmacotherapy in this area. Despite repeated calls for improved evidence throughout the literature, the progression of clinical trials in this field has been very slow.[36] Eccleston et al. pointed out that, at the current rate of one trial of 19 patients entering into evidence every 3.5 years, it will take around 1000 years to significantly lower the uncertainty in the effectiveness of pharmacological interventions for paediatric chronic pain management.[36] The lack of research in this area is likely due to practical and moral considerations of testing pharmacological interventions in children, coupled with the ethical concerns of withholding medication from young people in pain.[36]

These challenges mirror those encountered in other areas of paediatric research, suggesting the need for a revaluation of research methodologies and ethical considerations.

Based on the analysed studies, it can be concluded that there is no high-quality evidence for delivering any pharmacological intervention to a child or adolescent with chronic pain.[77] However, there is promising research on the analgesic effects of antidepressants and their potential to improve quality of life, which should not be overlooked. Although the quality of the systematic reviews themselves is good, the problem lies in the amount and quality of data available for analysis.[57,62]

The studies exhibit a high degree of heterogeneity, which does not facilitate cross-comparisons and the drawing of general conclusions. For instance, studies evaluated different aspects of chronic pain as their primary outcomes and the definition of reduction in pain score and pain intensity scales were different among the included studies. Some evaluated pain intensity in response to treatment, others sleep quality, others made a more holistic approach and evaluated also psychological comorbidities like anxiety and depression, but no single one evaluated the same outcomes. This underscores the need for more organised criteria of what outcomes should be assessed when studying the efficacy and safety of antidepressants for chronic pain in children and adolescents. The characteristics of the populations assessed, drug doses and duration of treatment were different among the included studies, which limits generalizability.

There were only a small number of studies with small sample sizes, compromising the quality of the evidence. The total number of studies was too small to draw meaningful conclusions, and no study contained over 100 patients per group. For example, the only study (Bahar, 2008) showing significant improvements in quality of life only included only 33 participants.[25,72] The follow-up period was also reduced throughout all studies, which is inadequate for a chronic pain condition with long-term consequences for children and their families.[57]

The types of data analysis also matter to the quality of the evidence that can be derived from it. For example, in the study comparing citalopram with placebo, responses to treatment were observed in both groups, with a more pronounced effect in the citalopram group according to per-protocol analysis. However, no significant difference was noted in the intention-to-treat analysis. Such an approach offers a more conservative estimation of an intervention's efficacy, reflecting a real-world scenario where not all patients adhere to the prescribed treatment. This suggests that while citalopram may exhibit efficacy under controlled conditions and with strict adherence, its effectiveness in a general, real-world population remains uncertain. A thorough examination of non-adherence and dropout reasons is essential for a comprehensive understanding of a drug's potential benefits and limitations.

In the evaluation of antidepressant efficacy, it is crucial to discern the relationship between the antidepressant's effects and those attributable to placebo. A predominant finding in these studies is the absence of a significant difference between the antidepressants and placebo groups. This lack of disparity is not necessarily indicative of the antidepressant's ineffectiveness in alleviating pain but rather

highlights the potent therapeutic effect of placebos.[63] When assessing criteria based on pain intensity improvement, the outcomes appear to be comparable, that is, in the reviewed studies, the number of individuals experiencing pain relief is nearly identical between those treated with placebos and those treated with amitriptyline.

Furthermore, only a select few antidepressant drugs (amitriptyline, duloxetine and citalopram) have been studied in this demographic, hindering any attempt to compare the effectiveness and safety profiles between different classes.

Considering all these factors, it can be concluded that there is an urgent need for more clinical trials and improved research on this topic. Future trials should aim for superior methodological quality, examining a wider range of outcomes and comparing different therapies, both pharmacological and non-pharmacological. It may also be appropriate to include other types of studies. For example, qualitative studies could be beneficial for investigating chronic pain, as it is a highly subjective experience. These studies can help to identify what patients value most when managing the condition, which can inform future research and improve outcomes for children and adolescents with chronic pain.

Furthermore, future research should focus on outcomes that are truly valued by young people and their families. For example, the duration of treatment and the long-term longevity of benefits are key aspects of great interest to patients. When treatments have equal efficacy, children and their families may still consider treatment with an earlier onset to be better. It is imperative to listen to their expectations and conduct research that addresses patient-centred outcomes. For instance, in one of the reviewed studies, more than half of the eligible adolescents or their guardians refused to participate.[72] Interestingly, despite a strong desire for immediate symptom relief, the main reason for this decision was not the possibility of receiving a placebo instead of amitriptyline, nor the length of the trial and the associated pre-treatment period. Instead, parents expressed discomfort with the idea of their child using any type of antidepressant medication, often influenced by reports in the lay press as the determining factor in their decision-making process. This feeling was amplified in 2004 after the United States Food and Drug Administration issued “black box” warnings regarding the potentially heightened risk of suicidal thoughts in children taking antidepressants.[55,72] In order to provide the best medical care, healthcare professionals need to understand the priorities, expectations and beliefs of patients and families about the treatment proposed.

Clinical Practice Guidelines

Clinical practice guidelines play a pivotal role in informing the management strategies for chronic pain, however, guidelines specifically targeting paediatric populations remain notably sparse. The Guidelines on the Management of Chronic Pain in Children, from the WHO, advocate for a cautious application of antidepressants, consistent with the unclear balance between the benefits and harms of pharmacotherapy in this population, emphasizing an interdisciplinary approach grounded in the

biopsychosocial model.[5] The WHO underlines the need for tailored therapeutic strategies based on individualized risk assessments that are age, context, and culturally appropriate for assessing pain and its impacts. Specific national guidelines, although very few available, suggest low-dose amitriptyline for a spectrum of functional and nociceptive/neuropathic pain conditions, citing its favourable risk-benefit profile at reduced dosages despite the limited quality of evidence.[28,29] The Direção Geral da Saúde only has guidelines for paediatric chronic cancer pain that recommend TCAs like amitriptyline for chronic cancer pain with a neuropathic component, aligning with previous reviews calling for an interdisciplinary treatment approach.[78]

The reliance on clinical experience and expert opinion, due to the dearth of robust evidence, accentuates the urgent need for comprehensive research to bridge the evidence gaps. The extant guidelines champion a cautious, evidence-informed utilization of antidepressants while highlighting the critical role of an interdisciplinary treatment strategy. This situation underscores the imperative for updated, evidence-based clinical practice guidelines to optimise individualized care for paediatric patients experiencing chronic pain.

The role of interdisciplinary treatment

The management of chronic pain in children and adolescents is inherently complex due to their unique biological, psychosocial and developmental characteristics.[79] The inadequacy of purely biomedical models in addressing this problem is consistent with the need for a more integrative approach.[23] Given that the efficacy and safety profiles of pharmacological treatments in paediatric populations remain understudied, interdisciplinary pain treatment programs have emerged as the standard of care in this patient population.[65] These programs advocate for a holistic approach, encompassing not only pharmacological interventions like antidepressants, but also psychological therapies, physical rehabilitation, and social support systems.[23] Such comprehensive care models have demonstrated promising outcomes,[22,40,45] improving both the quality of life for patients and cost efficiency.[10] Moreover, the integration of family and caregivers into the treatment process has emerged as a critical component,[3] emphasizing the influence of parental attitudes and behaviours on the child's pain experience and recovery trajectory. This model facilitates a paradigm shift towards value-based healthcare, where services are tailored to meet the unique needs of patients, rather than requiring patients to navigate the complexities of healthcare systems.

Conclusion

As stated by the WHO, access to pain management is a fundamental human right and children have the right to enjoyment of the highest attainable standard of health. Regrettably, as this review of the literature illustrates, the management of chronic pain, particularly in children and adolescents, remains a major gap in the medical field. Most countries lack a national policy or have inadequate policies for addressing pain as a health issue, including inadequate guidelines, research and education levels.

In the field of paediatric healthcare, the use of antidepressants as a treatment option for chronic pain management remains uncertain. The existing literature, characterized by its scarcity, fails to provide a robust foundation to draw definitive conclusions. The heterogeneity of study designs and populations further complicates the synthesis of the existing evidence. The frequent lack of inclusion of this population in studies exacerbates the challenge of developing universally applicable, evidence-based treatments for children and adolescents suffering from chronic pain.

Given the current state of evidence, healthcare professionals should proceed with caution when prescribing these medications for young patients, ensuring that treatment choices are tailored to the individual's specific needs and circumstances. It is recommended to be wary of the potential adverse effects of antidepressants, as there is insufficient evidence of their benefit in this population. Clinicians are encouraged to adopt a multidisciplinary approach, integrating both pharmacological and non-pharmacological interventions.

In addition, this review has highlighted several critical points that extend beyond its scope and into the broader field of pain management. There is a significant gap in understanding the biological mechanisms behind chronic pain and how they interact with psychological and social factors, leading to treatments that may not tackle the pain's root causes and hindering the development of targeted effective therapies. This is particularly problematic in paediatric populations, where developmental factors add another layer of complexity to pain perception and management. Furthermore, the inherent subjectivity of the pain experience requires a tailored approach to care that differs from conventional, broadly applicable treatments.

The limitations of this review, which reflect the wider constraints within paediatric pain research, highlight the urgent need for well-designed paediatric studies. Future research should focus on addressing current gaps through larger sample sizes, extended follow-up periods, and a broader consideration of outcomes that encompass quality of life, functional disability and mental health. As well as strengthening the evidence base for current treatments, research should aim to develop new therapeutic interventions that more effectively address the multifaceted nature of chronic pain in paediatric patients. The primary and secondary outcomes assessed must be of value to the children and adolescents with chronic pain.

In conclusion, this review underlines the critical need for more research on the efficacy and safety of antidepressants in managing chronic pain in children and adolescents. Addressing chronic pain in young people requires a unified effort from the scientific community, healthcare providers and policymakers to improve outcomes and defend the rights of children to comprehensive and empathetic care. It is important to acknowledge that the commitment to the research of chronic pain and its treatment, goes beyond the scope of medical research, and involves fundamental human rights. As we envision a future where children and adolescents can overcome the burden of chronic pain, let us prioritise empathy and innovation, address the depths of suffering, and empower young people to embrace the full potential of their developmental years, with hope and health.

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