NARRATIVE REVIEW

Chronic non-cancer pain in adolescents: a narrative review

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Abstract

Introduction: Chronic pain is defined as a pain lasting more than 3–6 months. It is estimated that 25% of the pediatric population may experience some kind of pain in this context. Adolescence, corresponding to a particular period of development, seems to present the ideal territory for the appearance of maladaptive mechanisms that can trigger episodes of persistent or recurrent pain.

Methods: A narrative review, in the PubMed/Medline database, in order to synthetize the available evidence in the approach to chronic pain in adolescents, highlighting its etiology, pathophysiology, diagnosis, and treatment.

Results: Pain is seen as a result from the interaction of biological, psychological, individual, social, and environmental factors. Headache, abdominal pain, and musculoskeletal pain are frequent causes of chronic pain in adolescents. Pain not only has implications on adolescents, but also on family, society, and how they interact. It has implications on daily activities, physical capacity, school performance, and sleep, and is associated with psychiatric comorbidities, such as anxiety and depression. The therapeutic approach of pain must be multimodal and multidisciplinary, involving adolescents, their families and environment, using pharmacological and non-pharmacological strategies.

Discussion and conclusion: The acknowledgment, prevention, diagnosis, and treatment of chronic pain in adolescent patients seem not to be ideal. The development of evidence-based forms of treatment, and the training of health professionals at all levels of care are essential for the diagnosis, treatment, and early referral of these patients.

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Introduction

The underappreciation of pain in pediatrics affects the health of children and adolescents, leading to physical disability and psychological distress in adulthood.1 Up to 60% of the children and adolescents with chronic pain end up having pain in adulthood, which is associated with a higher burden on healthcare services, affecting labor productivity, and causing social marginalization.2 However, the prevention and treatment of pain in children and adolescents does not seem to be ideal. It is often underdiagnosed and undertreated.

The International Association for the Study of Pain (IASP) defines pain as an unpleasant sensory and emotional experience associated with or similar to actual or potential tissue damage, thus demonstrating the difficulty to have an objective definition and description, given its multidimensional character.3,4 Chronic pain is defined as pain that lasts longer than 3–6 months.4

Adolescence corresponds to a specific period of physiological, psychological, emotional, and social development, and seems to present the ideal ground for the emergence of maladaptive mechanisms that trigger pain phenomena.4 All adolescents experience acute pain along their development. Although most of them recover without further complications, some end up having persistent or recurring pain, which culminates with the process of chronic non-cancer pain in adolescents. In this manner, it is urgent to know, understand, and work on the many factors that contribute to the chronification of pain in adolescents.5

The aim of this review is to summarize the evidence available on the etiology, pathophysiology, diagnosis, and treatment of chronic non-cancer pain in adolescents.

Methods

In this review, we followed the assumptions of a narrative review,6,7 aiming to answer the investigation question: what is the evidence available on the etiology, pathophysiology, diagnosis, and treatment of chronic non-cancer pain in adolescents?

We conducted a search on the PubMed/Medline database, on July 2nd, 2020, using natural language terms, and MeSH Subject Headings: “chronic pain”, “adolescent”, “paediatric”, and “pediatric”, combining them with the Boolean operators “AND” and “OR”, which led to a total of 405 results. After reviewing abstracts, 166 papers were initially selected and analyzed, which in turn, allowed identifying other relevant complementary publications. We included papers written in English and Portuguese published in the past ten years, whose titles stated they were experimental, observational prospective, or retrospective trials, clinical case reports, or systematic reviews that addressed adolescents with chronic pain.

We defined the concept of adolescence using the definition of the World Health Organization (WHO), as the period of development comprehended between 10 and 19 years of age.8 We did not apply geographical or cultural limitations for the studies included in this review.

Results

Epidemiology

Chronic pain is a global public health problem whose estimated average prevalence is approximately 35%. Globally, its etiology, type, and location seem to vary according to age, sex, and the age group considered. It is more frequent in the female sex, above 65 years of age, and located on the lumbar region or lower limbs.9,10

Chronic pain in the pediatric population is more expressive in adolescence and its prevalence is estimated to be 25%, with peak incidence between 14 and 15 years of age, affecting disproportionally more the female sex, with prevalence rates almost twice as high as that of the male sex.11 About 30% of adolescents show interference in their daily activities and 8% present severe incapacity.12,13 The most prevalent types of pain are headaches (23%–51%), abdominal pain (2%–41%), and musculoskeletal pain (4%–40%).11,14

In a multicenter trial coordinated by Gobina et al., which intended to assess the prevalence and demographic characteristics of chronic pain in adolescents, using questionnaires applied on 11-, 13- and 15-year-old students in secondary schools of 42 countries, they found that about 44.2% of them reported weekly chronic pain during the past 6 months, and chronic pain in several areas was more frequent (13.2%–33.8%), than pain on a single site.15

Current data allow the observation that, although chronic pain in adolescents is a global problem, there are differences in prevalence, whether due to sampling differences, form of description, and acquisition of data, or even due to the very definition of pain used, pain pattern, and demographic characteristics of adolescents, with age and sex being important predictors.15

Pathophysiology

Pain has been classified as to its mechanism in three major groups: nociceptive, neuropathic, and nocinocplastic (Table 1).3

Nociceptive pain results from tissue lesion with the activation of nociceptors and, depending on the area where the noxious stimulus occurs, it is differentiated in somatic pain and visceral pain. Visceral pain originates from the activation of nociceptors located in internal organs. Neuropathic pain is the result of a lesion or disease in the somatosensory nervous system.16 Nocinocplastic pain encompasses all situations in which there is a lesion that is not on the somatic tissue, visceral or somatosensory system, but in which there is an alteration in the nociception mechanism.17,18

Although practical and with predominant implications in the clinical and therapeutic approach, this classification of pain is increasingly seen as too reductionist because it is limited to only two dimensions, physical and functional. In that sense, in 2019, IASP and the WHO developed, through the International Classification of Diseases (ICD-11), a more robust, systematized, and dynamic classification system. In this manner, chronic pain is classified in 7 groups: (1) Chronic primary pain, which includes chronic pain whose etiology is unknown or cannot be attributed to another chronic condition; (2) Chronic cancer-related pain, which includes pain caused by oncological diseases or by their treatment; (3)
Table 1 Classification of pain according to the underlying mechanism. Pathophysiological and clinical differentiation of nociceptive, neuropathic, and nociplastic pain.

| Stimulation | Nociceptive pain | Neuropathic pain | Nociplastic pain |
|-------------|------------------|------------------|-----------------|
| Nervous system lesion | No lesion identified. | Abnormal central processing |
| Area | Visceral – smooth muscle, solid organs. Diffuse, poorly localized, referred | Burning, pins, and needles, breakthrough, hypoesthesia, hyperesthesia, allodynia, irradiation | Multiple areas, diffuse, undefined |
| Clinical Characteristics | Sharp/continuous, stabbing, throbbing, palpitating | Polyneuropathy, Neuralgia, Chemotherapy, Radiotherapy | Fibromyalgia, Irritable bowel syndrome, Headaches |
| Context | Trauma, Post-operative pain, Burn, Ischemic pain | | |

Chronic postsurgical or posttraumatic pain, when pain persists beyond normal healing time; (4) Chronic neuropathic pain, caused by a disease or lesion of the somatosensory nervous system; (5) Chronic headache or orofacial pain; (6) Chronic visceral pain, whose origin is secondary to internal organs (head, neck, chest, abdominal, and pelvis); and (7) Chronic musculoskeletal pain, secondary to diseases of the bones, joints or related soft tissues.

Today, chronic pain is interpreted as a complex, and sometimes dysfunctional, network resulting from neuronal communications between peripheral nerves, spine, and brain. All information is processed, and modulated in the brain, where consciousness of the experience of pain takes place. Patients with chronic pain present facilitation of the nociceptive circuits, with increased signal transduction and reduced response threshold to noxious stimuli, originating phenomena of peripheral and central sensitization, often without any identifiable structural cause. Currently, pain is interpreted as a complex multidimensional process with the integration of biological, psychological, individual, sociocultural, and environmental factors, based on the biopsychosocial model (Fig. 1). In this manner, the interaction of genetic and environmental aspects, like physical health, sex, maturity, cognitive development, emotions, cultural influences, and socioeconomic level results in pathophysiological mechanisms that perpetuate pain.

In chronic non-cancer pain in adolescents, these factors have yet to be interpreted from a developmental perspective.

The psychological dimension has been widely investigated and seems to play a predominant role in the pathophysiology of chronic non-cancer pain in adolescents. Several models try to explain the influence of these psychological processes in the augmentation and perpetuation of pain. The Fear Avoidance Model says that pain, when interpreted as a threat, leads to repetitive behaviors of fear and avoidance, which may result in loss of function. It is a vicious cycle that may condition more avoidance, more pain and incapacity, as well as an increased risk of persistent pain.

If, on one hand, catastrophizing (negative posture and mentality of overreacting to pain), depression, and anxiety are facilitators and individual risk factors in the chronic pain process, on the other hand, an overprotective family and chronic disease models are interpersonal risk factors and mechanisms, that is, they are important predictors for central sensitization, and persistence of pain.

However, not all psychological states are maladaptive. According to the Ecological Risk-Resilience Model of Pediatric Chronic Pain, several resources and mecha-
organisms may lead to adaptive experiences with chronic pain. This model identifies individual and interpersonal resilience as a key aspect. Resilience is defined as someone’s capacity to respond effectively to adversity and is influenced by developmental, social, cultural, and environmental factors. As an example, optimism, self-efficacy, cognitive flexibility (capacity to respond in an effective and flexible way to adverse events), and positive emotions are considered individual resilience resources. Positive relationships with peers, social engagement, and the support of family and teachers are interpersonal resilience resources. These specific resilience mechanisms may be activated when adolescents are confronted with pain and may modulate and positively influence nociceptive pathways.

In a more integrative way, and at the light of the models described above, the Self-determination Theory suggests that pain mechanisms influence three basic psychological needs: autonomy, competence/efficacy, and interpersonal relationships. Autonomy is considered a fundamental acquisition in adolescent development and may be negatively affected by pain. In the presence of pain, the incapacity to perform school, leisure, and mastery and physical activities may contribute to avoidance and frustration behaviors, leading to difficulties in social interaction, victimization, and rejection by peers.

Impact

Chronic non-cancer pain in adolescents impacts the adolescent’s individual, family, and social structure and dynamics, giving grounds for clinical assessment, diagnostic investigation, and referral, which sometimes generate or perpetuate uncertainty, stress, and anxiety.

The presence of comorbidities like anxiety, and depression is frequent, and more common in this group than in the general pediatric population. It is estimated that about 80% of the adolescents with chronic pain have anxiety in some phase of the treatment. The consequences of fear and anxiety, including attention biases, somatization, and avoidance behaviors, contribute to a vicious cycle that perpetuates and exacerbates pain.

This psychosocial aspect may be the only manifestation of the painful process adolescents go through at the time of assessment. In 2006, when John D. Loeser put forth the Onion Model, the author structured the pain experience in layers, comparing it to an onion formed, from the center to the periphery by: nociception, pain, suffering, and pain behaviors. The inner layers are not visible on the outside, being private experiences that only the adolescent is subjected to. The external layer is the pain behavior, which translates through words, actions, or expressions all the experience of the biopsychosocial process involved.

Pain may affect school performance, absenteeism, and academic progress, reason for which it should always be assessed. Adolescents with chronic pain tend to present a lower level of schooling in adulthood, higher probability of joining the labor market earlier, and of having precarious jobs.

Adolescents with chronic pain frequently show anxiety, a frail, dependent or obsessive-compulsive personality, delayed development, and difficulties in learning, concentration, memory and cognition, previous traumatic experiences, poor coping strategies, overprotective parents, chronic disease models, or dysfunctional families. They are exposed to a series of conditions, including the physical manifestations of pain, which translate into lower functional status, quality of life, school performance, and social life engagement.

Diagnosis

The care of adolescents with chronic pain is challenging, and as previously described, the problem goes beyond reporting their pain, often being associated with other symptoms, behaviors, and disabilities.

The assessment of pain should start with the adolescents’ report, in their own words, of their experiences, and beliefs. The information provided by parents, caretakers, peers, teachers, and other professionals is also fundamental, and essential to complement and provide details of the clinical history.

The thorough description of symptoms should include their location, distribution, time characteristics, intensity, character, and relief and worsening factors. A complete physical examination is an essential complement to the clinical history, including for example, the observation of the overall appearance of the adolescent, vital signs, growth, inspection, palpation, and neurological examination, which help define the etiological diagnosis. Additional diagnostic tests, upon the hypothesis of a structural cause or a specific disease, should be directed and complement the investigation.

The Pediatric Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials, in an attempt to standardize procedures, suggests the assessment of physical and emotional aspects, sleep, family interaction, quality of life, previous treatments, and history as key aspects to take into account in the diagnosis (Table 2).

State-of-the-art treatment

The therapeutic approach to chronic non-cancer pain in adolescents should be based on the biopsychosocial model, using a multimodal (pharmacological and non-pharmacological) and interdisciplinary strategy, integrating several professionals (physicians of different specialties, nurses, psychologists, physical therapists, occupational therapists, and social workers) contributing and sharing treatment objectives.

Initially, a plan of care is outlined with the active participation of the patient, both in the definition of the goals to reach, and in the acquisition and application of coping strategies (ideally active), in which the physician plays the role of a mentor. The goal of the treatment is to have an effective control of the pain, although frequently functional recovery (physical activity, regular sleep, school attendance, and social life) usually comes first. The family plays a key role in the results and should be involved in the treatment plan from the beginning.

Today, according to recommendations, the management, follow-up, and treatment of part of these patients do not require consultation at a Pediatric Chronic Pain Unit, that is,
Table 2  Examples of multidimensional assessment instruments for adolescents with chronic pain. Adapted from Liossi C. et al. (2016).50,51

| Dimension | Parameter | Assessment |
|-----------|-----------|------------|
| Biological | Pain symptom | Intensity, Characteristics, Distribution, Fatigue, Functional status, Quality of life, Sleep | VAS, NRS, Pain Diaries (DN4, LANS) |
| Comorbidities | | | PedsQL (MFS) |
| Psychological | Emotional status | Depression, Anxiety, Coping, Catastrophizing, Self-efficacy | CDI, RCADS, PI-ED, STAI, RCADS, PI-ED, PCS-C, PCS-P |
| Cognition | | | PSEQ |
| Social | Environment | Family dynamics, Parental catastrophizing, Parental anxiety, Parental depression | PSI-SF, BAI, STAI, HADS, BDII |

BAI, Backache Index; BDI-II, Beck Depression Inventory-II; CDI, Children’s Depression Inventory; CSHQ, Children’s Sleep Habits Questionnaire; DN4, Douleur neuropathique 4; FDI, Functional Disability Inventory; FPSS-R, Faces Pain Scale-Revised; HADS, Hospital Anxiety, and Depression Scale; LANS, Leeds Assessment of Neuropathic Symptoms, and Signs; MFS, Multidimensional Fatigue Scale; NRS, Numeric Rating Scale; PCQ, Pain Coping Questionnaire; PCS-C, Pain Catastrophizing Scale-Child; PCS-P, Pain Catastrophizing Scale-Parent; PedsQL, Pediatric Quality of Life; PI-ED, Paediatric Index of Emotional Distress; RCADS, Revised Child Anxiety, and Depression Scale; STAI, State-Trait Anxiety Inventory; PSI-SF, Parenting Stress Index/Short Form; STAI, State-Trait Anxiety Inventory; STAXI, State- Trait Anger Expression Inventory; STAXI-2, State-Trait Anger Expression Inventory-2; STAXI-2 C/A, State-Trait Anger Expression Inventory-2 Child, and Adolescent; VAS, visual analog scale; VRS, Verbal Rating Scale.

a Some of the abovementioned instruments have not yet been translated and validated in Portuguese.

these patients may be followed up in any context of primary or differentiated care. However, there is a recommendation that they should be referred early in cases of refractory or complex chronic pain.12,61

Education on pain neuroscience

The understanding of pain and its mechanisms, through education on the neuroscience of pain, may have a therapeutic benefit. When the origin of chronic pain is not understood, maladjusted beliefs may be developed (kinesiophobia and catastrophizing) that support the vicious cycle of chronic pain.52,61 These interventions intend to provide informational and emotional support that facilitates behavior change, and the acquisition of active coping strategies.64 It consists of using the knowledge on the neurobiology and neurophysiology of chronic pain, addressing (a) The nociceptive system and its operation, focusing on the role of the CNS in the interpretation, processing, and positive and negative modulation of nociceptive stimuli, under the influence of the biopsychosocial model; (b) The adaptation of the nociceptive system to persistent pain (central and peripheral sensitization); and (c) Its practical application in every-day life, especially the factors likely to worsen or attenuate pain.56,65 Empathetic adolescent-focused communication is fundamental, and evidence suggests that adolescents learn better through metaphor, metonymy, short stories, and images, adapted to their cognitive capacity and environment.66 Sometimes, educational interventions at school may also be beneficial.56,67

In parallel, education toward a healthy lifestyle, focusing on its fundamental pillars (ex., nutrition, bowel microbiota) should also be encouraged.

Pharmacological treatment

Despite the common use and clinical usefulness of many pharmacological agents, currently there is no evidence supporting their use in chronic non-cancer pain in adolescents. Systematic reviews conducted so far do not permit drawing conclusions about a beneficial or harmful effect of using drugs for chronic non-cancer pain in adolescents.51 Even though the absence of scientific evidence does not mean evidence of no effect, there is an urgent need for data on the efficacy, safety, and tolerability of analgesic drugs on the pediatric population, as well as the development and licensing of new drugs for this age group.68-72

Many drugs are used in this context: peripheral analgesic agents, Non-Steroidal Anti-inflammatory Drugs (NSAIDs), opioids, local anesthetics, and adjuvant medications like antidepressants, and anticonvulsants. This review does not intend to explore the characteristics of each option. However, they are available in the recommended literature (WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses), currently under revision.73 The decision to start a new pharmacological treatment must be based on the pathophysiology of pain and on the mechanism of action of the drug.74 The WHO’s analgesic ladder provides, depending on the intensity of the pain, an orientation for the prescription of drugs. It has two
steps: the first, mild to moderate pain for which the use of peripheral analgesic drugs and NSAIDs are recommended, in isolation or in combination; and for the second step, moderate to severe pain, the administration of an opioid should be considered.\textsuperscript{7,11} The correct use of analgesic drugs is also based on their administration at regular intervals, with the possibility of salvage doses, through the simplest, most effective, and least painful route of administration.\textsuperscript{73} Sometimes, for example in neuropathic pain, peripheral analgesic drugs may be insufficient and the association of adjuvant drugs (antidepressants, anticonvulsants) is possible.\textsuperscript{19,70} In refractory or complex pain, it may be necessary to resort to opioids.\textsuperscript{71} In this context, there is no consensus on their use in pediatrics. Today, it is suggested that they be prescribed in the context of consultations at Chronic Pediatric Pain Units, at the lowest effective dose and for the shortest time possible, in order to keep the surveillance of potential secondary effects.\textsuperscript{72} Morphine is the drug of choice and the rotation of opioids or route of administration is recommended whenever the analgesic effect is insufficient and/or intolerable secondary effects appear.\textsuperscript{72} Using mild opioids (codeine, tramadol) is not currently recommended by the Food and Drug Administration for children under 12 years of age nor for obese teens between 12 and 18 years with severe respiratory disease or Obstructive Sleep Hypopnea-Apnea Syndrome. European organizations recommend using low doses of tramadol.\textsuperscript{70}

Intervention techniques for peripheral nerves and neuroaxis may constitute a diagnostic and therapeutic strategy as part of the multimodal strategy, although there is not much evidence for their use.\textsuperscript{73}

Physical therapies

There is a wide variety of frequently used techniques, like the application of heat or cold, Transcutaneous Electric Neuromuscular Stimulation (TENS), desensitization, and cardio exercise.\textsuperscript{70} Every adolescent should have an individualized rehabilitation plan, supported on a cognitive-behavioral approach that includes active physical interventions, defining goals to be reached (ideally defined by the teenager), gradual physical exercise, rhythmic activity (progressing to regular physical exercise) that they are interested in so as to optimize compliance. Today, neuromuscular physical practice and cardio exercise are emerging as promising interventions.\textsuperscript{77}

Psychological interventions

Psychological interventions are the treatment modality that presents the highest level of evidence.\textsuperscript{51} They are based on cognitive or behavioral therapy or a combination of both (cognitive-behavioral therapy). Their focus are maladaptive emotions, cognitions, and behaviors related to pain, present in adolescents, and their families, and have as therapeutic goals: to prevent recurring pain; to mitigate severe pain; to reduce sociocultural, environmental, family, emotional (anxiety, depression, and post-traumatic stress), and behavioral (passive coping, pain fear-avoidance, kinesiophobia, catastrophizing, poor sleep hygiene, low acceptance of pain, parental overprotection, and other) risk factors, and to increase adaptative functioning.\textsuperscript{73} They may be provided individually or in group, and currently there is growing interest in their implementation with the use of digital tools (apps for cell phones, videos, websites), because of their accessibility and ease of use.\textsuperscript{79}

Integrative medicine

Integrative medicine is an emerging field that encompasses alternative and complementary medicine based on evidence, on conventional medicine, integrating individuals to their environment as a whole. It comprehends several approaches: utilization of natural products (vitamins, minerals, plant-based products); mind-body therapies (meditation, relaxation); physical and movement therapies (massage, yoga); energy therapies (acupuncture, reiki); traditional Chinese medicine, naturopathy, and others. The modalities most frequently used in the treatment of chronic non-cancer pain in adolescents are acupuncture, creative arts, herbal medicine, homeopathy, and massage, despite the scarce evidence for their use in the pediatric population.\textsuperscript{80}

Intensive interdisciplinary treatment

Some centers have instituted intensive interdisciplinary treatment for adolescents with severe incapacity. It consists of a treatment program lasting about 3 weeks, with 3 to 5 sessions per day, and involves several therapeutic modalities in an inpatient or outpatient regimen. Although parents do not stay in together, they are also focused by the intervention (family interventions/parenteral education/group therapy). The cost is high, but everything indicates good cost effectiveness and high satisfaction.\textsuperscript{81}

Discussion and conclusion

The current information on pain in the pediatric population, particularly on adolescence, makes it difficult to standardize and describe it because of the heterogeneity of this group.\textsuperscript{2,16,21} In this age group, the problem is particularly evident as to the epidemiological characterization and treatment of pain.

Overall, chronic non-cancer pain in adolescents seems to be frequent and have impact on several daily-life activities, and its underappreciation and perpetuation contribute to make it chronic, with physical limitations and psychological suffering in adulthood.\textsuperscript{1} However, this impact seems to be frequently ignored or underappreciated, and pain is accepted as something “normal”.

The study and description of the pathophysiology of pain is undergoing clear evolution. The approach according to its mechanism and based on the biopsychosocial model is fundamental for the institution of adequate treatments. However, it looks like this strategy is not yet generalized, which contributes to make chronic pain misunderstood, and mistreated, perpetuating its negative consequences.

Chronic non-cancer pain in adolescents should always be treated, regardless of the context or level of care. The capacity of health services to detect and respond to
these patients should be cross-sectional, and not exclusive with super dedicated and highly specialized teams. Primary health care, because of its community activity, constitutes a privileged area for the diagnosis and detection of chronic non-cancer pain in adolescents.\(^6,^7\) It should be an integral part of the initial approach, diagnosis, treatment, and whenever necessary, severe or complex pain should be referred.

Early detection and diagnosis, like interdisciplinary treatment, sharing common treatment goals, has a positive impact on the rational and effective use of health services, reduces costs, and translates into economic and social return to the country.

Chronic Pediatric Pain Units may also play an important role in the training of healthcare workers and to the population, and schools are an excellent environment to build awareness and promote intervention strategies for pain in adolescents.

On the other hand, it is urgent to study and design therapeutic measures with proven treatment effectiveness, considering the potential effects in the development and efficacy from the standpoint of patients.\(^6^1\)\(^-\)\(^6^5\)

In conclusion, the awareness of the problem of chronic pain in adolescents is fundamental for adequate treatment, requires joint work of several professional groups, with the aim of minimizing its impact on the day-to-day and future of adolescents.

### Conflicts of interest

The authors declare no conflicts of interest.

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