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Review

Exercise-induced hypoalgesia in chronic neck pain: A narrative review

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ABSTRACT

Chronic neck pain (CNP) is a worldwide health problem with several risk factors. One of the most widely used treatments for managing this condition is therapeutic exercise, which could generate a response called exercise-induced hypoalgesia (EIH). There is no consensus on the best exercise modality to induce hypoalgesia. Therefore, this review aims to analyze and synthesize the state-of-the-art about the hypoalgesic effect of exercise in subjects with CNP. We included articles on EIH and CNP in patients older than 18 years, with pain for more than three months, where the EIH response was measured. Articles that studied CNP associated with comorbidities or measured the response to treatments other than exercise were excluded. The studies reviewed reported variable results. Exercise in healthy subjects has been shown to reduce indicators of pain sensitivity; however, in people with chronic pain, the response is variable. Some investigations reported adverse effects with increased pain intensity and decreased pain sensitivity, others found no clinical response, and some even reported EIH with decreased pain and increased sensitivity. EIH is an identifiable, stimulable, and helpful therapeutic response in people with pain. More research is still needed on subjects with CNP to clarify the protocols and therapeutic variables that facilitate the EIH phenomenon. In addition, it is necessary to deepen the knowledge of the intrinsic and extrinsic factors that influence EIH in people with CNP.

1. Introduction

Neck pain is the sixth most common cause of years lived with disability in the United States.[1] It has an annual prevalence of 288.7 million cases globally. Latin American regions have the lowest age-standardized incidence; however, in the last 20 years, high-income countries have had the most significant increase in incidence, with the highest prevalence of neck pain in Scandinavian countries.[2] This latter finding could be related to the growing population of older people in these countries and the strong association between age and the prevalence of musculoskeletal disorders.[3]

Neck pain is a multidimensional condition since no precise or unique pathophysiological mechanism can explain its origin. Only a few clinical conditions (such as a history of trauma or degenerative neck pathologies during the working age) have been identified as potentially causative findings, so the evidence has highlighted its multifactorial nature.[4,5] Neck pain is related to several non-modifiable (e.g., age and female gender) and modifiable risk factors. The latter include psychological factors (e.g., stress, anxiety, depression) and cognitive factors (e.g., catastrophizing, low self-efficacy, and low resilience).[5–9] In addition, the intervention of social factors (such as low social, family, and work support),[10,11] behavioral factors (such as passive or avoidant coping strategies),[12–14] occupational factors (such as workload, time, and body positions at work)[9,15] and biological factors (such as neuromusculoskeletal problems, autoimmune diseases, sleep disorders, genetic susceptibility, and history of previous neck or low back pain)[16] have also been identified. Because neck pain tends to become chronic, identifying these factors becomes more important for prevention and early diagnosis.[9]

Chronic pain generates a personal and family burden, as well as the patient's environment, directly impacting their quality of life.[17,18]

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Abbreviations

CCF	Cranio-cervical flexion coordination exercise
CF	Cervical flexion resistance exercise
CNP	Chronic neck pain
CNS	Central nervous system
CNSNP	Chronic nonspecific neck pain
CPM	Conditioned pain modulation
EIH	Exercise-induced hypoalgesia
MHR	Maximum heart rate
NRS	Numeric rating scale for pain
OCP	Occlusion cuff pressures
PAG	Periaqueductal gray matter
PNS	Peripheral nervous system
PPT	Pressure pain thresholds
RVM	Rostral ventromedial medulla
TPT	Thermal pain threshold
TS	Temporal summation
VAS	Visual analogue scale for pain
WAD	Whiplash-associated disorders

Moreover, in most cases, the chronicity of pain has a considerable impact on the perception of health status and level of disability, interfering in the development of activities of daily living and social and family participation.[19]

People with chronic pain suffer a detriment to their quality of life, but this individual effect can also have social consequences, such as increased direct and indirect healthcare costs.[20] The estimated economic cost to the healthcare system differs between countries and their characteristics. However, across Europe, the cost of chronic pain has been estimated to be between 1.5% and 3.0% of the Gross Domestic Product (GDP).[21] Furthermore, while higher-income countries have a higher prevalence of chronic pain, the consequences are more devastating in lower-income countries: those with chronic pain in low-income countries generally have more significant activity limitations, substance abuse, and mood disturbances.[22]

The high cost associated with neck pain treatments has led to the search for interventions recommended by scientific evidence. A recent systematic review of clinical guidelines has provided evidence-based treatment recommendations for neck and back pain.[23] This review contemplates various interventions, such as musculoskeletal rehabilitation, medical treatments, and multidisciplinary approaches. The treatments used in musculoskeletal rehabilitation mentioned in clinical guidelines are counseling and education, manual therapy, exercise programs, therapeutic modalities, and ergonomic interventions.[23–26] On the other hand, medical treatments consider oral drugs, injectable drugs, and rest in acute phases.[23–26] Multidisciplinary treatments consider specialty approaches in the different areas of treatment required, including physical therapy, occupational therapy, surgery, psychology, and psychiatry.[23–26]

Therapeutic exercise is a commonly used treatment for chronic neck pain (CNP).[23,27] Among its possible effects, this intervention presents an acute response that facilitates the phenomenon known as exercise-induced hypoalgesia (EIH).[28,29] EIH corresponds to the decrease in pain during or after a single bout of exercise that will depend on different variables, including the type, frequency, and intensity.[29–31]

In healthy, pain-free subjects, EIH generated by aerobic and endurance exercise has been shown to decrease various indicators of pain sensitivity such as pressure, thermal, and electrical pain thresholds,[28] pressure pain tolerance,[32] and temporal summation of thermal and mechanical pain.[33]

The acute effect of exercise on pain sensitivity varies in populations with chronic pain. Some investigations show decreased pain,[34–37] others report increased pain,[36–42] and some even report no change in response to a single bout of exercise.[33] Increased sensitivity to pain following exercise (termed exercise-induced hyperalgesia) is thought to lead to pain in some people with chronic pain.[43–45] Exercise-induced hyperalgesia can be considered a barrier to treatment adherence, contributing to increased pain and long-term disability.[31,46,47] Considering the variability in the study protocols, the populations analyzed, the different diagnoses involved, and the results obtained, it becomes necessary to review the currently available research on exercise response in people with CNP since no publications have summarized the literature focusing on clinical practice. Therefore, this review aims to analyze and synthesize the state of the art on the hypoalgesic effect of exercise in subjects with CNP. To achieve this, we will give an overview of neck pain and its chronification process and describe the neurophysiological mechanisms of EIH. Finally, we will investigate the EIH response in subjects with CNP, reviewing the exercise protocols applied in different subgroups.

2. Materials and methods

The present study reviewed the literature available in the following databases: PubMed, EBSCO, CINAHL, Scopus, and Web of Science. For the specific review on EIH in patients with CNP, articles on these topics published from 2002 to March 2022 were selected. In the first instance, the articles were filtered by title and abstract and later by full text. The inclusion criteria corresponded to studies in patients older than 18 years, with CNP lasting more than three months, and where the response of EIH was measured. Articles that included neck pain with comorbidities and measured the response to treatments other than exercise were excluded from this review.

3. General information on chronic neck pain

3.1. Pain and chronic pain

Pain has been defined by the International Association for the Study of Pain (IASP) as “an unpleasant sensory and emotional experience associated with or resembling that associated with actual or potential tissue damage."[48] Meanwhile, chronic pain has been defined as pain that lasts longer than required for tissue recovery and has been established in practice as pain that persists beyond three months.[49]

Chronic pain is now recognized as a proper disease rather than a simple symptom.[50] As in other health conditions, chronic pain has shown specific changes in the central nervous system (CNS) and peripheral nervous system (PNS) with consequences on the quality of life of individuals[51] as it interferes with physical and psychological function, sleep, and social life.[17] These changes may be maintained by the persistence of nociceptive stimuli and other sensitizing mechanisms at the central level, including psychological factors. However, these changes may be reversible with appropriate treatment.[52]

3.2. General aspects of neck pain and CNP

Between 24% and 35% of people with neck pain tend to chronify their condition when it persists for at least 12 months.[53] There are three types of chronic neck pain based on their etiology: i) specific chronic neck pain, which lasts for more than three months and is attributed to specific causes such as symptomatic cervical hernias, radiculopathies, autoimmune diseases, spondyloarthropathies, Etc. ii) Chronic non-specific or idiopathic neck pain (CNSNP), which is characterized by lasting more than three months, inability to identify an underlying structural pathology, and presenting imaging findings commonly unrelated to the patient's symptoms. iii) Whiplash-associated disorders (WAD), which correspond to a chronic cervical pain condition that usually follows a traumatic event (commonly a vehicle collision) and is caused by acceleration and deceleration forces that generate varying degrees of affectation of the neuromusculoskeletal structures of the neck.[54,55] It has been shown that WAD patients tend to develop complications such as CNP,

headaches, dizziness, motor dysfunction, cognitive impairment, and central sensitization.[56–65] In fact, WAD is considered a central sensitization syndrome.[60,66] In patients with headaches secondary to WAD, it has been shown that, after three months of pain, morphological changes occur in the gray matter. These changes include decreased gray matter in the anterior cingulate and dorsolateral prefrontal cortex. In contrast, there is an increase in gray matter in the periaqueductal gray matter (PAG), thalamus, and cerebellum. However, these changes resolve after one year in conjunction with the remission of headaches secondary to WAD.[67] Equivalent morphological changes in the CNS have been observed in patients with CNSNP.[68] These changes have been attributed to central sensitization, which generates modifications in sensory processing,[69] alterations in pain inhibitory mechanisms, and increased pain facilitation.[70]

3.3. Diagnostic methods and classification of neck pain

Diagnosing cervical pain requires a complete examination, including clinical history, physical examination, and imaging tests to identify structural changes and determine potential dysfunction.[71] In addition, the clinical evaluation of the cervical spine should identify red flags, warning signs, and symptoms of severe pathologies and non-musculoskeletal diseases that may cause the clinical condition.[72,73] The heterogeneous nature of neck pain poses challenges for therapeutic planning, which has led to concerted efforts to categorize clinical conditions better and classify symptoms. Different classification systems have been created from this, one of which is the treatment-based classification system,[74] which focuses on treatment goals and the interventions required to achieve those goals. We also find the biomedical classification model based on clinical signs and symptoms.[71] The anatomopathological classification system is a structure-based medical model that does not always identify the specific cause of neck pain because the location of symptoms and imaging findings do not necessarily influence the prognosis.[75] Another classification system is the International Classification of Functioning, Disability, and Health of the World Health Organization (ICF-WHO), based on the type of musculoskeletal impairment.[76] Finally, we find the classification according to the neurobiological mechanism of neck pain, which can be nociceptive, neuropathic, or nociplastic.[77] This classification is clinically relevant, as it allows differentiation of the therapeutic approach. For example, it has been seen that pain associated with WAD presents alterations in nociceptive processing and generalized hypersensitivity, while CNSNP only shows hypersensitivity in the neck area. Thus, it is relevant to consider them as different clinical entities, not only from an etiological point of view but also from a neurobiological one.[78]

4. Exercise-induced hypoalgesia: neurophysiological mechanisms

One of the mechanisms underlying EIH is the descending pain inhibition system, where certain brain areas modulate nociceptive signals in the spinal cord.[79]

Several authors have suggested that hypoalgesia induced by regular physical activity is mainly due to a physiological change that enhances the descending inhibitory pathways of pain, thus generating a protective effect against peripheral injury or threat. In healthy subjects, this system is generally stimulated by vigorous physical activity.[80,81] The system may not produce such changes in physically inactive individuals; therefore, they may be at higher risk for persistent pain.[82] Experts believe that the functioning of the descending inhibitory system is a critical factor in explaining chronic pain.[83]

Through descending modulation, the inhibitory system strongly influences neuronal and glial plasticity, producing changes in the structure and function of the nervous system. Depending on the intensity, frequency, and duration of exercise, these changes could induce sensitization or desensitization of synaptic function, which is relevant for pain modulation.[84,85]

Descending pain pathways (from the cortex to the brainstem and spinal cord) can modulate the activity of ascending signals and, thus, the painful experience.[85] This experience varies among individuals, including pain sensitivity (peripheral nociceptor sensitivity) and variability in pain processing in the central nervous system. Therefore, peripheral impulses from tissue receptors can be modified in the medullary dorsal horn, inhibiting or facilitating the nociceptive pathway.[86] Descending facilitation and descending inhibition are critical mechanisms for linking pain-related neurons in different brain regions.[87]

The PAG and the rostral ventromedial medulla (RVM) are vital anatomical structures involved in the mechanism of descending inhibition. The PAG influences descending inhibition mainly through its connections with the RVM, which also can facilitate nociception.[88] This is supported by the fact that in the RVM, two types of neurons are responsible for pain modulation: on-cells and off-cells.[89–91] Off-cells trigger descending inhibition, and on-cells create descending facilitation.[83,88,92–94] The dynamic balance between on-cells and off-cells is dictated by behavioral priorities, fears, and other factors evaluated by higher structures in the brain.[92] It has been suggested that an imbalance in favor of facilitation may underlie pathological pain states.[83] In fact, there is evidence that pain facilitation is more prevalent than defective pain inhibition as a mechanism for processing nociplastic pain in subjects with moderate or severe neck disabilities.[95] Thus, pain sensitivity is determined in part by ascending sensory information (the amount of nociception from the periphery) but also by descending modulation of the PAG-RVM system.[83,88,92]

The PAG may exert descending facilitatory effects on spinal transmission, whereas cortical neurons could stimulate brainstem neurons and lead to the excitation of descending facilitation.[96] Therefore, inadequate descending inhibition and descending facilitation may be significant causes of central sensitization and chronic pain states.[83] Downward pain inhibition is assessed psychophysically using the conditioned pain modulation (CPM) paradigm.[97]

The CPM is a quantitative sensory test commonly used to assess the functionality of endogenous pain inhibition in the central nervous system.[97] It is based on the “pain inhibits pain” mechanism,[98] in which a reduction in pain perception of a test stimulus is induced by the simultaneous application of a noxious stimulus (conditioning stimulus) to another region of the body.[99] In subjects with a healthy nociceptive system, the intensity of pain experienced with the test stimulus will decrease during or after applying the noxious or conditioning stimulus, reflecting the efficacy of the endogenous pain inhibitory pathway.[97] CPM is a clinically meaningful measure of endogenous pain inhibition, and its reliability is fair to excellent when measured by heat contact.[99]

5. Exercise-induced hypoalgesia in patients with chronic pain

EIH has been well-documented in people without pain.[28,100] However, conflicting responses have been found in people with chronic musculoskeletal pain. Previous reviews report reduced pain sensitivity and intensity, other studies report no change, and some show hyperalgesia after exercise.[28,101,102] This variability may be due to several circumstances: factors associated with the patient's pain condition, immunological factors, psychosocial factors, exercise-related factors, demographic factors, and lifestyle factors.

5.1. Factors associated with the patient's pain condition

The patient's pain condition is relevant to the EIH response. Hypoalgesia after a single bout of exercise has been demonstrated in chronic pain conditions, including low back pain,[31,37] shoulder pain,[103] patellofemoral pain,[104] knee osteoarthrosis,[102,105] and rheumatoid arthritis.[106] However, in other conditions such as WAD,[38] chronic fatigue syndrome,[37,107] fibromyalgia,[36,40,108–111] painful diabetic neuropathy,[42] and Gulf War syndrome,[112] reduced hypoalgesia and even hyperalgesia

post-exercise have been shown. This response may also be influenced by the area where the exercise is performed: studies show that exercising in chronic pain areas could generate hyperalgesia. In contrast, if the exercise is performed in an unaffected region, it could generate hypoalgesia.[35,110] Finally, patients' responses to CPM evaluation should also be considered. In individuals with knee osteoarthritis, it has been seen that those who exhibit CPM alteration have a lower acute hypoalgesic effect and more significant hyperalgesia after isometric and aerobic exercise.[113]

5.2. Immunological factors

The immunological factors involved in EIH are associated with the appearance of immune cells such as macrophages and glial cells, which, through the release of inflammatory mediators, can generate increased excitability of the nociceptive system in the nervous system.[114,115] People with chronic widespread pain often show alterations in immune function responses and adaptations, such as the complement system, tumor necrosis factor-alpha (TNF-α), interleukins (IL-6, IL-8, and IL-11), interferon Gamma (INF-γ), C-reactive protein and oxidative stress. At the same time, anti-inflammatory markers may be decreased or unaltered.[116–119] The effects of the altered immune response in EIH are inconclusive, and the immune system's role remains unclear. However, the appearance of a proinflammatory response after a bout of exercise could be related to the non-appearance of EIH, as may occur in people with chronic pain.[27]

5.3. Psychosocial factors

A recent systematic review that included healthy subjects and those with chronic pain concluded that it is difficult to establish a clear relationship between psychosocial factors and EIH due to the high heterogeneity and risk of bias in the studies.[120] However, in other studies, psychosocial factors have been shown to interfere with endogenous descending modulation.[121] Because of the above, it has been suggested that they could affect the EIH response in people with chronic pain. In healthy subjects, it has been postulated that negative beliefs influence post-exercise hyperalgesia,[122,123] which can be modified through educational interventions, thus enhancing the EIH response.[123]

5.4. Exercise-related factors

The variables that determine exercise are at least four: frequency (number of times per week that exercise is performed), time (minutes of exercise performed per week), duration (number of weeks that the intervention is completed), and intensity.[101] When analyzing all these variables together, a recent meta-analysis showed that frequency could have a positive effect on pain reduction, suggesting increasing the number of times exercising each week until the exercise is practiced daily. Conversely, increasing the time of exercise in the week or the duration of individual exercise sessions could have decreased the effect of EIH.[101] There is controversial evidence on exercise duration,[124] as studies show that both longer and shorter exercise protocols can achieve a hypoalgesic effect.[31,125,126] These results suggest that the combination of exercise intensity and duration may be more important in promoting EIH than either variable alone.[124] There are reports that low to moderate-intensity exercise (50%–60% of maximum heart rate [MHR]) produces improvements in chronic pain symptoms[127,128]; however, initiating treatment with these doses of exercise in patients with musculoskeletal pain could result in avoidant behavior and kinesiophobia.[129,130] Therefore, it is suggested that the intensity should be initially adjusted to lower doses and then gradually increased toward moderate intensity.[131,132] In patients with fibromyalgia, pain reduction has been obtained with doses of preferred intensity (exercise intensity self-perceived as adequate and comfortable for the patient).[133,134] Finally, there is insufficient evidence about the effects of exercise dose concerning hypoalgesia.[101]

5.5. Demographic factors

Healthy older adults generally have lower EIH responses than younger adults. Higher levels of prior physical capacity may determine better EIH responses in older adults.[28,135,136] However, these findings have only been demonstrated in people without chronic pain.

In the case of the sex variable, the evidence is inconclusive. Most studies have been conducted on healthy individuals; some demonstrate significant differences in EIH, and others demonstrate no difference between men and women.[137–139] Studies demonstrating sex differences in EIH responses in healthy individuals show a dependence of this response on basal pain levels and stimulus type.[27,140,141]

In the case of people with chronic pain, there is little evidence comparing differences associated with age range or sex. In this regard, Ickmans et al. (2017) conducted a study on people with WAD and found no relevant differences in sex or age.[41]

5.6. Lifestyle factors

Healthy lifestyles such as regular physical activity are associated with a better hypoalgesic response to acute exercise in individuals with and without chronic pain,[124,142,143] which is consistent with studies in patients with chronic musculoskeletal pain showing that those who are more physically active experience less pain severity.[128,144] People who engage in regular physical activity exhibit higher pain tolerance, better CPM responses, and prevent the risk of developing acute and chronic pain conditions.[124] However, to date, no studies have demonstrated the effect of regular exercise on EIH responses in people with CNP.

6. Exercise-induced hypoalgesia in patients with chronic neck pain

6.1. Exercise-induced hypoalgesia in CNP: Protocols

After applying this literature review's inclusion and exclusion criteria, eight studies were selected for a specific analysis of EIH in CNP. Table 1 summarizes the studies protocols where exercise has been applied as a hypoalgesic therapeutic agent in CNP. These investigations considered different study variables. One of these variables was CNP condition, including WAD,[34,38,41,145,146] work-related neck pain,[95] neck/shoulder pain,[147] and CNSNP.[146,148] although, for the overall analysis, the last three were grouped as CNSNP.[54,55] Likewise, the modality of the exercise is another relevant variable, and four types can be found: isometric exercises,[34,95,145,148] aerobic exercises,[34,38,41,145,147] strength exercises,[148] and dynamic strength exercises.[146] The third and last variable of interest incorporated in the studies reviewed is associated with the type of exercise execution, with different modalities: isometric shoulder abduction,[95] isometric exercises of the lower extremities,[34,145] cycle ergometer of arms and legs,[34,38,41,145,147] cervical flexion and cranio-cervical flexion exercises,[148] and, finally, repeated abduction movement of the upper limbs.[146] The cycle ergometer is the most frequently used of the exercises mentioned above.[34,38,41,145,147] On the other hand, repeated arm movement was the least used.[146]

In the protocol of Xie et al.,[95] participants performed bilateral sustained isometric shoulder abduction at 90° without external weights until exhaustion or up to 3 min.

In the protocol of Smith et al.,[34] participants completed a submaximal ergometer cycling test at 25 w, and power output was increased by 25 w every minute until 75% of age-predicted MHR was reached. The participant continued pedaling at this power for 30 min. For the isometric exercise, participants performed an upright squat with their back against the wall and maintained this contraction until fatigue or for a maximum of 3 min.

The protocol of Grimby-Ekman et al.[147] consisted of 30 min of pedaling with the upper limbs at a constant rate of 25 laps/min. The initial load was 100 g for women and 200 g for men. After 10 min, the

Table 1
Protocols applied in the studies investigating exercise-induced hypoalgesia in chronic neck pain.

Author	Year	Chronic pain condition	Type of Exercise	Protocol	Sample	Outcome
O'Leary et al.[148]	2007	Neck Pain	Strength Isometric	Cervical Flexion Cranio-cervical Flexion	48	PPT, VAS, TPT PPT, VAS, TPT
Van Oosterwijck et al.[38]	2012	WAD	Aerobic Aerobic	Leg cycle ergometer for 15 min at 75% MHR Self-paced and physiologically limited leg cycle ergometer exercise	44	PPT PPT
Christensen et al.[146]	2017	Neck Pain	Dynamic strength	Repeated arm abduction movement	50	PPT, VAS
		WAD	Dynamic strength			PPT, VAS
Ickmans et al.[41]	2017	WAD	Aerobic	Leg Cycle ergometer less than 15 min.	52	PPT, VAS, OCP, TS
Smith et al.[34]	2017	WAD	Aerobic Isometric	30 min 75% MHR Wall squat for 3 min or until exhaustion.	40	PPT PPT
Grimby-Ekman et al.[147]	2020	Neck/shoulder pain	Aerobic	30 min of arm cycle ergometer with incremental resistance.	38	PPT, NRS
Smith et al.[145]	2020	WAD	Aerobic Isometric	30 min 75% MHR Isometric knee extension with dynamometer	70	PPT PPT
Xie Y et al.[95]	2021	Work-related neck pain (mild disability).	Isometric	Isometric shoulder abduction (90°) until exhaustion or 3 min.	92	PPT, NRS
		Work-related neck pain (moderate-severe disability)	Isometric	Isometric shoulder abduction (90°) until exhaustion or 3 min.		PPT, NRS

PPT: Pressure pain threshold; VAS: Visual analogue scale for pain; TPT: Thermal pain threshold; WAD: Whiplash associated disorders; MHR: Maximum heart rate; OCP: Occlusion cuff pressure; TS: Temporal summation; NRS: Numeric rating scale for pain.

load was increased to 300 g for women and 400 g for men. After another 10 min, the load was increased to 500 g for women and 600 g for men. Then, the participants cycled with this load for another 10 min.

In the Smith et al. study protocol,[145] a single session was executed to perform a submaximal aerobic treadmill exercise or an isometric knee extension exercise. In the aerobic exercise, participants completed a submaximal treadmill walking test. The participant began walking at 5–7 km/h or at a comfortable pace with a 0% incline. If after 4 min, 75% of MHR had yet to be reached, the slope was increased by 2%. The slope was increased by 2% per minute until 75% of the MHR was reached. The participant continued walking with this power output for 30 min. For isometric quadriceps exercise, participants were instructed to perform muscle contraction at 20% and 25% maximal voluntary contraction with a dynamometer until exhaustion or a maximum of 3 min.

O'Leary et al.[148] developed a protocol including cranio-cervical flexion coordination exercise (CCF) and cervical flexion resistance exercise (CF) in the supine position, using a pressure device for feedback. The highest-pressure increment at which the participant could comfortably maintain a painless contraction for 10 s (level ranging from 22 to 30 mmHg) was established. Then, the intervention was performed consisting of a 10-s sustained contraction at the selected level for 10 repetitions with a 10-s rest interval between each repetition.

For the cervical flexion resistance exercise, participants performed a supine head lift exercise with three sets of 10 repetitions. Each repetition lasted 3 s, with 2-s rest intervals between repetitions. Subjects rested for 30 s between sets.

In the study by Christensen et al.[146] repeated arm movements were performed and perceived pain sensitivity responses were measured. Participants performed shoulder abduction in the scapular plane to an angle of 140° with the arm straight in a sitting position. Three slow movements were performed with a 3-s ascending phase and a 3-s descending phase followed by three fast movements. Each movement had a 6-s rest before moving the opposite arm.

The exercise protocol used in the study by Van Oosterwijck et al.[38] was performed in a seated position on an ergometer bicycle. Patients were instructed to pedal at 60–70 revolutions per minute.

The protocol used in the study by Ickmans et al.[41] uses submaximal aerobic exercise performed on a cycle ergometer. The workload started at 25 w and was increased by 25 w every minute until the participant reached their submaximal level (75% of age-predicted MHR). Participants pedaled at a constant speed of approximately 60 revolutions per minute. At the end of each minute, the heart rate was recorded. The exercise ended when participants reached their target heart rates. Cool-down included 1 min of pedaling at a speed of 60 revolutions per minute and a workload of 25 w.

6.2. Exercise-induced hypoalgesia in CNP: Results according to the clinical condition

Evidence has reported diverse exercise responses depending on the clinical condition. In WAD, isometric wall squat exercise was effective in generating EIH, while aerobic exercise reported no significant differences.[34] Another study reports no difference in EIH between isometric and aerobic exercise for this condition. However, high self-reported levels of physical activity in the previous week and lower CPM efficiency predicted the deficiency of isometric exercise in inducing exercise hypoalgesia in the neck.[145]

For aerobic exercise using a leg cycle ergometer, a worsening of symptoms after exercise has been reported, although there is a decrease in symptom intensity when exercise is limited to its own physiological rate.[38] For the exercise of repeated arm abduction movements, there were differential responses in pain sensitivity and muscle activity between subgroups of patients with neck pain and healthy controls. In the WAD group, there was generalized exercise-induced hyperalgesia with increased pain intensity and decreased pressure pain thresholds (PPT) compared to asymptomatic controls.[146] In another study,[41] in which a leg cycle ergometer exercise of less than 15 min was performed, there were decreases in both PPT and occlusion cuff pressures (OCP) in patients with chronic WAD compared with healthy individuals. There was no sex- and age-associated differences in EIH response, PPT, OCP, and CPM in chronic WAD. However, there was greater self-reported pain in men and greater pain facilitation in younger individuals. Furthermore, exercise-induced hyperalgesia was not generated in the chronic WAD group, as reported in other studies.[38] This highlights that, despite alterations in pain processing in patients with WAD, it will not necessarily influence the hypoalgesic response to exercise.[41]

Regarding work-related neck pain and applying isometric shoulder abduction exercise (90°) until exhaustion or for 3 min, no differences were found for CPM and EIH between the different disability groups (mild, moderate, and severe).[95] Regarding intragroup differences, the

mild disability group had a significant increase in pain magnitude greater than the non-disability group. All groups increased PPT (decreased mechanical tenderness) at all sites assessed after exercise.[95]

In individuals with neck/shoulder pain, aerobic exercise with an arm cycle ergometer for 30 min with incremental resistance showed discouraging results. In the chronic pain group, there was increased pain intensity during exercise and the following two nights post-exercise, with decreased in pain thresholds immediately following activity.[147]

In individuals with CNSNP, specific isometric strength exercises of CCF provided an immediate change in local mechanical hyperalgesia of the neck, relieving perceived pain on movement.[148]

Finally, repeated arm elevation exercises up to 140° elicited generalized hyperalgesia in patients with CNSNP compared to pain-free subjects. At the same time, individuals in the control group showed increased PPT (hypoalgesia) at the cervical level and in the head.[136] In this study by Christensen et al.,[146] the exercise-induced generalized hyperalgesia response observed in patients with CNSNP also occurred in patients with WAD.

6.3. *Exercise-induced hypoalgesia in CNP: Results according to the type of exercise*

Tables 2 and 3 summarize the results of the exercise protocols reviewed, grouped by type of exercise (Table 2, resistance exercises; Table 3, aerobic exercises). Conclusions and analysis of the hypoalgesic response in consideration of the evaluated outcome are included.

None of the analyzed exercise protocols significantly reduced perceived pain intensity for the studied subjects carrying CNSNP.[34,95,145,146,148] Patients with CNSNP reported decreased mechanical sensitivity in dynamic strength and isometric resistance exercises when applied locally to the neck.[148] Something equivalent could be seen with isometric exercises of the upper extremities, which increased PPT.[95] In contrast, PPT decreased when dynamic strength resistance exercises were applied to the upper extremities.[146] Neither dynamic force nor isometric resisted exercises induced changes in thermal pain thresholds.[148]

When analyzing the case of patients with WAD, lower extremity isometric exercises presented contradictory results. Isometric knee wall squat induced decreases in both local and remote zone mechanical tenderness,[34] while isometric knee extension exercise failed to modify local cervical mechanical tenderness but did modify remote zone mechanical tenderness.[145] This could be related to the baseline pain level since the group with greater pain presented greater EIH than those with lower pain levels.[145] Finally, dynamic upper extremity strength exercises showed increased perceived pain and mechanical sensitivity.[146]

In aerobic exercise, only one study was performed with an upper extremity cycle ergometer with incremental resistance in patients with CNSNP,[147] where there was an increase in perceived pain intensity during exercise associated with increased mechanical sensitivity immediately after exercise. However, in a delayed manner, the mechanical sensitivity measured with PPT decreased to the level of the original measurement (105 min post-exercise).[147]

In the aerobic exercise protocols applied to patients with WAD, most exercises at submaximal intensity (75% MHR) were used, with none reporting EIH at the neck.[34,38,41,145] Only the study by Smith et al. (2020)[145] reported decreased mechanical sensitivity in a remote zone (hand) after 30 min of submaximal aerobic exercise. In turn, Ickmans et al.[41] showed decreased temporal summation after a leg cycle ergometer protocol. This could be interpreted as a decrease in downward facilitation when performing 15-min submaximal aerobic exercises. On

Table 2
Studies evaluating exercise-induced analgesia response in resistance exercise protocols.

Author	Chronic pain condition	Type of Exercise	Results	Conclusion	Analysis
O'Leary et al.[148]	Neck Pain	Dynamic Strength	= VAS ↑PPT* = TPT	This study shows that CCF-specific therapeutic exercise will likely provide an immediate change in local mechanical hyperalgesia in the neck, resulting in relief of perceived pain with movement in patients with chronic neck pain.	Pain measured with VAS did not change after exercise. However, during exercise, VAS was lower. Regarding mechanical sensitivity, there is an increase in PPT in the most symptomatic segments, but there were no changes in PPT at a distance (leg) or TPT. Therefore, isometric and dynamic strength exercises at the cervical spine level could favor decreased local pain sensitivity.
		Isometric	= VAS ↑PPT* = TPT		
Christensen et al.[146]	Neck Pain	Dynamic strength	↑VAS ↓PPT (AP)	In both groups, the subjects with WAD and those with CNSNP increased their pain intensity and mechanical sensitivity.	Considering that subjects with WAD and those with CNSNP increased pain intensity and mechanical sensitivity, it is concluded that dynamic strength exercises would generate generalized hyperalgesia in response to exercise in patients with chronic neck pain.
	WAD	Dynamic strength	↑VAS ↓PPT (AP)		
Smith et al.[34]	WAD	Isometric	↑PPT (AP)	Isometric wall squat exercise, but not aerobic cycling exercise, achieve EIH reducing mechanical sensitivity.	The isometric exercise protocol in this research decreased mechanical sensitization in all the measured points. An aerobic exercise protocol was applied in this same study, which did not modify mechanical sensitization.
Smith et al.[145]	WAD	Isometric	= PPT (CP) ↑PPT (HP)	Participants with chronic WAD did not show a significant change in the neck and tibialis anterior mechanical sensitivity after the isometric exercise protocol. However, they did increase PPT in hand during the exercise.	The isometric exercise protocol applied was successful in reducing mechanical sensitization globally. In addition, an aerobic exercise protocol was applied in the same study that achieved the same results.
Xie Y et al.[95]	Work-related neck pain (mild disability).	Isometric	↑PPT(AP) ↑NRS	Even though there is an increase in pain intensity in all groups, it exits a decrease in mechanical sensitivity in all of them. No between-group differences were found for EIH in work-related neck pain with different levels of disability.	There is a paradoxical behavior after applying the isometric exercise protocol in people with work-related neck pain (considered non-specific neck pain). Although there is an increase in pain intensity in all groups, a parallel decrease in generalized mechanical sensitivity is observed, independent of the level of disability associated with the pain.
	Work-related neck pain (moderate-severe disability)	Isometric	↑PPT(AP) ↑NRS		

VAS: Visual analogue scale for pain; PPT: Pressure pain threshold; TPT: Thermal pain threshold; CCF: cranio-cervical flexion coordination exercise; WAD: Whiplash associated disorders; AP: All points where the PPT were applied; CNSNP: Chronic nonspecific neck pain; EIH: Exercise-induced hypoalgesia; CP: Cervical point for PPT; HP: Hand point for PPT; NRS: Numeric rating scale for pain; ↑ Increase; ↓ Decrease; = Unchanged; * Significant differences.

Table 3
Studies evaluating exercise-induced analgesia response in aerobic exercise protocols.

Author	Chronic pain condition	Type of Exercise	Results	Conclusion	Analysis
Van Oosterwijck et al.[38]	WAD	Aerobic Aerobic (Self-paced)	↓PPT (AP) ↓PPT (AP) ↑PPT (CaP)	Individuals with WAD demonstrated lower PPT and symptom exacerbations after exercise, suggesting impaired downstream endogenous pain inhibition during exercise. Although WAD patients' symptoms increased in response to both types of exercise, self-paced and physiologically limited exercise will trigger less severe symptoms and therefore seems more appropriate for WAD patients.	Mechanical sensitivity to pain increased at all points measured in WAD patients who underwent submaximal exercise, suggesting impaired endogenous pain inhibition top-down control during exercise. In contrast, in patients who underwent self-paced and physiologically limited exercise, it was observed that there was a decrease in mechanical sensitivity at the calf point (distant from the painful region). Therefore, it is inferred that self-paced exercise could decrease generalized sensitization in WAD patients.
Ickmans et al.[41]	WAD	Aerobic	↓VAS*(Men) = PPT (CaP) = PPT (SP) = OCP ↓TS	Some altered pain processing changes are present in patients with WAD, which are not modified in response to exercise.	Men with WAD carriers showed lower self-reported pain intensity than the other groups. PPT and OCP had no significant changes in response to submaximal exercise. Calf TS decreased, and when groups were analyzed separately, women with WAD significantly reduced TS (in other words, downward facilitation), decreasing generalized sensitization in response to submaximal exercise.
Smith et al.[34]	WAD	Aerobic	= PPT (AP)	Isometric wall squat exercise, but not aerobic cycling exercise, achieve EIH reducing mechanical sensitivity.	Mechanical pain sensitivity (measured with PPT) was not modified after the aerobic exercise protocol applied in this study and therefore failed to generate the EIH response.
Grimby-Ekman et al.[147]	Neck/ Shoulder pain	Aerobic	↑NRS (during the exercise) 15 min: ↓PPT 105 min: ↑PPT (Original level)	Subjects with chronic neck/shoulder pain showed increased pain and mechanical sensitization after exercise.	Subjects with chronic neck/shoulder pain showed increased pain intensity and mechanical sensitivity after aerobic exercise. This study shows that arm cycling exercise increases local sensitization in people with neck/shoulder pain.
Smith et al.[145]	WAD	Aerobic	= PPT (CP) ↑PPT (HP)	Participants with chronic WAD did not show a significant change in mechanical sensitivity in the neck and tibialis anterior. However, they showed a significant hand change during the exercise.	Participants with WAD showed no significant changes in neck and posterior tibial mechanical sensitization but significant changes in hand mechanical sensitization during exercise. Considering that this study compared aerobic exercise with isometric exercise and that the results in both protocols were equivalent, it is estimated that both types of exercise would have the capacity to decrease generalized pain sensitization.

WAD Whiplash associated disorders; PPT Pressure pain threshold; AP: All points where the PPT were applied; CaP: Calf point for PPT; VAS: Visual analogue scale for pain; SP: Shoulder point for PPT; OCP: Occlusion cuff pressure; TS: Temporal summation; EIH: Exercise-induced hypoalgesia; NRS: Numeric rating scale for pain; MIN: Minutes; CP: Cervical point for PPT; HP: Hand point for PPT; ↑ Increase; ↓ Decrease; = Unchanged; * Significant differences.

the other hand, Van Oosterwijck et al.[38] observed that, although physiologically limited self-paced exercise generated an increase in mechanical sensitivity at various points of the body, it also managed to decrease this parameter in the calf, which could be associated with a lower exacerbation of symptoms. Finally, Ickmans et al.[41] found no change in pain thresholds with the occlusion cuff after aerobic exercise.

7. Discussion and perspectives for research

The present review synthesized the neurophysiological characteristics and mechanisms of EIH, the EIH response in general chronic pain conditions, and, as the main objective, delved into the analysis of such response in subjects with CNP, including the different exercise modalities applied in different subgroups.

Mixed results were reported in the studies considered for the EIH section in CNP. Some investigations reported adverse effects with increased pain intensity and decreased PPT,[34,38,145,147] others found no clinical response,[41,145] and some even reported EIH with decreased pain intensity and increased PPT.[34,95,148]

Findings varied among the different painful conditions; in the case of WAD, EIH was obtained by isometric wall squat exercise.[34] However, there were no equivalent results when other exercise modalities were applied,[135] i.e., aerobic and isometric quadriceps extension exercises with a dynamometer.[145] In the latter type of exercise, although participants did not achieve a generalized EIH, they did achieve EIH in areas remote to the exercise, consistent with the findings of Lannersten and Kosek,[110] who report a better EIH response when exercising in areas remote to the painful region. In addition, another explanation that could be behind the lack of consistency between the results in different exercise modalities is the fact that the initial pain intensity of the subjects was different, being higher in the study by Smith et al.[145,149] These results could be associated with the fact that people with WAD present an altered processing of pain and its downward modulation,[38] as observed in other populations with chronic pain.[37] However, in the study by Meeus et al.[37] people with chronic low back pain achieved a positive EIH response (with submaximal aerobic exercise on an ergometer bicycle). These results could be explained by the fact that the individuals who responded positively presented mild to moderate levels of disability in the cervical spine, which coincides with that reported by Smith et al.[34] The latter authors found an EIH response to isometric exercise in individuals with chronic WAD with mild to moderate levels of cervical pain and disability (without evidence of dysfunctional CPM). Additionally, they found reduced pain sensitivity in both the cervical spine and over the tibialis anterior following isometric wall squat exercise. They did not report EIH in any groups with aerobic exercise on an ergometric bicycle.

Another factor that could condition EIH is the pace of exercise. A positive long-term effect may be obtained when exercise is physiologically limited and self-paced in people with WAD. This effect could respond to the abrogation of local hyperalgesia in response to exercise.[38] Another element that could condition EIH in patients with WAD is the patient's level of physical activity.[142,143] It has been observed that in individuals with moderate levels of physical activity in the previous week, EIH could

be predicted. In contrast, in individuals with high or low levels of physical activity, EIH appeared to be altered.[145] Consistent with these findings, a meta-analysis found that increasing the duration of exercise (total weekly time) does not improve the EIH response, whereas increasing the frequency (number of days of exercise per week) does show improvements in EIH.[101] Finally, although differences in pain perception have been shown to exist between men and women[140] and between age groups,[149,150] studies concerning EIH have reported conflicting results when comparing sexes[137,138] and a lower hypoalgesic response of older adults relative to younger adults.[28,135,136] However, these studies have mainly been conducted in healthy individuals, so it is difficult to extrapolate these results to chronic pain conditions.[137] When we looked into studies performed in individuals with CNP, we only found investigations regarding the differences in EIH responses between age groups and sexes in patients with WAD. In these studies, it has been observed that these variables do not significantly influence the hypoalgesic response,[41] although the reason for these results has yet to be clarified.

Although most studies in individuals with WAD suggest that there is a relationship between post-exercise hyperalgesia, pain sensitivity, intensity, and level of disability,[38,145,151] a recent study in ultrasound workers with varying levels of disability from CNSNP (mild, moderate/severe) achieved EIH in all groups following isometric shoulder abduction.[95] This suggests that the EIH response in subjects with CNSNP has a different behavior than in subjects with WAD.[54] For example (in contrast to what occurred in studies in patients with WAD), an investigation in patients with CNSNP showed that none of the groups studied presented hyperalgesia in the cervical area (measured with PPT and pain threshold to cold),[95] which is consistent with what has been reported in other manual workers.[152–154] This could be because, in these subjects with mild disability, both CPM and EIH would be unaffected, indirectly indicating the optimal status of the descending pain inhibitory pathways. In contrast, in subjects with moderate/severe disability, there is a more significant response to temporal summation (TS), an indirect indicator of the pain facilitation phenomenon. Although this response could explain the greater disability and pain sensitivity in these subjects, the EIH response is not affected since it was observed that, after exercise, there was a decrease in mechanical sensitivity. This could provide novel information that increased pain facilitation rather than impaired pain inhibition may underpin the presence of nociplastic pain in individuals with CNSNP.[95]

Findings in CNSNP show variable responses to shoulder elevation exercises. Christiansen et al.[146] found that subjects tended to generate post-exercise hyperalgesia. Another CNSNP condition, such as chronic neck/shoulder pain, was also associated with increased pain intensity, decreased PPT, and altered EIH.[147] In contrast, O'Leary et al.[148] found a local EIH effect following CF and CCF exercise (with reduced PPT) but not a systemic one. In this study, the CCF exercise protocol was superior to the CF protocol in generating EIH. One explanation for this effect is that the study participants had symptomatic upper cervical spine dysfunction in 85% of the participants. CCF exercise produces an upper cervical spine flexor action, in contrast to CF exercise, which primarily involves lower cervical spine activity. Therefore, CCF exercise could facilitate EIH through a local stimulus on pain-sensitive structures of the upper cervical region, which would not occur with CF exercise.[148]

Another variable that could be considered a priori as a determinant in response to EIH is psychosocial factors. In the study by Xie et al.,[95] sonographers with moderate/severe disability had greater psychological impairments than those with lesser disability. It was found that 61% and 78% of them had anxious and depressive symptoms, respectively. This suggests that psychological factors could partly mediate the somatosensory changes identified in sonographers with disabilities.[95] However, no association was found between psychological variables such as pain catastrophizing and post-traumatic stress symptoms with EIH in persons with WAD.[145] Although catastrophizing could predict pain, it was associated with reductions in TS but not so in PPT. The lack of association between psychosocial factors and EIH found in this study is consistent with the analysis of a systematic review, which concluded that psychological factors are not associated with the strength of EIH in people with musculoskeletal pain.[120] It should be noted that in the studies included in the review by Munneke et al.,[120] there is high heterogeneity and a high risk of bias, making it difficult to generate associations between these factors and EIH.

The heterogeneity of the studies reviewed regarding differences in protocols, different populations, and insufficient sample sizes does not allow definitive and generalizable conclusions to be drawn. Therefore, future studies should consider in their design larger sample sizes and replicate already standardized protocols that allow the identification of subgroups of EIH responders and non-responders.[41,147,148] In addition, it is important to persevere with studies that measure long-term exercise response to clarify how the repetition of the stimulus influences the ability to produce EIH.[145,146] It is also important that future studies attempt to elucidate how psychosocial variables participate in the EIH response. Finally, the limitation most frequently mentioned in the studies in this review is the inconsistency in the sensory assessment of pain thresholds, CPM, and TS, which are measured differently and with different stimuli, which condition the post-exercise pain response.[34,41,95]

8. Conclusions

EIH is an identifiable, stimulable, and helpful therapeutic response in both persons with pain and healthy individuals. However, more research is still needed on subjects with CNP to clarify the protocols and therapeutic modalities that best facilitate the EIH phenomenon. In addition, the knowledge of the intrinsic and extrinsic factors that influence it should be deepened.

9. Key recommendations

- There are varied responses to exercise in CNP, which depend on variables such as the type of painful condition, the level of disability, the level of physical activity, and the pace and modality of the exercise to be applied.
- Moderate physical activity levels may be predictors of EIH response, and exercise frequency was shown to have a positive effect in generating it.
- In patients with CNSNP, both aerobic and dynamic strength exercises of the upper extremities failed to produce EIH. In contrast, local cervical exercises (isometric or dynamic strength types) and upper extremity isometric exercises did produce EIH.
- Although aerobic exercise does not generate EIH in WAD, exercising at a preferred intensity could elicit less hyperalgesia, which may be helpful for patients with CNP to engage in physical activity.
- WAD patients with increased tenderness, pain intensity, and disability have decreased EIH responses in CNP.
- No apparent influence of psychosocial factors on the ability to generate EIH in CNP has been evidenced.

Submission statement

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Authors' contributions

Fernando Rojas-Galleguillos: Conceptualization, writing – original draft/review & editing. **Cecilia Clark-Hormazábal**: Conceptualization, writing – original draft/review & editing. **Eduardo Méndez-Fuentes**: Conceptualization, writing – original draft/review & editing. **Francisco Guede-Rojas**: Writing – review & editing, visualization. **Cristhian Mendoza**: Writing – review & editing. **Andrés Riveros Valdés**: Writing –

review & editing. **Claudio Carvajal-Parodi**: Conceptualization, writing – original draft/review & editing, visualization, supervision.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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