

## Narrative Review

## Dysfunctional Endogenous Analgesia During Exercise in Patients with Chronic Pain: To Exercise or Not to Exercise?

Jo Nijs, PhD<sup>1,2,3</sup>, Eva Kosek, MD, PhD<sup>4</sup>, Jessica Van Oosterwijck, PhD,<sup>1,3</sup>  
and Mira Meeus, PhD<sup>1,2</sup>

From: <sup>1</sup>Chronic Pain and Chronic Fatigue Research Group (CHROPIVER), Department of Human Physiology, Faculty of Physical Education & Physiotherapy, Vrije Universiteit Brussel, Brussels, Belgium.

<sup>2</sup>Chronic Pain and Chronic Fatigue Research Group (CHROPIVER), Division of Musculoskeletal Physiotherapy, Department of Health Care Sciences, Artesis University College, Antwerp, Belgium.

<sup>3</sup>Department of Physical Medicine and Physiotherapy, University Hospital, Brussels, Belgium.

<sup>4</sup>Osher Center for Integrative Medicine, Stockholm Brain Institute, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden.

Address correspondence:  
to Jo Nijs  
Vrije Universiteit Brussel  
Building L-Mfys  
Pleinlaan 2, BE-1050  
Brussels, Belgium  
E-mail: Jo.Nijs@vub.ac.be

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**Background:** Exercise is an effective treatment for various chronic pain disorders, including fibromyalgia, chronic neck pain, osteoarthritis, rheumatoid arthritis, and chronic low back pain. Although the clinical benefits of exercise therapy in these populations are well established (i.e. evidence based), it is currently unclear whether exercise has positive effects on the processes involved in chronic pain (e.g. central pain modulation).

**Objectives:** Reviewing the available evidence addressing the effects of exercise on central pain modulation in patients with chronic pain.

**Methods:** Narrative review.

**Results:** Exercise activates endogenous analgesia in healthy individuals. The increased pain threshold following exercise is due to the release of endogenous opioids and activation of (supra)spinal nociceptive inhibitory mechanisms orchestrated by the brain. Exercise triggers the release of  $\beta$ -endorphins from the pituitary (peripherally) and the hypothalamus (centrally), which in turn enables analgesic effects by activating  $\mu$ -opioid receptors peripherally and centrally, respectively. The hypothalamus, through its projections on the periaqueductal grey, has the capacity to activate descending nociceptive inhibitory mechanisms.

However, several groups have shown dysfunctioning of endogenous analgesia in response to exercise in patients with chronic pain. Muscle contractions activate generalized endogenous analgesia in healthy, pain-free humans and patients with either osteoarthritis or rheumatoid arthritis, but result in increased generalised pain sensitivity in fibromyalgia patients. In patients having local muscular pain (e.g. shoulder myalgia), exercising non-painful muscles activates generalized endogenous analgesia. However, exercising painful muscles does not change pain sensitivity either in the exercising muscle or at distant locations.

**Limitations:** The reviewed studies examined acute effects of exercise rather than long-term effects of exercise therapy.

**Conclusions:** A dysfunctional response of patients with chronic pain and aberrations in central pain modulation to exercise has been shown, indicating that exercise therapy should be individually tailored with emphasis on prevention of symptom flares. The paper discusses the translation of these findings to rehabilitation practice together with future research avenues.

**Key words:** Whiplash, fibromyalgia, chronic pain, low back pain, exercise, rehabilitation, chronic fatigue syndrome, osteoarthritis, rheumatoid arthritis, sensitization, shoulder

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**C**hronic pain remains a challenging issue for clinicians and researchers. Over the past decades, scientific understanding of such unexplained chronic pain disorders has increased substantially. It has

now become clear that the majority of cases of chronic pain can be explained by alterations in central nervous system processing of incoming messages (1). More specifically, the responsiveness of central neurons

to input from unimodal and polymodal receptors is augmented, resulting in a pathophysiological state corresponding to central sensitization, characterized by generalized or widespread hypersensitivity to a variety of stimuli (i.e. mechanical, thermal, and chemical) (2).

The term central sensitization can be used to encompass altered sensory processing in the brain (3), long-term potentiation of brain synapses (4), impaired functioning of top-down anti-nociceptive mechanisms (5), and (over)activation of top-down pain facilitatory pathways which augment nociceptive transmission (3,6). Importantly, a different "pain signature" arises in the brain of those with chronic pain. This altered pain neuromatrix comprises of a) increased activity in brain areas known to be involved in acute pain sensations like the insula, anterior cingulate cortex, and the prefrontal cortex, but not in the primary or secondary somatosensory cortex (7); and b) brain activity in regions generally not involved in acute pain sensations like various brain stem nuclei, dorsolateral frontal cortex, and parietal associated cortex (7). Clinically central sensitization is characterized by non-segmental spreading of pain, "central" symptoms like concentration difficulties and fatigue, stress-intolerance and hypersensitivity to various stimuli like bright light, touch, and odors (8).

Exercise is frequently encountered as a central component of the treatment of patients with chronic pain. Exercise is an effective treatment for various chronic musculoskeletal pain disorders, including chronic low back pain (9), chronic whiplash associated disorders (10,11), osteoarthritis (12), and fibromyalgia (13,14). Although the clinical benefits of exercise therapy in these populations are well established (i.e. evidence based), it is currently unclear whether exercise therapy has positive effects on the processes involved in central sensitization. Is exercise capable of "treating" central sensitization in patients with chronic pain?

There is a strong theoretical rationale suggesting that exercise therapy can indeed "treat" central sensitization (or desensitize the central nervous system). In healthy individuals aerobic exercise of sufficient intensity ( $\pm 200$  W or 70 %  $VO_{2MAX}$ ) activates pain inhibition for up to 30 minutes post-exercise (15). Resistance exercise triggers endogenous analgesia as well, but it lasts for no more than a couple of minutes post-exercise (15). The exercise induced endogenous analgesia is presumed to be due to the release of endogenous opioids and growth factors (16,17) and activation of (supra)spinal nociceptive inhibitory mechanisms orchestrated by the brain (18,19).

Based on this theoretical rationale and on the evidence supporting the clinical benefits in various chronic musculoskeletal pain disorders, it is tempting to speculate that exercise can indeed desensitize the central nervous system. However, this hypothesis is not (yet) supported by scientific evidence. A recent systematic literature review showed that no conclusions can be made about the effect of exercise therapy on pain on pain-modulatory substances (e.g. serotonin, norepinephrine, opioids) or on its effects on altering brain activity of areas involved in pain processing in patients with musculoskeletal pain (20). Moreover, a dysfunctional response of some patients with chronic musculoskeletal pain to exercise has been shown. Several populations of chronic pain patients are unable to activate central descending nociceptive inhibition (endogenous analgesia or EA) during exercise (21-23), a dysfunction partly explaining symptom flares following exercise (22).

In what follows in this paper explains our current understanding of the biology of EA following exercise in humans. Next, it provides an overview of the studies addressing dysfunctional EA during local muscle and general aerobic exercise in patients with chronic pain. From this overview it will become clear that some chronic pain disorders (e.g. fibromyalgia) are characterized by a dysfunctional EA in response to both aerobic and local muscle exercises, while other chronic pain populations (e.g. chronic low back pain) show a normal activation of EA in response to exercise. The relevance of these findings to rehabilitation practice together with future research avenues will be discussed as well.

### **The Biology of Exercise-Induced Endogenous Analgesia**

Several partly overlapping mechanisms are suggested to play a role in exercise-induced EA, including release of endogenous opioids and growth factors (16,17), and activation of (supra)spinal nociceptive inhibitory mechanisms orchestrated by the brain (18,19). These mechanisms might be related to cardiovascular changes (i.e. increase in heart rate and blood pressure) during exercise, a notion supported by the finding that patients with hypertension show reduced pain sensitivity (24). The interaction can be explained by similar brain stem nuclei, neurotransmitters (e.g. monoamines) and peptides (e.g. opioids) (25). The exercise-induced blood pressure increase activates arterial baroreceptors, resulting in increased supraspinal inhibition (24,25) and stimulation of brain centers involved in pain modulation (26).

In addition, Hoffman and Thoren (27) have reported that once blood pressure is displaced out of the basal range, either by physiological stimuli or pathophysiological states, the endogenous opioid system becomes activated. Exercise triggers the release of  $\beta$ -endorphins from the pituitary (peripherally) and the hypothalamus (centrally), which in turn enables analgesic effects by activating  $\mu$ -opioid receptors peripherally and centrally, respectively (28). The hypothalamus, through its projections on the periaqueductal grey, has the capacity to activate descending nociceptive inhibitory mechanisms.

Nevertheless, it appears from animal research that multiple analgesia systems exist (opioid and non-opioid), and that properties of the exercise stressor are important in determining which system is activated during exercise. It has been shown that by manipulating the parameters of the exercise stressor, it is possible to elicit either naloxone-reversible or naloxone-insensitive EA following exercise (17,29).

The role of growth hormone and growth factors in exercise-induced EA remains unclear. Some authors hypothesize that growth hormone, via insulin-like growth factor and nerve growth factor, sensitizes rather than being involved in EA (30,31). Only one study evaluated the role of growth hormone in exercise-induced hypoalgesia, but suppressing growth hormone production during exercise did not alter exercise-induced hypoalgesia (32).  $\beta$ -endorphins and growth hormone are released after a certain exercise span, one hour and 10 to 40 minutes respectively, when lactate accumulation is leading to muscle acidosis (33-35).

Catecholamines also exert direct analgesic effects. Main descending inhibitory action to the spinal dorsal horn are noradrenergic. In the dorsal horn, norepinephrine, through action on alpha-2A-adrenoceptors, suppresses release of excitatory transmitters from central terminals of primary afferent nociceptors (36). In addition it may suppress postsynaptic responses of spinal pain-relay neurons (36). Besides catecholamines, the mediators of the long-term stress response, namely corticosteroids, are involved in exercise induced EA. Both opioid and non-opioid mechanisms would contribute to the development of EA induced by glucocorticoids (37). Hence, exercise can be viewed as a frequent stressor activating stress-induced analgesia.

Other possible explanations for exercise-induced EA involve an increased body awareness for somatic sensations after exercise. This awareness of more salient signals—for example, sweating and heart pounding—may divert attention away from the pain stimulus.

Distraction can significantly alter pain perception (38). Furthermore, traditional gate control mechanisms, due to skin or muscle afferents competing with nociceptive afferents in the dorsal horn, may account for exercise induced EA. Finally, conditioned pain modulation, formerly referred to as diffuse noxious inhibitory controls (DNIC), may be activated subsequently to the nociceptive barrage resulting from muscle ischemia and lactate accumulation. Peripheral mechanisms are less plausible as they typically result in sensitizing agents (prostaglandins, lactate, ischemia, growth factors, etc.).

### **Dysfunction of Endogenous Analgesia During Muscle Contraction in Patients with Musculoskeletal Pain**

Long-term, low intensity, static work is a well known risk factor for the development of work-related myalgias, and static contractions increase pain intensity in patients with myalgia (39) and fibromyalgia (39,40). Animal studies have revealed that muscle ischemia is a potent cause of sensitization of peripheral mechanonociceptors so that the increased intramuscular pressure caused by the contraction can become an effective nociceptive stimulus (41). Compared to healthy controls, patients with shoulder myalgia (42) and fibromyalgia (43) had reduced muscle blood flow during static contractions, which could lead to peripheral sensitization and explain the increased pain sensitivity reported in painful muscles in these patients (39). In accordance with this, increased sensitivity to pressure pain (i.e., increased tenderness) at the contracting muscle following static contractions was reported in fibromyalgia patients (44,45), suggesting dysfunctional EA during exercise in these patients. Indeed, healthy subjects exhibited decreased pressure pain sensitivity at the contracting muscle during and following contraction indicating that segmental or possibly plurisegmental (generalized) pain inhibitory mechanisms were activated (46). In a follow-up study, localized (at the contracting muscle) as well as generalized (at a distant resting muscle) pain inhibitory effects were seen during static contractions in healthy individuals (46). In addition, the decrease in pain sensitivity was of similar magnitude at the contracting and the distant resting muscle indicating the importance of generalized EA mechanisms (46).

To our knowledge, only a few studies have examined the effect of static contractions on pain sensitivity outside the contracting muscle. Staud et al (47) found a bilateral decrease in cutaneous (heat) and deep somatic (pressure) pain sensitivity during unilateral static

contractions sustained during 90 seconds corresponding to 30% of the individual maximal voluntary contraction force (MVC) in healthy subjects. A paradoxical increase in heat and pressure pain sensitivity was seen bilaterally in fibromyalgia patients during the unilateral contractions, providing evidence for widespread deficiency of EA or more pronounced pain facilitation in fibromyalgia patients during exercise (47).

The important question raised by Staud et al (47) regarding the importance of deficient EA versus augmented pain facilitation in pain patients during physical exercise was further addressed in another study assessing patients with shoulder myalgia and fibromyalgia, respectively, during static contractions corresponding to 20 – 25% MVC until exhaustion (maximum 5 minutes) (39). Patients and healthy controls performed static contractions with M. quadriceps femoris and M. infraspinatus. Pressure pain thresholds were assessed before and during contraction at the contracting muscle, the resting homologous contralateral muscle, and contralaterally at a distant site (M. infraspinatus during contraction of M. quadriceps and vice versa). Pressure pain thresholds increased at all sites during both contractions in healthy controls, but no increase was seen at any site during contractions in fibromyalgia patients, who even exhibited increased pain sensitivity. Myalgia patients had an increase in pressure pain thresholds at all sites during contraction of the non-painful M. quadriceps, but no increase in pressure pain thresholds was seen at any site during contraction of the painful M. infraspinatus. The authors suggested that nociceptive input from painful muscles induced central sensitization and activated descending pain facilitatory mechanisms. The facilitatory mechanisms could override the contraction-induced pain inhibition and explain the lack of generalized EA during contraction of painful muscles in myalgia patients and the increased pain sensitivity during contraction in fibromyalgia patients (39).

Interestingly, a pilot study in patients with rheumatoid arthritis indicates normal EA during static contraction in these patients (Fridén et al., submitted) and preliminary results also indicate normal function of these mechanisms in patients with osteoarthritis of the knee and hip (Kosek, Roos, Nilsdotter, manuscript in preparation). These findings are in accordance with the reported beneficial effects of exercise in these conditions (48,49).

As mentioned, many potential mechanisms have been implicated in pain regulation during muscle contractions. Conditioned pain modulation has been proposed as one possible mechanism for pain inhibition

during contraction. However, the low pain ratings during contraction in healthy controls (39) make this unlikely. Furthermore, although a dysfunction of conditioned pain modulation has been shown in fibromyalgia (50), normal function of conditioned pain modulation was shown in shoulder myalgia patients (51). Exercise induced pain modulation during static contractions has also been related to arterial baroreceptor activation in humans (52). However, a normal increase in heart rate and blood pressure has been reported in fibromyalgia patients during static contractions offsetting abnormal cardiovascular response to exercise as a likely explanation for the dysfunction of EA in these patients (40,53). Finally, hormonal factors of importance for regulation of muscle blood flow and pain sensitivity could be of interest. The findings of a hypo-active sympatho-adrenal system in combination with a hypo-reactive adrenal-hypothalamo-pituitary (HPA) axis in fibromyalgia patients during static contractions could contribute to the dysfunctional EA during exercise and subsequent exercise intolerance that is so characteristic for fibromyalgia patients (53).

It is concluded that muscle contractions activate generalized EA in healthy, pain-free humans and patients with either osteoarthritis and rheumatoid arthritis, but result in increased generalised pain sensitivity in fibromyalgia patients. In patients having local muscular pain (e.g. shoulder myalgia), exercising non-painful muscles activates generalized EA. However, exercising painful muscles does not change pain sensitivity either in the exercising muscle or at distant locations.

### **Dysfunction of Endogenous Analgesia During Aerobic Exercise in Patients with Musculoskeletal Pain**

The dysfunctional EA in response to aerobic exercise was first shown in a small study of patients with chronic fatigue syndrome and healthy controls in which participants performed a graded exercise with 3 stages on a treadmill (54). Every stage of the exercise consisted of 5 minutes walking at a constant pace of 5km/h, with an increasing incline of 5°. Dysfunctional EA was demonstrated by decreased pain thresholds following exercise in patients with chronic fatigue syndrome, while pain thresholds increased in healthy controls. These findings were later replicated in 2 larger studies using various types of exercise:

- 1) submaximal cycle exercise with a gradual increase of 25 W every minute until 75% of the age-predicted target heart rate was achieved (22),

- 2) 6 short bouts of aerobic cycling interrupted by short recovery breaks (21), and
- 3) physiologically limited (heart rate below 80% of the anaerobic heart rate, workload below 80% of the anaerobic workload) and self-paced aerobic cycling (22).

From these studies it is concluded that neither types of aerobic exercise were able to activate EA in patients with chronic fatigue syndrome who experience chronic widespread pain. Importantly, the dysfunctional EA partly explains symptom flares following exercise in patients with chronic fatigue syndrome having chronic widespread pain (22).

A similar dysfunctional EA in response to exercise and symptom flares following exercise was shown in patients with chronic whiplash associated disorders (23), suggesting this to be a feature of central sensitization. The dysfunctional EA in patients with chronic whiplash associated disorders was observed during submaximal cycle exercise with a gradual increase of 25 W every minute until 75% of the age-predicted target heart rate was achieved, as well as during physiologically limited and self-paced aerobic cycling (23). Remarkably, in the studies outlined above the various types of aerobic exercise did activate EA in healthy sedentary controls (21-23,54) and patients with chronic low back pain (21). The latter confirms an earlier study in chronic low back pain patients (55). Thus, the mechanism of EA in patients with chronic low back pain responds normally to aerobic exercise.

Some work has been performed to unravel the mechanisms behind the dysfunctional EA during exercise in certain chronic pain disorders. Nitric oxide (NO) plays a complex role in nociceptive processing (19). Although evidence exists regarding the beneficial effects of the release of small amounts of NO during inhibition of nociceptive pathways (56), excessive amounts of NO could contribute to central sensitization. Indeed, NO is able to reduce the nociceptive inhibitory activity of the central nervous system, leading to central sensitization of dorsal horn neurones (57). A single bout of physical activity triggers release of NO (58), leading to the hypothesis that the dysfunctional EA during exercise might be due to NO release. However, NO levels were unrelated to pain processing during aerobic exercise in healthy sedentary controls, patients with chronic fatigue syndrome and chronic low back pain (21).

While endogenous opioid and adrenergic pain-inhibitory mechanisms might account for activation of EA during exercise in healthy individuals (18,19), direct evidence is lacking. Therefore, a study was undertaken

to examine the contribution of endogenous opioid pain-inhibitory mechanisms during exercise in 2 chronic pain populations: rheumatoid arthritis and fibromyalgia/chronic fatigue syndrome (59). In a randomized and placebo-controlled cross-over study, we modulated endogenous opioid and serotonergic pain-inhibitory mechanisms during exercise by using selective serotonin reuptake inhibitor (SSRI; 2 mL of citalopram intravenously) during the DNIC and temporal summation model in response to exercise. SSRIs activate serotonergic descending pathways that recruit, in part, opioid peptide-containing interneurons of the dorsal horn (60). Unfortunately, significant side effects immediately after intravenous administration of citalopram resulted in early cessation of the study. Hence, currently no conclusions can be made addressing the role of serotonergic descending pathways in EA in response to exercise in chronic pain patients (59).

It is concluded that the dysfunctional EA during aerobic exercise is not characteristic for all chronic pain patients, but rather limited to those with clear evidence of central sensitization (e.g. chronic whiplash, fibromyalgia, chronic fatigue syndrome).

### **Analgesic Effects of Exercise Therapy in Patients with Chronic Musculoskeletal Pain: Opportunities and Challenges**

#### ***Applying these Findings to the Practice of Exercise Therapy for Chronic Pain***

When confronted with the cumulating evidence for a dysfunctional EA during exercise in some chronic pain disorders, one might wonder whether we should continue using exercise therapy in these patients. However, this should not be an issue. The studies summarized above address acute bouts of exercise, not findings from randomized clinical trials examining the effects of exercise as a therapeutic intervention. The studies showing dysfunctional EA during exercise in some chronic pain conditions do not contradict the clinical evidence favoring the use of exercise as an intervention for chronic pain. Exercise is an effective treatment for chronic whiplash associated disorders (10,11), fibromyalgia (13,14), chronic fatigue syndrome (61,62), osteoarthritis (48), and rheumatoid arthritis (49). Hence, its clinical use and benefits should not be questioned. To exercise or not to exercise patients with chronic pain, is no longer the question.

On the other hand, the dysfunctional EA during exercise in patients with chronic pain should not be

ignored. In fact, its clinical relevance is supported by studies showing that symptom flares following exercise are related to the dysfunctional EA during exercise (22). In addition, the dysfunctional EA during exercise might explain the low compliance with exercise interventions in chronic pain patients. Typically the early stages of exercise therapy programs are prone to dropouts.

Lack of exercise-induced analgesia implies a decreased pain threshold following exercise. This makes patients vulnerable for new nociceptive input. Exercise is typically associated with myofiber damage and substances released in response to exercise (e.g. oxidative stress, lactate), potentially providing increased nociceptive input in response to exercise (63). Hence, the dysfunctional EA during exercise increases the risk of severe symptom flares following exercise sessions. For all these reasons, we conclude that clinicians should account for the dysfunctional EA during exercise in certain chronic pain conditions.

But how? Given the dearth of studies examining the effects of exercise therapy on EA (20), this question can only be answered by applying logical (clinical) reasoning. Appropriately tailored and graded exercise therapy has been suggested as a treatment for central sensitization in patients with chronic pain (64), but evidence supporting this notion is lacking (20). Especially in the early stages of exercise therapy programs, exercise therapy should be individually tailored with emphasis on prevention of symptom flares.

This might be achieved by applying the following guidelines (Table 1): prefer aerobic exercise over eccentric or isometric muscle work, as the latter 2 are likely to increase the hyperexcitability of the central nervous system (47) and result in diminished blood flow increase in the working muscles (43). The findings from the studies explained above suggest that exercising preferably non-painful parts of the body could have pain-relieving effects in myalgia patients by reducing pain sensitivity in painful muscles, while low intensity training regimes would be expected to be favorable in fibromyalgia in order to avoid unnecessary exacerbations of pain (39).

In addition, exercise therapy for chronic pain patients should account for cognitive-emotional sensitization. Emotions, attention, expectations, depressive thoughts, and catastrophic thoughts each enhance descending facilitation (65-67), which in turn sustains the process of central sensitization. This is typically referred to as cognitive-emotional sensitization (68), which can imply increased forebrain activity that can exert powerful influences on various brainstem nuclei (69), including those identified as the origin of descending facilitatory pathways (70). Clinically cognitive-emotional sensitization is typically addressed in comprehensive pain management programs that include pain physiology education to address illness perceptions and maladaptive pain cognitions, stress management, time-contingent activity management (i.e. graded activity), and time-contingent exercise therapy (i.e. graded exercise therapy) (Table 1).

Table 1. *Practical guidelines to account for dysfunctional endogenous analgesia during exercise when applying exercise therapy in patients with chronic musculoskeletal pain.*

**Keep the following guidelines in mind when applying exercise therapy in patients with chronic musculoskeletal pain and dysfunctional endogenous analgesia during exercise:**

- ◆ exercise should be fun, not a burden
- ◆ Discuss the content of the exercise protocol with the patient; it should fit the needs and requests of the patient
- ◆ Use aerobic exercise as well as motor control training
- ◆ Be careful with eccentric exercise
- ◆ Include exercise of non-painful parts of the body
- ◆ Allow increased pain during and shortly following exercise but avoid continuously increasing pain intensity over time (i.e. modify exercise)
- ◆ Use a time-contingent approach with appropriate baseline
- ◆ Be conservative when setting the baseline; prefer a lower baseline to guarantee that is well within the capabilities of the patient's body
- ◆ Use multiple and long recovery breaks in between exercises
- ◆ Monitor symptom flares, especially during initiation of treatment and during grading, and adopt exercise modalities accordingly
- ◆ Minor symptom flares are natural during initial stages of exercise therapy, but should cease once an exercise routine is established
- ◆ Do not grade the exercise protocol in case of major symptom flares

### **Treatment of the Dysfunctional Endogenous Analgesia During Exercise by Combining Centrally Acting Drugs with Exercise Therapy?**

In addition to the guidelines for designing appropriate exercise therapy programs, it seems rational to combine centrally acting drugs with exercise therapy. Unraveling the mechanisms responsible for the dysfunctional EA in response to exercise in people with chronic pain is likely to be a crucial step towards well-balanced drug + exercise treatments. In the mean time, the following suggestions seems rational given our current understanding of dysfunctional EA during exercise and chronic pain management. First, opioid use in combination with (the early stages) of graded exercise therapy might be an option in some patients with nociceptive pain. In this respect, it is important to realize that evidence indicates that opioid withdrawal is unnecessary for effective pain rehabilitation programs (71). This is important as the early pain rehabilitation programs advocated operant methods to decrease opioid consumption in the early treatment stages.

Second, activation of serotonergic and/or noradrenergic descending pathways in conjunction with graded exercise therapy might be an option. A centrally acting analgesic like Duloxetine, a selective and balanced serotonin and norepinephrine reuptake inhibitor (SNRI), has proven its efficacy in a variety of chronic pain conditions characterized by central sensitization (e.g. fibromyalgia [72] and osteoarthritis [73]). It remains unclear whether these clinical effects can be reinforced by combining drug use with graded exercise therapy. Further work in this area is warranted.

Finally, the finding that peak exercise performance in healthy people improves when using acetaminophen (74) might provide a new avenue for combining analgesics with exercise therapy for patients with chronic pain

and dysfunctional EA during exercise. There is evidence suggesting that acetaminophen primarily acts centrally by reinforcing descending inhibitory pathways (75), namely the serotonergic descending pain pathways.

Still, future research should examine whether these proposed combinations of drug treatment and graded exercise therapy are able to treat the dysfunctional EA in patients with chronic pain. Moreover, the combined treatment programs should not only improve EA during exercise, it should benefit the patient at the level of daily functioning and quality of life as well.

### **CONCLUSION**

Exercise activates EA in healthy individuals, resulting in generalized increased pain tolerance during and immediately following exercise. This conclusion accounts for aerobic exercises like cycling, and for exercising local muscle groups. The physiological mechanisms explaining EA following exercise have not been studied in detail yet, but the available research data suggest that it is due to the release of endogenous opioids and activation of (supra)spinal nociceptive inhibitory mechanisms orchestrated by the brain. However, aerobic exercise activates pain facilitation rather than inhibition in some patients with chronic pain and central sensitization (fibromyalgia, whiplash, and chronic fatigue syndrome). Exercising local muscle groups results in increased generalised pain sensitivity in fibromyalgia patients, but recent data indicate that this might not be the case in those with osteoarthritis and rheumatoid arthritis. In shoulder myalgia, exercising non-painful muscles activates generalized EA, but exercising painful muscles does not activate EA. Further work is required to unravel the biology of the dysfunctional EA following exercise, and to establish how these findings should be applied to clinical practice.

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