**Exercise and Central Sensitization**

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**What is central sensitization?**

When the body is presented with an initial noxious stimulus or injury, this stimulates afferent receptors that excite central nociceptive pathways, resulting in the output of pain. In central sensitization (CS), these noxious inputs chronically increase the excitability of the neurons in those pathways. This causes the neurons to be hypersensitive to incoming stimuli and create pain in response to movements or sensations that would not normally elicit a pain response.1,2 Therefore, the pain is more the result of central sensitivity instead of peripheral damage or particularly noxious inputs. This pain typically fuels a cognitive-emotional sensitivity as well, which can contribute to fear avoidance behavior and catastrophizing.2 Overall, CS can limit a patient’s function and participation by perpetuating pain long after the initial cause has been resolved or when no one cause can be found, and can have a psychological impact as the patient experiences pain in response to previously harmless activities.

**How can exercise help?**

Though the use of medications is a common intervention choice for patients experiencing CS, exercise has received growing attention as a conservative treatment.3 Several theories, that may not be mutually exclusive, underlie the justification for using exercise in this population.

Exercise-induced endogenous analgesia (EA)- This is one of the most prominent theories in the literature. During exercise, the changes in cardiovascular factors such as blood pressure and heart rate are believed to cause the release of beta-endorphins that activate receptors in the endogenous opioid system, producing an analgesic effect.3,4 These cardiovascular changes can also spur inhibitory action in descending pain pathways.4 While exercise-induced EA has been reliably shown in healthy individuals, there is some research showing that these systems may not function similarly in those with CS.4,5 Therefore, this mechanism may not fully justify how exercise can help certain individuals with CS.

Regulation of neurotrophic factors- Brain-derived neurotrophic factor (BDNF) is a protein known for facilitating neuroplasticity, and it also increases hyperexcitability of peripheral nociceptors and central neurons in pain pathways.6 This gives BDNF a role in perpetuating sensitivity and pain responses in those with CS. While BDNF levels temporarily rise after a bout of exercise, regular exercise acts to stabilize levels, often resulting in lowered BDNF in CS patients.3,6

Anti-inflammatory effects- In acute pain or injury, the activation of glial cells causes the release of inflammatory cytokines and neurotrophic factors to help tissue heal. However, if this activation becomes chronic, the inflammation caused can increase long-term potentiation in pain pathways.7 Since BDNF is one of the factors released during this chronic neuroinflammation, this theory is related to the mechanism discussed above regarding the regulation of neurotrophic factors. Regular exercise has been shown to alter the activity of glial cells by stimulating an anti-inflammatory response.7

**Who can benefit?**

Given that CS is not a single condition in itself but rather a consequence of other conditions, it can be present in a wide variety of patients. It is estimated that 25% of low back pain cases, 30% of osteoarthritis (OA) cases, and 90% of whiplash associated disorders feature pain with CS.5 CS can also occur with migraines, fibromyalgia, multiple sclerosis, and neuropathic pain.1,5,6,8,9 Therefore, patients both in musculoskeletal and neurological settings may experience CS and are capable of performing exercise to some extent, resulting in a large population that can benefit from this intervention.

**Evidence**

While exercise is used as an intervention for the conditions described above and many more, there is a lack of studies that incorporate consideration of CS into their intervention and analysis. OA presents with the strongest evidence in this area, with favorable outcomes seen with use of both strength and aerobic exercise.4,5,10 CS in low back pain and cancer-related pain have also been demonstrated to respond favorably to exercise interventions.5,11,12 Results have been mixed in use with fibromyalgia and whiplash-associated disorders in studies that focus on measuring exercise-induced EA, as EA is not induced similarly in these populations compared to those with OA and low-back pain.4 However, results have been favorable in studies of aerobic exercise for fibromyalgia and in studies that do not focus on measuring a particular mechanism or theory.5,13 Conversely, whiplash-associated disorders have demonstrated improved outcomes with resistance-training and not aerobic exercise.5,14

**Current Recommendations**

The exact mode of exercise that can yield the most benefit varies based on the patient and their condition as seen in the evidence discussed above, yet certain approaches and parameters for exercise are more universal for use with CS. Creating the exercise plan with pain science in mind is crucial to meet the needs of this population, and this includes educating the patient on the mechanisms of CS and pain and addressing any of their fears or concerns that revolve around their pain before initiating exercise and throughout the program.1,12,15,16 Graded activity that progresses intensity slowly has been shown to be beneficial for both pain and compliance, but must be executed carefully to avoid perpetuating avoidance behavior by limiting activity in excess.2,5,11 Basing activities completion on time or number of repetitions, rather than the patient’s reported symptom of pain is another common recommendation with CS. This approach allows the patient to experience movements that are safe and should not cause pain, forcing the nervous system to desensitize with the repeated exposure.15

**Other Potential Benefits**

Beyond the neurological desensitization benefits, exercise may benefit this population psychologically through addressing the cognitive-emotional sensitization that often accompanies CS. Strong emotions such as fear, depression, or frustration due to pain can help fuel CS by increasing forebrain activity and increasing facilitation of descending pathways causing more pain.4 As exercise safely exposes the patient to activities and movements that they were fearful of and associated with pain, their perceptions can change to better accommodate these movements and face pain, thus interrupting the vicious cycle were negative thoughts can feed into CS.

Decreased sleep and increased stress are additional factors that can contribute to CS due to their potential to increase inflammation in the brain. Exercise can help patients achieve greater sleep efficiency, and has shown small effects on stress.5,7 So while the contributions of exercise in improving these factors may be small and still need further research, they may be additional mechanisms by which exercise can help combat CS.

**Indications, contraindications, precautions for its use**

Indications and precautions for using exercise are similar in this population as others, in which you want to consider factors such as baseline cardiovascular health, any weightbearing restrictions, and comorbidities when designing an individualized exercise plan. In those with CS, it is necessary to note that their pain may increase immediately following exercise, as increased BDNF can increase sensitivity temporarily increased levels of oxidation and lactate can provide additional input that can be interpreted as pain.4 This may be an important piece to include in education of the patient before and exercise, and should be remembered when interpreting the patient’s response to exercise.

**Resources required**

Specific costs and equipment needs depend on the individual exercise program designed, but overall exercise is generally a small burden in these areas as most facilities already own exercise equipment to some extent. The exercises used for CS do not differ from exercise prescribed for other purposes in their execution but in their target, so these patients can utilize equipment that already exists in the clinic, such as a treadmill or weights. Exercise can also be done without equipment, such as through a walking program or the use of body-weight exercises. There is no specific additional training required for a therapist to utilize exercise for CS, as therapists are already well educated in therapeutic exercise prescription and progression. However, it is recommended that the therapist have knowledge or experience with pain science, as this would allow them to better educate the patient and execute an exercise program with the specific nature of CS in mind rather than a generalized program that may not be as effective.

**Translation to practice**

With the widespread use of exercise for numerous other conditions, its use for CS is promising. High-quality literature specific to exercise in CS is still needed, as certain intricacies of its use still require research. For example, as discussed for the current evidence, aerobic exercise is more effective in certain conditions with CS such as fibromyalgia, while strength exercise has benefits for those with whiplash-associated disorders and CS and may be the preferred option for that population.4,13,14 In the context of strength exercise, there is also some ambiguity about whether to target painful or non-painful muscles for certain patient groups.4 Research into these types of questions can help make the translation into practice easier by providing clearer recommendations on use. However, this intervention is ready for use currently due to the demonstrated benefits and existing use of exercise, just in a manner less focused on CS.

**Summary about utility of intervention for current practice**

Overall, this intervention can prove to be extremely useful in current practice. Compared to other “novel” interventions, exercise is much easier for both therapists and patients to access due to its low-cost, pre-existing knowledge of therapists in its use, and the ease of personalization to each patient. When patients with CS come to physical therapy, CS may not often be considered or addressed in a deliberate fashion, yet these patients are often prescribed general therapeutic exercises anyway with another condition in mind (such as OA). If therapists consider principles of pain science and research findings specific to this population, it would be easy to apply these principles by modification of an exercise plan to address CS-related needs and not only the condition that presents on the surface. This modification can maximize benefits to the patient by addressing all aspects of their pain.

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