Many with Complex Regional Pain Syndrome experience disproportionate pain that is no longer being sustained by an injury or noxious event (even if an injury may have been the initial trigger) that remains contained to a single body area or they may develop widespread, disparate pain and dysfunction that can affect multiple body areas over the course of their condition. It is not uncommon for peers, bosses, loved ones, and providers alike to treat those with CRPS as if they are overdramatic, hysterical, psychologically disturbed, drug seeking, payout seeking, liars, or malingerers instead of experiencing a "real" condition.[1] However, just because a person cannot see the source of a disorder does not mean it does not exist and is therefore delegitimate.

One such source of pain and dysfunction in CRPS is the sensitization of the central nervous system.[7, 8, 9, 10, 11, 12] Central sensitization or centralized pain is an umbrella term that contains many different diagnoses under its wings, including CRPS and the more commonly recognized fibromyalgia; this dysfunction is considered to be a root cause and driver for continued, amplified pain and atypical behavior of the conditions covered by central sensitization mechanisms. Let's talk about it.

What's Going On

There are three main recognized drivers of pain sensation: nociceptive pain, or pain caused by damage to non-neural tissues, including inflammatory pain caused by activation of the immune system; neuropathic pain, or pain caused by damage or disease of neural tissues; and the relatively newly added nociplastic pain, or pain caused by an altered pain detection within the central nervous system that amplifies neural signals to create hypersensitivity.[1, 2, 4] This more newly recognised nociplastic pain is also routinely called central sensitization syndrome (CSS), central pain syndrome (CPS), centralized pain, and widespread or diffuse pain. Sometimes, particularly when children are involved, some circles prefer the term amplified musculoskeletal pain syndrome (AMPS) in lieu of central sensitization syndrome, fibromyalgia, or CRPS.

Primary markers for centralized pain are: allodynia, or pain from a normally non-painful sensation; hyperalgesia, or prolonged and excessive pain to a normally painful sensation; secondary hyperalgesia, or pain that spreads beyond the initial site of injury; and temporal summation, or the increase in perceived pain intensity in response to repeated stimuli of equal physical intensity.[1, 2, 3] If an individual experiences these four features, central sensitization may be involved. Centralized pain involves the central nervous system's pain facilitation "accelerator" being overactive and/or the descending pain inhibition pathway "brake" being underactive, resulting in amplified responses to little nociceptive input or normal non-nociceptive input from the somatosensory system.[5]

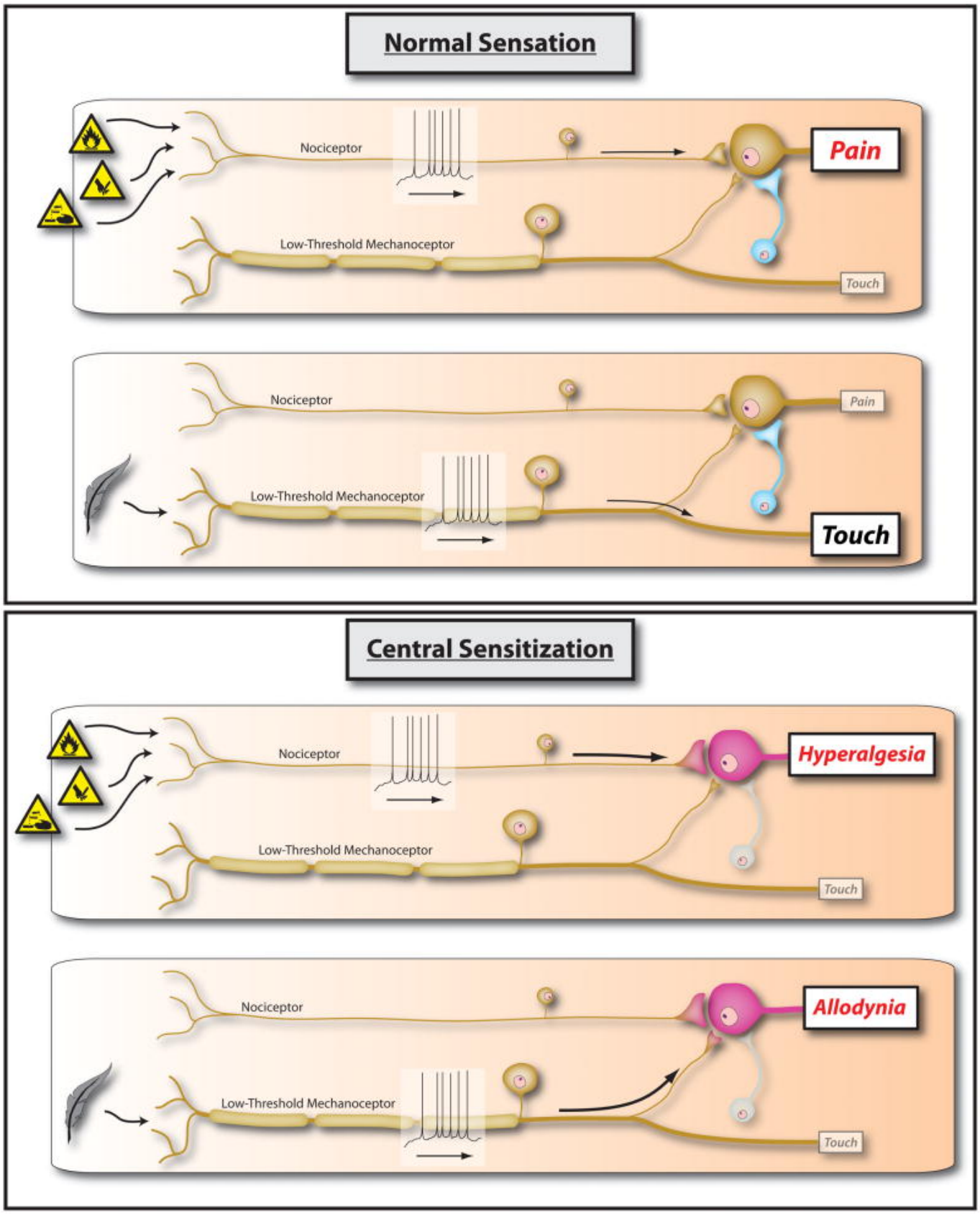

Image Credit: Woolf, Central sensitization: Implications for the diagnosis and treatment of pain (Pain, 2010)

In a normally functioning nervous system, when an injurious stimuli is detected in high threshold pain nerves, withdrawal reflexes are automatically activated to protect the person from sustaining any further harm. When subjected to a repeated conditioning stimulus, the nervous system can lower its activation threshold to fire more easily both during the stimulus and after it stops; windup is the term for progressively increasing nerve output during a conditioning stimulus, while sensitization is what happens after the conditioning stimulus stops being applied and it can remain active of its own accord for a sustained period or be perpetuated by low levels of nociceptive input. This amplification is what causes hyperalgesia (high pain from a mildly painful stimulus) and it creates a crossover in parallel signaling systems that usually run to different destinations, but in a sensitized system has non-noxious sensory information getting diverted to the pain detection system, causing allodynia (pain from a non-painful stimulus).[1]

This change in how the central nervous system operates can significantly alter and distort how pain is registered and can increase the intensity, length, and size of the area where pain is experienced, even if no tissue damage is occurring due to a noxious stimuli.[1] This hyper-responsiveness and sensitivity to any potential threat is an adaptive response by the nervous system to protect itself from further harm, especially in conditions and circumstances where risks are high;[3] however, if this state continues too long, it becomes maladaptive and loses its protective properties, becoming pathological instead.

When a person develops central sensitization, they can also develop many “unrelated” conditions that all come back to their overactive, overamplified central nervous system; these conditions are called Chronic Overlapping Pain Conditions (COPCs), or previously by other terms like affective spectrum disorder, central sensitivity syndromes, or chronic multisystem illnesses.[2] Some of the COPCs researchers consider to fall on the central sensitization spectrum, where CNS dysfunction plays a primary or exclusive role, include: fibromyalgia, CRPS, IBS, chronic migraine or tension headache, chronic fatigue syndrome, interstitial cystitis/bladder pain syndrome, endometriosis, vulvodynia/pelvic pain, temporomandibular disorder, dry eye disease, and low back pain. Other conditions have a central sensitization component while also clearly having additional mechanisms such as inflammatory nociceptive pain, such as autoimmune disorders, arthritis, sickle cell, cancer, and hypermobility syndromes.[1,2] In some cases, once the nociceptive input is removed, the central sensitization partially or entirely goes into remission, but this is not true for every case and every condition.[2]

While this topic is complex, fascinating, and has many parts we could focus on, there are a few major aspects of central sensitization that are worth mentioning within the scope and length of this article: top-down vs bottom-up differentiation, the spectrum of central sensitization as a continuum, a few different self-report scales, post-sugery recovery and pain management with opioid medication due to the dysfunction with the endogenous opioid system.

Fibromyalgia may be the most well-known disorder representing central sensitization to the

point that people used to be labeled as developing “secondary fibromyalgia” as a stand-in for describing their central sensitization due to their other chronic pain conditions or illnesses.[2] Fibromyalgia uses a self-report diagnostic tool called the Widespread Pain Index (up to 19 points) and the Symptom Severity Index (up to 12 points), whose scores are then combined for up to a total of 31 points to determine a patient’s degree of “fibromyalgianess.”[2]

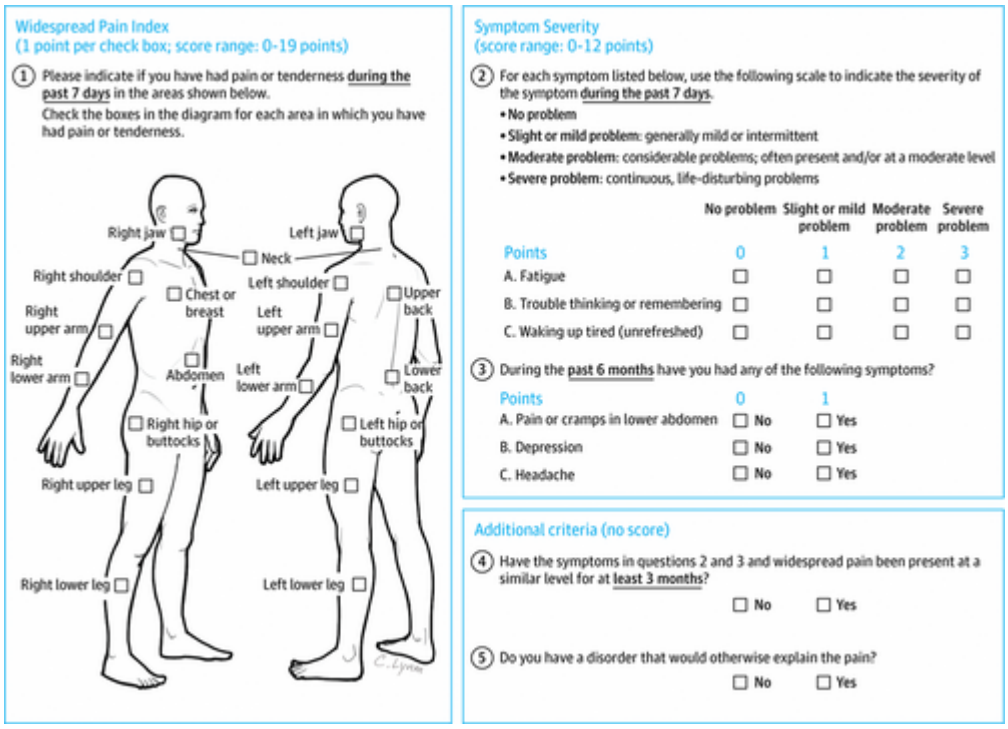

Image Credit: The 2011 Survey Criteria for Fibromyalgia (Wolfe et al., 2011) using the Michigan Body Map (Brummett, Bakshi et al., 2016)

While the official cutoff for a fibromyalgia diagnosis is 13, researchers are recognizing that central sensitization occurs on a continuum and even those who have subthreshold (below 13) scores can be experiencing a more mild degree on the spectrum of sensitization, which can be highly relevant information when it comes to treatment, post-operative care, and pain management. Studies have shown that for every one point on the 0-31 “fibromyalgianess” scale, a person would need 7-9 mg more oral morphine equivalent in the first 24-48 hours post-surgery, and they were 15-20% less likely to show pain improvement after the operation, after controlling for several demographic factors.[2] This response was shown in individual both above and below the official diagnostic criteria cutoff of 13 points.

The Central Sensitization Inventory (CSI) is another self-report tool of 25 multiple choice questions to find where individuals fall on the spectrum of sensitization. The results range from 0-100 with 40 or greater being considered as qualifying for meeting the central sensitization cutoff by the creators; while the cutoff correctly identifies over 80% of those with central sensitization, it also can provide a fair amount of false positives, and so utilizing this measure with another, more robust option is recommended.[4, 5]

Table 2. Central Sensitization Inventory

Name: _____ SS#: _____

Date: _____

Please circle the best response to the right of each statement.

1. I feel unrefreshed when I wake up from sleeping.	Never	Rarely	Sometimes	Often	Always
2. My muscles feel stiff and achy.	Never	Rarely	Sometimes	Often	Always
3. I have anxiety attacks.	Never	Rarely	Sometimes	Often	Always
4. I grind or clench my teeth.	Never	Rarely	Sometimes	Often	Always
5. I have problems with diarrhea and/or constipation.	Never	Rarely	Sometimes	Often	Always
6. I need help in performing my daily activities.	Never	Rarely	Sometimes	Often	Always
7. I am sensitive to bright lights.	Never	Rarely	Sometimes	Often	Always
8. I get tired very easily when I am physically active.	Never	Rarely	Sometimes	Often	Always
9. I feel pain all over my body.	Never	Rarely	Sometimes	Often	Always
10. I have headaches.	Never	Rarely	Sometimes	Often	Always
11. I feel discomfort in my bladder and/or burning when I urinate.	Never	Rarely	Sometimes	Often	Always
12. I do not sleep well.	Never	Rarely	Sometimes	Often	Always
13. I have difficulty concentrating.	Never	Rarely	Sometimes	Often	Always
14. I have skin problems such as dryness, itchiness, or rashes.	Never	Rarely	Sometimes	Often	Always
15. Stress makes my physical symptoms get worse.	Never	Rarely	Sometimes	Often	Always
16. I feel sad or depressed.	Never	Rarely	Sometimes	Often	Always
17. I have low energy.	Never	Rarely	Sometimes	Often	Always
18. I have muscle tension in my neck and shoulders.	Never	Rarely	Sometimes	Often	Always
19. I have pain in my jaw.	Never	Rarely	Sometimes	Often	Always
20. Certain smells, such as perfumes, make me feel dizzy and nauseated.	Never	Rarely	Sometimes	Often	Always
21. I have to urinate frequently.	Never	Rarely	Sometimes	Often	Always
22. My legs feel uncomfortable and restless when I am trying to go to sleep at night.	Never	Rarely	Sometimes	Often	Always
23. I have difficulty remembering things.	Never	Rarely	Sometimes	Often	Always
24. I suffered trauma as a child.	Never	Rarely	Sometimes	Often	Always
25. I have pain in my pelvic area.	Never	Rarely	Sometimes	Often	Always
Subtotal					

Total = _____

Image Credit: Roberts et al, Central Sensitization: Common Etiology In Somatoform Disorders

(MedCentral, 2014)[34]

It is thought that the reason for poor efficacy of external opioids may be related to a reduction of internal or endogenous opioid receptors within the nervous system, particularly mu opioid receptors. Other studies show higher levels of glutamate, the CNS's primary excitatory neurotransmitter, in certain brain regions, as well as low levels of the CNS's primary inhibitory neurotransmitter GABA. Brain imaging studies reveal clear evidence that the brain itself demonstrates structural, chemical, and functional alterations, substantiating that central sensitization and its related pain conditions caused in full or in part by these underpinning mechanisms are "real."[2]

Central sensitization is prevalent in many conditions to varying degrees. Some researchers have proposed a model that splits the condition into two subgroups for better classification: those who are "bottom-up" whose pain processing is amplified and who these researchers consider the "traditional central sensitization" being driven by ongoing nociceptive input; and those who are "top-down" whose main dysfunction is likely coming from within the brain itself and does not require ongoing nociceptive input to maintain the sensitization.[2, 5, 6, 7]

These researchers suggest the broader continuum of both bottom-up and top-down subgroups be renamed centralized pain, while the bottom-up group retains the central sensitization diagnosis and the top-down group gets a new term of central hypersensitivity.[2] They propose making this distinction will assist in pursuing proper treatment modalities, as those whose sensitization is maintained by peripheral nociceptive inputs would require aggressively treating those inputs to reduce them so the nervous system has the opportunity to eventually desensitize, whereas those with the top-down version would require interventions focused on the central nervous system. Many individuals likely have a combination-type of centralized pain and would need both peripherally- and centrally-focused approaches.

Central sensitization plays a critical role in maintaining CRPS, especially for those with widespread pain.[8, 9, 10, 11, 12] In 2022, a new classification for disorders was added to the ICD-11: Chronic Primary Pain;[13] CPP is the parent classification header for specific diagnoses, such as CRPS, that are maintained by centralized pain or by inefficient or dysfunctional internal opioid or pain inhibition systems.[14] CRPS's pathological mechanisms are also influenced by additional factors, including inflammation, immune alterations, brain changes outside of those within the standard view of central sensitization, genetic predisposition, and psychological state;[13] while centralized pain does appear to dominate in persistent CRPS cases, the "bottom-up" factors should not be ignored, particularly earlier in onset.

The CRPS Severity Score (CSS) is a 16-point measurement tool that can be utilized to help determine the degree of the syndrome based on a more specific counting of the eight diagnostic standards in the Budapest Criteria, both self-reported and observed; a higher score indicates the presence of more CRPS symptoms. Higher CSS scores were associated with both higher pain hypersensitivity and greater psychological distress, particularly

depression.[7, 14] Research reveals that the same pathways responsible for pain processing, amplification, modulation, and chronicity are also responsible for emotional processing, interoception, body awareness, and integrated pain; this creates an association between pain and emotional suffering, and an influence of pain on emotional distress and emotional distress on pain that is dependent on the degree of central sensitization and where a person falls on that continuum.[14] In CRPS, particularly for those with persistent cases and high severity scores, pain and emotional distress directly influence each other because they operate on the same brain pathways due to the sensitization of the central nervous system.

Table 2

CRPS severity score CSS.

Self-reported symptoms
Continuing disproportionate pain
Allodynia or hyperalgesia
Temperature asymmetry
Skin color asymmetry
Sweating asymmetry
Asymmetric edema
Trophic changes
Motor changes
Signs observed on examination
Hyperalgesia to pinprick
Allodynia
Temperature asymmetry
Skin color asymmetry
Sweating asymmetry
Asymmetric edema
Trophic changes
Motor changes

The maximum CSS score is 16. Every symptom and sign is counted with a score of 1.
CSS, CRPS severity score.

Image Credit: Birklein, Dimova, Complex regional pain syndrome–up-to-date (Pain Reports, 2017)

Practical Application

- Treatment recommendations for centralized pain should focus on long-term rather than short-term effects and include working within a biopsychosocial model of health and wellness and pursue a multimodal approach to target multiple mechanisms that are not sufficiently effective when working alone as monotherapies.[15]
- Several pharmacological approaches that have shown some effectiveness for

centralized pain, which are best utilized in some method of combined approached tailored to individual patient needs, include: SSRIs, SNRIs, NRIs, tricyclic antidepressants, gabapentinoids and other anti-convulsants, opioid agonists, the opioid antagonist naltrexone, the NMDA antagonist ketamine, beta antagonists, cannabidiol, HRT with testosterone, topical analgesics, and NSAIDs. Some of these are "top-down" focused while others are "bottom-up"; all of them can have adverse effects for some individuals, particularly the gabapentinoid class.[5, 16, 17, 18, 19, 20] Opioid agonists are another controversial medication class for centralized pain disorders, especially when it comes to long-term use, as they can further suppress a person's own internal opioid production and create a phenomenon known as opioid-induced hyperalgesia.[21, 22, 23]

- Non-pharmacological interventions include: transcutaneous electric nerve stimulation (TENS), repetitive Transcranial Magnetic Stimulation (rTMS), transcranial Direct Current Stimulation (tDCS), spinal cord stimulation (SCS), dorsal root ganglion stimulation (DRG), virtual reality (VR), manual therapy, graded exercise rehabilitation, sleep management, stress management, neuroscience education, and dietary intervention.[5, 15, 16, 17, 18, 19] Another non-invasive, electrostimulation approach that shows some promise for nociplastic and neuropathic pains is scrambler therapy, though it needs further study particularly in regards to nociplastic centralized pain.[24, 25, 26, 27, 28]
- Desensitization (a topic which will receive its own article in the future) or graded exposure are similar techniques to gradually turn down the hypersensitivity of the nervous system over time to reduce the overall intensity of pain and help a person create space for tolerating discomfort and unpleasant sensations so that the individual can have more functionality and independence even if pain remains a present part of daily life.[5] There are a few main approaches to desensitization, and it is my personal opinion that if not engaged with in a mindful manner that takes into account the neurobiological protective function of the sympathetic nervous system, particularly as it relates to CRPS, desensitization can further engrain pain and fear responses instead of reducing them. Desensitization's goal is about being able to tolerate things, even if they are unpleasant, without them causing such an extreme reaction that the individual cannot withstand the stimulus. It is meant to start low and slow and only once the hypersensitive area has begun to tolerate the current stimulus should the next, more intense stimulus be incorporated. Going too hard too fast for too long is detrimental and counterproductive for this treatment modality. The goal is to convince the body that while something may be uncomfortable, it isn't harmful; if a person is going outside of their window of tolerance (outside of the zone where they can emotionally regulate and healthily process even during challenging situations) during desensitization sessions, then the body registers that as a threat and the individual has moved beyond the neurobiological realm of safety they are trying to retrain and expand for the nervous system.
- Some cognitive therapies that have shown statistically significant results in assisting with managing and living with chronic pain caused by central sensitization are cognitive behavioral therapy (CBT), acceptance and commitment therapy (ACT), and mindfulness-based therapies (MBT), such as mindfulness-based stress reduction (MBSR),

mindfulness-based cognitive therapy (MBCT), and dialectical behavioral therapy (DBT).[19]

- Low dose naltrexone (LDN) is a medication that causes a small, temporary opioid blockade, encouraging the body to increase its own production of internal opioids and to increase its opioid receptors, which is where the real benefit comes for those who have an insufficient amount of receptors to provide appropriate pain relief. It also "turns down" the brain's immune cells, the microglia, assisting in the immune component for those whose microglia turn on healthy neural tissue. LDN has shown to decrease pain scores, improve mood, increase sleep, and improve functionality and quality of life in a majority of patients who take it; however, while 65% of patients reported benefits from taking LDN, 36% discontinued the medication and 11% reported adverse effects. LDN is generally well-tolerated with no major adverse effects and no known potential for abuse; the most commonly reported adverse effects are a period of vivid dreams, headaches, and diarrhea upon starting the medication. The dosage for chronic pain management generally ranges from 0.2-10mg, with the most common dose being 4.5mg. While LDN is inexpensive, it is often prescribed at doses that require compounding pharmacies to create it and may need to be covered out of pocket.[29, 30, 31, 32, 33]

Closing

Centralized pain plays a significant role in CRPS and many other conditions. It is a legitimate phenomenon that, while unseen, offers insight into many experiences that may seem disproportionate or unrelated. Centralized pain can have wide-reaching impacts that affect every area of life and can be difficult to treat, particularly for those with the top-down subtype. While stacking several treatment modalities over time for a long-term result of gradual desensitization to partial or complete remission is crucial for improved quality of life, first understanding what is going on so that a person can know what needs to be addressed, what options are available, and that they are experiencing a legitimate condition makes education an essential step for individuals to be able to make informed decisions in their own best interest.

Thanks for sticking with me, I hope you learned something, and I hope to see you next time.

References

1. Woolf, Central sensitization: Implications for the diagnosis and treatment of pain (Pain, 2010) ↩
2. Harte et al, The neurobiology of central sensitization (Applied Journal of Biobehavioral Research, 2018) ↩
3. Latremoliere, Woolf, Central Sensitization: A Generator of Pain Hypersensitivity by Central Neural Plasticity (Journal of Pain, 2009) ↩
4. Nijs et al, Central sensitisation in chronic pain conditions: latest discoveries and their potential for precision medicine (The Lancet Rheumatology, 2021) ↩
5. Nijs et al, Recognition and Treatment of Central Sensitization in Chronic Pain Patients:

Not Limited to Specialized Care (Journal of Orthopaedic & Sports Physical Therapy, 2016) ↩
6. Nijs et al, Central sensitisation in chronic pain conditions: latest discoveries and their potential for precision medicine (The Lancet Rheumatology, 2021) ↩
7. van Greinsven et al, Central Sensitization in Musculoskeletal Pain: Lost in Translation?, (Journal of Orthopaedic & Sports Physical Therapy, 2020) ↩
8. Shoenmacker et al, Central sensitization in CRPS patients with widespread pain: a cross-sectional study (Pain Medicine, 2023) ↩
9. Drummond, Sensory Disturbances in Complex Regional Pain Syndrome: Clinical Observations, Autonomic Interactions, and Possible Mechanisms (Pain Medicine, 2010) ↩
10. Wiemann et al, Evidence for converging pathophysiology in complex regional pain-syndrome and primary headache disorders: results from a case–control study (Journal of Neurology, 2023) ↩
11. Eldufani et al, A medical mystery of complex regional pain syndrome (Heliyon, 2020) ↩
12. Devarajan et al, Mechanisms of complex regional pain syndrome (Frontiers in Pain Research, 2024) ↩
13. Barke et al, Chronic Pain in the ICD-11: New Diagnoses That Clinical Psychologists Should Know About (Clinical Psychology in Europe, 2022) ↩
14. Karpin et al, Central Sensitization and Psychological State Distinguishing Complex Regional Pain Syndrome from Other Chronic Limb Pain Conditions: A Cluster Analysis Model (Biomedicines, 2023) ↩
15. Nijs et al, Treatment of central sensitization in patients with chronic pain: time for change? (Expert Opinion on Pharmacotherapy, 2019) ↩
16. Nijs et al, Treatment of central sensitization in patients with ‘unexplained’ chronic pain: an update (Expert Opinion on Pharmacotherapy, 2014) ↩
17. White, Robinson, A novel use for testosterone to treat central sensitization of chronic pain in fibromyalgia patients (International Immunopharmacology, 2015) ↩
18. Nijs et al, Treatment of central sensitization in patients with ‘unexplained’ chronic pain: what options do we have? (Expert Opinion on Pharmacotherapy, 2011) ↩
19. Nijs et al, Sleep disturbances and severe stress as glial activators: key targets for treating central sensitization in chronic pain patients? (Expert Opinion on Therapeutic Targets, 2017) ↩
20. Bazzari, Bazzari, Advances in targeting central sensitization and brain plasticity in chronic pain (The Egyptian Journal of Neurology, Psychiatry and Neurosurgery, 2022) ↩
21. Higgins et al, Evidence of opioid-induced hyperalgesia in clinical populations after chronic opioid exposure: a systematic review and meta-analysis (British Journal of Anaesthesia, 2019) ↩
22. Sampaio-Cunha, Martins, Knowing the Enemy Is Halfway towards Victory: A Scoping Review on Opioid-Induced Hyperalgesia (Journal of Clinical Medicine, 2022) ↩
23. Wilson et al, Mechanisms, diagnosis, prevention and management of perioperative opioid-induced hyperalgesia (Pain Management, 2021) ↩
24. D’Amato et al, Scrambler Therapy for the Treatment of Chronic Central Pain: A Case

Report (A & A Practice, 2018) ↩
25. Majithia et al, Scrambler Therapy for the management of chronic pain (Support Cancer Care, 2016) ↩
26. Marineo et al, Scrambler Therapy May Relieve Chronic Neuropathic Pain More Effectively Than Guideline-Based Drug Management: Results of a Pilot, Randomized, Controlled Trial (Journal of Pain and Symptom Management, 2012) ↩
27. Russo et al, Scrambler therapy in the management of somatosensory signs and symptoms related to neuropathic pain: an exploratory and prospective analysis (Acta Biomedica, 2018) ↩
28. Min et al, Differential response to scrambler therapy by neuropathic pain phenotypes (Scientific Reports, 2021) ↩
29. Younger et al, The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment for chronic pain (Clinical Rheumatology, 2014) ↩
30. Rupp et al, Low-dose naltrexone's utility for non-cancer centralized pain conditions: a scoping review (Pain Medicine, 2023) ↩
31. Noon et al, A novel glial cell inhibitor, low dose naltrexone, reduces pain and depression, and improves function in chronic pain: A CHOIR study (Journal of Pain, 2016) ↩
32. Chopra, Cooper, Treatment of Complex Regional Pain Syndrome (CRPS) Using Low Dose Naltrexone (LDN) (Journal of Neuroimmune Pharmacology, 2013) ↩
33. Driver, D'Souza, Efficacy of Low-Dose Naltrexone and Predictors of Treatment Success or Discontinuation in Fibromyalgia and Other Chronic Pain Conditions: A Fourteen-Year, Enterprise-Wide Retrospective Analysis (Biomedicines, 2023) ↩

34. Roberts et al, Central Sensitization: Common Etiology In Somatoform Disorders (MedCentral, 2014)

