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ALTERNATIVE TREATMENTS FOR PAIN MEDICINE (M JONES, SECTION EDITOR)

Novel Therapies for Centralized Pain: a Brief Review

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Abstract

Purpose of Review Centralized pain presents a complex pathology that many classic pharmacological agents for pain have not been able to sufficiently treat. To date, there are no clear guidelines for preferred treatment methods or comprehensive protocol that addresses confounding factors in this population. We sought to summarize the current field of knowledge around centrally mediated pain and to understand promising novel therapies.

Recent Findings Many treatments currently used address not only the centralized pain phenotypem but the impact of central sensitization and the common comorbidities that reside within this population. Some novel therapies with promising evidence include the following: low-dose naltrexone, IV ketamine, acupuncture, aerobic activity, and laser therapy. Non-interventional treatment options include aerobic exercise, cognitive-behavioral therapy, mind–body therapies, virtual reality, and patient education on disease expectations. Much of the literature further emphasizes the importance of patient-level predictors, including factors like pain catastrophizing and social history, on treatment compliance and reported pain relief.

Summary We found that there are many potential treatment options for patients with centralized pain, particularly those that can be used as adjunct or combination therapies. The introduction of new approaches should occur in a carefully controlled, titrated manner to avoid exacerbation of pain symptoms. This is successfully conducted through patient-physician communication as this is a highly complex and personalized pain category. Our examination shows that while physicians have many options with proven success, there is a need for studies with longitudinal and larger patient populations to better articulate treatment guidelines.

Keywords Centralized pain · Central sensitization · Nocioplastic pain · Low-dose naltrexone · Cognitive-behavioral therapy · Patient education

Introduction

Centralized pain includes any pain that stems from the central nervous system or is amplified by the central nervous system. This can be caused by environmental stressors, chronic pain conditions, severe infections, or psychological stressors. The biological basis and hereditary connection with these types of pain diagnoses have also been proven through the analysis of genetic mutations, bio-imaging studies, and twin studies [1]. Of significant note, many patients with centralized pain are unresponsive to surgical procedures or opioid medications [2].

The three main types of pain include neuropathic, nociceptive, and nociplastic pain. Neuropathic pain refers to dysfunction from confirmed disease or lesion in the nervous system, often classified by burning pain [3]. Nociceptive pain is generally related to trauma or injury that may resolve upon tissue healing [4]. This type of pain features inflammation and is worsened by movement. Nociplastic pain is pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain. It involves some level of hypersensitivity to non-noxious stimuli and is the basis for centralized pain states [5].

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There are several common co-occurring conditions for these patients, such as anxiety, depression, migraine headaches, dysmenorrhea, temporomandibular joint disorder (TMJD), chronic fatigue, irritable bowel syndrome (IBS), and other functional gastrointestinal (GI) disorders, interstitial cystitis/painful bladder syndrome, endometriosis, and other regional pain syndromes (especially back and neck pain). In fact, the phenotype of central pain often includes earlier episodes of acute pain or the occurrence of other (non-pain) symptoms or pain conditions [2]. For example, when looking at the change in diagnostic criteria in fibromyalgia from the 1990 America College of Rheumatology criteria to the 2011 survey, patients were now asked more about fatigue, sleep, memory, headaches, irritable bowel, and mood [2].

In many patients with chronic pain, central sensitization can explain why they suffer from pain in the absence of a clear origin of nociceptive input or in the absence of enough tissue damage to explain the experienced pain severity, disability, and other symptoms [2, 6]. It can be understood as a form of amplification of perceived signals, such that there is a continuum of altered nociceptive processing mechanisms in which greater symptoms of a certain condition are accompanied by more profound change [6]. Central sensitization is a well-established feature in patients with chronic traumatic neck pain (i.e., whiplash), fibromyalgia, osteoarthritis, migraine, irritable bowel syndrome, chronic fatigue syndrome, and pediatric pain conditions [6, 7]. By contrast, central sensitization is only present in a small subgroup of patients having conditions like acute low back pain, non-traumatic neck pain, tendinopathies, shoulder pain, and rheumatoid arthritis [6, 7].

One biological contributor to central sensitization may be increased glial activity. Activated microglia synthesizes and releases neurotrophic factors, which in turn increases neuronal excitability [2, 8]. Specifically, the increased availability of tumor necrosis factor-α (TNF-α) results in subsequent long-term potentiation and enhanced synaptic activity [2]. These are key mechanisms underlying central sensitization in patients with chronic pain, including chronic non-specific low back pain, fibromyalgia, and chronic lumbar radiculopathy pain [2, 8]. Aberrant glial activity also causes astrocyte activation in the central nervous system which leads to the production of proinflammatory substances by hypertrophied and activated astrocytes, with microglial cells possibly responding earlier than astrocytes [2, 8].

Patients with centrally mediated pain present a complex pathology that is still trying to be understood. The changing treatment options and the current lack of specified protocols to treat these patients are reflective of that.

Current Therapies

To date, pharmacological treatments have been only modestly successful in treating centrally mediated pain, partly due to being unresponsive in addition to generally having more severe side effects with this "pain-prone phenotype" [2, 6, 7].

Selective serotonin reuptake inhibitor drugs activate serotonergic descending pathways that may partially activate opioid peptide-containing interneurons in the dorsal horn [8]. Serotonin noradrenaline reuptake inhibitors are more effective than inhibiting serotonin alone, and these medications have been found to be more effective in treating otherwise difficult to treat painful conditions, including those associated with central sensitization [8].

Gabapentinoids bind to the α2δ subunit of voltage-gated calcium channels, which results in decreased Ca2 + influx during depolarization and decreased release of excitatory substances such as glutamate, noradrenaline, and substance P in the dorsal horn [8]. They have proven efficacy in reducing symptoms of central sensitization and hyperalgesia in both neuropathic and nociceptive pain stimulus; however, side effects often limit efficacy [9–11].

Opioids

The use of opioids, while currently less commonly prescribed than in years past, remains out of favor. In Clauw's 2014 review, he rated opioids as the least effective treatment due to their low efficacy and potential for adverse side effects [2]. The potential for adverse side effects is also mediated by other factors for patients with centralized pain. Pierce et al. found that these patients were more likely to report more adverse side effects to medication if they had a history of abuse, with the most significant effect from those who suffered from both childhood and adult abuse [7].

Novel Therapies

Low-Dose Naltrexone

Naltrexone was created as a mu opioid antagonist which is currently approved for use in treating opioid and alcohol dependence. It is commonly being used now for patients unresponsive to opioid treatments, potentially due to endogenous opioid systems at very low doses [2, 6]. Opioid medications have been shown in rats to induce Toll-like receptor 4 (TLR4) signaling, which can lead to

opioid-induced proinflammatory effects. In very small doses, both rat and in vitro studies have shown that naltrexone can inhibit this proinflammatory pathway by inhibiting TLR4 signaling [2, 6, 12].

Naltrexone inhibits production of the proinflammatory cytokine interleukin (IL)-6 and tumor necrosis factor (TNF)-alpha as well as inflammatory factor nitric oxide (NO) by inhibiting TLR4 signaling, which contributes to decreased pain sensation via processing of nociceptive signals [2, 6, 12]. The reduction in IL-6 and TNF-alpha has been shown in vitro and in vivo to result in a reduction of a variety of other cytokines implicated in central sensitization [2, 6, 12].

TLR4 is more prevalent on microglia than it is on astrocytes, which may suggest that LDN could have use as a potential immunomodulatory through the suppression of the innate immune cells of the nervous system [2, 6, 12]. This effect on microglia corresponds to the implication of microglial activation in those with chronic pain states, including those associated with centralized pain.

These proposed mechanisms of action suggest that LDN may operate as a novel nervous system anti-inflammatory and immunomodulator. Additionally, through the modulation of pain perception and sensitivity, LDN may also serve as a powerful analgesic. Immunomodulatory effects are suggested to help with inflammatory and autoimmune conditions, such as multiple sclerosis, Crohn's disease, ulcerative colitis, and SLE.

IV Ketamine

Ketamine exerts its analgesic and antidepressant effects via myriad pathways. Its primary mechanism is as a noncompetitive antagonist of N-methyl-D-aspartate (NMDA) receptors residing in the central nervous system (CNS), particularly those located in the prefrontal cortex and hippocampus [13–16].

The NMDA receptor is a ligand-gated channel whose major agonist is glutamate, the predominant excitatory neurotransmitter in the CNS; when this receptor is inhibited, decreased neuronal activity ensues [13–16]. Activation of this NMDA channel plays a key role in mood, pain perception, cognition, and opioid tolerance, and it is thought to be the principal receptor involved in phenomena of central sensitization and windup [13–16]. In other words, Ketamine seeks to "reboot" the systems responsible for the cycle of chronic pain.

Ketamine also has rapidly apparent antidepressant effects thought to also be a function of NMDA receptor modulation [13–16].

The dosing and specific protocols for IV ketamine use vary significantly, indicating that larger studies need to be completed in order to fully assess its use in treating chronic pain.

Acupuncture

There is conflicting evidence on the efficacy of acupuncture in treating chronic pain, particularly fibromyalgia [17–22]. There is low to moderate–level evidence that compared with no treatment and standard therapy, acupuncture improves pain and stiffness in people with fibromyalgia, while there is less evidence on the effect of acupuncture compared to sham acupuncture in reducing pain or fatigue, improving sleep, or global well-being.

Electroacupuncture is probably better than traditional acupuncture for pain and stiffness reduction and improvement of global well-being, sleep, and fatigue [23]. The effect lasts up to one month but is not maintained at 6 months follow-up.

Acupuncture appears safe. People with fibromyalgia may consider using electroacupuncture alone or with exercise and medication. The small sample size, scarcity of studies for each comparison, and the lack of an ideal sham acupuncture weaken the level of evidence and its clinical implications. Larger studies are warranted.

Aerobic Activity

Aerobic activity and strength training have been consistently shown to be a vital component of any centralized pain treatment protocol [20, 24–30]. addition to pain relief, exercise also helps to improve quality of life and functioning, which may in turn help alleviate some of the psychological factors in chronic pain [31]. This activity can be land- or water-based activity with slight to moderate intensity, two or three times per week at a minimum as according to the EULAR guidelines and Cochrane reviews [2, 26, 29].

For adults with fibromyalgia, studies have found that stretching exercises provides the greatest pain relief and increased functioning, though interestingly resistance training helps mental health status [27, 32, 33]. Bidonde et al.'s Cochrane review found that mixed exercise training may not provide clinically significant improvement for fibromyalgia patients [34].

Exercise must be carefully graduated and patients should be monitored for symptom exacerbation [34]. The most significant adverse effect from beginning exercise is the potential for symptoms to worsen when beginning training. This is often alleviated by the use of medications when beginning these programs [2].

Laser Therapy

Low-level laser therapy is now frequently being used for pain management, often in fibromyalgia patients, with positive effects [35, 36].

The analgesic effect of PBM has been reported to involve A-delta and C fibers. Low-power laser irradiation promotes proliferation of multiple cells primarily through the activation of mitochondrial respiratory chain and the consequent initiation of cellular signaling [37]. This includes leading to the activation of TPKR, which can go on to activate its downstream signaling elements, like Ras/Raf/MEK/ERK, PI3K/Akt/eIF4E, PI3K/Akt/eNOS, and PLC-gamma/PKC pathways [36–37].

Low-power laser irradiation also induces an immediate increase in mitochondrial membrane potential and ATP. [35–38, 39, 37]. This cascade potentially results in increased cell proliferation and inflammatory modulation. Specifically, it helps regulate the activity of HIF-1α in neuropathic inflammation and peripheral nerve repair through decreasing cytokines and HIF-1α levels while increasing relevant growth factor secretions [38]. This was further verified through improvement in pain relief and functional abilities.

Alternative/Complimentary Treatments

As pharmacological and interventional treatment becomes less effective and preferred, biopsychosocial approaches have become increasingly used to help treat central pain. Hawk et al. helped develop clinical practice guidelines with a 62-member Delphi panel reviewing the current substantive literature and clinical experience [40]. They emphasized using multidisciplinary approaches focused on treating, rather than curing pain conditions.

Additional therapies, like the use of TENS and heat, have evidence-based and research support for pain relief due to decreasing inflammatory reactions at specific painful sites [41].

Mind–Body Therapies

The mind–body connection is of particular emphasis to decrease pain levels and increase functioning across a variety of etiologies, such as with therapies like mindfulness training and osteopathic manipulative treatment [22, 42, 43]. This impact is deepened when integrative health is offered by or working in conjunction with physicians [44]. For example, Tai Chi has been found to have a greater impact on pain relief and quality of life compared to traditional exercise [45].

Therapy

Pain catastrophizing scores have been widely used in clinical and research settings as a way to quantify the potential for patients to have a heightened reaction to pain. Cognitive behavioral therapy (CBT) has been shown to be an important clinical tool for patients with a history of this.

Different forms of therapy are also important due to the connections between a history of abuse and chronic pain [6, 7, 46, 47]. Previous studies have shown that patients with a history of abuse are more likely to have more widespread symptoms and potentially increased healthcare utilization [7, 48]. Some other biological basis stems from hyperalgesia and difficulties modulating spinal nociception as proven when studying pain in those with and without previous adverse life events [49, 50].

This also harkens to the aforementioned text discussing central sensitization and peripheral nociceptive input as these patients are also more likely to have increased symptom load and worse adverse reactions to treatment. This is partly confounded by the frequency of mental health comorbidities in this population as some disorders, like anxiety, have been shown to make this phenotype worse or can present this feature prior to a pain diagnosis [6, 43, 51]. These multifactorial relationships are why alternative forms of treatment, like CBT, are critical in this population.

Education

In addition to the understanding and sense of control that can come from CBT or general therapy, education has been shown to play a significant role in chronic pain [6, 30, 40]. Upon receiving a diagnosis, even if they have not yet had successful treatment, patients may have a rapid decline in health utilization as they are no longer searching through different physicians to find an answer to what is causing their pain. This change in mindset from diagnosis to treatment both allows for better education as to the reasons and potential treatments for the pain, especially in having the patient understand the limitations of currently available treatments. When combining this with many options for both pharmaceutical and particularly non-pharmaceutical options for therapy, the shift of control back to the patient may increase the likelihood of the placebo effect relieving some of their pain [2].

Virtual Reality

Virtual reality (VR) is increasingly being studied as a method to help chronic pain patients with a variety of diagnoses. Integration of rehabilitation strategies with VR, including

more efficient graded exposure exercises, has been shown to reduce pain intensity and/or pain-related disability [52–57]. Some studies showed maintenance of pain during graded exercise programs, which is still significant for quality of life and ability to complete treatment options [58, 59]. The VERMONT trial further proved this point by comparing the walking distance of chronic pain patients with motor neglect using virtual environments compared to those without [60].

One common explanation for these therapeutic effects is that of embodiment. The illusion of control and ownership over one's virtual person, without pain, allows having tactile connections that is particularly important for amplifying the previously stated effects of VR [61, 62]. This treatment method has also been shown to improve kinesiophobia, which often is a significant deterrent for engaging and complying with recommendations for exercise [53, 58, 59, 63].

Another aspect of VR is that of gamification, in which report lower pain ratings due to the fun, distractable nature of a simulated game as well as the short-term goal-setting focus of games [64, 65]. Most effective when used in combination with first-person games or colocation embodiment techniques, the immersive experience can modulate sensory signals to aid in pain relief [65]. This has also been aptly labelled as a way of "recontextualizing sensory feedback" [52]. Important to note as well is that the distraction was the effect regardless of pain catastrophizing ratings or pain level [64].

Matamala-Gomez et al. reviewed clinical and experimental literature for the analgesic effect of VR in chronic pain patients with the most effective methods including colocation of the physical and virtual body, having the virtual body correct or overcompensate for common perceptual distortions of pain locations (based on personal pain phenotype), and a multisensory experience (i.e., auditory cues in addition to visual ones) [66]. One such multisensory experience involved heartbeat-enhanced VR where flashes on the painful limb in the virtual environment that were synchronous to the patient's own heartbeat led to reduced pain rating and increased motor function [67].

VR should be used in combination with traditional therapies and with attention to pain etiology for optimized analgesic effect [53, 57, 62, 68]. Cerritelli et al. found that the combination of manual therapies allowed for a more comprehensive approach that engaged parasympathetic tone and tactile movement to enhance the visual and auditory aspects of VR [62]. This alternative, non-invasive treatment offers potential success for pain relief and improved quality of life with little side effect for patients with centralized pain.

Patient Predictors

Many of these complimentary treatments involve more individualized treatment to attain the best outcome in patients with often complicated and multifaceted pathologies. Pierce et al. describe the importance of "patient-level predictors," including abuse history, in predicting and understand the effects of prescribed treatments for patients with centralized pain [7]. Other forms of testing, such as muscle strength, may also be indicators of disease progression and response [69]. Pain etiology, comorbidities, and pain catastrophizing all present unique barriers towards achieving pain relief in patients with centrally mediated pain [2, 6].

Conclusions

While we have summarized the recent findings in treatment options for centrally mediated pain, there is clearly a strong need for more research. Non-interventional treatment options with proven efficacy include aerobic exercise, cognitive-behavioral therapy (or any connection with a mental health professional), and patient education on disease expectations. The introduction of activity should be titrated to avoid relapse in pain levels. The use of interventions should only be chosen when there is a clear indication, and other factors should be considered like financial constraints, patient support system, and pain catastrophizing. Some first-line options include SNRI/SSRIs and low-dose naltrexone. All medications should be started at a low dose and increased slowly over time. If refractory to more conservative measures, IV ketamine and laser treatment may be used. Regardless of the treatment chosen, communication with therapy staff is vital for treatment compliance and patient success.

Declarations

Conflict of Interest Paul Ryan Haffey and Jade I Basem declare no conflict of interest.

Human and Animal Rights and Informed Consent. This article does not contain any studies with human or animal subjects performed by any of the authors.

References

1. Harris RE, Clauw DJ. How do we know that the pain in fibromyalgia is "real"? Curr Pain Headache Rep. 2006;10:403–7.
2. Clauw DJ. Fibromyalgia: a clinical review. JAMA. 2014;311:1547–55.
3. Treede RD, Jensen TS, Campbell JN, et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology. 2008;70:1630–5.
4. Armstrong SA, Herr MJ. Physiology, nociception. *StatPearls*. Treasure Island (FL): StatPearls Publishing Copyright © 2021, StatPearls Publishing LLC., 2021.
5. Fitzcharles MA, Cohen SP, Clauw DJ, Littlejohn G, Usui C, Häuser W. Nociplastic pain: towards an understanding of prevalent pain conditions. Lancet. 2021;397:2098–110.

6. Spiegel DR, Chatterjee A, McCroskey AL, et al. A review of select centralized pain syndromes: relationship with childhood sexual abuse, opiate prescribing, and treatment implications for the primary care physician. Health Serv Res Manag Epidemiol. 2015;2:2333392814567920.
7. Pierce J, Hassett AL, Schneiderhan JR, Divers J, Brummett CM, Goesling J. Centralized pain and pain catastrophizing mediate the association between lifetime abuse history and self-reported pain medication side effects. Reg Anesth Pain Med. 2020;45:293–300.
8. Nijs Jo, Leysen L, Vanlauwe J, Logghe T, Ickmans K, Polli A, Malfliet A, Coppieters I, Huysmans E. Treatment of central sensitization in patients with chronic pain: time for change? Expert Opin Pharmacother. 2019;20(16):1961–70. https://doi.org/10.1080/14656566.2019.1647166.
9. Gottrup H, Juhl G, Kristensen AD, et al. Chronic oral gabapentin reduces elements of central sensitization in human experimental hyperalgesia. Anesthesiology. 2004;101:1400–8.
10. Iannetti GD, Zambreanu L, Wise RG, et al. Pharmacological modulation of pain-related brain activity during normal and central sensitization states in humans. Proc Natl Acad Sci USA. 2005;102:18195–200.
11. Moore RA, Wiffen PJ, Derry S, McQuay HJ. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev. 2011;Cd007938.
12. Patten DK, Schultz BG, Berlau DJ. The safety and efficacy of low-dose naltrexone in the management of chronic pain and inflammation in multiple sclerosis, fibromyalgia, Crohn's disease, and other chronic pain disorders. Pharmacotherapy. 2018;38(3):382–9. https://doi.org/10.1002/phar.2086. (Epub 2018 Feb 23 PMID: 29377216).
13. Tauben D. Nonopioid medications for pain. Phys Med Rehabil Clin N Am. 2015;26(2):219–48. https://doi.org/10.1016/j.pmr.2015.01.005. (PMID: 25952062).
14. Orhurhu, Vwaire MD, MPH*; Orhurhu, Mariam Salisu MD, MPH†; Bhatia, Anuj MD, FRCPC‡; Cohen, Steven P. MD§,‖ Ketamine infusions for chronic pain: a systematic review and meta-analysis of randomized controlled trials, Anesthesia & Analgesia. 2019;129(1):241–254. https://doi.org/10.1213/ANE.0000000000004185.
15. Cohen SP, Bhatia A, Buvanendran A, et al. Consensus guidelines on the use of intravenous ketamine infusions for chronic pain from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Reg Anesth Pain Med. 2018;43(5):521–46.
16. Bell RF, Kalso EA. Ketamine for pain management Pain Rep. 2018;3(5): e674.
17. Kim J, Kim S-R, Lee H, Nam D-H. Comparing verum and sham acupuncture in fibromyalgia syndrome: a systematic review and meta-analysis. Evid Based Complement Alternat Med. 2019;8757685-This meta-analysis provides an nearly exhaustive representation of current data regarding the efficacy in the treatment of fibromyalgia.
18. Garrido-Ardila EM, González-López-Arza MV, Jiménez-Palomares M, García-Nogales A, Rodríguez-Mansilla J. Effects of physiotherapy vs. acupuncture in quality of life, pain, stiffness, difficulty to work and depression of women with fibromyalgia: a randomized controlled trial. J Clin Med. 2021;10: 3765.
19. Di Carlo M, Beci G, Salaffi F. Pain Changes Induced by Acupuncture in Single Body Areas in Fibromyalgia Syndrome: Results from an Open-Label Pragmatic Study. Evid Based Complement Alternat Med. 2021;9991144.
20. Garrido-Ardila EM, González-López-Arza MV, Jiménez-Palomares M, García-Nogales A, Rodríguez-Mansilla J. Effects of Physiotherapy vs. acupuncture in quality of life, pain, stiffness, difficulty to work and depression of women with fibromyalgia: a randomized controlled trial. J Clin Med. 2021;10.
21. Huang JF, Zheng XQ, Chen D, et al. Can acupuncture improve chronic spinal pain? A systematic review and meta-analysis. Global Spine J. 2021;11:1248–65.
22. Giannitrapani KF, Holliday JR, Miake-Lye IM, Hempel S, Taylor SL. Synthesizing the strength of the evidence of complementary and integrative health therapies for pain. Pain Med. 2019;20:1831–40.
23. Salazar AP, Stein C, Marchese RR, Plentz RD, Pagnussat AS. Electric stimulation for pain relief in patients with fibromyalgia: a systematic review and meta-analysis of randomized controlled trials. Pain Physician 2017;20:15–25. This meta-analysis provides a very thorough evaluation of the data regarding the effectiveness of electrical stimulation in this challenging patient population.
24. Andrade A, Dominski FH, Sieczkowska SM. What we already know about the effects of exercise in patients with fibromyalgia: An umbrella review. Semin Arthritis Rheum. 2020;50:1465–80.
25. Ketenci A, Evcik D, Sonel TB. What is the benefits flexibility exercise training for adults with fibromyalgia? A Cochrane review summary with commentary. Turk J Phys Med Rehabil. 2020;66:468–72.
26. Bidonde J, Busch AJ, Schachter CL, et al. Aerobic exercise training for adults with fibromyalgia. Cochrane Database Syst Rev. 2017;6:Cd012700.
27. Sato S, Ukimoto S, Kanamoto T, et al. Chronic musculoskeletal pain, catastrophizing, and physical function in adult women were improved after 3-month aerobic-resistance circuit training. Sci Rep. 2021;11:14939.
28. Hernando-Garijo I, Ceballos-Laita L, Mingo-Gómez MT, et al. Immediate effects of a telerehabilitation program based on aerobic exercise in women with fibromyalgia. Int J Environ Res Public Health. 2021;18.
29. Macfarlane GJ, Kronisch C, Dean LE, et al. EULAR revised recommendations for the management of fibromyalgia. Ann Rheum Dis. 2017;76:318–28.
30. Häuser W, Ablin J, Perrot S, Fitzcharles MA. Management of fibromyalgia: practical guides from recent evidence-based guidelines. Pol Arch Intern Med. 2017;127:47–56.
31. Izquierdo-Alventosa R, Inglés M, Cortés-Amador S, et al. Low-intensity physical exercise improves pain catastrophizing and other psychological and physical aspects in women with fibromyalgia: a randomized controlled trial. Int J Environ Res Public Health. 2020;17.
32. Assumpção A, Matsutani LA, Yuan SL, et al. Muscle stretching exercises and resistance training in fibromyalgia: which is better? A three-arm randomized controlled trial. Eur J Phys Rehabil Med. 2018;54:663–70.
33. Vilarino GT, Andreato LV, de Souza LC, Branco JHL, Andrade A. Effects of resistance training on the mental health of patients with fibromyalgia: a systematic review. Clin Rheumatol. 2021;40:4417–25.
34. Bidonde J, Busch AJ, Schachter CL, et al. Mixed exercise training for adults with fibromyalgia. Cochrane Database Syst Rev. 2019;5:Cd013340.
35. Ruaro JA, Fréz AR, Ruaro MB, Nicolau RA. Low-level laser therapy to treat fibromyalgia. Lasers Med Sci. 2014;29:1815–9.
36. Kholoosy L, Elyaspour D, Akhgari MR, Razzaghi Z, Khodamardi Z, Bayat M. Evaluation of the therapeutic effect of low level laser in controlling low back pain: a randomized controlled trial. J Lasers Med Sci. 2020;11:120–5.
37. Gao X, Xing D. Molecular mechanisms of cell proliferation induced by low power laser irradiation. J Biomed Sci. 2009;16(1):4. Published 2009 Jan 12. https://doi.org/10.1186/1423-0127-16-4.
38. Hsieh YL, Chou LW, Chang PL, Yang CC, Kao MJ, Hong CZ. Low-level laser therapy alleviates neuropathic pain and promotes function recovery in rats with chronic constriction injury: possible

involvements in hypoxia-inducible factor 1α (HIF-1α). J Comp Neurol. 2012;520:2903–16.
39. Maher DP, Chen L, Mao J. Intravenous ketamine infusions for neuropathic pain management: a promising therapy in need of optimization. Anesth Analg. 2017;124(2):661–74.
40. Hawk C, Whalen W, Farabaugh RJ, et al. Best practices for chiropractic management of patients with chronic musculoskeletal pain: a clinical practice guideline. J Altern Complement Med. 2020;26:884–901.
41. Honda Y, Sakamoto J, Hamaue Y, et al. Effects of physical-agent pain relief modalities for fibromyalgia patients: a systematic review and meta-analysis of randomized controlled trials. Pain Res Manag. 2018;2930632.
42. Skelly AC, Chou R, Dettori JR, et al. Noninvasive Nonpharmacological Treatment for Chronic Pain: A Systematic Review. Agency for Healthcare Research and Quality (US), Rockville (MD), 2018.
43. Galvez-Sánchez CM, Montoro CI, Duschek S, Del Paso GAR. Pain catastrophizing mediates the negative influence of pain and trait-anxiety on health-related quality of life in fibromyalgia. Qual Life Res. 2020;29:1871–81.
44. Urits I, Schwartz RH, Orhurhu V, et al. A Comprehensive Review of Alternative Therapies for the management of chronic pain patients: acupuncture, Tai Chi, osteopathic manipulative medicine, and Chiropractic care. Adv Ther. 2021;38:76–89.
45. Wang C, Schmid CH, Fielding RA, et al. Effect of tai chi versus aerobic exercise for fibromyalgia: comparative effectiveness randomized controlled trial. BMJ. 2018;360: k851.
46. Nicol AL, Sieberg CB, Clauw DJ, Hassett AL, Moser SE, Brummett CM. The association between a history of lifetime traumatic events and pain severity, physical function, and affective distress in patients with chronic pain. J Pain. 2016;17:1334–48.
47. Lumley MA, Schubiner H. Psychological therapy for centralized pain: an integrative assessment and treatment model. Psychosom Med. 2019;81:114–24.
48. Alexander RW, Bradley LA, Alarcón GS, et al. Sexual and physical abuse in women with fibromyalgia: association with outpatient health care utilization and pain medication usage. Arthritis Care Res. 1998;11:102–15.
49. Hellman N, Kuhn BL, Lannon EW, et al. Emotional modulation of pain and spinal nociception in sexual assault survivors. Psychosom Med. 2018;80:861–8.
50. Kell PA, Hellman N, Huber FA, et al. The relationship between adverse life events and endogenous inhibition of pain and spinal nociception: findings from the oklahoma study of native American pain risk (OK-SNAP). J Pain. 2021;22:1097–110.
51. Spiegel DR, Shaukat AM, McCroskey AL, et al. Conceptualizing a subtype of patients with chronic pain: the necessity of obtaining a history of sexual abuse. Int J Psychiatry Med. 2016;51:84–103.
52. Trujillo MS, Alvarez AF, Nguyen L, Petros J. Embodiment in virtual reality for the treatment of chronic low back pain: a case series. J Pain Res. 2020;13:3131–7.
53. Trost Z, Zielke M, Guck A, et al. The promise and challenge of virtual gaming technologies for chronic pain: the case of graded exposure for low back pain. Pain Manag. 2015;5:197–206.
54. Alemanno F, Houdayer E, Emedoli D, et al. Efficacy of virtual reality to reduce chronic low back pain: Proof-of-concept of a non-pharmacological approach on pain, quality of life, neuropsychological and functional outcome. PLoS ONE. 2019;14: e0216858.
55. Villiger M, Bohli D, Kiper D, et al. Virtual reality-augmented neurorehabilitation improves motor function and reduces neuropathic pain in patients with incomplete spinal cord injury. Neurorehabil Neural Repair. 2013;27:675–83.
56. Leemhuis E, Giuffrida V, Giannini AM, Pazzaglia M. A therapeutic matrix: virtual reality as a clinical tool for spinal cord injury-induced neuropathic pain. Brain Sci. 2021;11.
57. Darnall BD, Krishnamurthy P, Tsuei J, Minor JD. Self-administered skills-based virtual reality intervention for chronic pain: randomized controlled pilot study. JMIR Form Res. 2020;4: e17293.
58. Hennessy RW, Rumble D, Christian M, Brown DA, Trost Z. A graded exposure, locomotion-enabled virtual reality app during walking and reaching for individuals with chronic low back pain: cohort gaming design. JMIR Serious Games. 2020;8: e17799.
59. Tejera DM, Beltran-Alacreu H, Cano-de-la-Cuerda R, et al. Effects of virtual reality versus exercise on pain, functional, somatosensory and psychosocial outcomes in patients with non-specific chronic neck pain: a randomized clinical trial. Int J Environ Res Public Health. 2020;17.
60. de Villiers E, Stone T, Wang NW, Sarangi V, Pelah A, Shenker N. Virtual environment rehabilitation for patients with motor neglect trial (VERMONT): a single-center randomized controlled feasibility trial. Brain Sci. 2021;11.
61. Stanton TR, Gilpin HR, Edwards L, Moseley GL, Newport R. Illusory resizing of the painful knee is analgesic in symptomatic knee osteoarthritis. PeerJ. 2018;6: e5206.
62. Cerritelli F, Chiera M, Abbro M, et al. The challenges and perspectives of the integration between virtual and augmented reality and manual therapies. Front Neurol. 2021;12: 700211.
63. Nambi G, Abdelbasset WK, Alsubaie SF, et al. Short-term psychological and hormonal effects of virtual reality training on chronic low back pain in soccer players. J Sport Rehabil. 2021:1–10.
64. Matheve T, Bogaerts K, Timmermans A. Virtual reality distraction induces hypoalgesia in patients with chronic low back pain: a randomized controlled trial. J Neuroeng Rehabil. 2020;17:55.
65. Nierula B, Martini M, Matamala-Gomez M, Slater M, Sanchez-Vives MV. Seeing an embodied virtual hand is analgesic contingent on colocation. J Pain. 2017;18:645–55.
66. Matamala-Gomez M, Donegan T, Bottiroli S, Sandrini G, Sanchez-Vives MV, Tassorelli C. Immersive virtual reality and virtual embodiment for pain relief. Front Hum Neurosci. 2019;13:279.
67. Solcà M, Ronchi R, Bello-Ruiz J, et al. Heartbeat-enhanced immersive virtual reality to treat complex regional pain syndrome. Neurology. 2018;91:e479–89.
68. Matamala-Gomez M, Diaz Gonzalez AM, Slater M, Sanchez-Vives MV. Decreasing pain ratings in chronic arm pain through changing a virtual body: different strategies for different pain types. J Pain. 2019;20:685–97.
69. Sempere-Rubio N, Aguilar-Rodríguez M, Inglés M, Izquierdo-Alventosa R, Serra-Añó P. Physical condition factors that predict a better quality of life in women with fibromyalgia. Int J Environ Res Public Health. 2019;16.