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# Beyond Pills: Synergizing Pharmacological and Physical Activity Interventions in Fibromyalgia Treatment. A review

Oliwia Bochenek[1*], Mateusz Koper[2], Aleksandra Nowak[3], Jessica Kałuża[4], Adrian Konaszczuk[5], Klaudia Ratyna[6], Oliwia Kozyra[7], Zofia Szypuła [8], Katarzyna Paluch [9], Małgorzata Skarbek[10]

1. Grochowski Hospital, Grenadierów 51/59, 04-073 Warsaw, Poland
2. National Medical Institute of the Ministry of the Interior and Administration, Wołoska 137, 02-507 Warsaw, Poland
3. Infant Jesus Clinical Hospital UCC MUW, Lindleya 4, 02-005 Warsaw, Poland
4. University Clinical Centre of the Medical University of Warsaw, Banacha 1a, 02-097 Warsaw, Poland
5. Standalone Public Health Care Facility in Świdnik ul. Leśmiana 4, 21-040 Świdnik
6. Infant Jesus Clinical Hospital UCC MUW, Lindleya 4, 02-005 Warsaw, Poland
7. Praski Hospital of the Transfiguration of the Lord Sp. z o. o., Aleja Solidarności 67, 03-401 Warsaw, Poland
8. Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland
9. Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland

10. Provincial Hospital Center of the Jelenia Gora Valley, Oginskiego 6, 58-506 Jelenia Gora

* Corresponding author

Oliwia Bochenek: bochenekoliwia1998@gmail.com; ORCID: https://orcid.org/0009-0005-1482-2544

Mateusz Koper: mateusz.koper1998@gmail.com; ORCID: https://orcid.org/0000-0002-1048-2774

Aleksandra Nowak: aa.nowak17@gmail.com; ORCID: https://orcid.org/0009-0009-6602-4017

Jessica Kałuża: jkaluza@vp.pl; ORCID: https://orcid.org/0009-0002-5050-2538

Adrian Konaszczuk adrian.konaszczuk.nauka@gmail.com ORICID: https://orcid.org/0009-0006-5775-5035

Klaudia Ratyna: klaudiaratyna@gmail.com ORCID: https://orcid.org/0009-0005-2235-1105

Oliwia Kozyra: kozyraoliwia@gmail.com ORCID: https://orcid.org/0009-0004-4882-3126

Zofia Szypuła: zofia.m.szypula@gmail.com ORCID: https://orcid.org/0009-0007-1671-5587

Katarzyna Paluch: kasia.paluch48@gmail.com ORCID: https://orcid.org/0009-0004-2190-855X

Małgorzata Skarbek skarbek.malgorzata@gmail.com ORCID: https://orcid.org/0000-0001-6227-4283

**ABSTRACT**

**Introduction and purpose**

Fibromyalgia (FM) is a chronic condition characterized by widespread musculoskeletal pain, fatigue, sleep disturbances, and cognitive impairment, affecting 2-4% of the global population, with a higher prevalence among women and those of lower socioeconomic status. The pathogenesis of FM is complex and multifactorial, involving central sensitization and neurochemical dysregulation. This review highlights the latest advancements in pharmacological and behavioral therapies for fibromyalgia.

**State of knowledge**

Management of fibromyalgia currently is based on a combination of medication use and non-pharmacological approaches, primarily based on physical activity and cognitive-behavioral therapy. This review explores advancements in FM treatments, focusing on novel pharmacological agents such as vortioxetine, eslicarbazepine acetate, and tapentadol, which target specific neurochemical pathways to alleviate symptoms. Vortioxetine offers new mechanisms of action with potential cognitive benefits, while eslicarbazepine acetate and tapentadol provide alternative approaches for pain modulation and central sensitization. Additionally, non-pharmacological

therapies, including high-intensity interval training (HIIT) and virtual reality (VR) therapy, demonstrate promise in enhancing physical fitness, reducing pain, and improving quality of life for FM patients.

**Summary**

Overall, the integration of these novel therapies into comprehensive, individualized treatment plans can optimize outcomes and enhance the quality of life for individuals with FM. Ongoing research and personalized medicine approaches are essential to further refine and validate these emerging treatments.

**Keywords:** Fibromyalgia, Vortioxetine, Tapentadol, High-intensity interval training, Virtual Reality (VR) Therapy

## INTRODUCTION AND PURPOSE

Fibromyalgia is a chronic and complex condition characterized by widespread musculoskeletal pain, fatigue, sleep disturbances, and cognitive impairment [1]. It is a significant public health concern, affecting an estimated 2-4% of the general population worldwide [2], with women disproportionately affected compared to men global population, with a higher prevalence in women [3]. The prevalence of the condition is positively correlated with age and negatively correlated with socioeconomic status [2].

The pathogenesis of fibromyalgia is poorly understood, with studies indicating that it is a symptom of chronic widespread musculoskeletal pain and has genetic associations [4]. Recent research suggests that fibromyalgia may result from central sensitization, a neurophysiological process in which the central nervous system becomes hypersensitive to pain signals, amplifying of pain and other symptoms [5]. Additionally, numerous studies have shown that neurochemical dysregulation, including imbalances of serotonin, norepinephrine and dopamine, contributes to fibromyalgia symptoms [6]. Understanding FM's pathophysiology is crucial for developing effective treatments.

The diagnosis of fibromyalgia has evolved over time, with efforts to develop simple and practical diagnostic criteria that do not require a tender point examination [7]. Sleep disturbances are a significant symptom of fibromyalgia, with diagnostic criteria including symptoms like waking unrefreshed, fatigue, tiredness, and insomnia [8]. Fibromyalgia management often involves a multidisciplinary approach, including physical activity, exercise training, and mindfulness-based psychological interventions to improve pain management and quality of life [9]. Additionally, research has highlighted the importance of understanding and addressing depressive symptoms and quality of life in individuals with fibromyalgia [10]. Despite existing treatment guidelines, including the European League Against Rheumatism (EULAR) recommendations, new therapeutic strategies continue to emerge. The article discusses recent developments in pharmacological and behavioral therapies for FM, highlighting evidence-based approaches developed after the publication of recent EULAR recommendations.

## THE STATE OF KNOWLEDGE

### 1. Current treatment

The last European League Against Rheumatism (EULAR) revised recommendations for managing fibromyalgia from 2017 emphasize the importance of tailoring treatment to individual patients and highlight the need for self-management strategies [11]. These recommendations categorize treatment options into non-pharmacological and pharmacological therapies. Non-pharmacological interventions recommended include aerobic exercise, cognitive-behavioral therapy (CBT), mindfulness meditation, physiotherapy, and patient education programs [12-14]. These approaches aim to address the multidimensional nature of fibromyalgia, targeting not only physical symptoms but also psychological aspects such as pain perception and coping mechanisms. In terms of pharmacological treatments, the revised EULAR guidelines do not recommend non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, strong opioids, growth hormone, or sodium oxybate due to lack of efficacy Instead, they suggest considering medications like amitriptyline, duloxetine, milnacipran, and pregabalin for symptom management [15, 16]. Amitriptyline, in particular, has shown effectiveness in addressing various domains of fibromyalgia, including pain, sleep disturbances, fatigue, affective symptoms, functional limitations, and cognitive impairments [17]. The actions of amitriptyline on nociceptive and sensory processes at central and peripheral levels contribute to alleviating fibromyalgia symptoms [18].

Furthermore, the guidelines highlight the potential benefits of combining pharmacological treatments with psychological interventions. Cognitive-behavioral therapy (CBT) and mindfulness-based approaches have been shown to be effective in managing fibromyalgia symptoms [19, 20]. These therapies help patients develop coping strategies, improve pain perception, and enhance overall well-being. Overall, the EULAR revised recommendations underscore the importance of a comprehensive and individualized approach to managing fibromyalgia to optimize treatment outcomes and enhance the quality of life for individuals living with fibromyalgia.

## 2. Novel Therapeutic Strategies - Pharmacological Therapies

When it comes to medications for fibromyalgia, several pharmacological options have been explored. While amitriptyline is commonly used off-label for fibromyalgia, pregabalin, duloxetine, and milnacipran are the only FDA-approved medications for this condition [21]. Moreover, the use of sleep aids, selective serotonin reuptake inhibitors, opioids, and serotonin-norepinephrine reuptake inhibitors is prevalent among individuals with fibromyalgia, highlighting the high prevalence of polypharmacy in this population [22]. Additionally, other pharmacological interventions listed in this review, such as selective serotonin-norepinephrine reuptake inhibitors, anticonvulsants, muscle relaxants, and analgesics, have shown promise in alleviating fibromyalgia symptoms. The pharmacological management of fibromyalgia involves a range of medications targeting pain, neurotransmitter regulation, and symptom relief [23]. The use of multiple medications and the exploration of new pharmacological strategies underscore the complexity of treating fibromyalgia and the need for personalized approaches to address individual needs.

### 2.1.Novel Antidepresants - Vortioxetine

Vortioxetine, a novel multimodal antidepressant, has garnered attention for its potential in the treatment of fibromyalgia. Studies have highlighted vortioxetine's unique pharmacological profile, acting as a serotonin transporter inhibitor and interacting with various serotonin receptors, including 5-HT1A, 5-HT1B, 5-HT3, 5-HT7, and 5-HT1D receptors [24]. This multimodal action of vortioxetine sets it apart from traditional antidepressants, potentially offering a distinct mechanism of action in managing fibromyalgia symptoms. Research has demonstrated vortioxetine's ability to modulate serotonergic neurotransmission and enhance cognitive function through its effects on plasticity-related gene expression [25]. These

findings suggest that vortioxetine may have a broader impact beyond depression, making it a promising candidate for conditions like fibromyalgia that involve cognitive deficits and altered neurotransmitter function. Moreover, vortioxetine has shown efficacy in improving memory and cognitive impairments associated with psychiatric diseases, indicating its potential in addressing cognitive symptoms often present in fibromyalgia patients [26]. Additionally, vortioxetine's impact on neuroplasticity pathways and protein-interaction networks further supports its potential in managing conditions characterized by central sensitization, such as fibromyalgia [25]. Animal studies, evaluated the impact of dopaminergic and serotonergic system modulators including vortioxetine on the pain threshold, anxiety, depression-like behavior, and motor functions given subcutaneous reserpine (0.25 mg/kg) to induce fibromyalgia-like symptoms, revealed vortioxetine markedly reduced tactile allodynia [27]. While the direct effects of vortioxetine on fibromyalgia have not been extensively studied, its modulation of neurotransmitter systems, cognitive enhancement properties, and unique pharmacological profile make it a compelling candidate for further exploration in the management of fibromyalgia symptoms.

### 2.2.Anticonvulsants - Eslicarbazepine Acetate

Eslicarbazepine acetate, a novel voltage-gated sodium channel antagonist, has primarily been studied in the context of its efficacy and safety as an adjunctive therapy for partial-onset seizures [28]. However, its mechanism of action as a sodium channel antagonist may offer a unique approach to addressing the central sensitization seen in fibromyalgia. Central sensitization is a key feature of fibromyalgia, leading to increased pain perception and other symptoms [29]. By modulating sodium channels, eslicarbazepine acetate could potentially influence the pain processing pathways involved in fibromyalgia. Its potential role in modulating pain signals and central sensitization aligns with the need for diverse treatment options in fibromyalgia [30]. Moreover, it has also been associated with enhancing sleep quality in epilepsy patients [31]. Given the symptom overlap between epilepsy and FM, such as pain and sleep disturbances, it is conceivable that eslicarbazepine acetate could benefit FM patients in these areas. In summary, although eslicarbazepine acetate has been mainly researched in epilepsy, its mechanism of action and safety profile justify further investigation for potential use in conditions such as fibromyalgia.

### 2.3. Muscle Relaxants - Tizanidine

Tizanidine, an alpha-2 adrenergic agonist, has shown promise in the treatment of various pain conditions, including fibromyalgia. Studies have demonstrated that tizanidine exerts anti-nociceptive effects by inhibiting proinflammatory cytokines through the suppression of specific signaling pathways [32]. Besides, tizanidine has been found to increase the antinociceptive effect and prevent gastric damage induced by other pain medications [33]. Moreover, tizanidine has been combined with other medications like gabapentin in the treatment of myofascial pain, potentializing the analgesic effect of gabapentin and diclofenac in acute pain model [34]. Research has also indicated that intrathecal tizanidine may be more specific than morphine in reversing allodynia and hyperpathia associated with neuropathic pain states, suggesting its potential value in managing such conditions [35]. While tizanidine has shown promise in pain management, it is essential to consider individual variability in drug interactions and dosing for optimal therapeutic outcomes [36]. In conclusion, tizanidine's mechanism of action in inhibiting proinflammatory cytokines and its potential to alleviate pain without significant intrinsic muscle changes make it a promising candidate for fibromyalgia treatment. Thus, further research and clinical trials focusing on tizanidine's efficacy, safety, and optimal dosing regimens in fibromyalgia management are warranted to enhance its role in pain therapy.

### 2.4. Analgesics - Tapentadol

Tapentadol, a centrally acting analgesic, exhibits a unique dual mechanism of action that sets it apart from traditional opioids. The primary mechanisms of action of tapentadol involve both μ-opioid receptor (MOR) agonism and noradrenaline reuptake inhibition (NRI) [37]. This dual action allows tapentadol to address both nociceptive and neuropathic components of chronic pain [38]. Studies have shown that tapentadol's antinociceptive effects are predominantly mediated by μ-opioid receptor agonism, while its antihypersensitive effects are mainly due to noradrenaline reuptake inhibition [39]. The synergistic interaction between these two mechanisms of action contributes to tapentadol's analgesic efficacy. In the context of fibromyalgia, tapentadol has been found to enhance the descending pain inhibition in patients with this condition [40]. Furthermore, tapentadol's dual mode of action may make it particularly useful in the treatment of neuropathic pain [41]. To conclude, tapentadol's mechanism of action, involving both MOR agonism and NRI, provides a comprehensive

approach to pain management, making it a valuable option for conditions like fibromyalgia where traditional opioids may be less effective.

## 3. Novel Therapeutic Strategies - Non-Pharmacological Therapies

The relationship between exercise and fibromyalgia has been extensively studied in the literature. Research supports that exercise is an essential element in the management of fibromyalgia syndrome [23]. While some patients may initially avoid physical activity due to concerns about symptom exacerbation, evidence indicates that various forms of exercise can benefit individuals with fibromyalgia by helping to restore the body's neurochemical balance and promoting positive emotional well-being [42]. Studies have shown that exercise, including both aerobic and strength exercises, can have beneficial effects on health-related physical fitness parameters, depression, anxiety, and quality of life in patients with fibromyalgia [43]. Various types of exercises, including aerobic, strengthening, aquatic, pilates, tai chi and core muscle strengthening exercises, have been investigated for their effectiveness in managing fibromyalgia symptoms [44]. These exercises have been proven to be beneficial, cost-effective, and to promote improvements in pain and other fibromyalgia symptoms. Moreover, studies have shown that exercise can significantly improve pain and function in individuals with fibromyalgia [45]. In conclusion, the literature supports the positive impact of exercise on individuals with fibromyalgia. Various forms of exercise, when combined with education and proper guidance, can help alleviate symptoms, improve physical fitness, and enhance overall quality of life for individuals living with fibromyalgia. The newest approach to improving well-being in fibromyalgia patients by promoting physical activity is outlined below.

### 3.1.Exercise - High-Intensity Interval Training (HIIT)

High-intensity interval training (HIIT) has gained attention in various medical conditions due to its potential benefits. In the context of fibromyalgia, a condition characterized by widespread musculoskeletal pain and fatigue, exercise therapy plays a crucial role in management. Research suggests that exercise, including HIIT, can be beneficial for individuals with fibromyalgia [46, 47]. While traditional exercise modalities like aerobic training, muscle strengthening, and flexibility exercises are commonly used [48], recent studies have shown that HIIT can lead to improvements in aerobic capacity, fatigue, and other physiological parameters in patients and quality of life in different patient populations [49-51].

HIIT involves short bursts of intense exercise followed by brief recovery periods and has been shown to improve cardiorespiratory fitness and exercise capacity in various patient groups, including those with coronary artery disease [49]. Additionally, HIIT has been investigated in the context of conditions such as osteoarthritis, where it has shown potential in attenuating pain and improving hyperalgesia, but further studies are needed [52]. In conclusion, while traditional exercise therapies remain important in managing fibromyalgia, the emerging evidence on the benefits of HIIT in improving fitness, symptoms, and quality of life in various patient populations suggests that HIIT could be a valuable addition to the therapeutic approach for fibromyalgia. Therefore, further studies specifically focusing on the effects of HIIT in individuals with fibromyalgia are warranted to determine its efficacy and safety in this particular population.

### 3.2. Multidisciplinary Rehabilitation - Virtual Reality (VR) Therapy

Virtual Reality (VR) therapy has emerged as a potential treatment modality for fibromyalgia. Studies have explored the use of VR exercises in improving pain, functionality, cardiopulmonary capacity, and quality of life in fibromyalgia patients [53]. Moreover, research has indicated that combining neuromodulation with VR and targeted exercise regimens can effectively alleviate fibromyalgia symptoms, offering promising nonpharmacological management avenues [54]. Furthermore, VR technology has been considered an effective adjunctive therapy for treating fibromyalgia, providing a means to address the complex nature of the condition through a multimodal treatment approach [55]. The immersive nature of VR interventions can offer a unique approach to treating musculoskeletal pain resulting in reduced pain and increased activity levels, including in patients with fibromyalgia [56]. Additionally, the use of VR therapy in combination with physical exercises has been found to impact quality of life, fatigue, pain levels, and functional capacity in individuals with fibromyalgia [57]. In conclusion, the integration of VR therapy into the treatment of fibromyalgia holds promise in addressing the multifaceted nature of the condition. By leveraging the immersive and interactive capabilities of VR technology, healthcare providers can potentially enhance pain management, improve functionality, and positively impact the quality of life for individuals living with fibromyalgia.

### 3.3.Digital Therapeutics - Mobile Health (mHealth) Applications

Mobile health (mHealth) applications have garnered significant attention in the healthcare sector for their potential to support various aspects of patient care. In the context of fibromyalgia, the use of mHealth apps presents an opportunity to enhance treatment outcomes and patient self-management. Studies have indicated that mHealth apps can enhance self-efficacy, facilitate chronic disease management, and improve patient outcomes [58, 59]. In the case of fibromyalgia-like post-COVID-19 syndrome, the development of a specialized mHealth app aims to cater to the unique needs of patients with this condition [60]. Moreover, significant improvements in reducing pain were reported for patients FM [61]. These apps offer CBT, mindfulness exercises, pain tracking, and personalized exercise programs [62-64]. Such targeted interventions through mHealth apps can potentially provide personalized support and resources for individuals managing fibromyalgia. Despite existing literature highlighting promising benefits of integrating mHealth technologies into strategies for managing chronic diseases, further research focusing on the development and evaluation of mHealth applications tailored for treating fibromyalgia is needed [65].

## DISCUSSION

The management of fibromyalgia necessitates a multidimensional approach [66]. Current guidelines emphasize comprehensive approach, combining pharmacological treatment with complementary modalities such as cognitive behavioral therapy, aerobic and strengthening physical training, and meditative movement therapies [23, 67]. Advances published after the current 2017 EULAR recommendations introduced new drug options and innovative non-pharmacological interventions, providing a wider range of tools for clinicians and patients. Pharmacological treatments such as vortioxetine, eslicarbazepine acetate, and tapentadol offer new mechanisms of action and improved safety profile [68-71]. These medications could be used as an alternative for patients who cannot tolerate or do not respond to current therapies available in clinical practice. Behavioral therapies, including virtual reality therapies, HIIT and digital therapeutics, address the psychological and functional aspects of fibromyalgia. Additionally, the use of mobile devices and applications allows patients to enhance self-engagement, monitor symptoms, and understand their condition better, which directly translates to improved physician-patient collaboration and achieving optimal therapeutic outcomes. However, it should be noted that despite the promising results of new therapies, they do not provide better long-term outcomes than the non-pharmacological therapies present in current guidelines [72]. Nevertheless, they may impact other aspects of patient well-being,

leading to an improved quality of life. It is important to emphasize that continuous research and personalized medicine strategies are crucial for maximizing fibromyalgia treatment outcomes.

## CONCLUSION

Fibromyalgia remains a challenging condition to treat due to its complex etiology and heterogeneous symptomatology. Recent advancements in pharmacological and behavioral therapies provide new opportunities for improving patient outcomes. Novel pharmacological agents targeting specific neurochemical pathways and innovative behavioral interventions offer promising additions to existing treatment strategies. As our understanding of fibromyalgia's pathophysiology continues to evolve, it is crucial to integrate these insights into clinical practice to improve the quality of life for those affected by this debilitating. Notwithstanding these encouraging results, there is still much to be discovered. Further research is needed to explore the efficacy, long-term effects, and optimal combinations of these treatments to improve outcomes and quality of life for individuals with fibromyalgia.

**Author's contribution**

Conceptualization, OB; methodology, OB, JK, AN; software, MK, AK, KR, OK, MS; check, ZS, KP; formal analysis OB, MK, JK; investigation, AK, KR, OK; resources, MS, ZS, KP; data curation, AK, KR; writing – rough preparation OB, JK, AN; writing-review and editing, AN, MK; visualization, OK; supervision, ZS, KP; project administration, MS

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## References


1. Häuser, W., et al., *What are the key symptoms of fibromyalgia? Results of a survey of the German Fibromyalgia Association.* Der Schmerz, 2008. **22**: p. 176-183.
2. Arnold, L.M., et al. *A framework for fibromyalgia management for primary care providers*. in *Mayo Clinic Proceedings*. 2012. Elsevier.
3. Wolfe, F., et al., *The prevalence and characteristics of fibromyalgia in the general population.* Arthritis & Rheumatism: Official Journal of the American College of Rheumatology, 1995. **38**(1): p. 19-28.
4. Buskila, D. and P. Sarzi-Puttini, *Biology and therapy of fibromyalgia. Genetic aspects of fibromyalgia syndrome.* Arthritis research & therapy, 2006. **8**: p. 1-5.
5. Sluka, K.A. and D.J. Clauw, *Neurobiology of fibromyalgia and chronic widespread pain.* Neuroscience, 2016. **338**: p. 114-129.
6. Ablin, J., L. Neumann, and D. Buskila, *Pathogenesis of fibromyalgia–a review.* Joint Bone Spine, 2008. **75**(3): p. 273-279.
7. Wolfe, F., et al., *The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity.* Arthritis care & research, 2010. **62**(5): p. 600-610.
8. Roizenblatt, S., N.S.R. Neto, and S. Tufik, *Sleep disorders and fibromyalgia.* Current pain and headache reports, 2011. **15**: p. 347-357.
9. Saral, I., et al., *The effects of long-and short-term interdisciplinary treatment approaches in women with fibromyalgia: a randomized controlled trial.* Rheumatology international, 2016. **36**: p. 1379-1389.
10. Yepez, D., et al., *Fibromyalgia and depression: a literature review of their shared aspects.* Cureus, 2022. **14**(5).
11. Häuser, W., et al., *Efficacy of multicomponent treatment in fibromyalgia syndrome: a meta-analysis of randomized controlled clinical trials.* Arthritis Care & Research, 2009. **61**(2): p. 216-224.
12. Bernardy, K., et al., *Cognitive behavioural therapies for fibromyalgia.* Cochrane Database of Systematic Reviews, 2013(9).
13. Lakhan, S.E. and K.L. Schofield, *Mindfulness-based therapies in the treatment of somatization disorders: a systematic review and meta-analysis.* PloS one, 2013. **8**(8): p. e71834.
14. Langhorst, J., et al., *Efficacy and safety of meditative movement therapies in fibromyalgia syndrome: a systematic review and meta-analysis of randomized controlled trials.* Rheumatology international, 2013. **33**: p. 193-207.

15. Häuser, W., et al., *Comparative efficacy and acceptability of amitriptyline, duloxetine and milnacipran in fibromyalgia syndrome: a systematic review with meta-analysis.* Rheumatology, 2011. **50**(3): p. 532-543.
16. Lunn, M.P., R.A. Hughes, and P.J. Wiffen, *Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia.* Cochrane database of systematic reviews, 2014(1).
17. Nishishinya, B., et al., *Amitriptyline in the treatment of fibromyalgia: a systematic review of its efficacy.* Rheumatology, 2008. **47**(12): p. 1741-1746.
18. Lawson, K., *A brief review of the pharmacology of amitriptyline and clinical outcomes in treating fibromyalgia.* Biomedicines, 2017. **5**(2): p. 24.
19. Minelli, A. and A. Vaona, *Effectiveness of cognitive behavioral therapy in the treatment of fibromyalgia syndrome: a meta-analytic literature review.* Reumatismo, 2012. **64**(3): p. 151-157.
20. Glombiewski, J.A., et al., *Psychological treatments for fibromyalgia: a meta-analysis.* PAIN®, 2010. **151**(2): p. 280-295.
21. Farag, H.M., et al., *Comparison of amitriptyline and us food and drug administration–approved treatments for fibromyalgia: a systematic review and network meta-analysis.* JAMA network open, 2022. **5**(5): p. e2212939-e2212939.
22. Vincent, A., et al., *A cross-sectional assessment of the prevalence of multiple chronic conditions and medication use in a sample of community-dwelling adults with fibromyalgia in Olmsted County, Minnesota.* BMJ open, 2015. **5**(3): p. e006681.
23. Macfarlane, G.J., et al., *EULAR revised recommendations for the management of fibromyalgia.* Annals of the rheumatic diseases, 2017. **76**(2): p. 318-328.
24. Chen, G., et al., *Effects of intrinsic factors on the clinical pharmacokinetics of vortioxetine.* Clinical Pharmacology in Drug Development, 2018. **7**(8): p. 880-888.
25. Waller, J.A., et al., *Neuroplasticity pathways and protein-interaction networks are modulated by vortioxetine in rodents.* BMC neuroscience, 2017. **18**: p. 1-15.
26. McIntyre, R.S., S. Lophaven, and C.K. Olsen, *A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults.* International Journal of Neuropsychopharmacology, 2014. **17**(10): p. 1557-1567.
27. Sałat, K. and A. Furgała-Wojas, *Serotonergic neurotransmission system modulator, vortioxetine, and dopaminergic D2/D3 receptor agonist, ropinirole, attenuate fibromyalgia-like symptoms in mice.* Molecules, 2021. **26**(8): p. 2398.
28. Sperling, M.R., et al., *Eslicarbazepine acetate as adjunctive therapy in patients with uncontrolled partial-onset seizures: results of a phase III, double-blind, randomized, placebo-controlled trial.* Epilepsia, 2015. **56**(2): p. 244-253.
29. Yunus, M.B. *Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes*. in *Seminars in arthritis and rheumatism*. 2007. Elsevier.
30. Mezhov, V., E. Guymer, and G. Littlejohn, *Central sensitivity and fibromyalgia.* Internal Medicine Journal, 2021. **51**(12): p. 1990-1998.
31. Assenza, G., et al., *The ROME (Retrospective Observational Multicenter study on Eslicarbazepine) study: efficacy and behavioural effects of Eslicarbazepine acetate as adjunctive therapy for adults with partial onset seizures in real life.* Seizure, 2018. **58**: p. 35-40.
32. Pei, W., et al., *Tizanidine exerts anti-nociceptive effects in spared nerve injury model of neuropathic pain through inhibition of TLR4/NF-κB pathway.* International journal of molecular medicine, 2018. **42**(6): p. 3209-3219.
33. Patiño-Camacho, S.I., et al., *Low doses of tizanidine synergize the anti-nociceptive and anti-inflammatory effects of ketorolac or naproxen while reducing of side effects.* European journal of pharmacology, 2017. **805**: p. 51-57.

34. Zayed, A., et al., *Comparison between the analgesic effect of Tizanidine, Diclofenac and Gabapbentin on experimentally induced acute and chronic pain in male albino rats.* Zagazig University Medical Journal, 2021. **27**(5): p. 855-864.
35. Leiphart, J.W., et al., *A comparison of intrathecally administered narcotic and nonnarcotic analgesics for experimental chronic neuropathic pain.* Journal of neurosurgery, 1995. **82**(4): p. 595-599.
36. Ghanavatian, S. and A. Derian, *Tizanidine*, in *StatPearls [Internet]*. 2022, StatPearls Publishing.
37. Chang, E.J., E.J. Choi, and K.H. Kim, *Tapentadol: can it kill two birds with one stone without breaking windows?* The Korean journal of pain, 2016. **29**(3): p. 153.
38. Tzschentke, T., et al., *Tapentadol: with two mechanisms of action in one molecule effective against nociceptive and neuropathic pain: preclinical overview.* Der Schmerz, 2011. **25**: p. 19-25.
39. Tzschentke, T.M., T. Christoph, and B.Y. Kögel, *The mu-opioid receptor Agonist/Noradrenaline reuptake inhibition (MOR–NRI) concept in analgesia: the case of tapentadol.* CNS drugs, 2014. **28**: p. 319-329.
40. van de Donk, T., et al., *Cornea nerve fibre state determines analgesic response to tapentadol in fibromyalgia patients without effective endogenous pain modulation.* European Journal of Pain, 2019. **23**(9): p. 1586-1595.
41. Freo, U., P. Romualdi, and H.G. Kress, *Tapentadol for neuropathic pain: a review of clinical studies.* Journal of pain research, 2019: p. 1537-1551.
42. López-Pousa, S., et al., *Sense of Well-Being in Patients with Fibromyalgia: Aerobic Exercise Program in a Mature Forest—A Pilot Study.* Evidence-Based Complementary and Alternative Medicine, 2015. **2015**(1): p. 614783.
43. Masquelier, E. and J. D'haeyere, *Physical activity in the treatment of fibromyalgia.* Joint Bone Spine, 2021. **88**(5): p. 105202.
44. Busch, A.J., et al., *Exercise therapy for fibromyalgia.* Current pain and headache reports, 2011. **15**: p. 358-367.
45. Häuser, W., et al., *Efficacy of different types of aerobic exercise in fibromyalgia syndrome: a systematic review and meta-analysis of randomised controlled trials.* Arthritis research & therapy, 2010. **12**: p. 1-14.
46. Bodéré, C., et al., *A training program for fibromyalgia management: A 5-year pilot study.* SAGE Open Medicine, 2020. **8**: p. 2050312120943072.
47. Silva, L.C., et al., *Exercise Training for Women With Fibromyalgia Syndrome: A Scoping Review.* Topics in Geriatric Rehabilitation, 2024. **40**(2): p. 147-157.
48. Sosa-Reina, M.D., et al., *Effectiveness of therapeutic exercise in fibromyalgia syndrome: A systematic review and meta-analysis of randomized clinical trials.* BioMed research international, 2017. **2017**(1): p. 2356346.
49. Taylor, J.L., et al., *Short-term and long-term feasibility, safety, and efficacy of high-intensity interval training in cardiac rehabilitation: the FITR heart study randomized clinical trial.* JAMA cardiology, 2020. **5**(12): p. 1382-1389.
50. Lavín-Pérez, A.M., et al., *Effects of high-intensity training on the quality of life of cancer patients and survivors: a systematic review with meta-analysis.* Scientific Reports, 2021. **11**(1): p. 15089.
51. Alarcón-Gómez, J., et al., *Effect of high-intensity interval training on quality of life, sleep quality, exercise motivation and enjoyment in sedentary people with type 1 diabetes mellitus.* International journal of environmental research and public health, 2021. **18**(23): p. 12612.
52. Wang, X., et al., *High intensity interval training attenuates osteoarthritis-associated hyperalgesia in rats.* The Journal of Physiological Sciences, 2023. **73**(1): p. 8.

53. Polat, M., et al., *The effect of virtual reality exercises on pain, functionality, cardiopulmonary capacity, and quality of life in fibromyalgia syndrome: a randomized controlled study.* Games for Health Journal, 2021. **10**(3): p. 165-173.
54. Rubio-Zarapuz, A., et al., *Comparative Analysis of Psychophysiological Responses in Fibromyalgia Patients: Evaluating Neuromodulation Alone, Neuromodulation Combined with Virtual Reality, and Exercise Interventions.* Medicina, 2024. **60**(3): p. 404.
55. Shi, Y. and W. Wu, *Multimodal non-invasive non-pharmacological therapies for chronic pain: Mechanisms and progress.* BMC medicine, 2023. **21**(1): p. 372.
56. Gulsen, C., et al., *Effect of fully immersive virtual reality treatment combined with exercise in fibromyalgia patients: a randomized controlled trial.* Assistive Technology, 2022. **34**(3): p. 256-263.
57. Cortés-Pérez, I., et al., *Virtual reality-based therapy reduces the disabling impact of fibromyalgia syndrome in women: Systematic review with meta-analysis of randomized controlled trials.* Journal of personalized medicine, 2021. **11**(11): p. 1167.
58. Knitza, J., et al., *Patient's perception of digital symptom assessment technologies in rheumatology: results from a multicentre study.* Frontiers in Public Health, 2022. **10**: p. 844669.
59. Wang, H., et al., *The association of mobile health applications with self-management behaviors among adults with chronic conditions in the United States.* International Journal of Environmental Research and Public Health, 2021. **18**(19): p. 10351.
60. Blanchard, M., et al., *An mHealth App for Fibromyalgia-like Post–COVID-19 Syndrome: Protocol for the Analysis of User Experience and Clinical Data.* JMIR Research Protocols, 2022. **11**(2): p. e32193.
61. Lee, J., et al., *Application of a real-time pain monitoring system in Korean fibromyalgia patients: a pilot study.* International journal of rheumatic diseases, 2019. **22**(5): p. 934-939.
62. Denecke, K., N. Schmid, and S. Nüssli, *Implementation of cognitive behavioral therapy in e–mental health apps: literature review.* Journal of medical Internet research, 2022. **24**(3): p. e27791.
63. Mani, M., et al., *Review and evaluation of mindfulness-based iPhone apps.* JMIR mHealth and uHealth, 2015. **3**(3): p. e4328.
64. Lalloo, C., et al., *Capturing daily disease experiences of adolescents with chronic pain: mHealth-mediated symptom tracking.* JMIR mHealth and uHealth, 2019. **7**(1): p. e11838.
65. Gallego, A., et al., *Study protocol for a three-arm randomized controlled trial investigating the effectiveness, cost-utility, and physiological effects of a fully self-guided digital Acceptance and Commitment Therapy for Spanish patients with fibromyalgia.* Digital Health, 2024. **10**: p. 20552076241239177.
66. Hawkins, R.A., *Fibromyalgia: a clinical update.* Journal of Osteopathic Medicine, 2013. **113**(9): p. 680-689.
67. Häuser, W., et al., *Management of fibromyalgia: practical guides from recent evidence-based guidelines.* Pol Arch Intern Med, 2017. **127**(1): p. 47-56.
68. Guardiola-Lemaitre, B., et al., *Agomelatine: mechanism of action and pharmacological profile in relation to antidepressant properties.* British Journal of Pharmacology, 2014. **171**(15): p. 3604-3619.
69. Singh, D.R., et al., *Tapentadol hydrochloride: A novel analgesic.* Saudi journal of anaesthesia, 2013. **7**(3): p. 322-326.

70. Alvarez, E., V. Perez, and F. Artigas, *Pharmacology and clinical potential of vortioxetine in the treatment of major depressive disorder.* Neuropsychiatric disease and treatment, 2014: p. 1297-1307.
71. Galiana, G.L., A.C. Gauthier, and R.H. Mattson, *Eslicarbazepine acetate: a new improvement on a classic drug family for the treatment of partial-onset seizures.* Drugs in R&D, 2017. **17**: p. 329-339.
72. Atan, T. and Y. Karavelioğlu, *Effectiveness of high-intensity interval training vs moderate-intensity continuous training in patients with fibromyalgia: a pilot randomized controlled trial.* Archives of Physical Medicine and Rehabilitation, 2020. **101**(11): p. 1865-1876.