PHARMACOVIGILANCE AND OFF-GUIDELINE USE FOR GABAPENTIN IN FIBROMYALGIA: A REVIEW OF SAFETY PROFILES AND PRESCRIBING PATTERNS

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ABSTRACT

Fibromyalgia (FM) is a multifactorial chronic pain syndrome that significantly affects patients' quality of life. Despite the widespread use of gabapentinoids such as gabapentin, their off-label use in FM treatment remains controversial due to inconsistent efficacy and safety concerns. This systematic review aims to map the current state of knowledge in the field. of off-guideline use of gabapentin use in FM by synthesizing findings from four selected studies published between 2020 and 2025. The studies reviewed include clinical and preclinical trials assessing gabapentin monotherapy, its extended-release formulations, and combinations with osteopathic manipulative medicine (OMM) or natural compounds like sulforaphane. Results suggest that combination therapies offer superior pain relief compared to gabapentin alone. Notably, extended-release gabapentin demonstrated improved adherence and reduced side effects. Furthermore, mirogabalin, a novel gabapentinoid, was found to enhance both pain control and cognitive function ("fibro fog") in animal models. However, reported side effects such as dizziness and drowsiness, along with limitations in study design and sample size, emphasize the need for further randomized controlled trials. This review highlights the evolving role of gabapentinoids in FM treatment and underscores the importance of integrated therapeutic strategies for optimal patient outcomes.

Keywords: Fibromyalgia; Gabapentin; Mirogabalin; Off-Label Use; Pharmacovigilance; Sulforaphane.

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INTRODUCTION

Fibromyalgia (FM) is a complex and multifactorial chronic pain syndrome characterized by widespread musculoskeletal pain, fatigue, sleep disturbances, cognitive dysfunction, and common psychological comorbidities such as depression and anxiety. Affecting an estimated 2–7% of the global population, FM poses a substantial burden on patients' quality of life and healthcare systems. Despite various therapeutic options, the management of FM remains challenging due to inconsistent treatment responses and the limited efficacy or tolerability of many pharmacological agents. Gabapentinoids such as gabapentin and pregabalin are commonly prescribed, yet issues related to bioavailability and side effects have prompted the development of newer formulations, such as extended-release gabapentin, which offer improved pharmacokinetics and patient adherence. In parallel, the integration of conventional medications with natural compounds like sulforaphane and non-pharmacological approaches such as osteopathic manipulative medicine (OMM) has demonstrated synergistic potential in addressing FM symptoms more comprehensively. Furthermore, the emergence of novel agents like mirogabalin extends the therapeutic landscape by targeting both pain and cognitive impairments. This review aims to synthesize recent advancements in FM therapy, highlighting the efficacy, safety, and innovation of these evolving. The primary objective of this study was to evaluate the efficacy and safety

of a gastro-retentive, extended-release formulation of gabapentin (G-GR; Gralise®) in reducing pain severity in patients with fibromyalgia, as measured by the Numeric Pain Rating Scale (NPRS). Additionally, the study aimed to assess improvements in sleep quality and overall quality of life. This research also sought to pharmacological and integrative interventions.

METHODS

This study used a systematic review method, which refers to a research methodology conducted by collecting, evaluating, and interpreting various studies focusing on a specific topic using secondary data as samples. Literature collection was carried out based on the Recommended Reporting Items for Systematic Review Protocols and Meta-Analyses (PRISMA-P) guidelines in 2020. Literature searches were conducted in three public publication databases, namely PubMed, Science Direct, and Google Scholar, using the keywords "Gabapentin" AND "Fibromyalgia" AND " explore treatment outcomes in both gabapentinoid-naïve patients and those who had previously discontinued gabapentin due to adverse effects, while comparing adverse event profiles and medication adherence with those reported in previous studies of immediate-release gabapentin (North, J. M., et al., 2015).

Off-Label Use". The screening process was conducted using journal inclusion criteria, namely using Indonesian and English languages, published between 2020 and 2025, using and data obtained through clinical trials, research articles and with the search category open full access.. Meanwhile, exclusion criteria included studies that were written using review or systematic review methods. The literature obtained was then extracted by reviewing the general and specific aspects of the research. After several stages of matching with the criteria to be studied, 4 articles that met the criteria were selected for review.

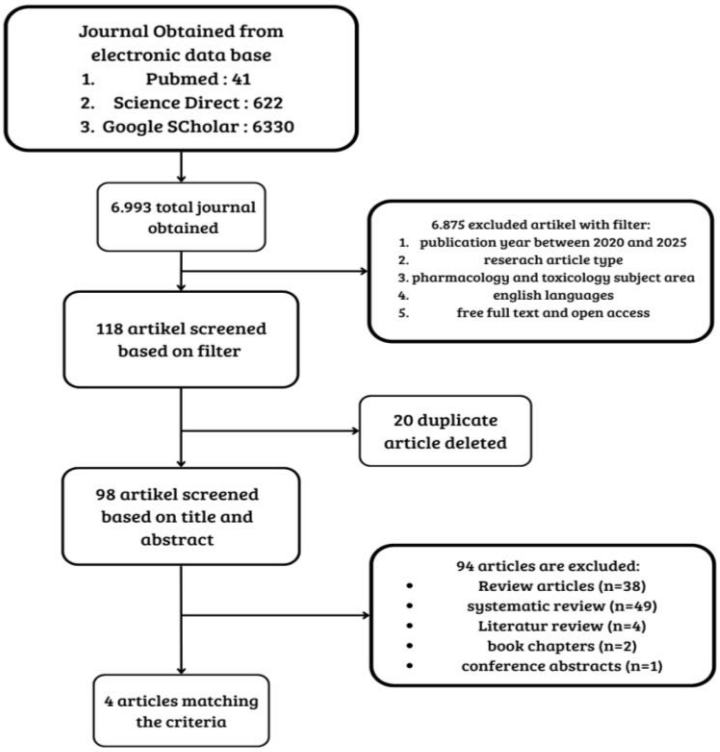

Figure 1. Stage of Literature Selection Based on PRISMA-P

Table 1. Comparative Summary of Journals

No.	Journal 1	Journal 2	Journal 3	Journal 4
Name of the Author and Year of Research	Cynthia Marske, DO, et al., 2018	Ik-Yahalcab Zamora-Díaz et al., 2025	Murasawa Hiroyasu et al., 2021	North et al., 2015
Journal Name	The Journal of Alternative and Complementary Medicine	Biomedicine & Pharmacotherapy	Biomedicine & Pharmacotherapy	Pain Practice
Research Title	Fibromyalgia with Gabapentin and Osteopathic Manipulative Medicine: A Pilot Study	Pharmacological interactions of sulforaphane and gabapentin in a murine fibromyalgia-like pain model	Mirogabalin, a novel ligand for α2δ subunit of voltage-gated calcium channels, improves cognitive impairments in repeated intramuscular acidic saline injection model rats, an experimental model of fibromyalgia	The Effect of a Novel Form of Extended-Release Gabapentin on Pain and Sleep in Fibromyalgia: An Open-Label Pilot Study
Study Design	Prospective pilot study, single-center, 8 weeks	Preclinical in vivo controlled experimental study using animal models	Preclinical in vivo controlled experimental study using animal models	Open-label, single-arm, single-center pilot study over 15 weeks

Drug Tested and Dosage	· Gabapentin: starting from 300 mg/day → 600 mg → 900 mg/day (divided into 3 doses of 300 mg if intolerant) · OMM: 30 minutes/week × 6 weeks	Gabapentin (GBP): · Doses: 17.8, 31.6, and 100 mg/kg · Route: Intraperitoneal (i.p.) Sulforaphane (SFN): · Doses: 3.16, 31.6, and 100 mg/kg · Route: Intraperitoneal (i.p.) Combination Treatments: · Doses: 3.16:17.8 ; 10:17.8 ; 31.6:17.8 ; and 31.6:31.6 (SFN:GBP)	Drug Tested: Mirogabalin besylate (a gabapentinoid class drug, which acts as a ligand on the α2δ subunit of voltage-gated calcium channels). Dosage: Doses of 3 mg/kg and 10 mg/kg, once daily for 13 consecutive days..	Extended-release gabapentin (G-GR), titrated over 2 weeks to 1800 mg/day, maintained for 10 weeks, followed by tapering
Research Sample	40 participants total; 29 completed study; inclusion: adults 18–65 years diagnosed with fibromyalgia per ACR 1990 criteria	· Tikus Wistar jantan: berat 180–200 gram (Number: 72) · Mencit Swiss Webster jantan: berat 25–30 gram, (Number not specified)	- Adult male rats (Crl:CD(SD)) acclimatized for 9 days prior to the study. - Weighing 123-137 grams, which were induced into a fibromyalgia model using pH injection. - Randomly divided into treatment groups with 12 rats per group.	34 fibromyalgia patients enrolled (29 completed starter pack); inclusion criteria included adults ≥18 years with FM diagnosis, gabapentinoid naïve or previously discontinued immediate-release forms due to side effects

Statistical Methods	ANOVA for between-group comparisons; paired t-test for within-group changes; no initial power calculation	Data were expressed as mean ± SEM. One-way ANOVA with Dunnett's or Tukey's post hoc test, and Student's t-test were used. AUC was calculated using the trapezoidal method. Significance was set at $p < 0.05$. Analysis used GraphPad Prism v8.0.2.	- Measured data are expressed as mean ± standard error of the mean (SEM). - one-way analysis of variance (ANOVA): For analysis of comparisons between groups - Tukey's multiple comparison test: post-hoc test to determine which groups are significantly different. A value of $p < 0.05$	T-test, Wilcoxon sign-rank test, nonparametric tests with Bonferroni adjustment for multiple comparisons; data analyzed using JMP statistical software
Research Conclusion	OMM and combined OMM + gabapentin significantly reduced pain (WBF scale). OMM alone showed significant improvements on CGI. Gabapentin alone did not show significant benefit. Side effects were higher in gabapentin groups. Larger studies with updated ACR 2010 criteria recommended.	This study shows that sulforaphane (SFN) effectively reduces fibromyalgia-related pain in rats, especially when combined with gabapentin (GBP), and may serve as a natural alternative for pain management. Compared to gabapentin alone, the combination of sulforaphane and gabapentin provided stronger and longer-lasting pain relief in fibromyalgia model rats, suggesting that sulforaphane enhances gabapentin's effectiveness.	- Mirogabalin significantly improved cognitive impairment in fibromyalgia model rats. - Oral administration effectively improves cognitive function. - Mirogabalin has the potential to treat pain and "fibro fog" in fibromyalgia. - Safety profile is good in animals, but further studies in humans are needed.	This study demonstrates that extended-release gabapentin (G-GR) is effective in reducing fibromyalgia (FM) pain, improving quality of life, and enhancing sleep quality in patients, including those with prior gabapentinoid treatment failure or intolerance. The treatment was generally well tolerated, with manageable side effects. Although limited by a small sample size, open-label design, and lack of a control group, the

findings support the potential role of G-GR in FM management and warrant further investigation through larger, randomized controlled trials to confirm these benefits.

RESULT

In 2018, Dr. Cynthia Marske and colleagues published a pilot study in *The Journal of Alternative and Complementary Medicine* titled "Fibromyalgia with Gabapentin and Osteopathic Manipulative Medicine: A Pilot Study." The study aimed to compare the safety and effectiveness of gabapentin (900 mg/day), osteopathic manipulative medicine (OMM), and their combination in treating fibromyalgia. This 8-week, single-center, randomized trial involved 29 adult participants who met the 1990 ACR criteria for fibromyalgia. Participants were divided into three groups: gabapentin only, OMM only, and combination therapy. OMM was administered once weekly for six weeks. Results showed that the OMM group and the combination group experienced a significant reduction in pain (WBF scale). The OMM-only group also showed significant improvement in overall health perception (CGI scale). In contrast, the gabapentin-only group did not show significant improvements and reported more side effects. The study concluded that OMM, alone or combined with gabapentin, may be a safe and effective option for managing fibromyalgia symptoms. However, larger, well-powered studies using updated diagnostic criteria are needed to confirm these findings.

In a 2025 study by Ik-Yahalcab Zamora-Díaz et al., published in Biomedicine & Pharmacotherapy, researchers investigated the effects of sulforaphane (SFN) and gabapentin (GBP) on fibromyalgia-like pain induced by reserpine in male Wistar rats and Swiss Webster mice. Animals received varying doses of gabapentin (17.8, 31.6, 100 mg/kg) and sulforaphane (3.16, 31.6, 100 mg/kg) intraperitoneally, both alone and in combination at ratios such as 3.16:17.8 and 31.6:31.6 (SFN:GBP). The study measured pain relief through behavioral assays, analyzing results with one-way ANOVA and post hoc tests, setting significance at $p < 0.05$. The data showed that sulforaphane alone significantly reduced pain ($p < 0.05$) compared to controls. More importantly, the combination treatments resulted in a greater reduction in pain scores with significant differences versus gabapentin alone ($p < 0.01$). Area under the curve (AUC) analyses of pain responses indicated prolonged analgesic effects in the combination groups, with the 31.6:31.6 mg/kg dose showing the most sustained relief. These findings support that sulforaphane enhances gabapentin's efficacy, providing stronger and longer-lasting analgesia in this fibromyalgia model, highlighting sulforaphane as a promising natural adjunct for pain management.

Murasawa et al in 2021, the use of gabapentinoids, specifically mirogabalin, shows potential as an off-label therapy for fibromyalgia, especially in addressing cognitive impairment ("fibro fog"). This study used a rat model of fibromyalgia (Sluka model) induced with repeated intramuscular acid injections, where the rats experienced a

decline in cognitive function similar to symptoms in fibromyalgia patients. Oral administration of mirogabalin at doses of 3 and 10 mg/kg for 13 days significantly improved the cognitive performance of rats on various behavioral tests, such as Y-maze, novel object recognition, Morris water maze, and step-through passive avoidance, so mirogabalin not only has potential as an analgesic for chronic pain in fibromyalgia, but can also improve cognitive impairment which is one of the main comorbidities in this syndrome. From a pharmacovigilance aspect, myrogabalin as part of the gabapentinoid group generally has a good safety profile in preclinical studies with minimal side effects in animal models, but off-label use of gabapentinoids in humans still requires close monitoring regarding the risk of side effects such as dizziness, drowsiness, impaired coordination, and potential drug interactions, so further studies in humans are needed to ensure its safety and clinical effectiveness.

The study by North et al in 2015, examined the effectiveness and safety of gabapentin extended-release (G-GR) in managing pain and sleep disturbances in fibromyalgia (FM) patients through a 15-week open study with 34 participants. Results showed significant reductions in pain scores (NPRS) and impact on quality of life (FIQ) from week 4, which persisted until the end of treatment. Improvements were also seen in sleep duration and quality based on the MOS Sleep Questionnaire, with significant improvement in sleep quality by week 12. Patient assessment via PGIC showed significant perceived improvement from week 8. Reported side effects were mostly mild and transient, such as drowsiness and dizziness, while the two serious events did not lead to disability. G-GR was also well tolerated by patients who were previously unable to continue gabapentinoid therapy due to side effects. Although the results are promising, limitations of this study include the non-controlled design, small sample size, short duration, and potential site bias, so larger, controlled clinical trials are needed for further confirmation.

DISCUSSION

Various therapeutic approaches have been evaluated in the management of fibromyalgia (FM), particularly focusing on the use of gabapentinoids. Research by Marske et al in 2018, showed that osteopathic manipulation therapy (OMM) and the combination of OMM with gabapentin had significant effectiveness in reducing pain and improving health perceptions of fibromyalgia patients, compared to the use of gabapentin alone which showed no significant changes. This indicates that non-pharmacologically based multimodal approaches may provide additional benefits in fibromyalgia patients, especially in the context of chronic musculoskeletal pain. Meanwhile, North et al in 2015, evaluated a new formulation of gabapentin extended-release (G-GR) and found that administration of G-GR significantly reduced pain scores, improved sleep quality, and improved the impact of fibromyalgia on patients' daily activities. The advantages of G-GR lie in its ease of use (single daily dose) and milder side effect profile, making it a more convenient option and potentially improving patient compliance.

Pre-clinical studies by Zamora-Díaz et al in 2025, provided evidence that the combination of sulforaphane (SFN), a bioactive compound from cruciferous vegetables, with gabapentin produced synergistic effects in relieving fibromyalgia pain in a rat model. This combination provided significant antihyperalgesic and antialodinic effects, even at lower doses of each drug when administered singly, as well as suggesting the involvement of calcium channels as a pharmacological mechanism. Meanwhile, Murasawa et al in 2021, evaluated mirogabalin-a novel ligand for the α2δ subunit of calcium channels-and found that it not only effectively relieved fibromyalgia pain, but also improved cognitive impairment (‘fibro fog’) in a mouse model. These four studies collectively emphasize the importance of holistic and innovative therapeutic approaches, both pharmacological and non-pharmacological, in managing the complexity of fibromyalgia

symptoms, as well as the need for continued research for broader clinical confirmation.

CONCLUSION

Based on the literature review of several analyzed studies, gabapentin, whether used alone, in combination with agents like OMM or sulforaphane, or in extended-release formulations, demonstrates significant potential in reducing pain and improving quality of life for fibromyalgia patients. Combination therapies tend to enhance pain relief compared to monotherapy, while extended-release gabapentin is effective even in patients who previously did not tolerate standard gabapentin. Additionally, mirogabalin, a newer gabapentinoid, shows promise in addressing cognitive impairments associated with fibromyalgia, with a favorable safety profile in preclinical studies. Despite these encouraging findings, limitations such as small sample sizes and open-label designs underscore the need for larger, randomized controlled trials to confirm long-term efficacy and safety. Overall, gabapentin and its derivatives represent promising treatment options for fibromyalgia, warranting further research to optimize their clinical use.

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