INTERNATIONAL JOURNAL OF MULTIDISCIPLINARY EVOLUTIONARY RESEARCH

Lithium in Fibromyalgia: Revisiting Historical Clinical Evidence, Potential Analgesic Mechanisms, and the Influence of Bipolar Disorder — A Critical Narrative Review

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Article Info

P-ISSN: 3051-3502
E-ISSN: 3051-3510
Volume: 07
Issue: 02
Received: 02-08-2026
Accepted: 03-09-2026
Published: 01-10-2026
Page No: 117-125

Abstract

Background: Fibromyalgia is a chronic condition characterized by widespread pain, fatigue, nonrestorative sleep, cognitive complaints, and functional impairment. Although lithium is primarily used as a mood stabilizer, historical clinical observations and contemporary findings have raised questions about its potential analgesic properties.

Objective: To critically evaluate the evidence concerning lithium and fibromyalgia, distinguishing direct clinical observations from indirect findings involving bipolar disorder, experimental models, and sleep-related outcomes.

Methods: A critical narrative review was conducted using historical full-text publications, identifiable contemporary observational studies, and experimental evidence. The literature was examined according to study design, diagnostic characterization, psychiatric comorbidity, concomitant treatment, reported outcomes, and methodological limitations. Particular attention was given to avoiding duplication of patients across related publications.

Results: Tyber described three women with fibromyalgia who experienced marked reductions in spontaneous pain and stiffness following lithium augmentation of ongoing antidepressant treatment. One patient also reported improvement in fatigability, whereas tender-point sensitivity persisted despite symptomatic relief. Subsequent publications by Lewis and Fontrier proposed mechanisms involving calcium–parathyroid hormone regulation without introducing additional treated patients. In 2004, Fontrier reported an individual experience of approximately 70–80% pain reduction, with rapid onset and limited duration. In the FACE-BD observational cohort, lithium exposure was associated with lower odds of reporting physical pain among patients with bipolar disorder (adjusted odds ratio 0.59; 95% confidence interval 0.35–0.95). Preliminary experimental findings and observational studies of sleep in bipolar disorder provide additional indirect evidence. However, controlled clinical evidence establishing lithium efficacy in fibromyalgia remains unavailable among the reviewed publications.

Conclusions: Historical clinical observations suggest a possible analgesic signal associated with lithium, but the available evidence is insufficient to establish causality, clinical efficacy, or independence from mood stabilization. The relationship between lithium and other fibromyalgia-related manifestations, including sleep disturbances, fatigue, cognition, and quality of life, remains inadequately investigated. Given the limited evidence and established safety concerns, lithium should remain an investigational intervention for fibromyalgia.

Keywords: Fibromyalgia, Lithium, Chronic Widespread Pain, Bipolar Disorder, Analgesia, Sleep Disturbances, Fatigue, Central Sensitization

1. Introduction

Fibromyalgia is a chronic pain condition characterized by widespread musculoskeletal pain accompanied by fatigue, nonrestorative sleep, cognitive complaints, and reduced physical functioning. Its clinical manifestations extend beyond pain and may substantially impair occupational performance, social participation, and health-related quality of life. The heterogeneity of symptoms and the absence of a single explanatory biological mechanism continue to complicate treatment, particularly among patients with persistent symptoms despite conventional interventions.

Current concepts emphasize altered central pain processing, including amplification of nociceptive signaling and disturbances in endogenous pain modulation. Nevertheless, these mechanisms do not fully account for the clinical complexity of fibromyalgia. Sleep disturbances, autonomic dysfunction, psychological factors, and neuroimmune interactions may contribute to symptom persistence and variability. This multidimensional framework has encouraged investigation of medications capable of influencing neuronal signaling and central pain regulation rather than acting exclusively through conventional peripheral analgesic mechanisms.

Lithium has attracted limited but longstanding interest in this context. Although primarily recognized for its role in the management of bipolar disorder, lithium influences several biological pathways involved in neuronal function, cellular adaptation, and circadian regulation. Its potential relevance to fibromyalgia emerged from historical observations suggesting that lithium augmentation might improve musculoskeletal pain in patients whose symptoms had responded inadequately to antidepressant treatment.

An earlier investigation by Tyber examined combined lithium and amitriptyline treatment in patients with painful shoulder syndrome, reporting clinical improvement in 44 of 56 treated individuals [1]. Although this population did not have fibromyalgia, the study illustrates the historical interest in lithium-containing treatment regimens for musculoskeletal pain. Because lithium was administered with amitriptyline, its independent contribution could not be determined.

In 1990, Tyber subsequently described three women with fibromyalgia who experienced substantial symptomatic improvement following lithium augmentation of ongoing tricyclic antidepressant treatment [2]. These observations were challenged in subsequent correspondence because of their uncontrolled design, incomplete reporting of patient selection, and potential psychiatric confounding [3]. Nevertheless, they introduced the hypothesis that lithium might influence fibromyalgia-related pain and stiffness.

Further interest developed through publications by Fontrier and Lewis, who initially explored potential associations between fibromyalgia and sunlight exposure [4] and later proposed mechanisms involving calcium and parathyroid hormone regulation [5, 6]. In 2004, Fontrier reported an individual experience of substantial pain reduction following lithium administration [7], providing an additional direct observation.

More recently, the FACE-BD study identified an association between lithium exposure and lower odds of reporting physical pain among patients with bipolar disorder [8]. Although this investigation did not specifically evaluate fibromyalgia, its findings renewed interest in whether lithium might influence pain perception through mechanisms extending beyond conventional mood stabilization.

The central question remains whether lithium has an intrinsic analgesic effect or whether historical improvements can be explained by antidepressant augmentation, stabilization of previously unrecognized affective symptoms, changes in sleep, or other uncontrolled influences. This distinction is particularly important because psychiatric comorbidity is common in chronic pain populations, whereas lithium has a narrow therapeutic index and potentially significant adverse effects.

The objective of this review is to critically reassess the historical clinical evidence concerning lithium in fibromyalgia, integrate relevant contemporary observational and experimental findings, and examine the biological plausibility of its proposed analgesic effects. Particular attention is given to psychiatric characterization, spontaneous pain versus evoked tenderness, and the limited evidence concerning fatigue, sleep, cognition, and quality of life.

2. Methods

2.1. Review Design and Scope

This article was developed as a critical narrative review addressing the potential relationship between lithium exposure and fibromyalgia-related symptoms. A narrative approach was selected because the directly relevant clinical literature consists predominantly of historical case reports, correspondence, and theoretical publications, whereas more recent quantitative investigations involve populations without confirmed fibromyalgia. The differences in study design, diagnostic characterization, and outcome assessment preclude meaningful quantitative pooling.

The review addressed three principal questions: whether lithium exposure has been associated with symptomatic improvement in patients diagnosed with fibromyalgia; whether findings in bipolar disorder provide indirect evidence of analgesic activity; and whether experimental or mechanistic observations offer plausible explanations for the reported clinical responses. Pain was considered the principal outcome, while sleep disturbances, fatigue, cognitive symptoms, and quality of life were examined when information was available.

2.2. Identification and Evaluation of Publications

The historical literature was evaluated through direct examination of the full texts of Tyber's 1990 case report [2], Teasell's subsequent correspondence [3], Fontrier and Lewis's 1998 communication [4], Lewis and Fontrier's 2003 research proposal [6], and Fontrier's 2004 letter [7]. These publications were considered central because they contain the principal historical observations connecting lithium with fibromyalgia and provide information that may be incompletely represented in bibliographic summaries.

Additional identifiable publications concerning lithium and physical pain in bipolar disorder, sleep-related outcomes, and experimental fibromyalgia models were incorporated to provide contemporary context. The evidence was organized according to its direct or indirect relevance to fibromyalgia, with particular emphasis on study design, psychiatric comorbidity, concomitant medication, reported clinical outcomes, and risk of bias.

This review was not conducted as a formally exhaustive systematic search across all international bibliographic databases. Accordingly, no claim is made regarding complete coverage of restricted or regional databases, and no systematic-review registration or PRISMA flow diagram is presented.

2.3. Evidence Classification and Synthesis

Direct clinical evidence required a reported diagnosis of fibromyalgia and an identifiable therapeutic observation involving lithium. Publications discussing previously reported patients without introducing new clinical observations were classified as commentary or hypothesis-generating literature. Studies involving bipolar disorder and nonspecific physical pain were classified as indirect

evidence, regardless of the strength of their statistical associations.

Psychiatric characterization was examined carefully because it represents an important potential source of confounding. In particular, the absence of a documented bipolar disorder diagnosis was not interpreted as evidence that bipolar disorder had been formally excluded. Similarly, improvements in sleep, fatigue, cognition, or quality of life were not inferred from reductions in pain unless those outcomes were explicitly described.

A qualitative synthesis was undertaken. No meta-analysis was performed because the available direct clinical evidence lacked controlled comparisons and standardized outcome measurements. Related publications were examined to avoid counting the same patients more than once.

3. Results

3.1. Historical Clinical Evidence Involving Fibromyalgia

The earliest directly relevant clinical publication was Tyber's 1990 report describing three women with fibromyalgia whose symptoms had responded inadequately to tricyclic antidepressants [2]. The author proposed lithium augmentation based partly on previous experience with antidepressant-resistant depression and musculoskeletal pain. All three patients subsequently reported substantial improvement in spontaneous pain and stiffness, although their clinical characteristics, psychiatric histories, and treatment responses differed.

The first patient was a 48-year-old woman with a long history of recurrent unipolar depression and three years of musculoskeletal symptoms, including widespread pain, stiffness, headaches, and reduced energy. At presentation, she was receiving amitriptyline and indomethacin without appreciable relief of pain. Following lithium augmentation, she experienced a marked reduction in pain, stiffness, and fatigability after approximately three months. However, previously identified tender points remained sensitive despite the improvement in spontaneous symptoms. Lithium was subsequently discontinued, and the patient continued to report only minimal intermittent symptoms 18 months later while remaining on amitriptyline [2].

This case is important because it documents improvement in fatigue in addition to pain and stiffness. It also suggests a possible dissociation between spontaneous pain and tenderness elicited during examination. Nevertheless, the coexistence of recurrent depression and ongoing antidepressant therapy complicates causal interpretation. Furthermore, persistent improvement after lithium discontinuation cannot establish a prolonged pharmacological effect because changes in the natural course of symptoms and concomitant treatment remain possible explanations.

The second patient was a 49-year-old woman with longstanding musculoskeletal pain following a motor vehicle accident. Her medical history included severe recurrent headaches and previous psychiatric hospitalizations, while clinical examination revealed motor restlessness, pressured speech, and unusual posturing. Lithium was added to ongoing trimipramine treatment, and approximately one year later she reported minimal joint symptoms and numerous pain-free days. Her affect and behavior also appeared more stable [2].

Among the three cases, this patient presents the greatest difficulty when attempting to separate analgesic effects from psychiatric influences. Although bipolar disorder was not formally diagnosed in the original publication, the psychiatric history and behavioral findings cannot be disregarded. Improvement in pain occurred alongside changes in affect and behavior, and the available information does not permit determination of whether these changes were causally related. Consequently, this case should not be interpreted as evidence of lithium efficacy in a patient with definitively excluded bipolar disorder.

The third patient was a 56-year-old woman with diffuse musculoskeletal pain and stiffness who had received several previous treatments, including amitriptyline and epidural corticosteroid injections. Perphenazine had previously produced symptomatic improvement but was discontinued because of akathisia. Following substitution with lithium, the patient experienced almost complete relief of spontaneous pain. However, treatment was complicated by tremor, and some pain and stiffness recurred after treatment adjustment. As in the first case, tenderness persisted at multiple sites despite substantial improvement in spontaneous symptoms [2].

Taken together, these observations suggest that lithium augmentation was temporally associated with improvement in spontaneous pain and stiffness in selected patients with fibromyalgia. Nevertheless, the report lacked a control group, blinded assessment, standardized outcome measurements, and systematic psychiatric evaluation. The use of concomitant medications further limits attribution of benefit specifically to lithium. Moreover, the total number of patients treated before these three favorable responses were identified was not reported, preventing estimation of response frequency and raising the possibility of selective reporting.

The individual clinical observations are summarized in Table 1.

3.2. Methodological Criticism and the Interpretation of Uncontrolled Observations

Teasell's 1991 correspondence challenged the interpretation of Tyber's findings and emphasized the risks of recommending lithium without controlled evidence [3]. The principal criticism concerned the absence of information about the total number of patients treated before the three favorable outcomes were observed. Without this denominator, the apparent success of the reported cases cannot be translated into an estimate of treatment effectiveness.

Tyber responded by defending the preliminary role of case reports and suggesting that lithium augmentation might warrant further investigation in patients with resistant fibromyalgia [3]. However, the exchange highlights an important distinction between observations capable of generating hypotheses and evidence sufficient to establish therapeutic efficacy.

Table 1: Direct clinical observations concerning lithium in fibromyalgia without confirmed bipolar disorder

Study / patient	Clinical and psychiatric characteristics	Main pain-related findings	Other outcomes	Principal limitations
Tyber, 1990 [2] — Case 1	48-year-old woman; recurrent unipolar depression; fibromyalgia refractory to ongoing treatment	Marked reduction in spontaneous pain and stiffness; minimal intermittent symptoms 18 months after lithium discontinuation	Reduced fatigability; tender-point sensitivity persisted	Concomitant antidepressant therapy; no standardized outcomes
Tyber, 1990 [2] — Case 2	49-year-old woman; longstanding pain after trauma; psychiatric hospitalizations and behavioral abnormalities	Minimal joint symptoms and numerous pain-free days after lithium augmentation	Improvement in affect and behavior	Major psychiatric confounding; bipolar disorder not formally characterized
Tyber, 1990 [2] — Case 3	56-year-old woman; diffuse musculoskeletal pain and stiffness	Near-complete initial relief of spontaneous pain; partial recurrence following treatment adjustment	Persistent tenderness; treatment-limiting tremor	Concomitant medication; adverse effects; uncontrolled
Fontrier, 2004 [7]	Individual self-report; longstanding fibromyalgia; bipolar disorder status not documented	Approximately 70–80% pain reduction; onset within 40 minutes; duration 4–5 hours	Pain-related sleep disruption described, but sleep response not independently measured	No control group, standardized assessment, or psychiatric characterization

Abbreviations: BD, bipolar disorder.

Note: The absence of a documented bipolar disorder diagnosis should not be interpreted as formal exclusion of the disorder. The four rows represent four individually described patients, not a prospective clinical cohort.

The correspondence did not introduce additional treated patients and should not be regarded as an independent clinical investigation. Its principal contribution was methodological, identifying concerns about uncontrolled treatment, uncertain reproducibility, incomplete patient selection information, and psychiatric confounding that remain relevant to the interpretation of the historical evidence.

3.3. Development of the Calcium–parathyroid Hypothesis

The publications by Fontrier and Lewis illustrate the evolution of a proposed biological explanation for fibromyalgia rather than the development of a substantial clinical evidence base. In 1998, the authors described observations concerning sunlight avoidance among women with fibromyalgia and proposed that reduced ultraviolet exposure might contribute to disease mechanisms through effects involving vitamin D metabolism and immune regulation [4]. Although historically relevant, this publication did not evaluate lithium treatment and should not be interpreted as evidence of therapeutic efficacy.

In 2001, Lewis and Fontrier published a further hypothesis concerning fibromyalgia [5]. Their subsequent 2003 publication explicitly revisited Tyber's three patients and proposed that lithium-associated changes in parathyroid hormone secretion might explain the reported symptomatic improvement [6]. The authors suggested that fibromyalgia could involve disturbances of calcium–parathyroid regulation and that the endocrine effects of lithium might therefore be therapeutically relevant.

The 2003 publication was a research proposal rather than a clinical trial. It did not describe a new patient series, independently assess treatment outcomes, or establish an endocrine abnormality as the cause of fibromyalgia. Consequently, the three patients discussed in that publication must not be counted separately from Tyber's original cases.

The proposed mechanism also requires critical interpretation. Lithium-associated changes in parathyroid hormone and calcium regulation are recognized pharmacological effects, but they may represent adverse endocrine consequences rather than beneficial therapeutic mechanisms. The observation that lithium can influence parathyroid physiology does not establish that such changes relieve fibromyalgia symptoms. Demonstrating this relationship would require prospective measurement of endocrine parameters and their association with clinical outcomes under controlled conditions.

3.4. Fontrier's 2004 Report: An Individual Observation of Rapid Pain Reduction

Fontrier's 2004 letter provides an additional direct clinical observation involving fibromyalgia [7]. Unlike the earlier theoretical publications, this communication described the author's personal experience with the condition over more than a decade. She reported that pain following excessive physical activity could become disabling, interfere with daily functioning, and prevent sleep. Previous treatments, including opioids, nonsteroidal anti-inflammatory drugs, and gabapentin, had not provided satisfactory relief.

The author reported approximately 70–80% pain reduction following lithium administration, with onset within 40 minutes and an effect lasting four to five hours. She described the response as reproducible and proposed that lithium-induced changes in parathyroid hormone secretion might contribute to the observed effect [7].

The rapid time course raises an interesting mechanistic question. If the reported response reflected a genuine pharmacological effect, it might involve processes distinct from the longer-term mood-stabilizing actions traditionally associated with lithium. However, the observation cannot establish such a distinction. The report did not include blinded assessment, a placebo comparison, standardized pain measurements, pharmacokinetic evaluation, or formal psychiatric characterization.

Furthermore, the fact that pain interfered with sleep does not demonstrate that lithium independently improved sleep quality. Similarly, no validated assessments of fatigue, cognitive function, or quality of life were reported. These outcomes must therefore remain classified as unassessed rather than assumed to have improved.

Fontrier was also a coauthor of the earlier theoretical publications. This relationship reinforces the importance of distinguishing the 2004 individual therapeutic observation from the preceding hypothesis-generating literature. Across the historical clinical publications examined, four individually described patients can be identified: three in Tyber's report and one in Fontrier's letter. This figure represents the number of published individual observations,

not the total number of patients who may have received lithium for fibromyalgia.

3.5. Lithium Exposure and Physical Pain in Bipolar Disorder

The FACE-BD study provides the most substantial quantitative evidence relevant to the hypothesis that lithium may influence pain perception. Risch and colleagues examined the association between lithium treatment and physical pain in a cohort of 760 individuals with bipolar disorder, including 176 lithium users [8]. Pain was assessed using the pain/discomfort dimension of the EQ-5D-5L questionnaire, and statistical analyses considered several potential confounding variables.

Lithium exposure was associated with lower odds of reporting physical pain, with an adjusted odds ratio of 0.59 and a 95% confidence interval of 0.35–0.95. A secondary analysis involving lithium concentrations of at least 0.5 mmol/L demonstrated a stronger association, with an adjusted odds ratio of 0.45 and a 95% confidence interval of 0.24–0.79 [8].

These findings are relevant because the association persisted after adjustment for several psychiatric and clinical variables. Nevertheless, statistical adjustment cannot eliminate all sources of confounding, and the cross-sectional design does not establish temporal sequence or causality. Differences in illness characteristics, concomitant medications, comorbid conditions, and other unmeasured factors may have influenced the results.

Most importantly, the study did not specifically evaluate patients with confirmed fibromyalgia or measure changes in fibromyalgia-related pain following lithium initiation. Physical pain in bipolar disorder encompasses heterogeneous conditions and cannot be assumed to represent fibromyalgia or central sensitization. Consequently, the FACE-BD findings constitute indirect evidence supporting further research rather than confirmation of lithium efficacy in fibromyalgia.

The concentration-related analysis also belongs to the same cohort and should not be counted as an independent investigation. These findings are summarized in Table 2.

Table 2: Evidence involving lithium and physical pain in bipolar disorder

Study	Population and design	Fibromyalgia-specific assessment	Main findings	Interpretation
Risch et al., 2024 [8] — FACE-BD	Cross-sectional observational study; 760 patients with bipolar disorder, including 176 lithium users	No confirmed fibromyalgia-specific treatment analysis	Lithium exposure associated with lower odds of physical pain: adjusted OR 0.59 (95% CI 0.35–0.95)	Indirect evidence; causality cannot be established
FACE-BD concentration analysis [8]	Secondary analysis of the same cohort	No fibromyalgia-specific treatment analysis	Lithium concentration ≥0.5 mmol/L associated with lower odds of physical pain: adjusted OR 0.45 (95% CI 0.24–0.79)	Not an independent cohort
Direct controlled studies in fibromyalgia with confirmed BD	No eligible controlled investigation established from the reviewed evidence	Not applicable	No reliable treatment estimate available	Major evidence gap

Abbreviations: BD, bipolar disorder; CI, confidence interval; OR, odds ratio.
Note: FACE-BD assessed physical pain in bipolar disorder rather than lithium efficacy in confirmed fibromyalgia.

3.6. Experimental Evidence and Potential Effects on Nociception

Experimental research provides an additional perspective on whether lithium may influence pain-related processes independently of its established psychiatric indications. Jha presented findings concerning lithium exposure in a reserpine-induced rat model intended to reproduce selected fibromyalgia-like nociceptive abnormalities [9]. The conference abstract reported antinociceptive findings, suggesting that lithium may influence behavioral responses to painful stimuli in an experimental setting.

This observation is relevant because experimental models permit investigation of nociceptive mechanisms without requiring a clinical diagnosis of bipolar disorder. Nevertheless, animal models reproduce only selected features of fibromyalgia and cannot fully capture the disorder's subjective, cognitive, emotional, and functional dimensions. Moreover, publication as a conference abstract limits assessment of methodological details, sample characteristics, statistical procedures, and reproducibility.

The experimental findings should therefore be considered preliminary. They support the biological plausibility of further investigation but cannot establish clinical analgesic efficacy or determine the benefit–risk balance in patients with fibromyalgia.

3.7. Sleep Disturbances and Circadian Regulation

Sleep disturbances are among the most clinically significant manifestations of fibromyalgia. Nonrestorative sleep may contribute to fatigue, cognitive complaints, reduced pain tolerance, and impaired daily functioning. The relationship between sleep and pain is bidirectional: persistent pain can disrupt sleep, while inadequate sleep may increase pain sensitivity and worsen symptom burden. Consequently, an intervention that modifies sleep regulation could theoretically influence several fibromyalgia-related outcomes.

Lithium has established effects on biological rhythms, and observational investigations in bipolar disorder have examined its relationship with sleep characteristics. Geoffroy and colleagues evaluated sleep and chronotype measures in 525 euthymic patients with bipolar disorder and reported associations between lithium exposure and selected sleep parameters, particularly sleep efficiency in certain subgroups [10].

More recently, Gokcay and colleagues compared sleep characteristics among 130 patients with bipolar disorder receiving lithium or valproic acid. The study identified better habitual sleep efficiency and fewer sleep disturbances among lithium-treated individuals, although total sleep duration and sleep latency did not differ significantly between groups [11].

These findings provide a rationale for investigating sleep-related outcomes in fibromyalgia, but their interpretation requires caution. Sleep disturbances in bipolar disorder may reflect mood instability, psychiatric comorbidity, medication effects, or circadian dysregulation that differs from the mechanisms underlying nonrestorative sleep in fibromyalgia. Furthermore, observational associations do not establish that lithium directly improves sleep or that any improvement is independent of mood stabilization.

The direct fibromyalgia literature provides even less information. Tyber did not systematically assess sleep outcomes [2], while Fontrier described pain severe enough to prevent sleep without demonstrating a separate therapeutic effect on sleep quality [7]. Thus, despite plausible biological links, there is insufficient direct evidence to conclude that lithium improves fibromyalgia-related sleep disturbances.

The experimental and sleep-related findings are summarized in Table 3.

Table 3: Historical hypotheses, experimental findings, and indirect evidence relevant to lithium and fibromyalgia

Publication	Study type	Domain	Principal contribution	Relevance to fibromyalgia
Tyber, 1974 [1]	Historical clinical study	Musculoskeletal pain	Examined combined lithium–amitriptyline treatment in painful shoulder syndrome	Not fibromyalgia-specific; lithium contribution cannot be isolated
Teasell, 1991 [3]	Methodological correspondence	Evidence appraisal	Identified limitations in the interpretation of Tyber's three cases	No independent treated patients
Fontrier and Lewis, 1998 [4]	Historical correspondence	Etiology	Proposed association involving sunlight avoidance and ultraviolet exposure	Mechanistic background; no lithium treatment data
Lewis and Fontrier, 2001 [5]	Research hypothesis	Pathophysiology	Proposed a theoretical explanation for fibromyalgia	No therapeutic trial
Lewis and Fontrier, 2003 [6]	Research hypothesis	Endocrine mechanisms	Proposed a role for lithium-associated parathyroid hormone changes	No new clinical patients or efficacy data
Jha, 2023 [9]	Experimental conference abstract	Nociception	Reported preliminary antinociceptive findings in a reserpine-induced animal model	Preclinical evidence
Geoffroy et al., 2016 [10]	Observational study	Sleep	Identified associations between lithium exposure and selected sleep parameters in bipolar disorder	Indirect evidence
Gokcay et al., 2025 [11]	Comparative observational study	Sleep	Reported favorable associations with selected sleep-quality measures among lithium-treated bipolar patients	Indirect evidence

3.8. Fatigue, Cognitive Symptoms, and Quality of Life

Fatigue is a major determinant of disability in fibromyalgia and frequently persists even when pain is partially controlled. It may involve physical exhaustion, reduced endurance, mental fatigue, and difficulties maintaining daily activities. The historical evidence concerning lithium and fatigue is limited but not entirely absent. In Tyber's first case, the patient experienced a marked reduction in fatigability alongside improvements in pain and stiffness [2]. This observation is relevant because it demonstrates that lithium-associated changes were not restricted to pain in every reported patient.

However, the improvement was described qualitatively and was not measured using a validated fatigue instrument. The patient's history of recurrent depression and continued antidepressant treatment also complicates interpretation. No controlled study established whether lithium independently improves fatigue in fibromyalgia, and potential adverse effects could themselves worsen energy levels or functional performance.

Cognitive symptoms represent another important but insufficiently investigated domain. Patients with fibromyalgia commonly report difficulties with attention, memory, concentration, and mental processing. Although lithium influences neuronal signaling and plasticity, these biological actions cannot be equated with clinical cognitive benefit. The historical reports did not systematically assess cognition, and no verified controlled evidence demonstrates improvement in fibromyalgia-related cognitive dysfunction attributable to lithium.

Similarly, reductions in pain do not necessarily imply improvements in overall quality of life. Fibromyalgia affects multiple domains, and a treatment that improves one symptom may have limited impact on global functioning or may introduce adverse effects that offset its benefits. The available direct clinical reports did not use validated multidimensional instruments to evaluate overall disease impact. Consequently, any conclusion regarding lithium-associated improvement in quality of life would exceed the evidence.

4. Discussion

4.1. Reappraising the Historical Evidence

The historical literature concerning lithium and fibromyalgia is more informative than its small size might initially suggest, but its findings require careful interpretation. Tyber's report provides individual clinical descriptions demonstrating substantial improvement in spontaneous pain and stiffness following lithium augmentation [2], while Fontrier's subsequent personal account describes a rapid and reproducible analgesic response [7]. Together, these observations provide a basis for generating hypotheses about lithium-related pain modulation.

Nevertheless, the evidence remains exceptionally limited. Four individually described patients cannot establish a reliable estimate of treatment efficacy, particularly when the total number of exposed patients is unknown and favorable responses may have been selectively reported. The absence of control groups, standardized assessments, and systematic

psychiatric characterization substantially limits causal inference.

An important contribution of the present reassessment is the clarification that several historical publications represent discussion of the same observations rather than independent therapeutic investigations. Lewis and Fontrier's 2003 article explicitly revisited Tyber's cases [6], while the 1998 communication concerned a different etiological hypothesis [4]. Recognizing these distinctions prevents an exaggerated impression of the evidence base and allows a more accurate account of how the lithium hypothesis developed.

The historical findings should therefore be regarded neither as proof of efficacy nor as observations without scientific value. Their principal contribution is to identify clinical phenomena that may justify carefully controlled investigation.

4.2. Can Lithium-Associated Analgesia Be Separated from Mood Stabilization?

The possibility of an analgesic effect independent of mood stabilization is the most important unresolved question raised by this literature. Lithium's established psychiatric effects provide a plausible alternative explanation for improvements in pain, particularly among patients with depression, affective instability, or previously unrecognized bipolar symptoms. Because mood, sleep, and pain perception are closely interconnected, improvement in one domain may influence the others without requiring a direct analgesic action.

Tyber's cases illustrate this difficulty. The first patient had recurrent unipolar depression, while the second had a significant psychiatric history and behavioral findings that were not fully characterized diagnostically [2]. Improvements in pain occurred during ongoing treatment with psychotropic medications, making it impossible to isolate lithium's contribution. The third patient had previously responded to perphenazine, further demonstrating that changes in symptoms occurred in a context involving centrally acting medications.

Fontrier's report offers a different perspective because the described analgesic response occurred rapidly [7]. Such a time course is not readily explained by the conventional long-term framework of mood stabilization, but it does not establish a direct nociceptive mechanism. Expectation effects, symptom variability, and other uncontrolled influences remain possible.

The FACE-BD study strengthens the rationale for further investigation by demonstrating an association between lithium exposure and lower pain reporting after adjustment for several psychiatric variables [8]. However, statistical adjustment cannot establish mechanistic independence. A definitive answer would require prospective studies measuring pain and mood simultaneously, with sufficient temporal resolution to determine whether analgesic changes precede, accompany, or occur independently of changes in affective symptoms.

4.3. Potential Mechanisms Involving Intracellular Signaling and Neuroplasticity

Lithium influences intracellular signaling pathways that participate in neuronal adaptation, cellular stress responses, and synaptic function. Among these, modulation of glycogen synthase kinase-3β has attracted attention because this enzyme contributes to processes relevant to neuronal signaling and plasticity. Such pathways may intersect with mechanisms implicated in chronic pain, including altered central processing and changes in neuronal responsiveness.

However, the relationship between lithium's molecular actions and fibromyalgia remains largely theoretical. Fibromyalgia is not a single-pathway disorder, and the presence of a pharmacological effect on a signaling system does not demonstrate that the same effect will improve clinical symptoms. In addition, the historical clinical reports did not measure intracellular signaling, inflammatory biomarkers, or neurophysiological correlates of treatment response.

A rigorous mechanistic investigation would therefore need to connect biological changes with clinically meaningful outcomes rather than relying on molecular plausibility alone. Experimental findings such as those reported by Jha [9] may help identify candidate pathways, but translation to human fibromyalgia requires controlled clinical evidence.

4.4. The Calcium–parathyroid Hypothesis: Historical Significance and Contemporary Limitations

The hypothesis proposed by Lewis and Fontrier deserves discussion because it represents a specific mechanistic explanation developed directly from the historical clinical observations. The authors suggested that lithium-associated increases in parathyroid hormone might account for symptomatic improvement and proposed that fibromyalgia could involve abnormalities of calcium–parathyroid regulation [5, 6].

This hypothesis is scientifically interesting but remains unsubstantiated. The fact that lithium can influence parathyroid hormone secretion does not establish that fibromyalgia is a form of hypoparathyroidism or that increasing parathyroid hormone would improve its symptoms. Moreover, lithium-associated hyperparathyroidism and hypercalcemia are recognized clinical concerns. Endocrine changes that might initially appear mechanistically relevant could therefore represent adverse effects rather than therapeutic benefits.

The distinction is important because a proposed mechanism should be evaluated against the complete pharmacological profile of the medication. Future studies examining this hypothesis would need to assess calcium and parathyroid hormone regulation alongside pain outcomes and determine whether any association is independent of other biological or psychiatric factors.

4.5. A Possible Distinction Between Spontaneous Pain and Evoked Tenderness

One of the most intriguing findings in Tyber's report is the apparent dissociation between spontaneous pain and tender-point sensitivity [2]. Patients described substantial relief of pain and stiffness, yet tenderness remained detectable at previously identified sites. Although the historical examination methods were not designed to distinguish contemporary pain-processing mechanisms, this observation raises questions about whether different components of fibromyalgia pain may respond differently to pharmacological intervention.

Spontaneous pain reflects an ongoing subjective experience, whereas tenderness elicited during examination depends on responses to applied mechanical stimulation. These outcomes may overlap but are not interchangeable. A treatment might

alter the intensity or unpleasantness of ongoing pain without producing an equivalent change in experimentally evoked sensitivity.

This possibility remains speculative, particularly because the historical reports lacked standardized quantitative sensory testing. Nevertheless, the observation supports a methodological recommendation for future trials: pain intensity should not be the only sensory outcome. Investigations could also assess evoked pain sensitivity and related measures, allowing researchers to determine whether any therapeutic effect is generalized or restricted to particular dimensions of pain.

4.6. Sleep, Fatigue, and the Broader Symptom Burden

A central limitation of the available literature is its predominant focus on pain. Fibromyalgia is a multidimensional condition, and clinically meaningful improvement requires consideration of fatigue, sleep, cognition, and daily functioning. The historical reports provide limited information concerning these domains, while the contemporary observational studies involve psychiatric populations rather than patients with confirmed fibromyalgia. Lithium's effects on circadian regulation make sleep a particularly relevant area for future investigation. Nevertheless, it remains unclear whether the associations observed in bipolar disorder [10, 11] would translate into improvements in nonrestorative sleep in fibromyalgia. Similarly, the reduction in fatigability reported in one of Tyber's patients [2] is insufficient to establish a reproducible effect on fatigue.

Future clinical trials should therefore avoid relying exclusively on pain reduction. A comprehensive assessment would allow investigators to determine whether lithium produces a broader improvement in fibromyalgia symptoms, has effects limited to pain, or introduces adverse effects that compromise other domains of functioning.

4.7. Safety Considerations and the Threshold for Clinical Adoption

Any potential benefit of lithium in fibromyalgia must be evaluated in the context of its established safety profile. Lithium has a narrow therapeutic index and may be associated with renal, thyroid, neurological, and metabolic complications. Changes in calcium and parathyroid hormone regulation are particularly relevant given the historical mechanistic hypothesis.

The third patient in Tyber's report developed tremor that limited treatment tolerability [2], illustrating that adverse effects were already apparent in the earliest clinical observations. Long-term safety is especially important in fibromyalgia because the condition commonly requires prolonged management and may coexist with other medical conditions and medication exposures.

The current evidence does not establish an acceptable benefit–risk balance for lithium in fibromyalgia. Historical reports of symptomatic improvement, even when clinically striking, are insufficient to justify routine use of a medication with substantial monitoring requirements and potentially serious adverse effects. Accordingly, lithium should be considered an investigational intervention rather than an established treatment for fibromyalgia.

4.8. Implications for Future Clinical Research

The most important next step is a prospective randomized controlled trial specifically designed to evaluate lithium in patients with fibromyalgia. Such a study should use contemporary diagnostic criteria, standardized psychiatric assessment, and clearly defined eligibility criteria. Patients with confirmed bipolar disorder should either be studied separately or incorporated into a design capable of examining psychiatric comorbidity as a prespecified factor.

Pain intensity should be assessed using validated instruments, with additional evaluation of pain interference, sleep quality, fatigue, cognitive symptoms, physical functioning, and health-related quality of life. The temporal relationship between changes in pain and mood should be examined to help determine whether any analgesic effect is independent of mood stabilization.

Safety monitoring would need to be comprehensive, and treatment-related adverse effects should be evaluated alongside potential benefits. Mechanistic substudies could explore endocrine parameters, neurobiological signaling, and measures of pain processing, but such investigations should complement rather than replace clinically meaningful outcomes.

Given the limited existing evidence, an initial feasibility study may be appropriate before undertaking a larger efficacy trial. Such a study could help determine whether the historical analgesic signal is reproducible under controlled conditions and whether further clinical development is justified.

5. Strengths and Limitations

The principal strength of this review is the direct reassessment of the historical publications that established the proposed relationship between lithium and fibromyalgia. Examination of the original reports allows a more accurate description of individual clinical responses, psychiatric comorbidity, concomitant treatment, adverse effects, and symptom domains. It also clarifies that the publications by Lewis and Fontrier do not constitute multiple independent clinical series, thereby preventing duplication of patients and overestimation of the available evidence.

The review also distinguishes direct observations in fibromyalgia from indirect findings in bipolar disorder and experimental models. This separation is particularly important because the FACE-BD study provides the strongest quantitative association involving lithium and pain [8] but does not establish efficacy in fibromyalgia. Similarly, sleep-related findings in bipolar disorder [10, 11] cannot be assumed to apply to nonrestorative sleep in fibromyalgia.

The limitations are substantial. The direct clinical evidence consists of uncontrolled historical observations involving only four individually described patients. The original publications did not use contemporary diagnostic criteria or standardized multidimensional outcome measures, and psychiatric comorbidity was incompletely characterized. Concomitant treatments, selective reporting, and other sources of bias prevent reliable causal interpretation.

Furthermore, the mechanistic evidence remains indirect, and the experimental findings are preliminary. The literature identification process was not a fully reproducible systematic search across all international databases. Therefore, this review should be interpreted as a critical narrative synthesis

of identifiable evidence rather than an exhaustive systematic assessment of all published and unpublished studies.

6. Conclusion

The historical literature suggests that lithium exposure may be associated with substantial reductions in spontaneous pain and stiffness in selected patients with fibromyalgia. The most informative direct observations involve three patients described by Tyber [2] and one individual described by Fontrier [7]. Although these reports are clinically intriguing, they are uncontrolled and insufficient to establish therapeutic efficacy. The persistence of tender-point sensitivity despite improvement in spontaneous pain, together with the rapid analgesic response described in the individual report, raises questions about potential effects on pain processing that warrant further investigation.

Contemporary observational findings in bipolar disorder [8] and preliminary experimental evidence [9] provide additional biological and clinical rationale for studying lithium-related analgesia. However, they do not demonstrate efficacy in fibromyalgia or establish that any analgesic effect occurs independently of mood stabilization. Evidence concerning fatigue, sleep, cognition, and quality of life remains particularly limited.

Given lithium's established adverse-effect profile and the absence of controlled efficacy data, routine treatment of fibromyalgia with lithium cannot be supported. The available evidence justifies carefully designed clinical research, but not clinical adoption.

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and materials: This narrative review is based on previously published literature. The historical publications examined are identified in the reference list.

Funding: To be confirmed by the authors.

Conflicts of interest: To be confirmed by the authors.

Authors' contributions: To be completed after confirmation of the authorship list.

Use of artificial intelligence: The manuscript was initially conceptualized in Portuguese and subsequently developed in English with AI-assisted language support. Responsibility for scientific interpretation, accuracy of the references, and approval of the final manuscript remains with the author.

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How to Cite This Article

De Carvalho JF. Lithium in fibromyalgia: revisiting historical clinical evidence, potential analgesic mechanisms, and the influence of bipolar disorder—a critical narrative review. International Journal of Multidisciplinary Evolutionary Research. 2026;7(2):117-125.

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