Jurnal Ners Volume 10 Nomor 1 Tahun 2026 Halaman 2238 - 2247
JURNAL NERS
Research & Learning in Nursing Science
http://journal.universitaspahlawan.ac.id/index.php/ners

NEUROPATHIC PAIN IN LEPROSY: PREVALENCE, PATTERNS, AND IMPACT IN THE WORLD'S THREE MOST AFFECTED COUNTRIES

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Abstract

Leprosy remains highly endemic in India, Brazil, and Indonesia, where neurological complications continue to drive long-term disability despite the availability of effective multidrug therapy. Neuropathic pain has increasingly been recognized as a major contributor to morbidity among individuals affected by leprosy; however, evidence from the highest-burden regions remains fragmented. This study aims to systematically synthesize current evidence on the burden, characteristics, and impact of neuropathic pain in people with leprosy in India, Brazil, and Indonesia. A systematic search was conducted in PubMed, Cochrane Library, and ScienceDirect using predefined terms related to leprosy and neuropathic pain. Eligible studies assessed neuropathic pain using validated diagnostic tools or structured clinical evaluation, with data extracted using a standardized template and risk of bias assessed based on observational study criteria. Thirteen studies met the inclusion criteria, reporting neuropathic pain prevalence ranging from 21.8% to 75%, depending on diagnostic methods. Common symptoms included burning pain, tingling, electric-shock sensations, and dysesthesia, frequently accompanied by sensory loss and nerve thickening. Notably, neuropathic pain often persisted after completion of multidrug therapy, indicating ongoing neural dysfunction beyond bacteriological cure. Overall, neuropathic pain represents a prevalent, disabling, and under-addressed complication of leprosy, highlighting the urgent need for routine screening, long-term follow-up, and integrated multidisciplinary care in high-burden countries.

Keywords: *Leprosy, Neuropathic Pain, DN4, Quality Of Life, India-Brazil-Indonesia*

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INTRODUCTION

Leprosy continues to pose a substantial clinical and public health challenge, particularly in countries where transmission remains entrenched despite sustained efforts to eliminate the disease. More than 200,000 new cases are detected annually, a figure that has remained relatively stable over the past decade and underscores the persistent endemicity of the disease (World Health Organization, 2021). The global distribution of leprosy is strikingly uneven: India, Brazil, and Indonesia collectively account for more than 80% of new cases, reflecting a combination of population size, environmental determinants, health system capacity, and historical transmission patterns (Smith & Aerts, 2014). In these settings, the focus of leprosy control has shifted from purely bacteriological cure to long-term management of neurological and functional consequences that continue to affect patients well beyond treatment completion.

The pathobiology of leprosy is uniquely characterized by the affinity of Mycobacterium leprae for Schwann cells, the glial cells responsible for nurturing and insulating peripheral nerve fibers (Scollard et al., 2006). Schwann-cell invasion disrupts their normal function, impairing myelination and leading to progressive axonal degeneration (Souza et al., 2022). Over time, this results in structural alterations of the nerve fascicles, such as edema, fibrosis, and fascicular distortion. These changes compromise neural conductivity and induce both sensory and motor deficits. Beyond direct bacterial invasion, immune-mediated mechanisms, particularly during type 1 (reversal) reactions, trigger inflammatory swelling that further compresses peripheral nerves. Type 2 reactions, including erythema nodosum leprosum, add another layer of inflammatory stress, exacerbating neural injury through immune complex deposition and systemic inflammatory cascades (Lockwood & Saunderson, 2012). These processes together help explain why patients frequently experience progressive neuropathy even after microbiological cure has been achieved with multidrug therapy (MDT).

Among the spectrum of neural complications in leprosy, neuropathic pain (NP) has emerged as one of the most disabling yet under-recognized manifestations. Studies across endemic countries indicate that NP affects a substantial proportion of patients, with prevalence estimates typically ranging from 20% to over 50% depending on diagnostic criteria and population characteristics (Lasry-Levy et al., 2011). Unlike numbness or motor impairment, which are often attributed to structural damage, NP reflects ongoing pathological activity within somatosensory pathways. Many patients describe burning, electric-shock sensations, pins-and-needles, tingling, and thermal dysesthesia, all of which are characteristic of small- and large-fiber dysfunction (Haroun et al., 2019). These symptoms may develop at any stage of the disease: prior to diagnosis, during MDT, or months to years after treatment completion. Their persistence is often a marker of unresolved or recurrent peripheral nerve inflammation.

A noteworthy complication in diagnosing and managing NP in leprosy is the dissociation between symptoms and neurophysiological findings. Traditional nerve conduction studies (NCS), which predominantly assess large-fiber function, may appear normal even in patients with severe subjective pain (Giesel et al., 2018). This discrepancy highlights the importance of small-fiber involvement, which cannot be reliably captured by routine electrophysiology. Advanced assessments such as quantitative sensory testing (QST) and sensory profiling have demonstrated early and pronounced abnormalities in cold, warm, and tactile thresholds in affected patients, supporting the presence of significant small-fiber pathology even when NCS results are within normal limits (Giesel et al., 2018; Haroun et al., 2019). These insights underline the need for more sensitive tools and standardized approaches to detecting NP in leprosy.

The diagnosis of neuropathic pain relies considerably on validated screening instruments. The Douleur Neuropathique 4 (DN4) questionnaire is the most widely adopted tool in leprosy-endemic regions due to its ease of use and high diagnostic accuracy (Bouhassira et al., 2005). Other tools, such as the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), Neuropathic Pain Symptom Inventory (NPSI), and structured neurological examinations, are also employed in different research contexts. Despite the availability of these instruments, substantial heterogeneity in diagnostic methodologies persists across studies. Some investigations rely heavily on symptom-based screening, while others incorporate detailed clinical, electrophysiological, or psychophysical assessments. This inconsistency complicates the comparison of NP prevalence across settings and limits the ability to generalize findings globally.

Beyond physical discomfort, neuropathic pain in leprosy has profound consequences for daily functioning, social participation, and psychological well-being. Functional impairments include reduced hand dexterity, difficulty walking due to lower-limb neuropathy, and limitations in performing essential tasks that affect occupational roles and independence (Haroun et al., 2019; Lasry-Levy et al., 2011). Chronic NP contributes heavily to diminished quality of life, with patients frequently reporting restrictions in mobility, sleep disruption, fatigue, and general health decline (Araújo et al., 2024). Psychological morbidity, including depression, anxiety, and emotional distress, has been repeatedly documented among individuals living with chronic leprosy neuropathy, reinforcing the multifaceted nature of the burden imposed by NP. These psychosocial sequelae often persist in parallel with physical symptoms, creating a cycle of disability that significantly impacts long-term outcomes.

Despite growing awareness of these issues, the literature on neuropathic pain in leprosy remains fragmented and unevenly distributed. Many studies originate from single-center research

programs with limited generalizability, and few cross-national comparisons exist. Variability in assessment tools, study populations, and reporting practices further complicates efforts to synthesize existing knowledge. As a result, there is a clear need for a structured and region-focused synthesis that integrates evidence from the countries most affected by leprosy.

To address this gap, the present systematic review synthesizes available data from India, Brazil, and Indonesia, the three highest-burden countries worldwide. The objective is to provide a comprehensive and regionally relevant overview of the prevalence, clinical characteristics, sensory profiles, functional consequences, and psychological impact of neuropathic pain in individuals living with leprosy. By consolidating evidence from these diverse but high-priority settings, this review aims to support improved screening strategies, inform clinical decision-making, and guide future research and policy in neuropathic pain management within leprosy-endemic regions.

METHOD

This systematic review was conducted to synthesize evidence on the prevalence, clinical characteristics, and functional consequences of neuropathic pain among individuals affected by leprosy in India, Brazil, and Indonesia. The review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and followed a predefined protocol. Eligibility criteria were developed using the PICO framework, including individuals diagnosed with leprosy across all Ridley–Jopling classifications and disability grades, involving adults and adolescents residing in the three target countries. The exposure of interest was neuropathic pain, identified through validated screening tools such as DN4, LANSS, NPSI, or painDETECT, structured neurological examinations, or explicit clinical diagnosis by trained examiners. Eligible studies included cross-sectional, cohort, and retrospective designs, while case reports, reviews, editorials, conference abstracts, animal studies, and studies without pain-related outcomes were excluded.

A comprehensive literature search was conducted in PubMed, Cochrane Library, and ScienceDirect from inception to November 2025 using combinations of controlled vocabulary and free-text terms related to leprosy, neuropathic pain, and endemic countries, without language or year restrictions. All retrieved records were managed in a reference manager, duplicates were removed, and two reviewers independently screened titles, abstracts, and full texts for eligibility. Data extraction was performed using a standardized form capturing study characteristics, participant profiles, diagnostic methods, neuropathic pain prevalence and severity, sensory descriptors, functional impairment, disability, and quality-of-life or psychological outcomes.

Risk of bias was assessed using a modified checklist for observational studies, focusing on sampling methods, clarity of neuropathic pain diagnosis, completeness of outcome reporting, handling of confounding factors, and appropriateness of statistical analyses. Studies were categorized as having low, moderate, or high risk of bias, and quality assessments were incorporated into result interpretation. Due to heterogeneity in diagnostic tools, populations, and outcome measures, a qualitative narrative synthesis was undertaken, grouping findings where comparable instruments were used, while quantitative pooling was not performed.

RESULT AND DISCUSSION

Study Selection

Database searching identified 450 records (PubMed 349, Cochrane Library 5, ScienceDirect 96). After screening titles and abstracts, 432 articles were excluded for not addressing neuropathic pain, involving non-leprosy populations, or lacking clinical relevance. Eighteen articles were reviewed for duplication, and three duplicates were removed. A total of 15 full-text articles underwent eligibility assessment, of which two were excluded due to inappropriate participant characteristics or interventions unrelated to neuropathic pain evaluation. Consequently, 13 studies met the inclusion criteria and were synthesized qualitatively (Figure 1).

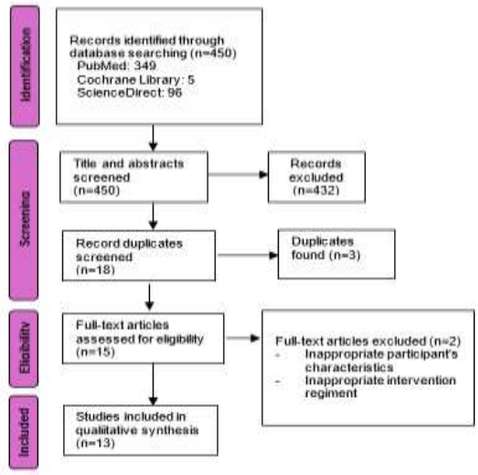

Figure 1. Diagram flow of literature search strategy for this systematic review

Characteristics of Included Studies

Table 1. Characteristics and Summary of Findings of Included Studies on Neuropathic Pain in Leprosy Across India, Brazil, and Indonesia

First Author (Year)	Country	Study Design	Population & Setting	Sample Size (N)	NP Data Reported	Key Findings

Dalimunthe et al. (2023)	Indonesia	Cross-sectional descriptive	Adults with leprosy neuropathy attending three referral hospitals in Medan	21	Yes	Neuropathic symptoms were reported by 95.2% of participants, predominantly affecting bilateral lower extremities with symptom duration ≤1 year. All patients were multibacillary, many had prior reactions, and neuropathy persisted after completion of MDT (RFT).
Tiago et al. (2021)	Brazil	Cross-sectional	Adults with relapse or treatment-failure leprosy at a referral hospital; compared with healthy controls	55	Yes	Neuropathic pain prevalence was 52.7%, mostly moderate–severe. Sensory symptoms were common, motor impairment and disability affected 81.4%, and thermography demonstrated limb temperature asymmetry consistent with autonomic dysfunction.
Raicher et al. (2018)	Brazil	Cross-sectional comparative	Adults with leprosy-related NP compared with NP from other etiologies	94 leprosy NP + 75 controls	Yes	Leprosy-related NP showed symptom profiles comparable to other neuropathic conditions, was chronic and often persisted after MDT, and responded best to amitriptyline among treatments used.
Santos et al. (2016)	Brazil	Cross-sectional	Adults attending two leprosy reference centers, during and after MDT	260	Yes	Pain prevalence was 75%, with neuropathic pain in 85% of pain cases. NP was associated with disability, leprosy reactions, and significantly reduced quality of life; inappropriate steroid use was common.
Pitta et al. (2022)	Brazil	Retrospective cohort	Pure neural leprosy vs other clinical forms at Fiocruz	119	Yes	NP occurred in 25% of pure neural leprosy and 19.2% of other forms, often after MDT, and was strongly associated with prior neuritis and multiple nerve involvement.
Somensi et al. (2022)	Brazil	Prospective cross-sectional	Adults with DN4-positive NP recruited from referral centers	21	Yes	Despite high pain severity, electrophysiological abnormalities were modest. Absent sympathetic skin response indicated autonomic involvement, and pain intensity was higher in women and corticosteroid users.
Toh et al. (2018)	Nepal	Cross-sectional	Adults previously treated for leprosy (RFT)	85	Yes	NP prevalence was 35.3% and was strongly associated with poor sleep, reduced quality of life, and higher depression scores, indicating substantial long-term psychosocial burden.
Lubis et al. (2023)	Indonesia	Cross-sectional analytical	Adults with multibacillary leprosy at a referral center	43	Yes	Neuropathic symptoms were common, especially numbness, tingling, and burning pain. Higher serum neurofilament light levels correlated with greater neuropathy severity.
Lasry-Levy et al. (2011)	India	Cross-sectional prevalence	Adults who completed MDT at Bombay Leprosy Project clinics	101	Yes	NP prevalence was 21.8%. Symptoms included numbness and tingling, and NP was associated with nerve enlargement and psychological morbidity. DN4 showed high diagnostic accuracy.
Haroun et al. (2019)	India	Cross-sectional phenotyping	Adults with and without leprosy pain undergoing sensory testing	86	Yes	Sensory loss to thermal and tactile stimuli with preserved deep pressure suggested small-fiber involvement. NP was associated with poorer quality of life.
Giesel et al. (2018)	Brazil	Cross-sectional	Adults with leprosy-related NP at a referral clinic	42	Yes	Severe burning pain was common, with marked sensory impairment and frequent persistence after MDT. Normal nerve conduction in some cases

					supported small-fiber neuropathy.
Pallavi et al. (2024)	India	Cross-sectional	Adults with Hansen's disease evaluated for peripheral neuropathy	126	No	The study focused on electrophysiological neuropathy patterns and did not assess neuropathic pain prevalence or characteristics.
Juliyanti et al. (2019)	Indonesia	Cross-sectional analytical	Adults with leprosy undergoing ENMG evaluation	50	No	Mixed axonal–demyelinating polyneuropathy was observed, but neuropathic pain outcomes were not assessed.

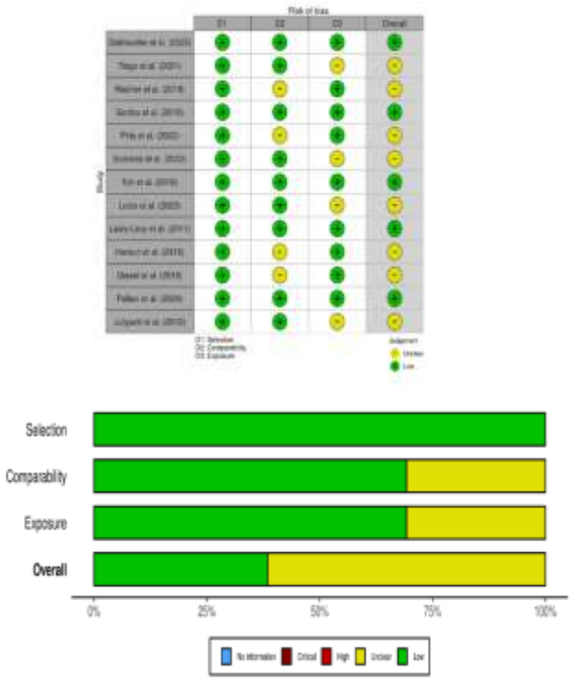

Figure 2. Risk of bias assessment result of the included studies

The 13 included studies encompassed research from India, Brazil, and Indonesia, representing the world's highest leprosy-burden regions. Study designs were predominantly cross-sectional, supplemented by a retrospective cohort and several deep phenotyping studies. Sample sizes varied substantially, from narrow clinic-based samples of 30–50 individuals to larger community or referral-based cohorts exceeding 200 participants.

The studies showcased heterogeneous diagnostic approaches to neuropathic pain. Most Indian and Brazilian cohorts used validated instruments such as DN4, LANSS, NPSI, Brief Pain Inventory, and clinical neurological examination. Brazilian studies frequently incorporated electrophysiological tests (nerve conduction studies) and quantitative sensory testing (QST) consistent with DFNS (German Research Network on Neuropathic Pain) standards, providing granular insights into thermal, tactile, and vibration thresholds. Indonesian cohorts primarily relied on DN4, monofilament sensory testing, and structured clinical examination.

The included populations ranged from post-MDT treated patients, patients with new neuropathy symptoms, individuals with pure neural leprosy (PNL), and those experiencing type 1 or type 2 leprosy reactions. Such heterogeneity contributed to differences in neuropathic pain burden across settings.

Prevalence of Neuropathic Pain in Leprosy

The prevalence of neuropathic pain (NP) across the 13 studies ranged from 21.8% to 75%, reflecting diversity in case mix, diagnostic tools, and stages of disease.

1. India

Indian studies commonly reported NP prevalence between 22% and 53%. In treated cohorts, NP remained prevalent despite completion of MDT, highlighting persistent or progressive neural damage. A key Indian deep-phenotyping study involving 86 treated patients demonstrated that NP affected both clinically stable and reaction-prone individuals, supporting the notion that NP does not necessarily correspond with active inflammation.

2. Brazil

Brazilian studies reported some of the highest NP prevalence values, especially in chronic or pure neural leprosy cohorts. Prevalence reached 75% in a large Brazilian sample using DN4 and clinical examination. Brazilian studies tended to involve older patients with longstanding neuropathy and complicated histories of repeated reaction episodes, which may partly explain the higher NP burden.

3. Indonesia

Indonesian cohorts demonstrated consistently high neuropathic symptom profiles, with DN4-positive neuropathy reported in >90% in some samples. However, these studies often involved tertiary-referral hospital populations, which might enrich for more severe or complicated cases.

Across all regions, many studies noted that NP often emerged after MDT completion or persisted long-term, suggesting that bacteriological cure does not halt ongoing nerve dysfunction.

Neuropathic Pain Characteristics

The clinical characteristics of neuropathic pain demonstrated both shared features and region-specific nuances.

1. Sensory Qualities

Across almost all included studies, the most frequently reported neuropathic pain descriptors were burning pain, electric shock–like sensations, tingling or pins-and-needles, numbness, sharp or stabbing pain, and the presence of allodynia and dysesthesia in more advanced neuropathy. Studies from Brazil employing DFNS-based quantitative sensory testing consistently identified thermal hypoesthesia to cold and warm stimuli, often accompanied by tactile hypoesthesia with relative preservation of deep pressure sensation, supporting a pattern of predominant small-fiber neuropathy. Similar sensory profiles were reported in studies from India, although comprehensive quantitative

sensory testing was less frequently applied. In Indonesia, DN4-based studies demonstrated a high prevalence of tingling, numbness, and pins-and-needles sensations, reflecting a symptomatic neuropathic profile consistent with small-fiber involvement.

2. Nerve Involvement

Across studies, the ulnar nerve was most frequently thickened or tender, followed by the peroneal and tibial nerves. Motor impairment, especially ulnar clawing or weakness in wrist/finger extension, was described in several studies and strongly correlated with neuropathic pain severity.

Several Brazilian studies highlighted that even patients with normal nerve conduction could exhibit marked NP symptoms, reinforcing the central role of small-fiber dysfunction, which cannot be captured by routine NCS.

3. Temporal Patterns

europathic pain was reported to emerge at various stages of the disease course, including during multidrug therapy, after completion of treatment, or following episodes of type 1 lepra reactions or neuritis. Several cohorts described patients in whom neuropathic pain persisted for years despite bacteriological cure, indicating that symptom chronicity is not solely dependent on active infection. This prolonged persistence suggests ongoing neural remodeling, irreversible nerve damage, or immune-mediated injury to peripheral nerves that continues beyond microbiological clearance.

Functional Impact and Disability

Functional impairment was consistently observed across the included studies, although the severity of disability varied according to regional context and population characteristics. Individuals with neuropathic pain frequently reported difficulty performing fine motor tasks such as writing or gripping utensils, reduced hand dexterity associated with sensory loss in the ulnar nerve territory, and unsteady gait or difficulty climbing stairs resulting from lower-limb neuropathy. These impairments often translated into a reduced capacity to engage in employment or carry out daily household activities. Studies from Brazil commonly employed objective functional assessment scales and demonstrated significantly higher disability scores among patients with neuropathic pain. In contrast, cohorts from India and Indonesia more frequently relied on Brief Pain Inventory functional subscales or clinical judgment; however, they similarly documented substantial functional limitations. Across settings, functional disability was consistently more pronounced among patients with longer durations of neuropathic pain, particularly those experiencing recurrent episodes of neuritis.

Quality of Life

Quality-of-life (QoL) findings across the studies indicate that NP exerts a substantial burden on general health perception, emotional well-being, physical functioning, and social roles. Brazilian studies using the Brief Pain Inventory (BPI) demonstrated pronounced reductions in general activity, mood, and sleep among NP patients. Indian studies using GHQ-12 and WHOQoL highlighted poorer psychological, social, and physical QoL domains in patients with active NP. Indonesian studies echoed these findings, linking NP severity to more profound daily activity impairment. Across all regions, QoL impairment correlated strongly with pain intensity, duration, and extent of sensory loss.

Psychological Morbidity

Five studies assessed psychological outcomes, revealing notable but heterogeneous findings. Depressive symptoms were reported in 15–41% of patients with neuropathic pain. In some Brazilian studies, moderate-to-severe depression was significantly more common among NP patients than among those with nociceptive pain or no pain at all. Indian cohorts demonstrated a broader spectrum while some studies noted higher GHQ-12 positivity in NP patients, one deep phenotyping study found no major psychological differences between NP and non-NP groups, suggesting possible sociocultural or population differences. Anxiety symptoms were less frequently measured but tended to co-occur with chronic neuropathic pain patterns.

Summary of Key Patterns

Across the three highest-burden countries, neuropathic pain in leprosy emerges as a highly prevalent condition affecting a substantial proportion of both treated and untreated individuals. It represents a multidimensional clinical problem characterized by overlapping sensory deficits, motor impairment, and chronic inflammatory or immune-mediated nerve damage. Neuropathic pain is a major driver of disability, leading to reduced hand dexterity, impaired mobility, and limitations in daily functioning, and it substantially contributes to diminished quality of life across physical, psychological, and social domains. Importantly, neuropathic pain frequently persists long after completion of multidrug therapy, indicating that it constitutes a sustained clinical burden rather than a transient treatment-related phenomenon. Despite considerable heterogeneity in diagnostic approaches and patient populations, the collective findings consistently underscore the complexity, severity, and long-term impact of neuropathic pain among people affected by leprosy in India, Brazil, and Indonesia.

Discussion

Summary of Main Findings

This systematic review demonstrates that neuropathic pain (NP) is a highly prevalent, clinically impactful, and chronically under-recognized complication of leprosy across the three highest-burden countries, India, Brazil, and Indonesia. Across the 13 included studies, NP affected anywhere from one-fifth to nearly three-quarters of individuals with leprosy, with variation largely attributable to differences in diagnostic instruments, clinical populations, and disease stages. The consistent identification of burning pain, electric-shock sensations, tingling, and dysesthesia highlights a characteristic sensory

profile that transcends geographic boundaries. Importantly, NP was frequently documented long after completion of MDT, reinforcing the chronicity of neural injury and the inadequacy of bacteriological cure alone to address ongoing neural morbidity. Functional limitations, diminished quality of life, and significant psychological distress were repeatedly observed, suggesting that NP contributes more substantially to long-term disability and social burden than previously appreciated. Collectively, these findings underscore that NP represents a core component of the clinical spectrum of leprosy, not merely an ancillary symptom.

Comparison With Previous Evidence

The results of this review align with and further extend prior evidence describing the protracted neurological course of leprosy. Earlier literature has long documented that nerve impairment remains the principal driver of leprosy-associated disability even decades into the MDT era (Scollard et al., 2006; Smith & Aerts, 2014). The prevalence estimates synthesized here, frequently exceeding 30–50%, mirror findings from previous cross-sectional cohorts, particularly those from India and Brazil, where NP has been consistently reported as a prominent complaint among both newly diagnosed and post-treatment individuals (Lasry-Levy et al., 2011). Deep-phenotyping investigations employing sophisticated sensory testing have demonstrated patterns of hypoesthesia, thermal threshold abnormalities, and tactile dysfunction consistent with small-fiber involvement (Giesel et al., 2018; Haroun et al., 2019). The studies from Brazil included in this review corroborate these findings, revealing distinct somatosensory loss profiles even in patients whose electrophysiological studies showed preserved large-fiber function. This reinforces the notion that traditional NCS alone systematically underestimates neuropathic burden.

Psychological consequences observed in this review, including depressive symptoms, anxiety, and social withdrawal, are consistent with broader literature describing the intersection of leprosy, chronic pain, stigma, and mental health (Araújo et al., 2024; Sharma et al., 2022). Studies from South Asia and Brazil have similarly highlighted how chronic NP reinforces self-stigma and limits reintegration, even after medical cure. Importantly, our synthesis integrates Indonesian data, which has historically been underrepresented in global NP research, revealing that neuropathic symptoms and psychosocial distress are pervasive even in community-based or mixed-age cohorts. This tri-national integration advances the field by providing a truly global perspective grounded in the populations most affected by the disease.

Possible Mechanisms Underlying Neuropathic Pain

The underlying mechanisms driving NP in leprosy are complex and multifactorial, involving direct microbial invasion, immune-mediated injury, inflammatory cascades, and maladaptive neuroplasticity. M. leprae selectively invades Schwann cells due to its affinity for laminin-2 and glycolipid receptors, disrupting axonal homeostasis and myelin integrity (Scollard et al., 2006; Souza et al., 2022). Early involvement of small unmyelinated fibers explains the typical clinical pattern: patients often present with burning pain, cold or warm dysesthesia, and prickling sensations long before detectable abnormalities appear on nerve conduction studies (Giesel et al., 2018; Haroun et al., 2019).

Type 1 reactions impose additional insult by precipitating acute inflammation in peripheral nerves, leading to swelling, endoneurial edema, and ischemia. Type 2 erythema nodosum leprosum (ENL) introduces systemic inflammation driven by immune complex deposition and cytokine surges, further destabilizing neural function (Lockwood & Saunderson, 2012). The persistence of NP after MDT highlights that nerve injury in leprosy is not solely attributable to bacterial presence but also reflects chronic immunological processes and post-inflammatory remodeling.

Central nervous system mechanisms may also contribute. Chronic nociceptive input from injured peripheral nerves can induce central sensitization, characterized by amplified pain processing within the spinal dorsal horn and higher centers (Cui et al., 2023; Nery et al., 2019). Although underexplored in leprosy, central sensitization may explain the disproportionate pain severity observed in some individuals with relatively limited peripheral impairment. Moreover, psychological stress, prevalent among patients facing stigma or long-term disability, can modulate pain perception via neuroimmune pathways, suggesting a bidirectional relationship between neural injury and emotional distress (Nery et al., 2019; Sharma et al., 2022). These mechanisms collectively illustrate that NP in leprosy represents not a single pathological process but an interplay of peripheral, immune, central, and psychosocial factors.

Completeness and Applicability of Evidence

The evidence base synthesized in this review is notable for its geographical breadth and methodological diversity. Studies from India, Brazil, and Indonesia offer complementary perspectives across clinical, demographic, and socioeconomic contexts. Many used validated screening instruments such as DN4 or LANSS, increasing internal validity and facilitating

meaningful comparisons across settings (Aarão et al., 2018; Bouhassira et al., 2005). However, the consistency of NP patterns across diverse populations enhances the external validity, suggesting that the burden reported here likely reflects broader patterns in other endemic regions across Africa and Southeast Asia.

Nevertheless, the evidence is not without gaps. Few studies incorporated objective assessments of small-fiber function such as skin biopsy or corneal confocal microscopy, and only a subset employed comprehensive QST methodologies. The scarcity of longitudinal designs limits understanding of NP evolution over time, particularly the transition from acute neuritis to chronic NP. Variation in inclusion criteria and sampling strategies across studies also narrows generalizability; many cohorts were drawn from tertiary referral centers where more severe cases cluster. Despite these limitations, the consistency of findings across settings with differing diagnostic capacity supports the robustness and applicability of the synthesized evidence.

Potential Biases and Limitations

Methodological constraints introduce several potential biases. The predominance of cross-sectional designs limits causal inference, and many studies lacked adjustments for confounders such as diabetes, alcohol use, HIV, or nutritional deficiencies, conditions that may influence neuropathic symptoms. Diagnostic variability is another source of heterogeneity: while DN4 offers strong diagnostic performance, reliance on symptom-based tools alone may inflate NP prevalence in settings where clinical overlap with nociceptive pain is substantial. Conversely, absence of advanced diagnostic tools may underestimate early small-fiber involvement.

Reporting bias is also likely, as psychological and quality-of-life outcomes were inconsistently measured across studies. Many cohorts underreported socioeconomic factors, stigma, and patient-reported barriers to care, all of which influence pain experience and health-seeking behavior. Regional differences in study rigor were evident; for example, Indonesian studies generally used smaller samples and fewer diagnostic tools than Indian or Brazilian cohorts. Finally, publication bias cannot be excluded, as studies with negative or inconclusive findings may be less likely to be published.

Implications for Clinical Practice and Public Health

The findings of this review have important implications for clinical practice, service delivery, and policy formulation in endemic regions. First, routine screening for neuropathic pain should be integrated into leprosy programs using simple, validated tools such as DN4, enabling early recognition and targeted intervention. Given that NP frequently persists beyond MDT, long-term follow-up must be incorporated into post-treatment surveillance to mitigate disability progression. Rehabilitation services, including physiotherapy, occupational therapy, and assistive devices, should be made accessible to address functional limitations (Araújo et al., 2024; Wilder-Smith & van Brakel, 2008).

From a public health perspective, addressing NP requires a multidimensional approach that encompasses medical, psychological, and social dimensions. Chronic pain management should include psychological counseling, community-based support systems, and anti-stigma interventions (Nery et al., 2019; Wilder-Smith & van Brakel, 2008). Policymakers should recognize NP as a significant contributor to leprosy-related disability and allocate resources for training health workers in pain management, early detection of reactions, and prevention of neural damage. Improved awareness of NP may also enhance patient engagement, reduce treatment delays, and support reintegration.

Future Research Directions

Future research should prioritize well-designed longitudinal studies to elucidate the natural history of NP, including the transition from acute neuritis to chronic pain syndromes. Standardization of diagnostic thresholds and development of culturally adapted NP tools will improve comparability across settings. Incorporating objective assessments such as QST, nerve ultrasound, or skin biopsy may clarify the contribution of small-fiber pathology and refine diagnostic accuracy. Clinical trials evaluating pharmacological (e.g., gabapentinoids, tricyclics) and non-pharmacological interventions (e.g., cognitive behavioral therapy, neuromodulation) are urgently needed. Additionally, investigation into the interplay between neuropathic pain, mental health, stigma, and socioeconomic status could inform integrated care models that better address the holistic needs of individuals affected by leprosy.

CONCLUSION

Neuropathic pain represents a persistent and substantial contributor to long-term morbidity among individuals affected by leprosy in India, Brazil, and Indonesia. Across varied clinical settings, neuropathic pain was consistently prevalent, often emerging or persisting after completion of multidrug therapy and frequently accompanied by sensory abnormalities, functional limitations, and psychological distress. The convergence of evidence across these high-burden countries underscores the chronic, multidimensional nature of leprosy-related neuropathic pain and highlights significant unmet needs in early detection, long-term surveillance, and comprehensive pain management.

Strengthening routine neuropathic pain screening, integrating multidisciplinary rehabilitation, and expanding research into underlying mechanisms and targeted treatments are essential steps toward reducing disability and improving quality of life for affected populations.

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