Act Farma Terap. 2025; 23(3): 161-169

Hanseniase (Leprosy): Epidemiology and Pharmacology. Global Burden and Therapeutic Strategies

Wilson C. Santos[1,2]

1 Universidade Federal Fluminense, Faculdade de Farmácia, , Niterói, RJ, Brasil.
2 Instituto Teófilo Hernando, Facultad de Medicina, Universidad Autónoma de Madrid.

Resumen

RESUMEN

La farmacología de la hanseniase se centra en la acción de agentes antimicrobianos específicos, dirigidos a erradicar *Mycobacterium leprae* del organismo y limitar las complicaciones clínicas y neurológicas asociadas. El régimen terapéutico convencional recomendado por la OMS incluye la combinación de dapsona, rifampicina y clofazimina, que actúan de manera sinérgica para reducir la carga bacteriana y prevenir la aparición de cepas resistentes. La dapsona interfiere en la síntesis de folato bacteriano, la rifampicina inhibe la ARN polimerasa de M. leprae, y la clofazimina presenta actividad antimicrobiana e inmunomoduladora, contribuyendo al control de las reacciones inflamatorias asociadas a la enfermedad.

En los últimos años, han surgido investigaciones enfocadas en el desarrollo de nuevas alternativas terapéuticas, como el uso de fluorquinolonas, minociclina y claritromicina, que han mostrado eficacia en casos resistentes o intolerantes al tratamiento estándar. Además, se exploran estrategias combinadas con agentes inmunomoduladores y la integración de terapias que favorecen la regeneración neural y reducen el daño progresivo.

La adherencia al tratamiento sigue siendo un reto, y la aparición de resistencia bacteriana plantea la necesidad de vigilancia epidemiológica y ajuste de protocolos. El abordaje multidisciplinario, que incorpora aspectos farmacológicos, sociales y de rehabilitación, resulta esencial para optimizar los resultados terapéuticos, mejorar la calidad de vida de las personas afectadas y avanzar hacia la erradicación definitiva de la hanseniase.

Palabras clave

Hanseniase, *Mycobacterium leprae*, Resistencia bacteriana.

Conflicto de intereses

Este artículo no presenta conflicto de interés.

Summary

The pharmacology of leprosy focuses on the action of specific antimicrobial agents, aimed at eradicating *Mycobacterium leprae* from the body and limiting associated clinical and neurological complications. The conventional therapeutic regimen recommended by the WHO includes the combination of dapsone, rifampicin, and clofazimine, which act synergistically to reduce bacterial load and prevent the emergence of resistant strains. Dapsone interferes with bacterial folate synthesis, rifampicin inhibits M. leprae RNA polymerase, and clofazimine exhibits antimicrobial and immunomodulatory activity, contributing to the control of inflammatory reactions associated with the disease.

In recent years, research has focused on the development of new therapeutic alternatives, such as the use of fluoroquinolones, minocycline, and clarithromycin, which have shown efficacy in cases resistant to or intolerant of standard treatment. In addition, combined strategies with immunomodulatory agents and the integration of therapies that promote neural regeneration and reduce progressive damage are being explored.

Treatment adherence remains a challenge, and the emergence of bacterial resistance raises the need for epidemiological surveillance and protocol adjustments. A multidisciplinary approach, incorporating pharmacological, social, and rehabilitation aspects, is essential to optimize therapeutic outcomes, improve the quality of life of affected individuals, and advance toward the definitive eradication of leprosy.

Key words

Leprosy, *Mycobacterium leprae*, Bacterial resistance.

Conflict of interests

This article does not present a conflict of interest.

1. Introduction

Hanseniase, more commonly known as leprosy, is a chronic infectious disease caused by the bacterium *Mycobacterium leprae*. Despite being one of the oldest diseases known to humanity, leprosy continues to impact communities worldwide, particularly in low- and middle - income countries. The multidimensional challenges posed by the disease — ranging from its epidemiological dynamics to its evolving pharmacological management — demand persistent scientific inquiry and public health vigilance.

Leprosy is currently classified as a neglected tropical disease, with more than 200,000 new cases reported globally each year (WHO, 2020). The highest prevalence rates are found in India, Brazil, and Indonesia, which together account for most new cases. While global incidence has declined in recent decades due to the widespread implementation of multidrug therapy (MDT), leprosy remains endemic in certain regions, where socioeconomic factors, limited healthcare infrastructure, and stigma perpetuate its persistence (Scollard et al.,2006).

- India: Continues to report the greatest number of annual cases, with pockets of high endemicity in rural and marginalized communities.
- Brazil: Maintains significant incidence, particularly in the Amazon region and northeastern states.
- Indonesia: Faces ongoing transmission, especially in islands with restricted access to health services.

Leprosy is transmitted primarily through prolonged close contact, likely via respiratory droplets (Richardus & Habbema, 2007). However, household exposure remains the strongest predictor of transmission. Immunological susceptibility, genetic factors, and associated conditions such as malnutrition or coinfection with other diseases (e.g., tuberculosis or HIV) increased risk (Britton & Lockwood, 2004). Children are particularly vulnerable, as are individuals in densely populated or impoverished settings. The manifestation of the disease presents a spectrum of clinical forms, determined by the host's immune response. The Ridley-Jopling classification (1966, see the reference list) divides cases into:

- Tuberculoid leprosy (TT): Characterized by localized skin lesions and nerve involvement, associated with strong cellular immunity.
- Lepromatous leprosy (LL): Extensive skin nodules and diffuse nerve damage, typically seen in individuals with poor immune response.
- Borderline forms: Exhibit features between the two poles and may shift with changes in immunity.

Peripheral nerve damage is a hallmark of the disease, often resulting in sensory loss, muscle weakness, and deformities (Ridley & Jopling, 1966). Stigma and discrimination further compound the psychological and social burden.

2. Pharmacology of Hanseniase Treatment

Multidrug Therapy (MDT): The Cornerstone

The advent of MDT revolutionized leprosy treatment, reducing transmission and preventing resistance. The standard WHO-recommended MDT regimen comprises (Noordeen, 2016):

- Rifampicin: A bactericidal agent targeting *M. leprae*, administered monthly under supervision. It is a naphthoquinone core connected to an aliphatic chain, forming an ansamycin compound, as depicted in Figure 1:

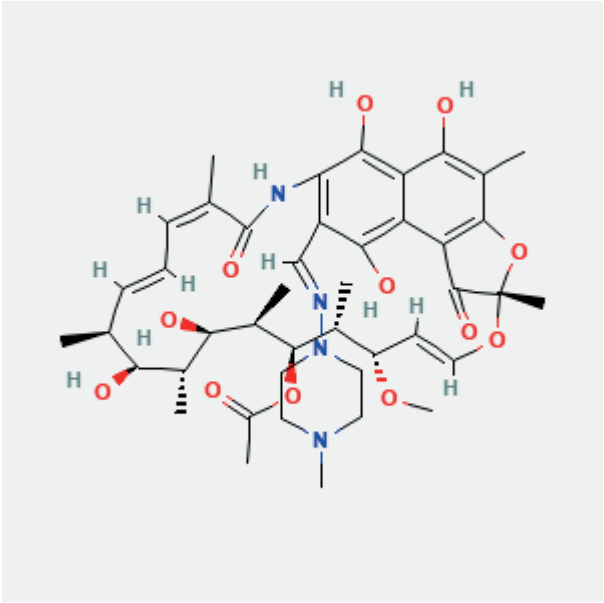

Figure 1. Rifampicin chemical structure. Source: https://pubchem.ncbi.nlm.nih.gov/compound/Rifampicin, accessed on August 31st 2005.

- Dapsone: An antimicrobial and anti-inflammatory drug, taken daily. This compound belongs to the class of organic compounds known as benzenesulfonyl compounds.

Figure 2. Dapsone chemical structure. Source: https://go.drugbank.com/drugs/DB00250, accessed on August 31st, 2025.

Clofazimine: A dye with bactericidal and anti-inflammatory properties, responsible for the characteristic skin discoloration. This compound belongs to the class of organic compounds known as phenazines and derivatives.

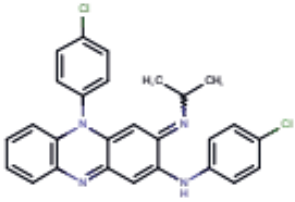

Figure 3. Clofazimine chemical structure. Source: https://go.drugbank.com/drugs/DB00845 , accessed on August 31st 2025.

Treatment duration ranges from six months (paucibacillary disease) to twelve months or more (multibacillary disease). MDT is generally well tolerated and highly effective, though adverse reactions—such as dapsone hypersensitivity or clofazimine-induced pigmentation—may occur. Understanding the pharmacological mechanisms of the principal drugs within multidrug therapy (MDT) for hanseniase illuminates their synergistic effects and the rationale for their combined use:

- Rifampicin: A potent bactericidal antibiotic that inhibits the DNA-dependent RNA polymerase of *Mycobacterium leprae*, effectively blocking transcription and halting bacterial protein synthesis. Rifampicin's rapid action leads to a swift reduction in viable bacilli, making it the most powerful agent in the MDT regimen (Brennan, 2001).
- Dapsone: Dapsone functions as a structural analogue of para-aminobenzoic acid (PABA), competitively inhibiting dihydropteroate synthase in the bacterial folate pathway. By disrupting folic acid synthesis, dapsone limits nucleotide production and impedes bacterial replication, exerting a primarily bacteriostatic effect against *M. leprae* (Krismawati et al., 2025).

- Clofazimine: Clofazimine demonstrates both bactericidal and anti-inflammatory actions. Its primary mechanism involves binding to mycobacterial DNA, thereby interfering with template function and inhibiting bacterial proliferation. Additionally, clofazimine modulates immune responses by suppressing neutrophil migration and the release of inflammatory mediators, which aids in managing lepra reactions (Garrelts, 1991).

The combined use of these agents in MDT not only enhances antimicrobial efficacy but also minimizes the emergence of drug resistance, ensuring effective and sustained management of hanseniase.

Drug	Dosage	Administration Frequency	Key Role	Common Side Effects	Molecular Target	Primary Action	Monitoring Recommendations
Rifampicin	600 mg	Monthly (supervised)	Rapid bactericidal action	Hepatotoxicity, flu-like symptoms	RNA polymerase	Inhibits transcription, blocks protein synthesis	Liver function tests
Dapsone	100 mg	Daily (self-administered)	Bacteriostatic, anti-inflammatory	Hemolysis, hypersensitivity	Dihydropteroate synthase	Blocks folic acid synthesis, impedes DNA synthesis	CBC, monitor for rash
Clofazimine	50 mg (daily), 300 mg (monthly)	Daily/monthly	Bactericidal, anti-inflammatory	Skin discoloration, GI upset	Mycobacterial DNA	Interferes with replicatio; modulates inflammation	Patient counseling, monitor for GI intolerance

Figure 4. Overview of MDT Regimen for Hansen Disease

Pharmacokinetics of Drugs Used in Hansen's Disease

The success of multidrug therapy (MDT) for Hansen's disease depends not only on the efficacy of the selected agents but also on their pharmacokinetic characteristics, which influence absorption, distribution, metabolism, and excretion. Understanding these properties is vital for optimizing dosing regimens, minimizing toxicity, and improving patient adherence, especially given the prolonged courses required for cure.

Rifampicin

Rifampicin is rapidly absorbed after oral administration, reaching peak plasma concentrations within 2–4 hours. Its high lipid solubility allows for extensive tissue penetration, including effective concentrations in skin and peripheral nerves. Rifampicin undergoes hepatic metabolism primarily via deacetylation, with metabolites excreted in bile and, to a lesser extent, urine. It is a potent inducer of hepatic cytochrome P450 enzymes, leading to significant drug-drug interaction potential.

Dapsone

Dapsone is well absorbed from the gastrointestinal tract, with bioavailability exceeding 80%. It has a large volume of distribution and accumulates in skin, muscle, liver, and kidneys. Dapsone

is metabolized in the liver via acetylation and hydroxylation, and both the parent drug and its metabolites are excreted in urine. The drug has a prolonged half-life (20–30 hours), contributing to its suitability for once-daily dosing but also raising the risk for cumulative toxicity, such as hemolysis, particularly in G6PD-deficient individuals.

Clofazimine

Clofazimine displays slow and variable gastrointestinal absorption, with peak concentrations observed 6–24 hours after dosing. It is highly lipophilic, leading to extensive tissue sequestration, especially in fatty tissues and the reticuloendothelial system. Clofazimine's elimination is remarkably slow, with a terminal half-life of up to 70 days, accounting for its skin discoloration side effects and persistent tissue staining. Excretion is primarily via bile into feces.

Implications for Clinical Practice

Variability in absorption and elimination, potential for drug-drug interactions, and the necessity for prolonged therapy all underscore the importance of individualized pharmacokinetic monitoring in Hansen's disease (Vernal & Gomes, 2024). Patient-specific factors such as comorbidities, hepatic or renal impairment, and concomitant medications can significantly affect drug levels, efficacy, and toxicity risk. Ongoing research into pharmacokinetic modeling and therapeutic drug monitoring promises to further refine leprosy treatment and promote safer, more effective regimens.

3. The Development and Nature of Drug Resistance

Leprosy treatment has evolved from monotherapy to the World Health Organization's recommended MDT, a strategy designed to prevent resistance by targeting different bacterial mechanisms simultaneously. Despite these efforts, resistance to key drugs — particularly dapsone and rifampicin — has been documented worldwide.

Mechanisms of Resistance

Drug resistance in *M. leprae* primarily arises through genetic mutations that reduce drug efficacy. The following mechanisms are most notable (Gosset, 1985; Joppling 1991):

- Dapsone Resistance: Linked to mutations in the *folP1* gene, which encodes dihydropteroate synthase, the enzyme targeted by dapsone. These mutations decrease the drug's ability to inhibit folate synthesis, allowing bacterial survival.
- Rifampicin Resistance: Associated with alterations in the *rpoB* gene, which codes for the β-subunit of RNA polymerase. Mutations here prevent rifampicin from binding effectively, leading to treatment failure.
- Clofazimine Resistance: While not as well-documented, resistance can develop through changes in bacterial redox systems or efflux pumps, though clinical resistance remains rare compared to dapsone and rifampicin.

Resistance can be further exacerbated by incomplete or erratic treatment, suboptimal dosing, and the presence of comorbidities that affect drug absorption and metabolism.

Clinical Implications of Drug Resistance: Impact on Patient Outcomes

Drug-resistant Hansen's disease poses significant clinical challenges:

- Prolonged Infectiousness: Patients harboring

resistant strains can remain infectious longer, increasing transmission risks within communities.
- Therapy Failure: Resistance leads to persistent lesions, continued nerve damage, and increased risk of disability and stigma.
- Limited Treatment Options: Resistance to first-line agents restricts available therapies, complicating disease management, especially in resource-limited settings.

Detecting drug resistance traditionally relied on clinical suspicion following poor response to therapy. However, advances in molecular diagnostics now allow for direct identification of resistance mutations from patient samples, enabling earlier and more precise interventions.

Pharmacokinetic Considerations and Their Role in Resistance

Individual drug absorption, distribution, and elimination can influence the development and management of resistance (Aubry et al., 2022). Variability in these pharmacokinetic parameters may result in subtherapeutic drug levels, promoting the survival of resistant bacterial populations.

- Rifampicin: Its potent induction of hepatic cytochrome P450 enzymes increases drug-drug interaction risk, which may lower effective plasma concentrations if co-administered with other agents.
- Dapsone: Prolonged half-life supports once-daily dosing but raises cumulative toxicity risk. In patients with G-6PD deficiency or hepatic impairment, altered metabolism may decrease drug effectiveness.
- Clofazimine: Slow elimination and extensive tissue sequestration could contribute to selective pressure for resistance, particularly with irregular dosing.

Thus, individualized pharmacokinetic monitoring and dose adjustment are crucial, particularly in patients with renal or hepatic dysfunction, to maintain optimal drug levels and reduce resistance risk.

Strategies to Combat Drug Resistance

Optimizing Treatment Adherence

Ensuring consistent and complete MDT adherence is the cornerstone of resistance prevention. Strategies include:

- Directly Observed Therapy (DOT): Healthcare providers supervise patient dosing to enhance compliance.
- Patient Education: Clear communication about the importance of full treatment courses and potential consequences of missed doses.

Pharmacokinetic Monitoring and Individualization

Advances in therapeutic drug monitoring and pharmacokinetic modeling now allow for personalized treatment regimens based on patient-specific factors. This approach can help maintain effective drug concentration, reduce toxicity, and minimize resistance risk.

Molecular Surveillance and Rapid Diagnostics

Routine molecular screening for resistance mutations in suspected cases enables timely therapy adjustment and can inform public health strategies. Integration of these techniques into national leprosy programs is key to curbing resistance spread.

Research and Drug Development

Ongoing research aims to identify new thera-

peutic agents and drug combinations effective against resistant *M. leprae* strains. This includes novel antimicrobials, immunomodulators, and adjunct therapies that may enhance host response and limit bacterial adaptation.

4. Alternative Drugs and Repurposed Agents in Leprosy Therapy

In recent decades, the concept of drug repurposing — finding new therapeutic uses for existing medications — has gained significant momentum in tackling neglected diseases, including leprosy. Drug repurposing offers the potential to expedite the development of new treatments by leveraging established pharmacological knowledge, safety profiles, and manufacturing infrastructure (Rosa & Santos 2020). For a disease such as leprosy, where drug resistance and treatment limitations persist, repurposing alternative agents can provide new hope for effective, safe, and accessible therapies. Several alternative and repurposed drugs have been studied or are currently under investigation for use in leprosy, either as substitutes for standard MDT drugs or as adjuncts to enhance efficacy, reduce treatment duration, or manage complications. A growing body of literature explores the clinical application of repurposed drugs in leprosy (Maia et al., 2013; Sharma et al. 2022).

Minocycline

Minocycline, a second-generation tetracycline antibiotic, has demonstrated significant bactericidal activity against *M. leprae*. Initially used for other bacterial infections, minocycline has been considered for leprosy due to its:

- Broad antimicrobial spectrum
- Suitable tissue penetration, especially in the skin and nerves
- Immunomodulatory and anti-inflammatory properties

Clinical studies suggested that minocycline, when combined with other agents such as ofloxacin and clarithromycin, can be effective in treating both lepromatous and multibacillary leprosy, especially in patients with resistance or intolerance to first-line drugs.

Ofloxacin

Ofloxacin, a fluoroquinolone antibiotic, inhibits bacterial DNA gyrase and has demonstrated in vitro activity against *M. leprae*. It has been used as part of alternative regimen for patients who cannot tolerate standard MDT. The World Health Organization recognizes ofloxacin as a second-line agent, especially valuable in cases of drug-resistant leprosy.

Clarithromycin

Clarithromycin, a macrolide antibiotic, has shown promise in the treatment of leprosy due to its activity against atypical mycobacteria and its ability to reach high concentrations in skin tissue. When combined with other agents, clarithromycin has been effective against both dapsone-sensitive and dapsone-resistant strains of *M. leprae*.

Thalidomide

Thalidomide is well known for its teratogenic effects, but its potent anti-inflammatory and immunomodulatory properties make it invaluable in the management of leprosy reactions, particularly erythema nodosum leprosum (ENL). Its use in leprosy is closely monitored due to its side effect profile, but it remains an important example of drug repurposing (Walker et al., 2007).

Other Potential Agents and Future Opportunities

The search for additional therapeutic agents has led researchers to evaluate drugs used for tuber-

culosis, other mycobacterial infections, and unrelated conditions. Some promising candidates include (Shyam et al., 2024):

- Linezolid: An oxazolidinone with activity against various mycobacteria.
- Bedaquiline and delamanid: Newer anti-tubercular drugs with potential efficacy against *M. leprae*.
- Azithromycin: Another macrolide with broad-spectrum activity.
- Immunomodulators: Drugs that modulate the host immune response to enhance clearance of the bacteria or reduce nerve damage.

5. Conclusion

Hanseniase remains a significant public health concern despite dramatic advances in treatment. Multidrug therapy remains the foundation of leprosy treatment, but its continued effectiveness depends on adherence, individualized dosing, and rapid detection of resistance. The integration of alternative agents such as minocycline, ofloxacin, clarithromycin, and thalidomide into leprosy management has expanded therapeutic options, especially for individuals with resistance or intolerance to standard therapies. However, continued research, vigilant pharmacovigilance, and equitable access are essential to fully realize the benefits of repurposed drugs for all individuals affected by this ancient and neglected disease. Ongoing surveillance, improved health education, and destigmatization efforts will be necessary to achieve global elimination and improve the quality of life of people living with hanseniase. The emergence and spread of drug-resistant Hansen's disease underline the need for vigilant clinical and public health action. Research into new drugs, improved diagnostics, and innovative treatment approaches promises hope for the future. Ultimately, a collaborative effort — spanning clinicians, researchers, public health officials, and affected communities — will be required to prevent drug resistance from reversing decades of progress in leprosy control.

References

1. Aubry A, Sammarco Rosa P, Chauffour A, Fletcher ML, Cambau E, Avanzi C. (2022) Drug resistance in leprosy: An update following 70 years of chemotherapy. Infect Dis Now. 52 (5):243-251. doi: 10.1016/j.idnow.2022.04.001.
2. Brennan, P.J. (2001). Structure, function, and biochemistry of the cell wall of Mycobacterium leprae. Leprosy Review, 72 (2), 143-159.
3. Britton, W.J., & Lockwood, D.N.J. (2004). Leprosy. The Lancet, 363 (9416), 1209-1219.
4. Garrelts, J.C. (1991) Clofazimine: a review of its use in leprosy and Mycobacterium avium complex infection. DICP, 25 (5): 525-31. doi: 10.1177/106002809102500513
5. Grosset, J.H. (1985). The pathogenesis of drug-resistant Mycobacterium leprae. Leprosy Review, 56 (Suppl), 51-57.
6. Jopling, W.H. (1991). Drug resistance in leprosy. Leprosy Review, 62 (1), 1-10.
7. Krismawati, Hana et al. (2025). Challenges associated with dapsone for leprosy treatment in Indonesia - urgent need for access to alternative antimicrobial drug. The Lancet Regional Health - Southeast Asia, Volume 34, 100555
8.
9. Maia, M.V. , Cunha, M.G.S., Cunha C.S. (2013). Adverse effects of alternative therapy (minocycline, ofloxacin, and clofazimine) in multibacillary leprosy patients in a recognized health care unit in Manaus, Amazonas, Brazil. An. bras. dermatol. 88 (2). https://doi.org/10.1590/S0365-05962013000200003
10.
11.
12. Noordeen S. K. (2016). History of chemotherapy leprosy. Clin Dermatol. 34(1):32-6.
13. Richardus, J.H., & Habbema, J.D.F. (2007). The impact of leprosy control on the transmission of M. leprae: is elimination feasible? Leprosy Review, 78(4), 330-337.
14. Ridley D. S. and Jopling W. H. (1966). Classification of Leprosy According to Immunity A Five-group System. International Journal of Leprosy, 31(3), 255-273.
15. Rosa S.G.V., Santos W.C. (2020) Clinical trials on drug repositioning for COVID-19 treatment. Rev. Panam. Salud Publica, 44:1. doi: 10.26633/RPSP.2020.40
16. Scollard, D.M., Adams, L.B., Gillis, T.P., Krahenbuhl, J.L., Truman, R.W., & Williams, D.L. (2006). The continuing challenges of leprosy. Clinical Microbiology Reviews, 19(2), 338-381.
17. Sharma M. & Singh P. (2022).
18. Repurposing Drugs to Combat Drug Resistance in Leprosy: A Review of Opportunities. Combinatorial Chemistry & High Throughput Screening, Volume 25, Issue 10, p. 1578 – 1586. https://doi.org/10.2174/1386207325666211007110638
19. Shyam M., Kumar, S., Singh, V. (2024). Unlocking Opportunities for Mycobacterium leprae and Mycobacterium ulcerans. ACS Infectious Diseases 10 (2), 251-269. DOI: 10.1021/acsinfecdis.3c00371
20. Vernal, S. & Gomes C.M (2024). Editorial: New insights in leprosy (Hansen's disease). Front Med (Lausanne) 11:1372149. doi: 10.3389/fmed.2024.1372149
21. Walker, SL; Waters, MF; Lockwood, DN (2007) The role of thalidomide in the management of erythema nodosum leprosum. Leprosy review, 78 (3). pp. 197-215. ISSN 0305-7518
22. World Health Organization. (2020). Global leprosy update, 2019: time to step-up prevention initiatives. Weekly Epidemiological Record, 95(36), 417–440.