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LINEZOLID-ASSOCIATED PERIPHERAL NEUROPATHY IN DRUG-RESISTANT TUBERCULOSIS: A CLINICAL AND ELECTROPHYSIOLOGICAL ASSESSMENT

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ABSTRACT

Background:
Linezolid is a key component of all-oral longer regimens for drug-resistant tuberculosis (DR-TB), but its use is frequently limited by neurotoxicity.

Objective: To evaluate the incidence, clinical and electrophysiological characteristics, time to onset, severity, and management outcomes of linezolid-associated peripheral neuropathy in patients receiving linezolid-containing DR-TB regimens.

Methods: This prospective observational study included adult DR-TB patients initiated on linezolid at a tertiary DR-TB Centre. Patients were monitored clinically for neuropathic symptoms and underwent neurological examination and EMG–NCV testing when neuropathy was suspected. Neuropathy was classified as mild, moderate, or severe based on clinical and electrophysiological findings. Data on exposure duration, pattern of nerve involvement, and management decisions were recorded and analysed descriptively.

Results: Among 50 patients receiving linezolid, peripheral neuropathy developed in 26 (52%). Moderate neuropathy was most frequent (57.7%), followed by mild (30.8%) and severe forms (11.5%). EMG–NCV confirmed motor-predominant neuropathy in 40%, with sensory, autonomic, and mixed patterns in 16%, 4%, and 2% respectively. Neuropathy occurred early, with 73.1% of cases developing within 0–2 weeks of treatment and the remainder between 2–6 weeks. All affected patients required permanent discontinuation of linezolid despite initial dose reduction attempts.

Conclusion: Peripheral neuropathy occurred commonly and developed rapidly among DR-TB patients receiving linezolid-containing regimens. Motor involvement predominated, and most cases were moderate in severity. Early onset and the need for permanent drug withdrawal highlight the importance of proactive neurological monitoring and individualized risk assessment in patients receiving linezolid.

Keywords: Linezolid, Drug-resistant tuberculosis, Peripheral neuropathy, EMG–NCV, Neurotoxicity, Adverse drug reaction

INTRODUCTION

Drug-resistant tuberculosis (DR-TB) remains a major global health challenge, requiring prolonged multidrug treatment regimens that are often limited by significant toxicity.[1] Linezolid, an oxazolidinone with potent activity against *Mycobacterium tuberculosis*, has become an essential component of contemporary all-oral longer regimens recommended by the World Health Organization.[2] Its inclusion has improved culture conversion rates and overall treatment outcomes in multidrug-resistant and extensively drug-resistant tuberculosis.[3] However, the therapeutic benefits of linezolid are counterbalanced by its well-recognized adverse effects, particularly myelosuppression and neurotoxicity, which frequently necessitate dose reduction or premature discontinuation of therapy.[4]

Peripheral neuropathy is one of the most common and clinically consequential toxicities associated with linezolid. Reported prevalence varies widely across studies, ranging from 20% to 40%, depending on treatment duration, comorbid conditions, and monitoring practices.[5,6] The pathophysiology is linked to mitochondrial dysfunction within peripheral nerves, leading to axonal injury that may be partially or entirely irreversible. Early symptoms may be subtle, yet progression can lead to marked motor, sensory, or autonomic impairment. The risk appears to increase with longer exposure, higher cumulative doses, diabetes mellitus, HIV infection, and other factors compromising nerve health.[5,6,7] Electromyography and nerve conduction velocity testing provide objective confirmation of neuropathy and help define nerve involvement, though their routine use varies across programs. With increasing reliance on linezolid in DR-TB regimens, clarifying the real-world frequency, onset, electrophysiological features, and outcomes of linezolid-related peripheral neuropathy is vital for safe treatment. Early detection and management of neurotoxicity are necessary to prevent disability and maintain effective therapy. This study therefore assessed the incidence, pattern, severity, and early onset of linezolid-associated peripheral neuropathy in patients on an all-oral longer regimen at a tertiary DR-TB centre, while also documenting management approaches and treatment changes required due to neurotoxicity to support safer, individualized use of linezolid in routine practice.

MATERIALS AND METHODS

Study Design and Setting: This observational, prospective study was carried out at the Drug-Resistant Tuberculosis (DR-TB) Centre of a tertiary care teaching hospital. All patients receiving an all-oral longer regimen containing linezolid were systematically evaluated for the development of peripheral neuropathy during the treatment course.

Study Population: The study population consisted of adult patients diagnosed with multidrug-resistant or rifampicin-resistant tuberculosis who were initiated on linezolid as part of their standardized regimen. Patients aged 18 years or older who were willing to participate and undergo neurological evaluation were included. Individuals with pre-existing neuropathy attributable to diabetes, HIV infection, alcoholism, nutritional deficiencies, or other neurological disorders were excluded. Patients receiving medications known to cause neuropathy, and those who declined electrophysiological testing, were also excluded.

Sample Size and Sampling Technique: The sample size was determined by the total number of eligible patients who commenced a linezolid-containing regimen during the study period. Every patient fulfilling the inclusion criteria and consenting to neurological assessment was enrolled consecutively. A total of fifty patients constituted the final study cohort.

Exposure to Linezolid: All participants received linezolid as part of the national program's all-oral longer regimen for drug-resistant tuberculosis. Details regarding dose, duration of therapy, and any changes such as dose reduction or treatment interruption were recorded prospectively. The duration of exposure before the onset of neuropathic symptoms was documented in all patients who developed neurological adverse effects.

Assessment for Neuropathy: Patients were monitored clinically at regular intervals for symptoms indicative of neuropathy, including tingling, numbness, burning sensations, weakness, or gait disturbances. Those with suspected symptoms underwent a detailed neurological examination to

assess the extent of peripheral nerve involvement. Electrophysiological evaluation using Electromyography (EMG) and Nerve Conduction Velocity (NCV) testing was performed to confirm the diagnosis and categorize neuropathy into motor, sensory, autonomic, or mixed types.

Classification of Severity: Neuropathy severity was determined based on clinical findings and EMG–NCV results. Sensory symptoms without significant functional limitation were categorized as mild. Cases exhibiting motor involvement or interference with daily activities were considered moderate. Severe neuropathy was identified when autonomic dysfunction, marked weakness, or significant impairment necessitating immediate discontinuation of linezolid was present.

Management of Neuropathy: Management decisions were guided by institutional protocols. Dose reduction was attempted initially in patients presenting with neuropathic symptoms; however, progression or persistence typically required permanent discontinuation of linezolid. Supportive therapy, including vitamin supplementation and symptomatic management, was provided when indicated. All treatment modifications and patient outcomes following neuropathy onset were documented prospectively.

Data Collection: Data were recorded using a structured proforma designed for the study. Information collected included demographic characteristics, comorbidities, duration of linezolid exposure, clinical presentation, EMG–NCV findings, severity grading, and management outcomes. Only those neurological adverse events directly attributable to linezolid were included in the final analysis.

Outcome Measures: The primary outcome measure was the incidence of peripheral neuropathy during linezolid therapy. Secondary outcomes included the electrophysiological pattern of neuropathy, the time to onset following treatment initiation, the severity at presentation, and the management strategy employed.

Statistical Analysis: Data entry and analysis were performed using Microsoft Excel. Descriptive statistics were used to summarize the dataset. Categorical variables were expressed as frequencies and percentages, while continuous variables were presented as mean and standard deviation.

RESULTS

A total of 50 patients receiving linezolid-containing regimens for drug-resistant tuberculosis were evaluated. Peripheral neuropathy was the most frequently observed adverse effect associated with linezolid therapy.

Table 1. Prevalence and Severity of Peripheral Neuropathy (n = 50)

Variable	Number	Percentage (%)
Peripheral Neuropathy – Present	26	52.0
Peripheral Neuropathy – Absent	24	48.0
Severity (among neuropathy cases, n = 26)		
• Mild	8	30.8
• Moderate	15	57.7
• Severe	**3**	**11.5**

Table 1 shows that peripheral neuropathy occurred in 26 of 50 patients (52%). Among those affected, moderate neuropathy was most frequent (57.7%), followed by mild (30.8%) and severe forms (11.5%).

Table 2. EMG–NCV Pattern Among Neuropathy Cases (n = 26)

Neuropathy Type	Number	Percentage (%)
Motor Neuropathy	20	40.0
Sensory Neuropathy	8	16.0
Autonomic Neuropathy	2	4.0
Mixed / Combined	1	2.0

Table 2 shows a clear dominance of motor neuropathy, observed in 40% of cases. Sensory involvement was noted in 16%, whereas autonomic and mixed patterns were uncommon, occurring in 4% and 2% respectively. This distribution underscores the strong motor predominance in linezolid-associated neuropathy.

Table 3. Categorized Time to Onset of Neuropathy After Linezolid Exposure (n = 26)

Time Interval	Number	Percentage (%)
0–2 weeks	19	73.1
>2–6 weeks	7	26.9
>6 weeks	0	0.0

Table 3 indicates that neuropathy appeared early in the treatment course, with 73.1% of cases arising within the first 0–2 weeks and the remaining 26.9% between 2–6 weeks. No patient developed symptoms beyond six weeks of therapy.

Table 4. Management of Linezolid-Induced Neuropathy (n = 26)

Management Step	Number	Percentage (%)
Initial dose reduction → permanent discontinuation	26	100.0
Temporary discontinuation with re-challenge	0	0.0
Continuation without modification	0	0.0

Table 4 shows that all patients with neuropathy required permanent discontinuation of linezolid. Although dose reduction was attempted initially, none could be re-challenged or continue therapy after symptom onset.

DISCUSSION

The present study evaluated the incidence, electrophysiological features, time-to-onset, and management of linezolid-associated peripheral neuropathy in patients receiving all-oral longer regimens for drug-resistant tuberculosis.

Peripheral neuropathy occurred in 52% of the cohort, with moderate neuropathy being the predominant severity grade. This incidence is higher than the pooled rate of approximately 31% reported in meta-analyses of linezolid toxicities. Zhang P et al.[8] reported neuropathy in around 32% of patients receiving long-term linezolid therapy, while Jaspard M et al.[9] documented a comparable incidence in their French cohort. The higher proportion seen in the present study may be attributed to rigorous monitoring practices, early EMG–NCV confirmation, and the higher prevalence of comorbidities such as diabetes and HIV—both known to increase susceptibility to neurotoxicity. In addition, Saibannavar A et al.[10] have emphasized that the likelihood of neuropathy increases with longer exposure and higher cumulative dosing, suggesting that regimen structure and patient factors may influence observed incidence.

Motor-predominant neuropathy (40%) was the striking electrophysiological pattern in this study. Sensory and autonomic neuropathies were less frequent. This observation is consistent with the mechanistic understanding that linezolid-induced mitochondrial dysfunction preferentially affects long-axon, high-energy-demand motor neurons. Similar findings have been highlighted by Anger HA et al.,[11] who noted a significant burden of motor impairment among patients developing neurological toxicities on linezolid. Reports by Maniyar A et al.[12] and Saibannavar A et al.[10] also describe motor involvement as a key clinical feature, reinforcing the reproducibility of this pattern across diverse populations.

Neuropathy developed unusually early in the present study, with 73.1% of cases manifesting within the first two weeks of therapy. This contrasts with several earlier studies. For instance, Zhang P et al.[8] reported a broader onset window extending over several months, while Jaspard M[9] described neuropathy typically emerging after prolonged exposure. The rapid onset in the current cohort may reflect higher baseline vulnerability due to comorbidities or heightened provider vigilance leading to

early diagnosis. These results underscore the need for active neurological surveillance from the start of therapy, rather than relying solely on monthly evaluations.

Every neuropathy case in this cohort required permanent discontinuation of linezolid, despite initial attempts at dose reduction. This is a more definitive intervention pattern compared to some published series, where re-challenge or dose tapering occasionally allowed continuation of therapy. Saibannavar A et al.[10] observed delayed recovery in many cases but did not report universal discontinuation. The 100% discontinuation rate in the present study may reflect the severity of early-onset symptoms or institutional policies prioritizing prevention of irreversible deficits. The finding highlights the substantial functional impact of linezolid-related neuropathy and the importance of timely recognition to avoid long-term morbidity.

LIMITATIONS

The sample size was modest, limiting the power to evaluate multiple risk factors. Long-term follow-up data on neurological recovery were not available, preventing assessment of reversibility. Standardized scoring scales such as CTCAE or INCAT were not used prospectively and severity classification was derived from clinical features. Additionally, potential confounders such as nutritional status or alcohol use were not systematically evaluated.

CONCLUSION AND IMPLICATIONS

The findings of this study highlight the clinical importance of early recognition and proactive monitoring of linezolid-associated neuropathy in drug-resistant tuberculosis. Given the high proportion of early-onset cases and the predominance of motor involvement, clinicians should incorporate baseline neurological assessment, frequent early follow-up, and consideration of alternative regimens in high-risk patients such as those with diabetes or HIV. Routine electrophysiological evaluation may aid in detecting subclinical dysfunction, and future research on neuroprotective strategies is warranted, as all affected patients in this cohort ultimately required permanent discontinuation of linezolid. Overall, the study underscores that linezolid-induced neuropathy is common, emerges rapidly, and carries significant functional consequences, necessitating vigilant surveillance and individualized therapeutic planning.

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