

# Linezolid-Associated Neuropathy in Patients with MDR/XDR Tuberculosis in Shenzhen, China

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**Objective:** Linezolid is one of the key drugs for the treatment of multidrug-resistant/extensively drug-resistant tuberculosis (MDR/XDR-TB). We aimed to describe the incorporation of the Michigan Neuropathy Screening Instrument (MNSI) and serum trough concentration as screening tools for neurotoxicity in the management of MDR/XDR-TB patients receiving a linezolid-based treatment regimen in Shenzhen, China.

**Methods:** A total of 73 patients on a linezolid-containing anti-MDR/XDR-TB regimen were prospectively enrolled. The MNSI was used for peripheral neuropathy screening. Optic neuropathy was diagnosed by ophthalmologists. Serum trough concentration was recorded and its relationship with neuropathy analyzed.

**Results:** Of all patients, neuropathy was observed in 40% (29) during anti-TB treatment. Of these, 20 (69%) had peripheral neuritis, seven (24%) optic neuritis, and two (7%) both. Serum trough concentration >2 mg/L was observed in 17 (59%) patients with neuropathy and 13 (30%) patients without neuropathy. There was a significant statistical difference between the two groups ( $P=0.013$ ). Time to onset of neuropathy from initiation of the linezolid-containing regimen was within 2 months for eight (28%) patients, 2–6 months for 18 (62%) patients, and >6 months for three (10%) patients. Sixteen (55%) patients were adjusted to a lower dose of 300 mg linezolid daily. Four (14%) patients had linezolid permanently removed from their regimen.

**Conclusion:** Neuropathy is a commonly reported adverse event associated with long-term use of linezolid. MNSI and serum trough-concentration monitoring can be adopted as simple screening tools for early detection of neuropathy to balance linezolid efficacy and tolerability.

**Keywords:** linezolid, MDR/XDR-TB, neuropathy, MNSI, serum trough concentration

## Introduction

An increasing incidence of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant TB (XDR-TB) worldwide calls for focused efforts by the End TB program. China has one of the highest TB burdens.<sup>1</sup> Disease management has been a challenge, as treatment options are limited. The efficacy and favorable treatment outcomes of linezolid, a group A antimicrobial endorsed by the WHO for MDR/XDR-TB in 2018,<sup>2,3</sup> have been well documented in the treatment of DR-TB in numerous studies. However, adverse events have also been reported in patients with prolonged use of the drug,<sup>4–7</sup> with neurotoxicity the most frequent.

Some studies have shown that dosage of linezolid is directly correlated with the risk of adverse events and trough concentration of linezolid associated with the risk of neurotoxicity.<sup>2,5,8–10</sup> Peripheral neuropathy has been reported to be as high as 81% in patients at a dose of up to 1,200 mg/day.<sup>5</sup> A randomized control trial of 33 MDR/XDR-TB patients on an initial daily dose of 1,200 mg linezolid for 4–6 weeks followed by 300–600 mg at the continuation phase reported significantly higher odds of adverse events of peripheral (24.2%) and optic (18.2%) neuropathy in patients on linezolid than a control group.<sup>6</sup> A meta-analysis reported development of neuropathy in 30% of patients during anti-MDR-TB treatment.<sup>4</sup> Neuropathy is one of the key causes of early or permanent discontinuation of linezolid in a regimen.<sup>7</sup>

Traditional diagnostic methods for peripheral neuropathy include nerve-conduction studies and electromyography, and optical examinations performed by an ophthalmologist in cases of optic neuropathy.<sup>6,11,12</sup> However, these are expensive, and have to be performed by specialized personnel. Referrals are usually necessary, as the equipment is not readily available in all clinical settings. As such, it would be beneficial if an easy-to-use screening tool could be adopted to monitor drug toxicity to allow early interventions in optimizing treatment outcome and completion.

Self-administered screening tools have been introduced to detect early development of neuropathic disorder. The Subjective Peripheral Neuropathy Screen was developed to monitor painful sensory neuropathy in HIV-positive patients.<sup>13</sup> The Michigan Neuropathy Screening Instrument (MNSI) was designed to provide a straightforward self-administered tool to screen for early sensorimotor polyneuropathy in diabetic patients.<sup>14</sup> With its simple and noninvasive nature and sensitivity of up to 80%, the MNSI has been translated into over ten languages and is used in different countries for screening of early peripheral neuropathic symptoms.<sup>15,16</sup> No study has described the use of the MNSI in screening linezolid-induced peripheral neuropathy in TB patients. In this study, we describe in more detail the neuropathic adverse effects associated with linezolid and evaluate the occurrence and management of neuropathy among MDR/XDR-TB patients receiving a linezolid-based treatment regimen.

## Methods

### Study Setting and Participants

We prospectively studied patients aged >18 years with clinically confirmed rifampicin-resistant TB (RR-TB), MDR-TB, and XDR-TB during January 1, 2020 to January 1, 2021 who were on a linezolid-based regimen and had agreed to have their trough linezolid concentration monitored during treatment. Exclusion criteria were HIV-positivity, severe cardiovascular, liver, or blood-system disease, other serious illness, and pregnancy or lactation. All participants were admitted to the Third People's Hospital of Shenzhen, China when treatment was initiated and then followed up in the outpatient unit for >12 months after treatment completion.

An anti-TB regimen was tailored for each patient based on their results on drug-susceptibility testing and after review and approval by the MDR-TB care team in the hospital for compliance with guidelines and recommendations of the WHO and Antituberculosis Committee of China. Management of adverse events were based on physician consensus and guidelines from the Antituberculosis Committee of China. Demographic, clinical, and laboratory data were obtained from medical records for all eligible patients. All 73 participants provided written consent to take part (ChiCTR190002662). This study was approved by the ethics committee of the Third People's Hospital. The hospital undertook that in using these statistics, no personal information of any patient would be revealed. It also complied with the Declaration of Helsinki in regard to confidentiality and ethics.

### Patient Care and Key Definitions

Molecular testing and phenotypic susceptibility testing were used to determine drug-resistance profiles of *Mycobacterium tuberculosis* isolates. RR-TB is defined as resistance of *M. tuberculosis* to rifampicin only, MDR-TB as resistance to at least rifampicin and isoniazid, pre-XDR-TB as resistance to isoniazid and rifampicin and either a fluoroquinolone or a second-line injectable agent, but not both, and XDR-TB as MDR-TB plus resistance to at least one fluoroquinolone and a second-line injectable agent.<sup>3</sup>

Linezolid was a common agent in regimen compositions of all participants in this study. Dosage was set at 600 mg, administered once daily on treatment initiation for all participants, except one on dialysis, who was administered a lower dose of 300 mg once daily. To screen for the presence of neuropathy during treatment, the MNSI was adopted, and patients were assessed by their attending clinicians for peripheral and optic neuropathy on a monthly basis. Referral to a neurologist and ophthalmologist was arranged when deemed necessary. The MNSI consists of two parts. The first is a self-administered questionnaire for patients on foot sensation, with higher scores indicating more neuropathic symptoms. The second part is a physical examination performed by a health professional that includes assessment of the patient's feet on appearance and ulceration, ankle reflexes, and vibration perception using a 128 Hz tuning fork. A patient is considered peripheral neuropathic when their score is  $\geq 2$  (on an 8-point scale).

Optic neuropathy includes visual acuity loss, blurred vision, or diminution of vision. Patients presenting with any susceptible neuropathic symptoms would be referred to an ophthalmologist for thorough clinical assessment. For this analysis, only adverse events associated with peripheral and optic neuropathy were included. Dosage adjustment and follow-up interval were determined by the physician depending on the severity of neuropathy. Trough concentration of linezolid was measured at least once during treatment. Planned time points to measure serum trough concentration were at the end of 1, 3, and 6 months of treatment or when neuropathy was highly suspected. Time from treatment initiation to onset of neuropathy was classified as  $\leq 2$  months,  $>2$  to  $\leq 6$  months, and  $>6$  months.

## Pharmacokinetics

Venous blood (2 mL) was collected 0–30 minutes before oral linezolid administration for linezolid trough concentrations. Plasma was separated and analyzed within 1 hour. High Performance Liquid Chromatography (HPLC) was used for measuring serum concentration. As the reference for linezolid trough concentration is  $<2$  mg/L,<sup>10</sup> we considered linezolid trough concentration  $>2$  mg/L at least once at baseline or during treatment to be high and associated with neuropathy.

## Statistical Analysis

Data analysis was conducted using SAS 9.2. Chi-squared tests were used to measure differences between the two groups.  $P < 0.05$  was regarded as statistically significant.

## Results

### Patient Characteristics and Incidence of Neuropathy in RR/MDR/XDR-TB Patients

Of the 73 patients, 36% (26) were female and 64% (47) male. Mean age was  $37.6 \pm 13.93$  years, seven (10%) had a history of treated TB, 56 (77%) were infected with an MDR strain of *M. tuberculosis*: ten (14%) with an RR strain, five (7%) with a pre-XDR strain, and two (3%) with an XDR strain. Six (8%) were coinfecting with HBV, five (7%) with type 2 diabetes mellitus, and two (3%) had had a kidney transplantation. A total of 66 patients had pulmonary TB, six had pulmonary and extrapulmonary TB (bone, lymph node, urinary, or genital), and 40% (29) were diagnosed with neuropathy (Table 1). A list of medicines administered for  $>1$  month for the 73 patients in this study is given in Table 2.

### Serum Linezolid Trough Concentration in Patients with and without Neuropathy

Thirty patients were observed to have  $>2$  mg/L trough concentration at least once in the study period. Based on results of the MNSI and optic neurological examination, we divided patients into two groups: neuropathic and nonneuropathic. Comparison between these two groups showed that linezolid trough concentration  $>2$  mg/L had a higher prevalence in patients with neuropathy (59%, 17) than those without neuropathy (30%, 13). There is a significant statistical difference between the two groups ( $P = 0.013$ , Table 3). Another comparison using baseline characteristics showed that serum linezolid trough concentration had no relationship to age, weight, albumin level, eGFR, or coexisting diabetes on the first visit (Supplement Figure 1). We further compared trough concentration between patients on daily linezolid dosages of 300 mg and 600 mg and found that trough concentration was lower in patients on a 300 mg/day dose, but the difference was not statistically significant ( $P = 0.26$ ; Figure 1).

### Types of Neuropathy and Dosage Adjustment

We further analyzed presentation among types of neuropathy. Of the 29 patients with neuropathy, 20 (69%) had peripheral neuritis, seven (24%) had optic neuritis, and two (7%) had both. For patients with peripheral neuropathy, five (25%) reported neuropathy within 2 months, 13 (65%) 2–6 months, and two (10%) after 6 months. Ten (50%) patients were adjusted to a lower dose of 300 mg linezolid daily. Four (20%) patients had linezolid permanently removed from their regimen. For patients with optic neuropathy, three (43%) reported neuropathy within 2 months and four (57%) 2–6 months. Three (43%) patients were kept on the original dose and four (57%) were adjusted to a lower dose of 300 mg linezolid daily. None of them had linezolid permanently removed from their regimen. The median duration from linezolid withdrawal to recovery from neuropathy was 4–6 months (Table 4).

**Table 1** Participant demographic and clinical characteristics

<b>Age (mean ± SD), years</b>	37.6±13.93
<b>Sex</b>	
Male	47 (64%)
Female	26 (36%)
<b>History of treated tuberculosis</b>	7 (10%)
<b>Comorbidities</b>	
HBV coinfection	6 (8%)
Diabetes mellitus	5 (7%)
End-stage renal disease (on dialysis)	1 (1%)
Liver cirrhosis	1 (1%)
Kidney transplantation	2 (3%)
<b>BMI on presentation, mean ± SD, kg/m<sup>2</sup></b>	20.8±1.4
<b>Albumin level on presentation, mean ± SD, g/L</b>	40.89±4.103
<b>eGFR on presentation, mean ± SD, mL/min</b>	101.41±28.24
<b>Drug resistance</b>	
RR-TB	10 (14%)
MDR-TB	56 (77%)
Pre-XDR	5 (7%)
XDR-TB	2 (3%)
<b>Type of tuberculosis</b>	
Pulmonary	66 (90%)
Extrapulmonary TB	1 (1%)
Pulmonary and extrapulmonary	6 (8%)
<b>Reported neuropathy</b>	29 (40%)

**Abbreviations:** HBV, hepatitis B virus; BMI, body-mass index; eGFR, estimated glomerular filtration rate; RR-TB, rifampicin-resistant tuberculosis; MDR-TB, multidrug-resistant tuberculosis; pre-XDR, pre-extensively drug-resistant tuberculosis; XDR-TB, extensively drug-resistant tuberculosis.

## Discussion

Peripheral and optic neuropathy is a common toxic effect reported with long-term use of linezolid for treatment of MDR/XDR-TB.<sup>17</sup> In the existing literature, prescribed daily linezolid doses range from 300 mg to 1,200 mg. All dosages have been proven to be effective and suit patients' specific conditions with precise monitoring. Nonetheless, adverse events have been reported, and they seem to be linearly correlated with dosage. Daily administration of 1,200 mg has been reported to be associated with the presence of peripheral neuropathy in >80% of patients.<sup>5</sup> A lower dose of 300 mg/day is believed to induce less toxicity; however, acquired drug resistance would become another concern with prolonged use.<sup>9,11</sup> To balance regimen efficacy and safety, a daily dose of 600 mg for 12–18 months is recommended for MDR/XDR-TB,<sup>18</sup> but this does not rule out the development of neuropathy completely. Forty percent of MDR/XDR-TB patients in our study showed neuropathy susceptible to be linezolid-associated. This was a little higher than the reported incidence of 30% (95% CI 20.53%–40.25%) in a systematic review in 2016.<sup>4</sup> A recent study by Marie et al. reported an incidence of 32% in linezolid-related

**Table 2** Regimen composition with duration >1 month

Drug*	n (%)
Linezolid	73 (100%)
Bedaquiline	10 (14%)
Isoniazid	3 (4%)
Ethambutol	6 (8%)
Ethionamide	8 (11%)
Levofloxacin	33 (45%)
Moxifloxacin	52 (71%)
Cycloserine	65 (89%)
Amikacin	5 (7%)
Pyrazinamide	52 (71%)
Clofazimine	58 (79%)

**Notes:** \*Regimen composition was tailored for every participant based on results of drug-susceptibility testing, guidelines from the WHO and Antituberculosis Committee of China, and affordability of drugs in reference to patients' financial well-being.

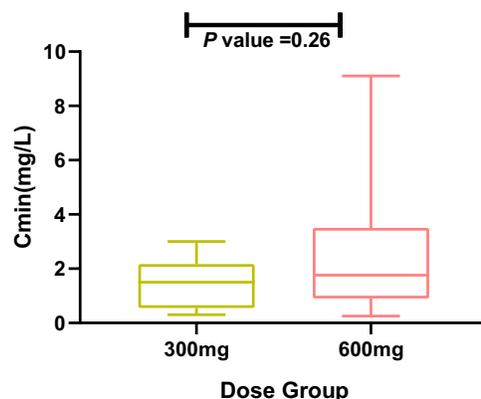
**Table 3** Univariate analysis of determinants of neuropathic development

	Neuropathic	Not neuropathic	P
	n=29	n=44	
Age, mean $\pm$ SD, years	37.54 $\pm$ 13.89	37.7 $\pm$ 14.26	0.961
Diabetes mellitus	0	5	0.068
End-stage renal disease (on dialysis)	1	0	0.403
BMI, mean $\pm$ SD, kg/m <sup>2</sup>	20.6 $\pm$ 2.2	21 $\pm$ 1.5	0.124
Albumin level at presentation, mean $\pm$ SD, g/mL	42.28 $\pm$ 3.96	40.02 $\pm$ 3.99	0.017
eGFR at presentation, mean $\pm$ SD, mL/min	93.44 $\pm$ 28.9	105.60 $\pm$ 27.33	0.111
Trough linezolid concentration >2 mg/L, n (%)	17 (59)	13 (30)	0.013

peripheral neuropathy confirmed by electromyography and nerve conduction–velocity testing.<sup>12</sup> A confirmed diagnosis of peripheral neuropathy requires professional device and knowledge, which may result in delayed diagnosis.

We suggest the introduction of a screening tool to identify neuropathy at an early stage and allow effective intervention. The MNSI is designed for peripheral neuropathy screening in patients with diabetes. It has been proven to be a simple and reliable assessment tool in the early diagnosis of diabetic peripheral neuropathy.<sup>15</sup> In our study, we extended the use of the MNSI to cover TB patients in monitoring the use of linezolid, which has been reported to be effective but limited by side effects. We expect the incorporation of a systematic assessment tool can assist with early identification of drug toxicity and provide data to assist physicians with close therapeutic monitoring and treatment management to optimize therapy efficacy and balance the drug's side-effect profile.

Optic neuropathy is another adverse event reported with extended use of linezolid.<sup>6,19</sup> In our study, seven patients developed optic neuropathy alone and two had both optic and peripheral neuropathy. As diagnosis of optic neuropathy is



**Figure 1** Serum trough concentration ( $C_{min}$ ) in patients on daily linezolid dosages of 300 mg and 600 mg.

more complicated and involves optical examination by a professional, referral to ophthalmologists is needed in any susceptible cases, so it is not included in the MNSI. Elimination of linezolid from the body occurs by both renal and nonrenal mechanisms. Nonrenal clearance accounts for 65% of the linezolid dose, and 30% of the dose is excreted as unchanged drug in the urine. It has been shown that renal dysfunction is associated with high linezolid trough concentration.<sup>20</sup> Our findings showed demographic characteristics and comorbidities did not seem to be associated with the development of neuropathy or serum trough concentration. The only dialysis patient in our study was prescribed a lower linezolid dose of 300 mg/day. His serum trough concentration was 1.5 mg/L, and a diagnosis of neuropathy was confirmed at 6 months of treatment. This reminds us that more attention should be paid to prioritizing high-risk patients to minimize complications.

Peripheral neuropathy is a common complication of diabetes, but the five diabetic patients in our study did not develop peripheral or optic neuropathy. It seems that linezolid does not increase the incidence of neuropathy in diabetes

**Table 4** Clinical characteristics of linezolid-associated neuropathy

	Peripheral neuropathy, n=20	Optic neuropathy, n=7	Both, n=2	P
	n (%)*	n (%)	n (%)	
<b>Linezolid trough concentration</b>				0.120
>2 mg/L	14 (70)	3 (43)	0	
≤2 mg/L	6 (30)	4 (57)	2 (100)	
<b>Time to onset from treatment initiation</b>				0.735
≤2 months	5 (25)	3 (43)	0	
>2 to ≤6 months	13 (65)	4 (57)	1 (50)	
>6 months	2 (10)	0	1 (50)	
<b>Therapy modification</b>				0.001
None	6 (30)	3 (43)	0	
Dose lowered to 300 mg/day	10 (50)	4 (57)	2 (100)	
Discontinuation of linezolid	4 (20)	0	0	
<b>Months from linezolid withdrawal to recovery (median)</b>	6	4	4	0.643

patients. Until now, no published studies have described higher incidence of neuropathy or neuropathy deterioration being associated with long-term use of linezolid in MDR-TB patients with diabetes. As it is difficult to identify whether neuropathy is induced by diabetes itself or by drugs, we suggest closer monitoring of the onset of neuropathy and precise hyperglycemic control in MDR-TB patients with diabetes.

Whether linezolid trough concentrations  $>2$  mg/L can be used as an indicator for the occurrence of neuropathy is still debated.<sup>20</sup> An early study by Song et al demonstrated a direct correlation between trough concentration and clinical toxicity.<sup>10</sup> In a retrospective study, Bolhuis et al. speculated that peripheral neuropathy was mediated by cumulative dose and days of exposure to linezolid.<sup>21</sup> A recent study by Jaspard et al. in France reported no significant association between trough concentration and neurologic toxicity.<sup>12</sup> In our study, serum trough concentration  $>2$  mg/L was more commonly observed in patients with peripheral and optic neuropathy. There was no significant difference in serum trough concentration among patients who developed peripheral or optic neuropathy or both. Most had onset of neuropathy within 6 months. Patients who did not develop neuropathy were observed to have good tolerability to linezolid over a treatment course  $>12$  months, but a few patients showed neuropathy within 2 months. The rapid onset of neuropathy reminds us that mitochondrial genetic heterogeneity may contribute to the development of neurotoxicity.<sup>22–24</sup> Trough concentration can be used as an indicator of linezolid accumulation in the body, and explains some side effects of the drug to a certain extent.

Although neurotoxicity is one of the major factors leading to the temporary or permanent withdrawal of linezolid for some patients, numerous studies have described the relief of neuropathic symptoms after linezolid has been discontinued.<sup>19</sup> Persistent irreversible neuropathy has also been reported.<sup>25</sup> A majority of patients with neuropathy in our study also reported gradual relief of symptoms after cessation of linezolid regimen. Consistently with other studies, the median time for elimination of neuropathic symptoms in our study was about 6 months.<sup>12</sup> Only two patients complained of pain and numbness persisting  $>1$  year following the completion of linezolid therapy.

There are several limitations to our study. Firstly, it was monocentric with a limited number of participants, though it was of prospective design and the clinical data of the patients were recorded in detail. Secondly, how trough concentration reflected the accumulation of linezolid over time could not be established, as measurement of trough concentration for all patients were not taken at identical time intervals over the whole treatment. Thirdly, optic neuropathy was diagnosed according to clinical examinations by an ophthalmologist, resulting in a lack of a systematic algorithm data set, and so can be biased as to the exact number of patients being affected.

In summary, we have described the characteristics of neuropathy in patients with long-term use of linezolid. We illustrated that the MNSI can be adopted as a simple and reliable screening tool for peripheral neuropathy. Systematic monitoring of serum trough concentration can be used as a supportive indicator for toxicity and therapy management. In the event of suspected neuropathy, dose adjustment or withdrawal can be considered to balance therapy efficacy and safety. Further studies are needed to explore the possible genetic factors associated with linezolid tolerability and predict the rapid onset of severe adverse effects.

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## Disclosure

The authors declare no conflicts of interest in this study.

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