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# The Role of Pyridoxine in the Prevention and Treatment of Neuropathy and Neurotoxicity Associated with Rifampicin-Resistant Tuberculosis Treatment Regimens: A Topic Review

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## Abstract

Rifampicin-resistant tuberculosis (RR-TB) is a global public health problem caused by mycobacterium tuberculosis resistant to Rifampicin. Drug-induced peripheral neuropathy and neurotoxicity are well-known adverse effects of treatment regimens that cause significant morbidity. Pyridoxine is often added to treatment regimens for the prevention and/or treatment of these side effects. The basis and effectiveness of this practice are unclear. We conducted a systematic review to evaluate the effectiveness of pyridoxine in preventing and/or treating neuropathy and neurotoxicity associated with RR-TB treatment. We included studies with patients with RR-TB who experienced neuropathy or neurotoxicity attributed to RR-TB regimens and were given pyridoxine. Our findings showed contradicting evidence on the use of pyridoxine for preventing or treating neurotoxicity due to cycloserine in the treatment of RR-TB. Moreover, pyridoxine did not have a protective effect against neuropathy and/or neurotoxicity caused by other RR-TB regimens that do not contain isoniazid. In conclusion, we found that withdrawing or withholding medications such as linezolid, cycloserine, thioamides, fluoroquinolones, and ethambutol, implicated in causing neuropathy or neurotoxicity was more effective than using pyridoxine to stop the progression of symptoms, and in some instances, led to their reversal over time.

## Keywords

Rifampicin-Resistant Tuberculosis, Pyridoxine, Vitamin B6, Neuropathy,

Neurotoxicity, Multidrug-Resistant Tuberculosis, Extensively Drug-Resistant Tuberculosis

## 1. Introduction

Rifampicin-resistant tuberculosis (RR-TB), including multi-drug resistant (MDR) and extensively drug-resistant (XDR) forms, is a significant global health concern. The World Health Organization (WHO) estimates that there were almost 400,000 new cases of MDR-TB in 2018, with 3.4% of all new TB cases and 20% of retreatment cases being MDR-TB [1]. Compared to drug-sensitive tuberculosis, RR-TB has a higher morbidity and mortality rate. However, as with other forms of TB, the cure rates vary between regions and the trend in the burden of RR-TB remains disproportionately worse in resource-limited areas, such as in Turkmenistan where the age-standardized incidence rate of MDR-TB increased by 67%, in East Africa where the prevalence is six times higher than the global average, and in Tugela Ferry in South Africa, where the mortality rate for immune-compromised patients with MDR-TB was 63% and 80% for those with XDR-TB [2] [3] [4] [5].

The treatment of RR-TB often requires complex drug regimens for which the WHO publishes recommendations for the use of specific medications in different combinations depending on several patient and mycobacterial factors [6] [7]. RR-TB treatment is further complicated by poor adherence due to the high cost of treatment, the high pill burden, and the occurrence of adverse events caused by medications among others [8] [9] [10].

Neuropathy and neurotoxicity are common complications of TB that can be caused by certain anti-RR-TB medications *i.e.* isoniazid, linezolid, cycloserine (Cs), thioamides, fluoroquinolones, and ethambutol. Pyridoxine, also known as vitamin B6, has been proposed and is often used, as a treatment or preventative measure for neuropathy and neurotoxicity caused by RR-TB regimens [11].

### 1.1. Neuropathy and Neurotoxicity

Neuropathy is often used synonymously to mean peripheral neuropathy (PN) but is defined as damage to the peripheral or central nervous system [12]. The causes of neuropathy differ (and are not fully understood) but their mechanisms of nerve damage can be classified into three main categories: segmental demyelination, Wallerian degeneration, and axonal degeneration [13] [14].

Neurotoxicity leads to a range of symptoms including coma, seizures, paralysis, dementia, impaired reasoning, memory loss, and disturbances in communication, motor functions, and attention [15]. Neurotoxic agents can directly injure nerve cells or interfere with the metabolic processes required for normal functioning, and in some cases, cause poor nervous system development [16] [17].

Neuropathy and neurotoxicity are common adverse events seen in tuberculosis (TB) patients. Moreover, the prevalence of PN in patients with drug-resistant TB is almost four times higher [11] [18]. These adverse events negatively affect patients' quality of life and can cause lifelong disability and morbidity [11].

### 1.2. Vitamin B6 in the Management of Neuropathy and Neurotoxicity

Vitamin B6 (often used to mean pyridoxine and vice versa) is routinely used for the management of neuropathy and neurotoxicity in TB patients. It is an essential water-soluble vitamin that is involved in various biological functions in the body, including the synthesis and breakdown of amino acids, biosynthesis of fatty acids, carbohydrates, nucleic acids, hemoglobin, sphingolipids, and neurotransmitters [19].

The World Health Organization (WHO) recommended the use of pyridoxine for the prevention of neurological side effects caused by Cs, linezolid, and isoniazid in DR-TB regimens containing these drugs [6]. Several researchers have advocated for its use in patients who experience neuropathy, and other neurological side effects of linezolid, Cs, streptomycin, ethionamide, and fluoroquinolones when used in RR-TB treatment [11] [18] [20] [21] [22].

Pyridoxine is costly, its addition to RR-TB regimens increases the pill burden, and it is known to cause neurotoxicity and can interact with other medications in the regimens potentially exacerbating side effects [23] [24]. Despite the above recommendations, the basis and effectiveness of adding pyridoxine to RR-TB treatment regimens for the management or prevention of these adverse events have remained unclear. We conducted a scoping literature review to examine the role of pyridoxine in preventing and/or treating neuropathy and neurotoxicity induced by RR-TB treatment regimens. This article will give an overview of the same.

## 2. Methods

This scoping review included review articles, case studies, case-control studies, and randomized and non-randomized studies published in English, Russian, or German in PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com/), Cochrane Library (https://www.cochranelibrary.com/), Web of Science (https://www.webofscience.com/), PsycINFO (https://www.proquest.com/products-services/psychology-database.html), and CINAHL (https://www.ebscohost.com/nursing/products/cinahl-databases/cinahl-complete). The study population in the included studies consisted of patients with RR-TB who experienced neuropathy and/or neurotoxicity attributed to RR-TB treatment regimens, not including isoniazid, and were given pyridoxine for prophylaxis or treatment of these side effects. The study setting included both hospital and community settings. We excluded studies that were conducted on animals

or on non-human samples, studies whose full-text versions were unavailable, and studies published in a language other than the languages specified in the inclusion criteria.

All the references of the identified articles were transferred to EndNote and then to the RAYYAN QCRI, an online data management web-based resource that allows for online collaboration with researchers around the world. Duplicate articles and titles in other languages were removed, and the eligibility of the remaining articles was determined using the PICO (Population, Intervention, Comparison, and Outcome) tool. However, due to the limited number of relevant studies and the disparity in study designs, the standard PICO criteria were followed only where appropriate, and the focus was on evaluating the effect of pyridoxine on RR-TB patients with neuropathy and/or neurotoxicity.

The selection of relevant studies was conducted using a double review system with the primary researcher and the thesis supervisor. Initial screening was done by title, and irrelevant studies were excluded. The remaining studies were then screened by abstract, and those deemed a "close fit" were sourced for full-text review. The bibliographies of these studies were also reviewed for relevant articles. Any conflicts on the inclusion or exclusion of an article were resolved through discussion between the two reviewers.

Data extraction and quality assessment of the studies were performed by two researchers independently, using the Cochrane Risk of Bias tool for randomized studies and the Newcastle-Ottawa Scale for observational studies. Any discrepancies were resolved through discussion and consensus.

Descriptive statistics were used to summarize and describe the characteristics of the included studies. This involved calculating the frequencies and percentages of the different variables of interest, as well as computing population summary characteristics of the reviewed studies. Data were further analyzed with the help of the RAYYAN QCRI online application. The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach was used to assess the quality of the evidence where possible. Comorbidities, such as diabetes, HIV, hypertension, hepatitis B and C, and underlying neuropathy at the onset of treatment, were explored as potential confounders for the occurrence of neuropathy and/or neurotoxicity. The outcomes of these studies were assessed and discussed, with a focus on the effect of using pyridoxine for the prevention and/or treatment of neuropathy or neurotoxicity induced by the implicated drugs.

## 3. Results

Nine articles were identified in the review, including one review, two retrospective cohort studies, four case series, and three case studies.

The studies were geographically diverse, with 22% taking place in Europe, 44% in Asia, 22% in North America, and 11% in Africa (**Figure 1**).

Based on the World Bank classification of countries by income, 44% of the

studies took place in high-income countries, 33% in low- and middle-income countries, and 22% in upper-middle-income countries (Figure 2).

The age of study participants was divided into two categories: adults (age 18 and above) and children. 67% of the studies focused on adults, and 33% on children. The sample sizes in the studies ranged from 1 (in single case studies) to 30 (in the case series), and the drug resistance patterns explored included 44% MDR, 33% XDR, and 22% MDR and XDR (Figure 3).

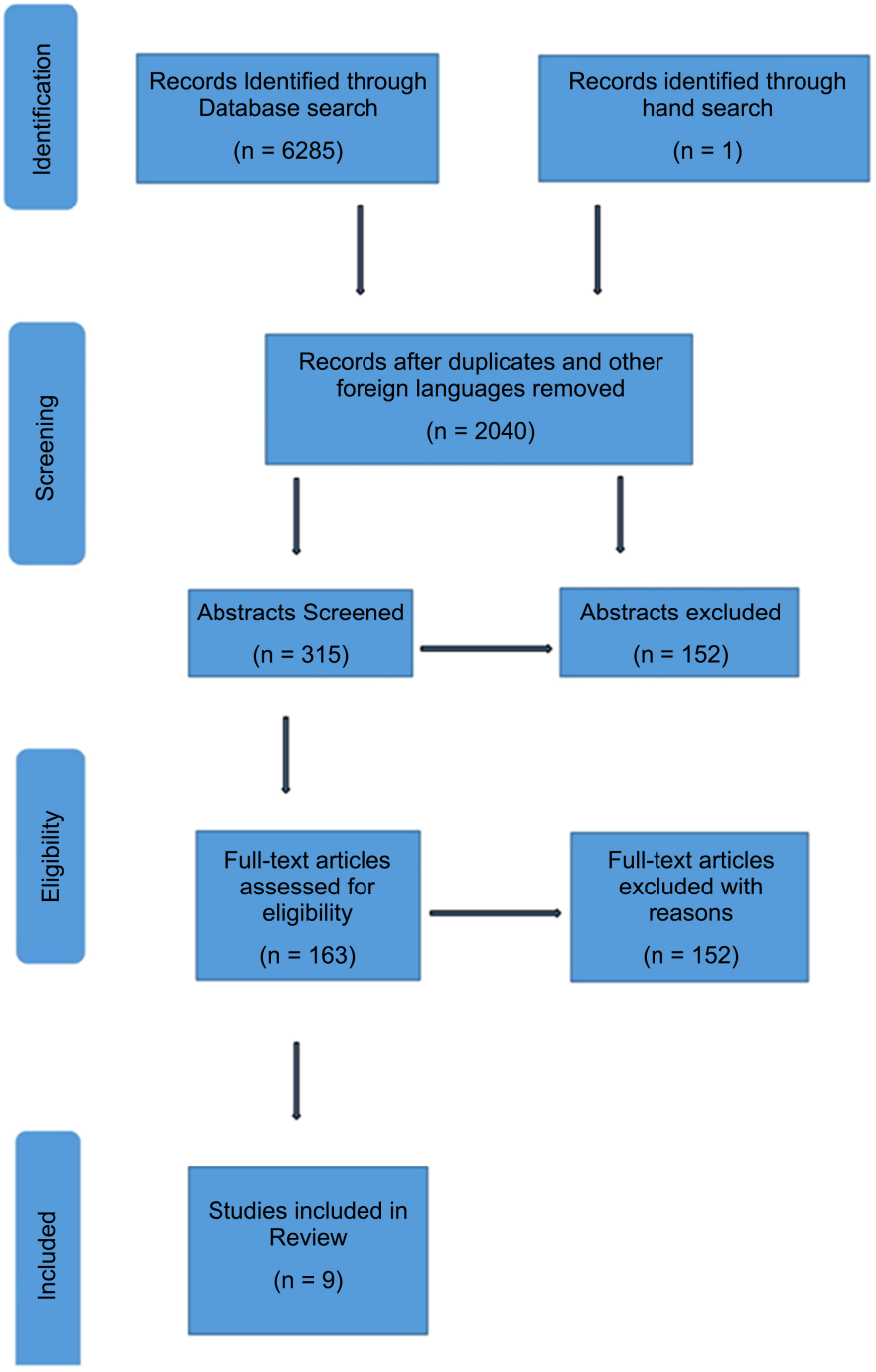


Figure 1. Inclusion/Exclusion criteria selection process.

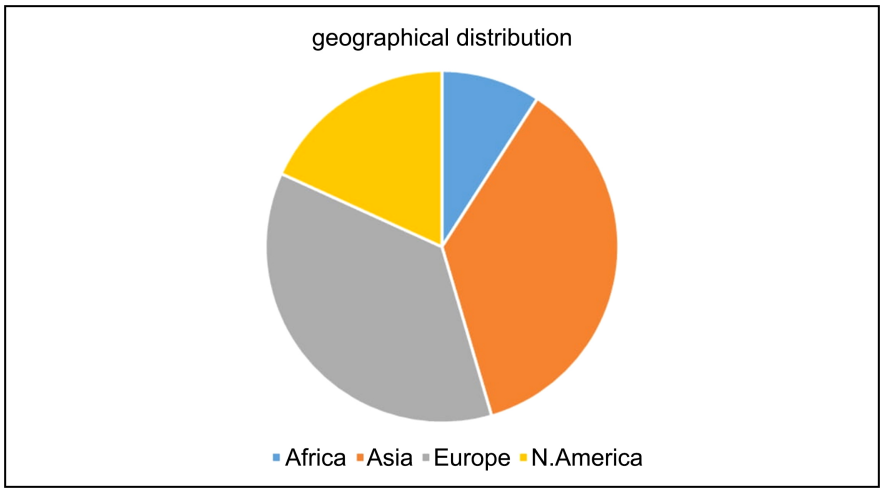


**Figure 2.** Geographical distribution of included studies.

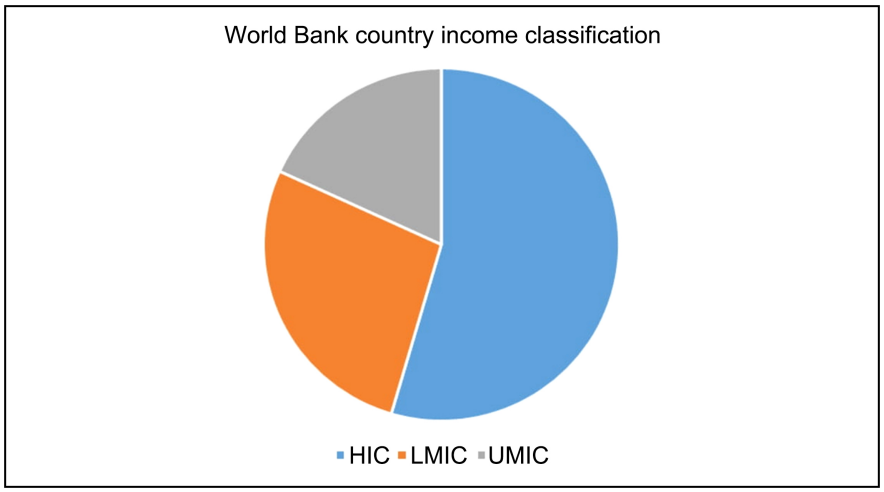


**Figure 3.** World Bank country income classification of included studies.

Linezolid-induced neuropathy in patients undergoing RR-TB was the most studied adverse event, appearing in 78% of the studies. Cs-induced neurotoxicity was the second most studied, making up 22% of the studies (**Figure 4**).

Only 44% of the studies described the presence or absence of comorbidities, with 50% of these studies reporting the presence of HIV and 50% reporting the presence of diabetes among patients with the adverse events of interest. None of the studies reported performing vitamin B6 level testing or a neurological exam on their patients before treatment (**Figure 5**).

Only 30% of the studies used a grading system to describe the intensity of the adverse events, and the grading system was not standardized, making it difficult to analyze the intensity of the adverse events. Of the studies analyzed, 66% mentioned the doses of vitamin B6 given to patients for the prevention of adverse events, while 33% stated the doses given for treatment. The prophylactic doses ranged from 50 to 250 mg daily, while those given for treatment ranged from 100 to 200 mg.

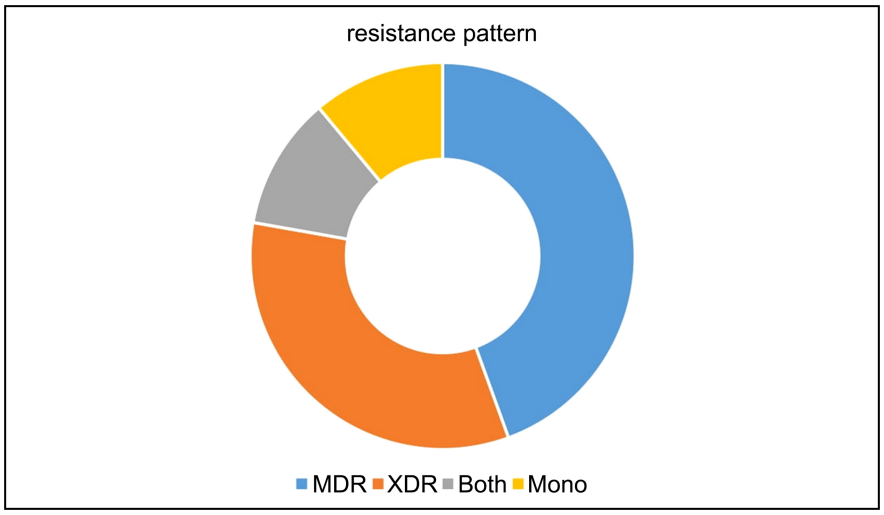


**Figure 4.** Mycobacteria tuberculosis resistance patterns of patients in the included studies.

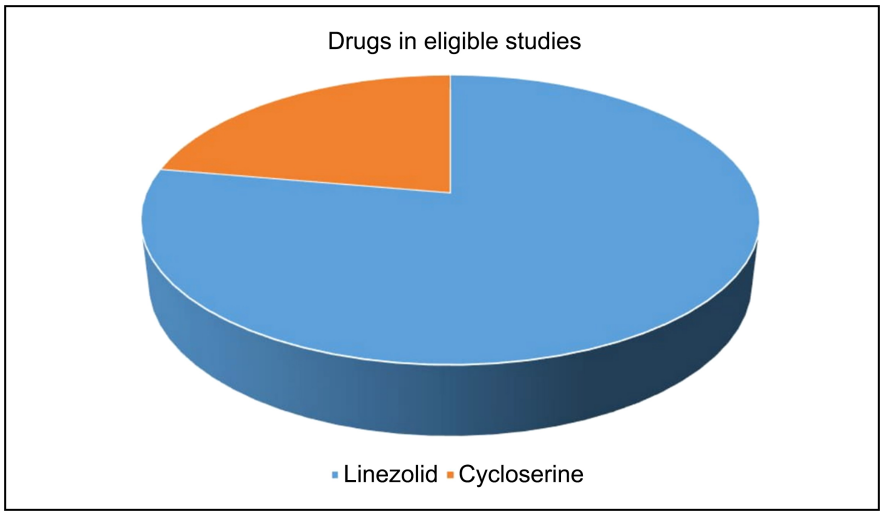


**Figure 5.** The RR-TB drug implicated for causing neuropathy/neurotoxicity in included studies.

In 44% of the studies, the doses of the implicated drugs were reduced in patients who experienced adverse events of interest, while 66% of the studies reported that the implicated drugs were withheld to stop or reverse the side effects.

## 4. Discussion

This study synthesizes evidence on the drugs implicated in causing peripheral neuropathy and the potential benefit of pyridoxine in treating and/or preventing them. We found two studies on Cs that fit our inclusion criteria. Sharma and colleagues (2017) reported that all patients suffered from neurotoxicity in the form of depression and about 70% of the patients had suicidal ideations despite all of them being on pyridoxine. They increased the dose of pyridoxine for this patient (though they did not specify the dosage) and noted some improvement [25]. In the second study by Manjeet *et al.* (2018) suicidal ideations dissipated

only to return when Cs was reintroduced into his regimen [26]. In both studies, neurological exams were not done nor were pyridoxine levels assessed prior to initiation of treatment nor were comorbidities that may have influenced the occurrence of the adverse events reported.

Other studies have also reported neurotoxic adverse events associated with Cs. Cohen *et al.* (1969) reported one patient who experienced convulsions and several other patients who experienced neurotoxic adverse events e.g. psychosis, requiring Cs to be discontinued or withheld. Girgis *et al.* (1962) reported that 12% of their patients had to discontinue Cs due to its neurotoxic effects. Kwon *et al.* (2008) reported a case of a patient who developed neurotoxic symptoms with associated organic brain changes seen on MRI after starting a TB treatment regimen containing Cs, despite being on 100 mg pyridoxine for prophylaxis that only resolved after Cs was stopped [27] [28] [29].

The search revealed seven studies on linezolid that fit our inclusion criteria. One of the studies was in China by Liu, Y. *et al.* (2015) was a retrospective hospital-based study on the clinical outcomes of XDR patients treated with linezolid [30]. In another study, Dauby, N. *et al.* (2011) the patient on linezolid for XDR-TB had been on 250mg of pyridoxine and was reported to have suffered from moderate PN necessitating a reduction in the linezolid dose [31]. Ramirez-Lapausa, M. *et al.* [32] peformed a retrospective study on patients treated with linezolid for MDR-TB in Madrid Spain from 1998-2014 and found PN was in close to 10% of the patients yet all of them were on vitamin B6 prophylaxis. The authors also noted that 14% of their patients had HIV however it was not implicated to influence the occurrence of PN [32].

Schecter, G.F. *et al.* [33] in California conducted a record review of 30 patients treated with linezolid as part of an MDR-TB regimen and found that 17% of the patients experienced PN. All the patients in the study had been put on vitamin B6 at a dose of 50 - 100 mg. They noted that one of the patients who suffered from neuropathy improved when the dose of pyridoxine was increased from 150 mg - 200 mg. Additionally, another patient suffered from optic neuropathy which resolved when linezolid was withheld [33]. Swaminathan, A. *et al.* [34] reported a case of a 15-year-old boy who was suffering from MDR-TB with additional resistance to injectable TB medication and diabetes mellitus (DM) type 1. The patient developed PN after 8 months affecting predominantly his lower limbs. He had been taking pyridoxine at a dose of 150 mg for prophylaxis and the dose was increased to 200 mg to treat the neuropathy without success. The symptoms only reduced when linezolid was withdrawn [34].

Anger, H. A. *et al.* [35] performed a retrospective review of public health and medical records of 16 RR-TB patients who underwent treatment in New York City between January 2000 and December 2006. They found that the incidence of neurotoxicity was 44% despite the use of pyridoxine. Furthermore, they noted that none of the patients who suffered from PN fully recovered [35]. Finally, Garcia-Pratts, A. *et al.* (2014) reported on linezolid treatment for drug-resistant

TB in children and thought it unlikely that the use of pyridoxine would prevent linezolid-induced PN in children [36]. Pyridoxine is useful in the prevention of linezolid-induced cytopenias but not PN and should be administered to RR-TB patients for this purpose [33] [37] [38].

We did not find studies that fit our inclusion criteria for thioamides, ethambutol, and fluoroquinolones, however using other articles, we synthesized evidence on the occurrence of the adverse events of interest and the role of pyridoxine in treating and preventing the same. Thioamides (prothionamide and ethionamide) are known to cause the adverse events of interest. Leggat P.O. [39] described a case of PN in a 54-year-old man secondary to ethionamide use. He had drug-resistant TB and had been put on a regimen containing Cs 1.0 g, streptomycin 1.0, and ethionamide at 0.5 g. The patient was reported to have begun experiencing tingling and later on burning sensations in both hands and feet after being on this regimen for 8 months. His symptoms only disappeared after ethionamide was stopped. Later on, ethionamide was reintroduced alongside 200 mg of pyridoxine and the patient did not complain of the same [39]. The effectiveness of pyridoxine, in this case, is difficult to judge because treatment was stopped after only 8 days because he developed severe persistent nausea that was attributed to ethionamide.

Tugwel, P. *et al.* [40] described a three-case series of patients who suffered from PN attributable to ethambutol. The first case described a 52-year-old man who developed both ocular toxicity as well as PN while on treatment with a regimen containing isoniazid. When the symptoms of PN worsened isoniazid was stopped and he continued treatment by taking the other drugs with the addition of vitamins B1, B2, B6, and B12. His symptoms persisted and he only improved showed when ethambutol was withheld. The second case was a 50-year-old woman who was also on a regimen containing ethambutol and isoniazid and suffered from progressive PN. Her symptoms persisted even after cessation of isoniazid and only stopped when ethambutol was withheld. The third patient was another 52-year-old man who developed neuropathy while on an isoniazid and ethambutol-based regimen. Ethambutol was withheld and the PN stopped despite the patient still being on isoniazid. Notably, this patient was receiving vitamin B6 but PN still occurred [40].

We analyzed the mechanisms by which these drugs cause the adverse events of interest to elicit how they interfere with pyridoxine metabolism leading to its deficiency. We found that this remains a controversial area due to the many theories that have been put forward [41]-[60]. Several authors have suggested that Cs can interfere with the metabolism of pyridoxine [61]-[67]. Imam *et al.* (2020) suggested that ethambutol causes neuropathy by causing pyridoxine deficiency while Nair *et al.* suggested that Cs-induced neurotoxicity was not due to pyridoxine antagonism [68] [69]. Further research is needed in this area to shed light on effective ways of preventing and treating neuropathy and neurotoxicity induced by RR-TB regimens.

We found strong evidence that suggests that neuropathy and neurotoxicity caused by ethambutol, thioamides, and linezolid are concentration and duration dependent [42] [70]-[76]. Neurotoxicity caused by Cs, on the other hand, is only concentration-dependent but does not seem to depend on the duration of use and paradoxically, it has been related to taking higher pyridoxine doses [77]. Evidence also suggests that the occurrence of comorbidities, especially diabetes mellitus, predisposes patients to neuropathy when using ethambutol and linezolid [34] [78]. We found strong evidence that suggests that most patients recover from neurotoxicity after withdrawal/stopping the implicated drug, however, PN induced by linezolid and ocular neuropathy have been found to persist long after the drugs are stopped and is irreversible in some cases [33] [38] [47] [72] [79] [80] [81].

While conducting this review, we encountered some limitations that must be acknowledged. The small number of included studies is mostly due to the fact that these adverse events have not been extensively researched in relation to RR-TB treatment. As a result, the findings of this review may not provide a comprehensive overview of the available literature on the topic. Moreover, the heterogeneity in the study designs and methodologies used across the included studies may have affected our ability to draw firm conclusions from the results. Additionally, it is possible that our search strategy did not capture all relevant unpublished studies or studies published in languages not included in our review. Nonetheless, this review provides valuable insights into the adverse events of interest and emphasizes the need for further research to enhance our understanding and management of these events.

## 5. Conclusion

The current body of evidence is limited and more research is needed to fully understand how to prevent and manage the neuropathy and neurotoxicity as side effects of RR-TB drugs. Based on the available literature, we did not find enough evidence to support the use of pyridoxine in the prevention or treatment of adverse events caused by RR-TB treatment regimens that do not contain isoniazid. Dose reduction, withholding, or discontinuing the implicated medications are effective ways to manage these events. Neuropsychiatric evaluations should be performed on all patients with RR-TB before initiation of treatment regimens containing drugs known to cause neuropathy and neurotoxicity should be routinely assessed for the same. Furthermore, comorbidities that predispose them to develop these adverse events should be routinely assessed and, when elicited, adequately managed.

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## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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