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ORIGINAL RESEARCH

Risk Assessment of Linezolid-Associated Neurological Adverse Drug Reactions Based on the Food and Drug Administration Adverse Event Reporting System Database

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Objective: To conduct data mining and analysis on neurological adverse drug reactions (ADRs), defined as any unwanted neurological effects caused by the use of linezolid, affecting both the central and peripheral nervous systems. This study also aims to investigate potential drug–drug interactions that may increase the risk of these ADRs when linezolid is used in combination with other medications. The findings aim to provide guidance for the safe clinical use of linezolid.

Methods: Data from the US Food and Drug Administration Adverse Event Reporting System between 1 July 2014 and 30 June 2024 were analysed to identify linezolid-related neurological ADRs. The Ω shrinkage measure was used to detect drugs associated with an elevated risk of neurological ADRs.

Results: A total of 8521 reports of linezolid-related ADRs were retrieved, of which 20.12% (1720 cases) involved neurological ADRs. Forty-five signals of neurological ADRs were detected, with serotonin syndrome (436 cases, reporting odds ratio [ROR] = 43.66, representing 25.35%) and peripheral neuropathy (413 cases, ROR = 7.88, representing 24.01%) being the most prevalent. Additionally, 23 previously undocumented ADR signals and 21 drugs associated with an increased risk of neurological ADRs (Ω 025 > 0) were identified.

Conclusion: This study highlights the need for careful monitoring of neurological ADRs associated with linezolid, vigilance regarding previously undocumented ADRs and the prudent management of concomitant medications. These findings provide essential guidance for the safe clinical use of linezolid.

Keywords: linezolid, signal detection, neurotoxicity, adverse drug reaction

Introduction

Linezolid, an effective oxazolidinone antibiotic, has demonstrated substantial antimicrobial activity against Gram-positive bacteria, including drug-resistant pathogens. This broad-spectrum antimicrobial activity has led to its widespread use in the treatment of severe and resistant infections.[1–3] However, with the increasing clinical application of linezolid, its adverse drug reactions (ADRs) have become more apparent, particularly its neurological ADRs. These reactions are not only diverse but also often severe, making them one of the primary reasons for discontinuation of linezolid in clinical practice,[4] sometimes even posing a threat to patient safety.

Studies have shown that the most common adverse reactions to linezolid include gastrointestinal symptoms (eg nausea, vomiting and diarrhoea) and bone marrow suppression (eg anaemia and thrombocytopenia).[5] The occurrence of bone marrow suppression is closely associated with the dosage and duration of treatment, highlighting the necessity for regular haematological monitoring during long-term therapy.[6] Similarly, prolonged use of linezolid has been linked to an increased risk of neurological adverse effects, particularly peripheral neuropathy, optic neuritis and seizures. Clinical

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studies indicate that treatment exceeding 28 days substantially raises the likelihood of developing these complications, with some cases resulting in irreversible damage.[7]

The mechanism underlying these neurological ADRs is believed to involve mitochondrial dysfunction, as linezolid inhibits mitochondrial protein synthesis, leading to impaired neuronal energy metabolism. Additionally, oxidative stress and axonal degeneration have been implicated in cases of peripheral and optic neuropathy.[8] These reactions are more frequently observed in patients undergoing prolonged linezolid therapy, and in severe cases, discontinuation of the drug is required.[9]

Despite ongoing research, the exact mechanisms of linezolid-induced neurological adverse effects remain poorly understood. Current findings suggest that linezolid disrupts neuronal energy metabolism by inhibiting mitochondrial protein synthesis, thereby contributing to neurotoxicity.[10] This hypothesis partially explains the peripheral neuropathy and optic nerve damage observed in some patients; however, further studies are needed to confirm these findings.

Furthermore, exacerbation of neurological adverse effects due to drug–drug interactions (DDIs) when linezolid is co-administered with other medications have been frequently reported in clinical practice. This underscores the need for further investigation into these interactions.[11]

To gain a deeper understanding of the characteristics of linezolid-related neurological ADRs, this study conducted data mining and analysis using the Food and Drug Administration Adverse Event Reporting System (FAERS).

Furthermore, the study conducts an in-depth exploration of linezolid's co-medication interactions, evaluating potential associations between its combined use with other drugs and an increased risk of neurological ADRs. This quantitative analysis provides a more scientifically grounded basis for assessing the safety of linezolid in complex treatment regimens. The study aims to offer new insights into the safe and rational use of linezolid in clinical practice.

Materials and Methods

Data Collection and Processing

Adverse drug reaction reports related to linezolid were obtained from the publicly available US FAERS database, covering the period between 1 July 2014 and 30 June 2024. These reports were collected using the search terms 'LINEZOLID' and its brand name, 'ZYVOX'. Reports, where linezolid was identified as the primary suspected drug, were selected, and data cleaning was performed using SAS 9.4 software.

According to the Medical Dictionary for Regulatory Activities (MedDRA) terminology (V26.1), ADR data were categorised based on system organ class (SOC), high-level group term (HLGT) and preferred term (PT). Reports related to neurological disorders were identified using the SOC code for neurological diseases (10029205), and duplicate reports were excluded based on fields such as report ID, retaining only the most recent version to avoid redundant signal counting.

Next, records where 'LINEZOLID' or 'ZYVOX' were listed as the primary suspected drug were retained, whereas reports with unclear drug names were excluded using fuzzy matching. Adverse drug reaction reports related to neurological disorders were further filtered based on MedDRA V26.1 codes, and records unrelated to the drug's indications, usage or storage were removed. This process ensured that the final dataset contained only reports of clear adverse reactions caused by linezolid, enhancing the reliability of the analysis.

Since this study exclusively utilises publicly accessible, de-identified data from the FAERS database, it does not involve direct patient contact or identifiable personal data. In accordance with Article 32, Items 1 and 2 of the *Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects* (China, 2023), this research is exempt from ethical approval.

Signal Detection

Signal detection in the FAERS database was conducted using both the reporting odds ratio (ROR) and proportional reporting ratio (PRR) methods. The frequency of ADRs associated with other drugs in the database served as the control to calculate the risk ratio for neurological ADRs linked to linezolid. The formulas for ROR and PRR calculations as well as the signal detection threshold criteria used in this study are provided in Table 1.[12]

Table 1 ROR and PRR Calculation Formulas and Signal Detection Threshold Criteria

Method	Formula	Signal Detection Threshold Criteria
ROR	$ROR = \frac{(a/c)}{(b/d)} = \frac{ad}{bc}$	a ≥ 3 and 95% CI (lower limit) > 1
	$95\%CI = e^{ln(ROR)\pm 1.96\sqrt{\left(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}\right)}}$	
PRR	$\mathrm{PRR} = \frac{a/(a+b)}{c/(c+d)}$	a ≥ 3 and PRR ≥ 2 and $\chi^2 \geq 4$
	$x^2 = \frac{(ad-bc)^2(a+b+c+d)}{(a+b)(a+c)(c+d)(b+d)}$	

Notes: a = Number of reports for the target drug with the target ADR. b = Number of reports for the target drug with other ADRs. c = Number of reports for other drugs with the target ADR. d = Number of reports for other drugs with other ADRs. e = Base of the natural logarithm, approximately equal to 2.718.
Abbreviations: ROR, Reporting Odds Ratio; PRR, Proportional Reporting Ratio.

To minimise false-positive results, only ADRs that met the signal generation criteria for both ROR and PRR were considered valid signals. A stronger signal indicates a stronger association between the drug and the ADR, suggesting a more substantial relationship.

Drug–Drug Interaction Detection Methods

The Ω shrinkage measure was used to identify drugs that, when combined with linezolid, increase the risk of neurological ADRs. Signal detection for co-medications was based on the frequency statistics of different drug combinations, primarily using a 4×2 contingency table, as shown in Table 2. The signal detection threshold for the Ω shrinkage measure was defined as Ω 025 > 0 for the lower limit of the 95% confidence interval (CI). The calculation method is as follows:

$$\Omega = log_2 \frac{n_{111} + 0.5}{E_{111} + 0.5}$$

$$f_{00} = \frac{n_{001}}{n_{00+}},\ f_{10} = \frac{n_{101}}{n_{10+}},\ f_{01} = \frac{n_{011}}{n_{01+}},\ f_{11} = \frac{n_{111}}{n_{11+}}$$

n = total number of reports displayed in the 4×2 contingency table

$$g_{11} = 1 - \frac{1}{\max\left(\frac{f_{00}}{1-f_{00}}, \frac{f_{10}}{1-f_{10}}\right) + \max\left(\frac{f_{00}}{1-f_{00}}, \frac{f_{01}}{1-f_{01}}\right) - \frac{f_{00}}{1-f_{00}} + 1}$$

$$\Omega_{025} = \Omega - \frac{\phi(0.975)}{\ln(2)\sqrt{n_{111}}}$$

$$E_{111} = g_{11} \times n_{11+}$$

Table 2 The 4×2 Contingency Table for Signal Detection of Drug-Drug Interaction

Co-medication	Target ADR	Other ADRs	Total
Both drugs A and B exposed	n111	n110	n11+
Only drug A exposed	n101	n100	n10+
Only drug B exposed	n011	n010	n01+
Neither drug A nor B exposed	n001	n000	n00+

Notes: drug A: linezolid; drug B: a co-administered drug; n: the number of reports.
Abbreviation: ADR, Adverse Drug Reactions.

Outcome Measures

Adverse drug reaction reports that met the risk signal detection criteria underwent the following analyses. 1) Demographic characteristics of the reported cases, including age, gender, reporting year, reporting region and the severity of adverse reactions, were summarised. 2) Adverse drug reaction signals identified through the ROR and PRR methods were ranked according to the number of reports, ROR values and PRR values, with corresponding HLGT classifications assigned to each identified signal. 3) A comparison was conducted with the most recent version of the linezolid drug label to determine whether any ADRs were not previously documented. 4) The Ω shrinkage measure was applied to evaluate potential DDIs that may increase the risk of neurological ADRs when linezolid is co-administered with other medications.

Statistical Analysis

Data cleaning and statistical analyses were performed using SAS 9.4 software to ensure accuracy and efficiency in data processing. The data cleaning process combined automated scripts with manual verification to remove duplicate reports, non-linezolid reports, reports with ambiguous drug names and records unrelated to drug indications or usage.

For signal detection, the ROR and PRR methods were employed to calculate the risk ratios for neurological ADRs associated with linezolid, thereby ensuring the specificity and sensitivity of the detected signals. Additionally, the Ω shrinkage measure was applied to evaluate the significance of co-medication signals, with a threshold of $\Omega\ 025 > 0$ for the lower limit of the 95% CI used for signal detection. These statistical methods were employed to enhance the reliability of the signal detection process and ensure its clinical relevance.

Results

Data Inclusion

Given the extensive coverage of the FAERS database, which contains a large number of spontaneous reports, data were collected for linezolid-related ADR reports between 1 July 2014 and 30 June 2024. A dual-filter approach was applied to ensure the dataset remained focused on the target ADRs while minimising interference from irrelevant information. A total of 8521 ADR reports were retrieved in which linezolid was identified as the primary suspected drug. Of these, 1720 reports involved various neurological ADRs, accounting for 20.12% of the total.

Basic Characteristics of Included Adverse Drug Reaction Reports

The number of linezolid-related ADR reports exhibited an overall increasing trend, with a notable rise in 2018, peaking in 2020 (Figure 1A). Among the 1720 included reports, the number of cases from men (763 cases) and women (713 cases) was comparable (Figure 1B). Geographically, the majority of reports originated from Europe, followed by North America and Asia (Figure 1C). In terms of age distribution, elderly individuals aged over 65 years constituted the largest proportion of reported cases (Figure 1D). Severe ADRs accounted for 82% of the reports, with the most common outcomes in severe ADR cases being ‘hospitalization or extended hospitalization’, which comprised 61% of the severe outcomes (Figure 1E).

Signal Analysis of Included Adverse Drug Reaction Reports

The ADR reports were ranked in descending order of report frequency. The top 10 adverse reactions, based on the number of reports, were serotonin syndrome (SS), peripheral neuropathy, dysgeusia, optic neuritis, polyneuropathy, encephalopathy, altered level of consciousness, myoclonus, generalised tonic–clonic seizures and reversible posterior leukoencephalopathy syndrome (PRES; Tables 2 and 3).

A risk signal analysis of the ADR reports identified 45 distinct adverse reaction signals, of which 23 were not listed on the drug’s official label (Table 4). Figure 2 illustrates the distribution of neurological ADR signals associated with

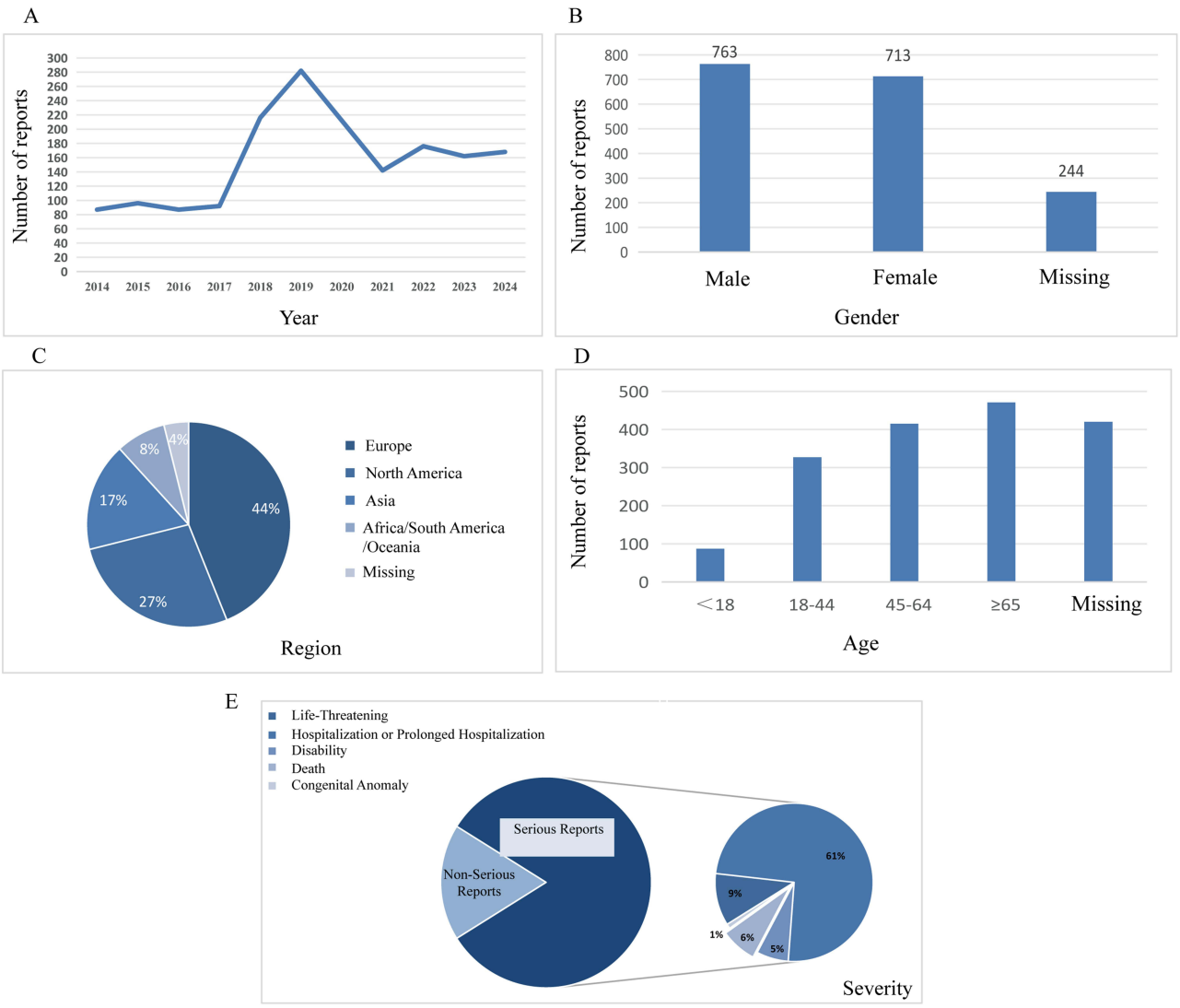

Figure 1 Basic characteristic on linezolid-related adverse event of nervous system. (**A**) Reporting time; (**B**) Gender; (**C**) Reporting region; (**D**) Age; (**E**) Severity of reports.

linezolid. Notable strong signals included SS (N = 436, ROR = 43.66, χ^2 = 17,019.77), peripheral neuropathy (N = 413, ROR = 7.88, χ^2 = 2384.35), optic neuritis (N = 101, ROR = 18.119, χ^2 = 1606.93), polyneuropathy (N = 96, ROR = 14.52, χ^2 = 1186.92) and axonal neuropathy (N = 12, ROR = 24.46, χ^2 = 265.12).

Table 3 Preferred Terms of Top 10 Linezolid-Related Adverse Event of Nervous System in FAERS

PT	Report Count	Percentage (%)	HLGT
Serotonin syndrome	436	25.35%	Neuromuscular Diseases
Neuropathy peripheral	413	24.01%	Peripheral Nerve Disorders
Dysgeusia	114	6.63%	Neurological Disorders (Unspecified)
Optic neuritis	101	5.87%	Cranial Nerve Disorders (Excluding Tumors)
Polyneuropathy	96	5.58%	Peripheral Nerve Disorders
Encephalopathy	68	3.95%	Various Brain Diseases
Depressed level of consciousness	51	2.97%	Various Brain Diseases
Myoclonus	44	2.56%	Various Brain Diseases
Generalised tonic-clonic seizure	39	2.27%	Seizures (Including Various Subtypes)
Posterior reversible encephalopathy syndrome	36	2.09%	Various Brain Diseases

Abbreviations: PT, Preferred Term; HLGT, High-Level Group Term.

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Table 4 Signal Intensity Analysis for Linezolid-Related Adverse Event of Nervous System in FAERS

PT	Report Count	ROR Value (95% CI Lower Limit)	PRR value (χ^2)
Seizures (incl subtypes)			
Generalised tonic-clonic seizure[a]	39	2.50 (1.82)	2.49 (34.80)
Generalised tonic-clonic seizur[a]	30	4.57 (3.19)	4.56 (83.18)
Partial seizures[a]	12	4.04 (2.29)	4.04 (27.34)
Tonic convulsion	6	7.96 (3.57)	7.96 (36.30)
Seizure like phenomena[a]	6	6.59 (2.96)	6.59 (28.33)
Tonic clonic movements[a]	4	5.25 (1.97)	5.25 (13.71)
Convulsive threshold lowered	3	11.99 (3.85)	11.99 (29.97)
Change in seizure presentation[a]	3	8.41 (2.70)	8.41 (19.46)
Encephalopathies NEC			
Encephalopathy[a]	68	4.77 (3.75)	4.75 (200.57)
Posterior reversible encephalopathy [a]	36	6.24 (4.49)	6.22 (157.12)
Hepatic encephalopathy [a]	13	2.28 (1.32)	2.27 (9.28)
Metabolic encephalopathy[a]	11	6.30 (3.48)	6.29 (48.77)
Spinal cord and nerve root disorders			
Spinal cord disorder[a]	5	4.96 (2.06)	4.96 (15.76)
Cranial nerve disorders (excl neoplasms)			
Optic neuritis	101	18.19 (14.94)	18.05 (1606.93)
Neuromuscular disorders			
Serotonin syndrome	436	43.66 (39.63)	42.14 (17,019.77)
Hypertonia	9	2.42 (1.26)	2.42 (7.50)
Anticholinergic syndrome[a]	6	6.80 (3.05)	6.79 (29.50)
Autonomic nervous system imbalance[a]	5	3.10 (1.29)	3.10 (7.08)
Myasthenia gravis crisis[a]	4	6.79 (2.54)	6.79 (19.64)
Neurological disorders NEC			
Dysgeusia	114	2.45 (2.04)	2.44 (96.62)
Depressed level of consciousness	51	2.14 (1.63)	2.14 (30.89)
Myoclonus	44	6.14 (4.56)	6.12 (187.71)
Altered state of consciousness	35	2.88 (2.07)	2.88 (42.76)
Neurotoxicity	27	2.86 (1.96)	2.86 (32.57)
Clonus	15	9.04 (5.44)	9.03 (106.42)
Hyperreflexia	12	5.50 (3.12)	5.49 (43.92)
Allodynia	8	17.75 (8.84)	17.74 (124.84)
Dysmetria	7	21.00 (9.95)	20.99 (131.29)
Neurological decompensation	6	4.68 (2.10)	4.68 (17.28)
Dysaesthesia	5	2.80 (1.16)	2.80 (5.77)
Apallic syndrome[a]	4	8.28 (3.10)	8.28 (25.44)
Coma hepatic[a]	3	5.84 (1.88)	5.84 (11.98)
Dysdiadochokinesis[a]	3	38.60 (12.26)	38.59 (106.94)

(*Continued*)

Table 4 (Continued).

PT	Report Count	ROR Value (95% CI Lower Limit)	PRR value (χ^2)
Peripheral neuropathies			
Neuropathy peripheral	413	7.88 (7.14)	7.65 (2384.35)
Polyneuropathy	96	14.52 (11.87)	14.41 (1186.92)
Peripheral sensory neuropathy	27	8.22 (5.63)	8.20 (169.87)
Axonal neuropathy[a]	12	24.46 (13.82)	24.43 (265.12)
Peripheral motor neuropathy[a]	11	13.17 (7.27)	13.16 (122.44)
Toxic neuropathy[a]	5	20.52 (8.48)	20.51 (91.46)
Small fibre neuropathy[a]	4	11.53 (4.31)	11.53 (38.15)
Peripheral sensorimotor neuropathy	4	6.38 (2.39)	6.37 (18.04)
Polyneuropathy chronic	3	90.35 (28.12)	90.32 (249.10)
Movement disorders (incl parkinsonism)			
Quadriplegia[a]	6	4.92 (2.21)	4.92 (18.69)
Quadriparesis[a]	3	3.13 (1.01)	3.13 (4.35)
Central nervous system vascular disorders			
Embolic cerebral infarction	5	12.33 (5.11)	12.33 (51.59)

Note: [a]refers to ADRs not listed in the linezolid product label.
Abbreviations: PT, Preferred Term; ROR, Reporting Odds Ratio; PRR, Proportional Reporting Ratio.

To further examine the relationship between dose, treatment duration and ADR occurrence, an additional analysis was conducted, with results presented in Table 5. This table categorises ADR incidence based on different dosage and treatment duration intervals, providing a more comprehensive view of risk factors associated with prolonged linezolid

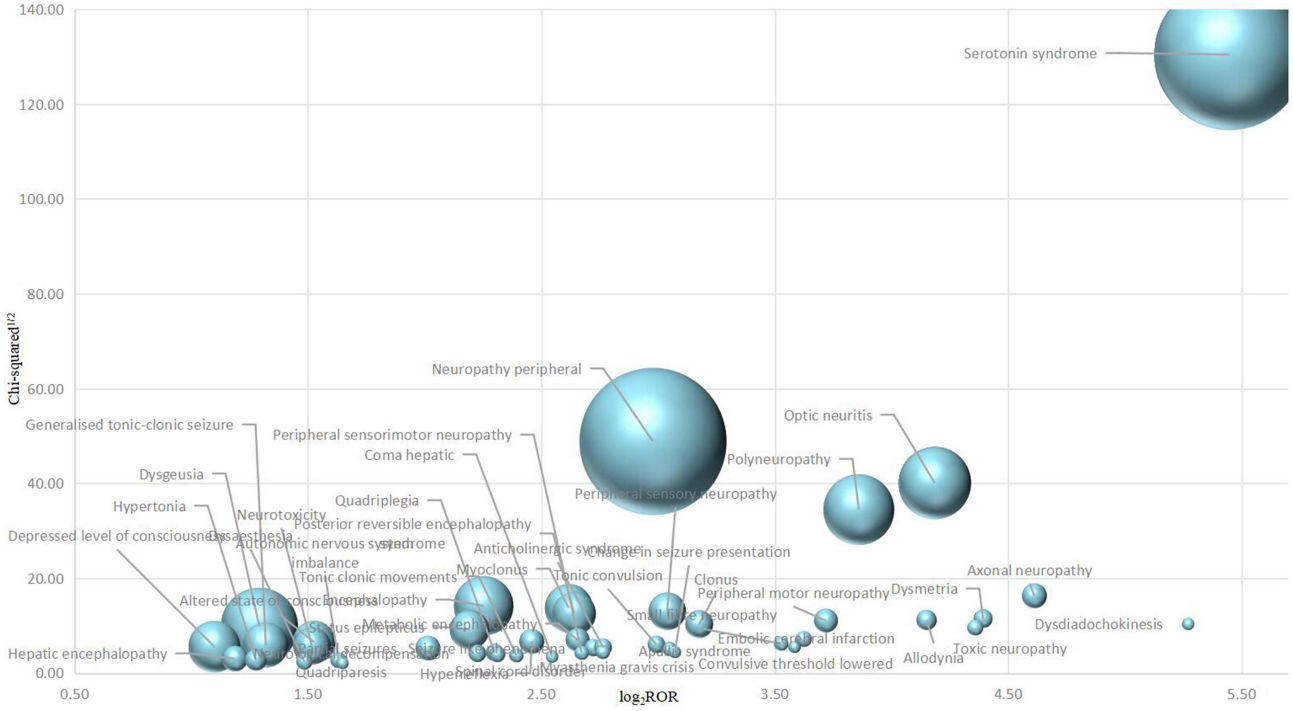

Figure 2 Signal distribution of linezolid-related adverse event of nervous system.

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Table 5 Distribution of Adverse Drug Reactions (ADRs) by Duration of Linezolid Therapy

Duration of Linezolid Use (Days)	Number of ADR Cases (n)
0–30	279
31–60	36
61–90	24
91–120	22
121–150	32
151–180	17
181–360	25
>360	12
Missing Data	1273
Total	**1720**

exposure. The analysis highlights a notable increase in ADR frequency with extended therapy duration, consistent with prior studies on linezolid-associated neurotoxicity.[13]

Drug–Drug Interaction Analysis

Using the Ω shrinkage measure, 21 drugs, including adalimumab, fentanyl, azithromycin, moxifloxacin and atorvastatin, were identified as increasing the risk of neurological ADRs when co-administered with linezolid.

Among these interactions, notable findings include the following. Adalimumab (Ω = 2.77, 95% CI: 1.95–3.58), a TNF-α inhibitor primarily used for autoimmune diseases, may enhance neurotoxicity due to its immunosuppressive effects when co-administered with linezolid, potentially increasing susceptibility to central nervous system complications. Fentanyl (Ω = 2.37, 95% CI: 1.85–2.90), an opioid analgesic, may elevate the risk of SS, a serious condition characterised by confusion, hyperreflexia and autonomic instability, when co-administered with linezolid.

Azithromycin (Ω = 2.06, 95% CI: 1.40–2.73), a macrolide antibiotic, may disrupt mitochondrial function, which, when combined with linezolid, could exacerbate oxidative stress and lead to neuropathy. Moxifloxacin (Ω = 1.61, 95% CI: 1.05–2.16), a fluoroquinolone antibiotic, may affect GABA receptor activity, potentially leading to increased neurological adverse effects, when combined with linezolid. Atorvastatin (Ω = 2.28, 95% CI: 1.02–3.55), a statin medication for cholesterol management, has been linked to neurotoxic effects such as myopathy and neuropathy, which may be exacerbated when used with linezolid.

Table 2 presents the 4×2 contingency table categorising patient reports based on exposure to linezolid and co-administered drugs, enabling the calculation of the Ω shrinkage measure. The Ω values derived from this analysis are further visualised in Figure 3, which displays the estimated Ω values and their 95% CIs for each drug combination.

Higher Ω values with positive lower confidence bounds (Ω 025 > 0) indicate a statistically significant increased risk of neurological ADRs when linezolid is used concomitantly with these medications. These findings suggest that the co-administration of linezolid with certain drug classes, particularly opioids, immunosuppressants and mitochondrial function-affecting drugs, may increase the risk of severe neurological adverse effects. Careful monitoring and risk assessment are recommended when prescribing linezolid with these agents.

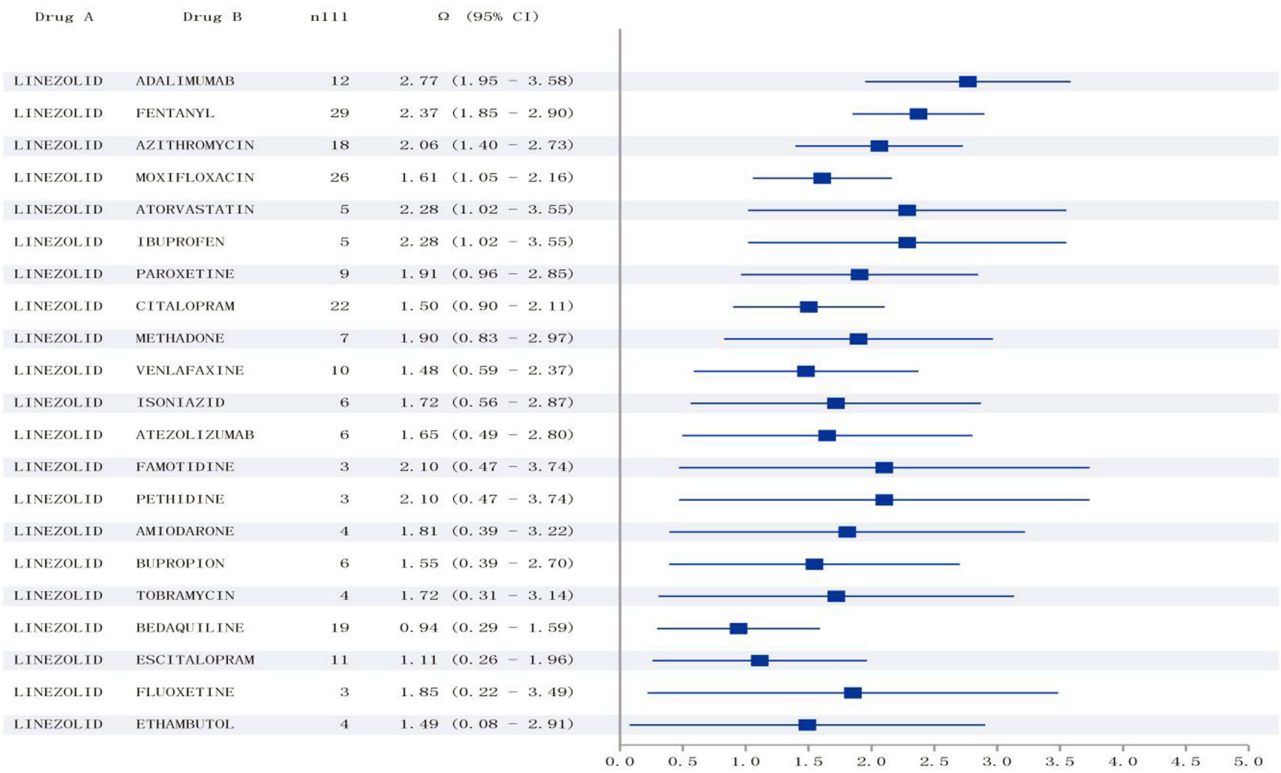

Figure 3 Statistical results of drugs that increase the risk of neurological adverse drug reactions when co-administered with linezolid (Ω025 > 0).

Discussion

Basic Overview of Adverse Drug Reaction Reports

A total of 1720 ADR reports related to linezolid were retrieved from the FAERS database, accounting for 20.12% of all reports. Since 2018, the number of neurological ADRs associated with linezolid has shown a gradual increase, likely due to its widespread use and the growing number and range of patients receiving treatment. The age distribution predominantly includes patients aged 65 and older, which may be attributed to age-related physiological decline and the presence of underlying health conditions.

According to the ADR risk signal analysis, 82% of the reports were classified as severe ADRs, consistent with the findings of Paton et al[14] Figure 1 presents the distribution of ADR cases by age and sex. However, it is important to note that the FAERS database primarily collects spontaneous ADR reports rather than comprehensive drug exposure data. As a result, precise ADR incidence rates across different demographic subgroups could not be calculated. This limitation should be considered when interpreting the data.

Additionally, recent studies, such as that by Hafez et al (2023), have highlighted that certain populations, including patients with chronic kidney disease, may be more vulnerable to drug-induced cognitive decline. This suggests that underlying conditions may contribute to ADR susceptibility, warranting further investigation.[15]

Adverse Drug Reaction Risk Signal Detection Results

Peripheral Nervous System Adverse Drug Reaction

In this study, the top five PTs by report count and signal strength included peripheral neuropathy, polyneuropathy, dysgeusia and axonal neuropathy, all of which are associated with peripheral nervous system toxicity.

Recent research has highlighted an increased incidence of peripheral neuropathy with linezolid use. A study by Conradie et al[16] found that 25% of participants experienced or reported peripheral neuropathy (≤grade 3). Similarly, Imperial et al[17] reported that 77% of participants experienced peripheral nervous system-related ADRs (≥grade 1).

Animal studies[18] have suggested that linezolid-induced peripheral neurotoxicity is related to the inhibition of autophagic flux. Experiments have demonstrated that rats treated with linezolid exhibited sparse sciatic nerve arrangements, accompanied by neuronal and myelin sheath damage, as well as downregulation of autophagic structural proteins. Additionally, other studies[19–21] have shown that linezolid can decrease the mitochondrial membrane potential of sensory axons and induce excessive calcium influx, leading to mitochondrial toxicity, axonal damage and other peripheral nervous system-related ADRs.

The product label indicates that linezolid treatment for more than 28 days can induce peripheral neuropathy; however, related adverse reactions have also been reported with short-term use. A study on the mitochondrial toxicity of linezolid found that 67% of patients experienced related adverse reactions despite receiving treatment for less than 28 days.[22] The mechanism involves linezolid's mitotoxic effects, which are tissue-dependent and cause damage to neural cells, with patients carrying the mtDNA haplotype U being genetically susceptible.

These findings suggest that genetic factors, such as mtDNA haplotypes, can influence susceptibility to peripheral neuropathy. Even with short-term use, clinicians should remain vigilant for peripheral nervous system toxicity when prescribing linezolid. Furthermore, polymorphisms affecting mitochondrial function and drug metabolism may contribute to the variability in ADR occurrence.

Central Nervous System Adverse Drug Reaction

In this study, the top 10 central nervous system-related ADRs by report count primarily included SS, optic neuritis, epilepsy and encephalopathy. Among these, epilepsy and encephalopathy are newly identified ADRs not listed on the product label.

Serotonin syndrome is a cluster of symptoms caused by excessive serotonin activity in the nervous system.[23] Linezolid is a reversible, non-selective monoamine oxidase A inhibitor. Monoamine oxidase is involved in the metabolism of monoamine neurotransmitters, and its inhibition can lead to an excess accumulation of serotonin in the central nervous system, thereby triggering SS. Additionally, linezolid crosses the blood–brain barrier, allowing it to exert direct effects on the central nervous system, which may contribute to the development of central nervous system-related ADRs such as SS.

Optic neuritis is an inflammatory condition affecting the optic nerve and is a leading cause of vision impairment and blindness. Several studies[24–26] have shown that linezolid can induce optic neuropathy in some patients, primarily presenting as varying degrees of vision loss, with a relatively high incidence. The underlying mechanism is believed to involve linezolid-induced inhibition of mitochondrial protein synthesis. Since the optic nerve is highly dependent on mitochondrial function, this inhibition could lead to nerve damage. Additionally, linezolid has strong ocular permeability, further increasing the risk of optic nerve toxicity.[27]

This study identified 103 cases of seizures, with generalised tonic–clonic seizures being the most common. Shneker et al[28] reported two cases of seizures induced by linezolid. One patient developed myoclonus and tremors, whereas the other experienced generalised tonic–clonic seizures. Both patients had a history of epilepsy. Although the mechanism remains unclear, these findings suggest that clinicians should exercise caution when administering linezolid to patients with a history of epilepsy.

This study also identified 68 cases of encephalopathy, primarily including reversible PRES and metabolic encephalopathy. Posterior leukoencephalopathy syndrome is a form of brain white matter oedema that predominantly affects the posterior brain regions.[29] It is diagnosed through neuroimaging and may present clinically with headache, altered consciousness, visual disturbances and seizures.

Nagel et al[30] reported a 71-year-old woman who developed PRES after 5 days of linezolid treatment for a hip joint prosthesis infection. The patient exhibited clinical and neuroimaging features of PRES, and after ruling out other causes, such as renal failure, inflammatory syndrome and central nervous system infections, her condition rapidly improved following the discontinuation of linezolid.

Tomar et al[31] reported a case of a 45-year-old woman with disseminated tuberculosis who developed altered consciousness 2 days after receiving linezolid and other anti-tuberculosis medications. Brain imaging confirmed a diagnosis of PRES. The mechanism of PRES remains unclear but is thought to involve disruption of the blood–

brain barrier, leading to cerebral oedema.[32,33] Since linezolid crosses the blood–brain barrier, it may contribute to this disruption, thereby increasing the risk of PRES and other central nervous system-related ADRs.

In addition to PRES, other neurological events, such as metabolic encephalopathy, have been reported with linezolid therapy. Upadhyay et al[34] described a 65-year-old woman with diabetes who developed altered sensation, respiratory distress and elevated bilirubin after 1 week of linezolid treatment. Her symptoms improved following drug discontinuation, suggesting a reversible metabolic encephalopathy induced by linezolid.

The exact mechanism remains unclear; however, it is speculated that linezolid may interfere with mitochondrial function, leading to metabolic disturbances affecting brain function.[35] Genetic variations affecting mitochondrial function may play a key role in the occurrence of metabolic encephalopathy and other neurotoxic effects, as these variations may alter the body's response to linezolid. Furthermore, the half-life of linezolid could vary between individuals, which may influence the severity of these adverse effects.

Drug Interaction Analysis

Increase in Linezolid Blood Levels

According to expert consensus on therapeutic drug monitoring for linezolid, the effective therapeutic range of its blood trough concentration is 2–8 mg/L. Linezolid is partially eliminated through the intestines via the P-glycoprotein (P-gp) efflux mechanism and is primarily metabolised by the liver and excreted through the gut. When co-administered with P-gp inhibitors such as omeprazole or amiodarone, these drugs inhibit P-gp activity, reducing linezolid's intestinal elimination, which may lead to elevated blood concentrations.[36,37] Increased linezolid blood levels may exceed the safe therapeutic range, raising the risk of central nervous system side effects, particularly with long-term or high-dose use. This drug interaction highlights the importance of therapeutic monitoring in patients receiving combination therapy, particularly when drugs with potential inhibitory effects are involved.

Increase in Serotonin Blood Levels

As a monoamine oxidase inhibitor, linezolid interferes with serotonin (5-HT) metabolism. When used in combination with serotonin reuptake inhibitors, such as citalopram, paroxetine or venlafaxine, it can greatly increase central nervous system serotonin levels. Cumulative effect raises the risk of SS, which presents severe symptoms such as hyperthermia, muscle rigidity, excessive nervous system activity and autonomic dysfunction. Additionally, co-administration with opioid analgesics, including fentanyl or methadone, can further exacerbate the risk of SS due to their 5-HT2A agonist action. Patients receiving these drug combinations should be closely monitored for signs of serotonin toxicity.

High Neurotoxicity of Concomitant Medications

Certain drugs, such as adalimumab, azithromycin, moxifloxacin, ibuprofen, isoniazid, apricizumab, ethambutol and tobramycin, exhibit high neurotoxicity. When used alongside linezolid, these medications may exacerbate neurotoxic side effects through a synergistic effect. Adalimumab and apricizumab may increase neurotoxicity by modulating immune responses, whereas NSAIDs such as ibuprofen could alter neuroprotective mechanisms by inhibiting prostaglandin synthesis. Azithromycin induces apoptosis in primary human neuronal cells, causing oxidative damage and mitochondrial dysfunction, which contribute to neurotoxicity.[38] Moxifloxacin increases neural excitability by inhibiting GABA receptor binding.[39] Isoniazid-induced neurotoxicity may be related to its inhibition of vitamin B6, affecting neurotransmitter synthesis. However, this study has certain limitations in analysing linezolid-related neurotoxic ADRs. Despite including 8521 ADR reports, the voluntary reporting nature of the FAERS database may introduce reporting bias, potentially underestimating the actual incidence of adverse reactions. Additionally, relying solely on FDA reports may not fully reflect real-world clinical applications. Although the ROR and PRR methods are effective, they may not entirely control for confounding factors. The absence of clinical trial-based evidence underscores the need for further prospective research. Future studies should aim to expand sample sizes, integrate multiple data sources and employ more rigorous statistical methods to enhance the reliability of the findings.

Conclusion

This study, through data mining and analysis of linezolid-related neurotoxic ADRs from the FAERS database between 1 July 2014 and 30 June 2024, highlights safety concerns regarding the clinical use of linezolid. A total of 8521 ADR reports were analysed, with 1720 (20.12%) related to neurotoxic ADRs. Signal detection identified 45 ADR signals associated with linezolid, with SS and peripheral neuropathy being the most prevalent, accounting for 25.35% and 24.01%, respectively. Additionally, 21 drugs were found to greatly increase the risk of neurological ADRs when co-administered with linezolid, underscoring the importance of monitoring DDIs.

These findings highlight the need for careful clinical monitoring, particularly in patients requiring prolonged linezolid therapy or receiving concomitant medications with potential neurotoxic effects. To minimise risks, clinicians should assess treatment duration, screen for high-risk drug interactions and monitor patients for early signs of neurotoxicity.

Future research should focus on further elucidating the mechanisms underlying these ADRs and refining risk mitigation strategies. By integrating pharmacovigilance data and real-world evidence, this study contributes to enhancing the safe clinical use of linezolid, aligning with its intended aim of providing guidance for optimised patient management.

Data Sharing Statement

All data generated or analyzed during this study are included in the article.

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Disclosure

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