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Linezolid and serotonin syndrome

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Abstract

Linezolid, a synthetic oxazolidinone antibiotic, is used to treat gram-positive bacterial infections, including methicillin-resistant *Staphylococcus aureus*. Despite its efficacy, linezolid can cause serotonin syndrome, a potentially fatal condition associated with excessive serotonin activity in the brain. This narrative review examined the pharmacological mechanisms of this interaction, particularly linezolid's mild monoamine oxidase-inhibitory activity, which can trigger serotonin syndrome in combination with serotonergic drugs. Serotonin syndrome causes cognitive, autonomic, and somatic symptoms ranging from mild (tremors, diarrhea) to severe (hyperthermia, seizures, multiorgan failure). The Hunter Serotonin Toxicity Criteria have superior sensitivity and specificity over the Sternbach Criteria for diagnosis. Clinical evidence indicates that although the incidence of linezolid-induced serotonin syndrome is low, the risk justifies careful monitoring and risk assessment. This review emphasizes enhanced pharmacovigilance and standardized reporting criteria to better capture and analyze data on linezolid-induced serotonin syndrome. Assessments of the pharmacological mechanisms, large-scale clinical trials, and cohort studies are essential to elucidate risk factors and outcomes. Developing comprehensive clinical guidelines and education programs for healthcare providers is crucial to improve linezolid's safety profile. Exploring pharmacogenomic approaches and alternative therapies with lower serotonin syndrome risks is recommended to enhance patient outcomes while maintaining linezolid's efficacy in treating severe bacterial infections.

Keywords

Linezolid, serotonin syndrome, methicillin-resistant *Staphylococcus aureus*, monoamine oxidase inhibitor, serotonin toxicity criteria, selective serotonin reuptake inhibitor, serotonin–norepinephrine reuptake inhibitor

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Introduction

Linezolid is an important antibiotic used to treat serious gram-positive bacterial infections, including methicillin-resistant *Staphylococcus aureus* (MRSA).[1] However, linezolid has been linked to the development of serotonin syndrome, a potentially life-threatening condition caused by excessive serotonin activity in the brain.[1] Serotonin syndrome can occur when linezolid is co-administered with other serotonergic medications, such as selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), and monoamine oxidase inhibitors (MAOIs).[1] This narrative review examined the pharmacological mechanisms underlying the interactions of linezolid with serotonergic agents, summarizes the available clinical evidence on the incidence and risk factors of linezolid-induced serotonin syndrome, and provided guidance on the appropriate clinical management of patients receiving concomitant linezolid and serotonergic therapy.

Methods

This narrative review was guided by the Scale for the Assessment of Narrative Review Articles.[2] A copy of the scale presenting the quality rating of this narrative review is provided in the supplement (Appendix A). The literature search was performed using PubMed and Google Scholar with the following keyword combinations: (linezolid OR antibiotics) AND (serotonin syndrome OR serotonin toxicity); (linezolid AND drug interactions) OR (monoamine oxidase inhibitors AND serotonin syndrome); (adverse effects OR side effects) AND (linezolid AND clinical outcomes); (CNS effects OR neurological effects) AND (linezolid OR serotonin syndrome). Studies written in languages other than English were excluded. Studies with no full-text access were also excluded.

Pharmacological overview of linezolid

Linezolid is a synthetic oxazolidinone antimicrobial drug that has been approved for treating bacterial pneumonia, skin and skin structure infections, and vancomycin-resistant enterococcus (VRE) infections, including those complicated by bacteremia. It has a broad spectrum of *in vitro* activities against gram-positive organisms, including methicillin-resistant staphylococci and VRE.[3] Linezolid was the first oxazolidinone found to inhibit the initiation of protein synthesis in bacteria, a mechanism of action unique to this class.[1,4] This is achieved through binding to the 50S subunit of the bacterial ribosome, specifically the peptidyl transferase center. This inhibition prevents the formation of the functional 70S initiation complex, ultimately preventing bacteria from producing essential proteins for growth and replication, making it highly effective against gram-positive pathogens.[5] Linezolid is well absorbed, and it has high bioavailability, allowing conversion to oral therapy. It is generally well tolerated, with myelosuppression being the most serious adverse effect.[4]

Definition of serotonin syndrome

Serotonin syndrome is a potentially life-threatening condition resulting from increased serotonin activity in the central nervous system (CNS). It typically occurs because of the use of serotonergic medications, either alone or in combination, leading to excessive serotonin accumulation.[6,7] This syndrome is characterized by a triad of cognitive, autonomic, and somatic effects. Symptoms can range from mild (e.g., tremors, diarrhea) to severe (e.g., hyperthermia, seizures, rhabdomyolysis). Common manifestations include agitation, confusion, hyperreflexia, myoclonus, diaphoresis, shivering, and gastrointestinal symptoms.[6]

Pathophysiology of serotonin syndrome

Serotonin syndrome occurs because of excessive serotonergic activity in the CNS and peripheral systems, often attributable to drug interactions or overdose. Several key aspects of its pathophysiology have been identified.

Serotonin receptors

The syndrome is primarily caused by the overstimulation of serotonin receptors, particularly the 5-HT1A and 5-HT2 receptors. When serotonergic drugs are used in combination, they can lead to an increase in serotonin levels at synapses, enhancing receptor activation.[8]

Mechanism of action

- Activation of 5-HT1A receptors is associated with mood regulation and anxiety. Overstimulation can lead to cognitive and behavioral changes.[6]
- 5-HT2 receptors are linked to autonomic functions and neuromuscular activity, and their overactivation can result in symptoms like hyperreflexia, tremor, and agitation.[9]

Neurotransmitter imbalance

An imbalance between serotonin and other neurotransmitters, particularly dopamine, might contribute to symptoms resembling neuroleptic malignant syndrome (NMS). This imbalance can exacerbate motor symptoms and autonomic instability.[6]

Clinical presentation

The syndrome typically presents with a triad of symptoms: cognitive/behavioral symptoms including confusion, agitation, and an altered mental status;[6] autonomic symptoms including hyperthermia, tachycardia, diaphoresis, and gastrointestinal disturbances;[9] and neuromuscular symptoms including myoclonus, hyperreflexia, and rigidity.[8]

Onset of symptoms

Symptoms usually develop within hours of initiating serotonergic agent treatment or increasing its dosage. The rapid onset is linked to the acute increase in serotonin levels, which can overwhelm the regulatory mechanisms of the CNS.[9]

Clinical significance of serotonin syndrome

Serotonin syndrome is significant because of its potential to cause severe, life-threatening complications if not promptly recognized and treated. Serotonin syndrome can develop rapidly, often within hours of initiating or increasing the dose of one serotonergic drug or adding another serotonergic agent. This rapid onset necessitates high vigilance among healthcare providers when prescribing or managing medications.[6] The severity of serotonin syndrome varies widely. Mild cases can involve tremors, diarrhea, and mild hypertension, whereas severe cases can involve hyperthermia, seizures, and multiorgan failure, potentially leading to death.[7,10] Understanding this spectrum is crucial for appropriate and timely intervention.

Serotonin syndrome, NMS, and anticholinergic toxicity

Serotonin syndrome, NMS, and anticholinergic toxicity are three distinct but potentially overlapping conditions that can arise from the use of certain medications. Serotonin syndrome is characterized by a hyperadrenergic state resulting from excessive serotonergic activity in the CNS. Key symptoms include an altered mental status, autonomic instability, and

neuromuscular abnormalities. The onset is typically rapid, occurring within hours of introducing a serotonergic agent or increasing its dosage.[6] NMS is primarily associated with antipsychotic medications and is characterized by extreme muscle rigidity, hyperthermia, autonomic dysregulation, and an altered mental status. Unlike serotonin syndrome, NMS develops more slowly, often over days to weeks after introducing or increasing the dose of a neuroleptic. The pathophysiology of NMS is believed to involve dopamine receptor antagonism and is associated with significant morbidity and mortality if not promptly treated.[11] Anticholinergic toxicity arises from the blockade of acetylcholine at muscarinic receptors, leading to symptoms such as dry mouth, urinary retention, constipation, and confusion. The presentation can mimic both serotonin syndrome and NMS, complicating the differential diagnosis. Anticholinergic toxicity usually occurs after the use of medications with anticholinergic properties, and it can also lead to severe complications if untreated.[12] Understanding the differences and similarities among these conditions is crucial for accurate diagnosis and management. Prompt recognition of the underlying syndrome is essential to guide appropriate treatment and improve patient outcomes.

Diagnostic criteria of serotonin syndrome

Several diagnostic criteria for serotonin syndrome exist, and the Hunter Serotonin Toxicity Criteria are among the most widely used criteria. The Hunter Serotonin Toxicity Criteria comprise a set of clinical guidelines designed to diagnose serotonin syndrome with high sensitivity and specificity. These criteria were developed by Dunkley *et al.* in 2003 through the analysis of a large cohort of patients with suspected serotonin toxicity. The goal was to establish a simple and accurate diagnostic tool that could be used in clinical settings.[13]

According to the Hunter criteria, serotonin syndrome is diagnosed if a patient meets one of the following conditions after taking a serotonergic agent: spontaneous clonus; inducible clonus and agitation or diaphoresis; ocular clonus and agitation or diaphoresis; tremor and hyperreflexia; and hypertonia, temperature $> 38^{\circ}C$, and ocular clonus or inducible clonus. The Hunter criteria are highly valued because of their simplicity and accuracy. They are particularly useful in emergency settings, in which rapid diagnosis is crucial. Compared with other diagnostic criteria, such as the Sternbach criteria, the Hunter criteria have displayed better diagnostic performance, including higher sensitivity (84% vs. 75%) and specificity (97% vs. 96%).[13]

The Sternbach criteria were proposed by Horowitz and Sternbach in 1991 to diagnose serotonin syndrome. These criteria predate the Hunter Serotonin Toxicity Criteria, and they were widely used before the latter's development.[14] Although the Sternbach criteria were instrumental in increasing awareness of serotonin syndrome, they are considered less specific and sensitive than the Hunter criteria. According to Sternbach, a diagnosis of serotonin syndrome can be made if a patient exhibits at least three of the following symptoms after the recent addition or increase of the dose of a known serotonergic agent: mental status changes, including confusion, hypomania, and agitation; autonomic dysfunction, including diaphoresis (excessive sweating), shivering, hyperthermia, hypertension, tachycardia, nausea, and diarrhea; and neuromuscular abnormalities, including myoclonus (muscle jerks), hyperreflexia, tremor, and incoordination.

Additionally, the Sternbach criteria require the exclusion of other etiologies,

such as infections, metabolic disorders, and substance abuse, as well as the absence of NMS. As they are less specific and sensitive than the Hunter criteria, the Sternbach criteria can miss mild cases or falsely attribute symptoms to serotonin syndrome when another diagnosis is more appropriate. Excluding other potential causes of symptoms, such as infections or metabolic disorders, can be challenging in acute setting, potentially delaying diagnosis.[15]

Challenges in diagnosing serotonin syndrome in critically ill patients

The diagnosis of serotonin syndrome can be particularly challenging in critically ill patients because of several factors inherent to this population. Critically ill patients often present with multiple comorbidities, and their clinical status can fluctuate rapidly. This complexity can obscure the clinical signs and symptoms typically associated with serotonin syndrome, leading to potential misdiagnoses or delayed recognition.[16]

One significant challenge is that only some patients fulfill the current diagnostic criteria for serotonin syndrome, which typically rely on the identification of specific clinical features such as an altered mental status, autonomic instability, and neuromuscular abnormalities.[17] In critically ill patients, these symptoms can overlap with manifestations of other conditions, such as septic shock, metabolic disturbances, or adverse effects from polypharmacy.[18] Consequently, clinicians might overlook serotonin syndrome or attribute its symptoms to more common complications of critical illness.

Additionally, the use of various medications, including opioids, sedatives, and other psychoactive drugs in the intensive care setting, can further complicate the assessment of serotonin syndrome. The potential for drug interactions and the presence of different syndromes that mimic serotonin syndrome can lead to diagnostic confusion.[19] Healthcare providers need to maintain a high index of suspicion for serotonin syndrome, especially in patients receiving serotonergic agents, and to consider the possibility of serotonin syndrome even when patients do not meet all diagnostic criteria.

Given these challenges, a more nuanced approach to diagnosis is warranted. Clinicians should be encouraged to evaluate the overall clinical picture, consider the pharmacological history, and use adjunct diagnostic tools when appropriate. This comprehensive assessment might improve the recognition of serotonin syndrome in critically ill patients, facilitating timely interventions and improving patient outcomes.

Epidemiology of serotonin syndrome caused by linezolid

Linezolid, primarily known for its antibacterial properties, has been implicated in the development of serotonin syndrome because of its mild MAOI activity. It is a reversible, non-selective inhibitor of monoamine oxidase, an enzyme responsible for the degradation of serotonin, norepinephrine, and dopamine. Monoamine oxidase inhibition can lead to increased levels of these neurotransmitters.[20] Patients who are concurrently taking other serotonergic medications, especially SSRIs, MAOIs, or SNRIs, are at increased risk.[21] The incidence of serotonin syndrome associated with linezolid is relatively low but clinically significant given the potential severity of the syndrome, although the exact incidence rates are not well defined.

Incidence data from cohort studies

Bai *et al*. examined the incidence of serotonin syndrome in patients aged 66 years or

older who were prescribed oral linezolid while also taking antidepressants. Among the 1134 patients, 215 (19.0%) concurrently received antidepressants. The study found that serotonin syndrome occurred in fewer than six patients (<0.5%), and the incidence was numerically but not significantly lower in the antidepressant group. In a propensity score-matched cohort, the adjusted risk difference for serotonin syndrome between patients who did and did not receive antidepressants was −1.2% (95% confidence interval [CI] = −2.9–0.5), and similar rates of mental status alteration, hospitalization, and death were observed between the two groups.[22] SanFilippo *et al*. investigated the association between serotonin toxicity and the combination of linezolid and serotonergic agents through a systematic review and meta-analysis. This study aimed to determine the incidence of serotonin toxicity when linezolid is used alone or in combination with serotonergic agents and compare the risk of serotonin toxicity when linezolid is combined with one or multiple serotonergic agents. The analysis, which included data from 14 studies, with five meeting the criteria, found that the concomitant use of linezolid and serotonergic agents increased the odds of serotonin toxicity, with odds ratios of 1.78 for linezolid monotherapy versus combination therapy and 5.18 for linezolid combined with multiple serotonergic agents versus a single agent. The findings suggest that the number of serotonergic agents used concomitantly with linezolid is a significant risk factor for serotonin toxicity, highlighting the need for careful consideration and risk–benefit analysis in clinical practice.[23]

Lawrence *et al*. reviewed post-marketing data from the FDA Adverse Event Reporting System (FAERS) to assess cases of serotonin toxicity associated with linezolid use. Of the 29 identified cases of serotonin toxicity linked to the concurrent administration of linezolid and drugs that increase CNS serotonin concentrations, the patients' ages ranged from 17 to 83 years, and the female-to-male ratio was 1:1. In total, 43 serotonergic drugs were involved, most commonly SSRIs (26 of 43 patients), followed by tricyclic antidepressants (6 patients) and atypical antidepressants (4 patients). The outcomes included three deaths, six interventions to prevent permanent impairment, and seven instances of initial or prolonged hospitalization. This study underscored the need for caution and awareness among prescribers when combining linezolid with serotonergic medications because of the significant risk of serotonin toxicity.[24]

Elli *et al*. analyzed 8997 reported cases of serotonin syndrome using FAERS data. In the study, SSRIs accounted for the highest number of reports, followed by opioids and other antidepressants. The reporting odds ratio (ROR) was 45.99 (95% CI = 41.21–51.33) for MAOIs, compared with 32.66 (95% CI = 31.33–34.04) for SSRIs. Among individual substances, moclobemide had the highest ROR (ROR = 388.36 95% CI = 314.58–479.46), followed by tryptophan (ROR = 44.19, 95% CI = 25.38–76.94). The study illustrated that the risk for serotonin syndrome is notably higher in older adults (aged 65 and older) and men, underscoring the need for careful monitoring of serotonergic drugs, including lesser-known risks associated with linezolid and triptans.[25]

Gatti *et al*. explored serotonin syndrome induced by drug–drug interactions (DDIs) with linezolid through pharmacovigilance and pharmacokinetic/pharmacodynamic analysis. Using FAERS data, this study identified 669 reports of serotonin syndrome linked to linezolid, representing 5.9% of the 11,429 total reports. The most frequent DDIs were linezolid and citalopram (69 patients; 10.3%). Citalopram, methadone, and escitalopram were classified as high-risk ("red-zone") medications,

with citalopram having the highest proportion of serotonin syndrome reports (0.277%) and methadone having the lowest mean number of DDIs (1.41). A significant correlation was found between the VD/Ki SERT ratio and the mean number of DDIs ($\rho = -0.53$; $P = 0.05$). The results suggest that linezolid is more likely to cause serotonin syndrome when co-administered with these high-risk serotonergic agents, emphasizing the need for tailored management to mitigate the risk of serotonin syndrome in clinical practice.[26]

Karkow *et al*. examined the incidence of serotonin syndrome in patients receiving linezolid, either alone or in combination with SSRIs or SNRIs. This retrospective case–control study was conducted at the University of Iowa Hospitals and Clinics and included 348 patients treated between 2010 and 2014. Of these, 87 patients received combination therapy with SSRIs or SNRIs, whereas 261 received linezolid monotherapy. Only one patient in each group (1.1% in the combination therapy group and 0.4% in the monotherapy group) was diagnosed with serotonin syndrome, revealing no significant difference in incidence ($P = 0.438$). The study found that the overall incidence of serotonin syndrome was low and raised questions about the practicality of the FDA guidelines, which recommend discontinuing SSRIs or SNRIs before starting linezolid therapy. The findings suggested that the risks associated with concomitant use might not be as high as previously believed.[27]

The retrospective cohort study by Mitwally *et al*. investigated the incidence of serotonin syndrome among 106 acutely ill patients receiving concomitant linezolid and opioids at Hamad Medical Corporation from March to September 2020. The findings revealed a low incidence of serotonin syndrome, with only one patient (1.6%) meeting the criteria, and this case was associated with post-cardiac arrest, making a direct link to the linezolid–opioid combination unlikely. The authors concluded that the co-administration of linezolid and opioids appears to be safe, although they emphasized the need for larger prospective studies to further explore and validate these results in critically ill populations.[28]

Traver *et al*. conducted a cross-sectional analysis of 494 hospitalized adults to evaluate the incidence of serotonin toxicity associated with the concurrent use of linezolid and opioids (methadone or buprenorphine). Over the study period from November 2015 to October 2019, two possible cases of serotonin toxicity were identified, both occurring in patients who received linezolid and methadone for more than 3 days, with no definite cases reported. The results indicated that serotonin toxicity was rare, occurring in 0.40% of all encounters and 1.89% of those with prolonged overlap of medications. The authors concluded that although serotonin toxicity can occur, it is infrequently observed in clinical practice, highlighting the need for further investigation of the risks associated with this combination in hospitalized patients.[29]

Incidence data from case reports

Table 1 summarizes findings from case reports on serotonin syndrome. Masbough *et al*. reported a case of serotonin syndrome induced by the concomitant use of linezolid and methadone in a 60-year-old man with a history of drug addiction and bipolar disorder. The patient was admitted to the poisoning department with dizziness, nausea, and vomiting, and his clinical findings included blood pressure of 95/61 mmHg, a heart rate of 110 bpm, a respiratory rate of 7 breaths per minute, and a Glasgow Coma Scale score of 7. Laboratory findings included a white blood cell count of 14.2×10^9/L, platelet count of 183×10^9/L, creatinine level of 6.8 mg/dL, potassium level of 7.3 mg/dL, and creatine phosphokinase level of

Table 1. Summary of the findings from case reports of serotonin syndrome.

Study/report	Patient demographics	Medications involved	Symptoms observed	Outcome
Masbough *et al.* (2022)	60-year-old man, drug addict	Linezolid, methadone	Fever, agitation, tremor, spontaneous clonus, tachycardia	Improved within 48 hours after linezolid discontinuation
Samartzis *et al.* (2013)	68-year-old woman	Linezolid, amitriptyline, fentanyl	Restlessness, diaphoresis, tremor, shivering, myoclonus, confusion, coma	Improved after medication withdrawal
Kulkarni and Kulkarni (2013)	65-year-old woman	Linezolid, escitalopram, clonazepam	Restlessness, diaphoresis, tremor, myoclonus, diarrhea, confusion, hallucinations	Improved after treatment cessation
Tahir (2004)	85-year-old woman	Linezolid, citalopram	Confusion, agitation, tremor, restlessness, dysarthric speech	Improved after citalopram withdrawal

4218 U/L. On the third day of hospitalization, after initiating linezolid 600 mg twice daily intravenously for ventilator-associated pneumonia, the patient developed symptoms of serotonin syndrome, including a fever of 39°C, agitation, tremor, spontaneous clonus, and a pulse rate of 115 bpm. Linezolid was discontinued, and vancomycin (1000 mg, twice daily) was administered together with supportive therapies, leading to symptom resolution within 48 hours. The report underscores the importance of recognizing drug interactions leading to serotonin syndrome and the need for careful patient education and monitoring to prevent such adverse reactions.[30]

Samartzis *et al.* reported a case of serotonin syndrome in a 68-year-old woman with advanced ischemic peripheral arterial disease and sepsis who was treated with 25 mg of amitriptyline twice daily and a 25 µg/hour fentanyl transdermal patch every 72 hours. Upon the addition of 600 mg of linezolid every 12 hours to her treatment regimen on the 10th day of hospitalization, the patient exhibited rapid clinical deterioration within the first 24 hours, including restlessness, diaphoresis, tremor, shivering, myoclonus, high fever (40°C), disorientation, confusion, and coma. The Hunter and Sternbach diagnostic criteria confirmed serotonin syndrome, which improved after discontinuing linezolid and amitriptyline. The patient exhibited signs of improvement within a few hours and gradual recovery of consciousness and orientation within 48 hours. This case underscored the risk of serotonin syndrome when linezolid is used in conjunction with serotonergic medications, such as amitriptyline and fentanyl, despite the lack of previously reported interactions involving these combinations. The authors suggested that linezolid should be avoided in patients receiving both amitriptyline and fentanyl because of the predictable and preventable risk of serotonin toxicity.[31]

Another case involved near-fatal serotonin syndrome induced by the concomitant use of linezolid (600 mg twice daily) and the antidepressant escitalopram (10 mg/day) in a 65-year-old woman. The patient was treated for depression with escitalopram for 2 months and developed severe serotonin syndrome symptoms, including restlessness, tremors, shivering, myoclonus, diarrhea, and mental status changes, within 24 hours of linezolid administration for sepsis. Her initial presentation included a temperature of 101°F, a pulse rate of 126/minute, and blood pressure of 136/88 mmHg, with leukocytosis (15,640/mm^3) and neutrophilia (80%). Serotonin syndrome was diagnosed on the basis of the exclusion of other CNS pathologies and the sequence of symptom onset following linezolid administration. Treatment involved discontinuing both linezolid and escitalopram, administering cyproheptadine (4 mg thrice daily), and supportive care, leading to the patient's recovery within 48 hours.[32]

In addition, Tahir reported an 85-year-old woman who developed serotonin syndrome because of the interaction between linezolid and citalopram, an SSRI prescribed at 20 mg/day for depression. The patient was initially treated for systemic infection with oxacillin-resistant *Staphylococcus aureus* using linezolid (600 mg twice daily) after she refused vancomycin. The patient exhibited symptoms of worsening tremor, confusion, restlessness, dysarthric speech, hyperreflexia, and autonomic instability (tachycardia, elevated blood pressure) shortly after being transferred to a skilled nursing facility. Her Mini-Mental Status Examination score decreased to 27/30. Upon identifying the DDI, citalopram was discontinued, leading to the resolution of serotonin syndrome symptoms within 72 hours. The patient also developed pancytopenia, which resolved after the completion of the linezolid course. This article highlighted the challenges in treating drug-resistant infections in older adults, the importance of recognizing potential DDIs, and the need for cautious use of serotonergic agents to prevent serotonin syndrome.[33]

Mortality rate of serotonin syndrome

Recent studies highlighted the variability in mortality rates associated with serotonin syndrome, emphasizing the importance of prompt recognition and management. The systematic review by Prakash *et al*. investigated fatal serotonin syndrome, analyzing 56 cases from the literature to characterize its epidemiology, clinical features, and risk factors. The study identified a mean patient age of 42.3 years, with a predominance of females and cases primarily from North America and Europe. Symptoms typically appeared rapidly within 24 hours of serotonergic drug administration, with fever (61%), seizures (36%), and tremors (30%) being the most common manifestations. High creatine kinase levels and severe complications, including cardiopulmonary arrest, were frequently observed, leading to a high mortality rate, with approximately 50% of patients dying within 24 hours. The findings highlighted the importance of early recognition and management of serotonin syndrome despite its rarity.[34]

Management of serotonin syndrome

The management of serotonin syndrome primarily involves the prompt recognition of symptoms, immediate discontinuation of serotonergic agents, and supportive care tailored to the severity of the condition. Early diagnosis is crucial for effective management. Clinicians should be aware of signs such as mental status changes (agitation, confusion), autonomic hyperactivity (hyperthermia, hypertension), and

neuromuscular abnormalities (tremor, hyperreflexia).[6]

The first step in managing serotonin syndrome is to immediately discontinue all serotonergic medications. These include commonly implicated drugs, such as SSRIs, SNRIs, tricyclic antidepressants, MAOIs, and certain opioids such as tramadol and fentanyl.[6,35] Discontinuing these agents reduces the serotonergic activity that causes the syndrome.

Supportive care is the cornerstone of treatment, and it varies according to symptom severity. In mild cases, management typically involves observation and symptomatic treatment, including oral or intravenous fluids, to maintain hydration and external cooling measures to manage hyperthermia.[6,35] Benzodiazepines such as lorazepam and diazepam are often administered to control agitation and decrease muscle rigidity, which can significantly improve patient comfort and reduce the risk of complications.[6,36]

In moderate-to-severe cases, hospitalization is often required for intensive monitoring and treatment. Aggressive cooling measures, such as cooling blankets or ice packs, are necessary if the patient's body temperature exceeds 41°C (105.8°F).[6,36] Short-acting antihypertensive agents such as esmolol and nitroprusside can be used to manage severe hypertension. Pharmacological management can include the administration of serotonin antagonists. Cyproheptadine, a histamine-1 receptor antagonist with antiserotonergic properties, is commonly used in moderate-to-severe cases. The initial dose is usually 12 mg, followed by 2 mg every 2 hours if symptoms persist, up to a maximum of 32 mg over 24 hours.[37,38] Chlorpromazine is another serotonin antagonist, although it is less commonly used because of its potential side effects, including hypotension.[6,36]

In the most severe cases, advanced interventions, such as intubation and mechanical ventilation, might be necessary, particularly if there is significant hyperthermia, an altered mental status, or respiratory failure.[6,35] Non-depolarizing neuromuscular blockers, such as vecuronium, can be used to control severe hyperthermia and muscle rigidity, but they should only be administered to intubated patients to ensure safety.[35,36]

Continuous monitoring of patients' vital signs, mental status, and neuromuscular function is essential until the symptoms are resolved. Long-term follow-up includes evaluating the potential underlying causes or contributing factors and educating patients about the risks associated with serotonergic medications. This education is vital to prevent recurrence and ensure that patients are aware of the symptoms of serotonin syndrome to ensure that they seek immediate medical attention if they experience these symptoms.[6,36]

Pharmacological options: Cyproheptadine and chlorpromazine

Cyproheptadine is an antihistamine with antiserotonergic properties that has been used to treat serotonin syndrome. Its antiserotonergic action can effectively reduce serotonin activity, making it beneficial in managing this condition. Additionally, cyproheptadine has a relatively quick onset of action, making it suitable for acute management. Although case reports suggest its efficacy, robust clinical trials are lacking, limiting its widespread acceptance in clinical guidelines.[6] Common side effects include sedation, dizziness, and dry mouth, which might not be ideal for all patients, particularly those who are already compromised.

Chlorpromazine, an antipsychotic, has also been used to manage serotonin syndrome, although its application is less

common. Its dopaminergic action might be beneficial in addressing agitation and muscle rigidity. Nevertheless, only a few case reports have demonstrated the efficacy of chlorpromazine in treating serotonin syndrome, raising questions about its reliability as a treatment option.[39] Furthermore, chlorpromazine can cause significant side effects, including sedation, orthostatic hypotension, and extrapyramidal symptoms, which can complicate treatment for vulnerable patient populations.

Future directions

Given the significant implications of linezolid-induced serotonin syndrome, future research and clinical practice should focus on several key topics. Enhanced pharmacovigilance and reporting systems are essential to better capture and analyze data on cases of serotonin syndrome related to linezolid, especially in combination with other serotonergic agents. Developing standardized reporting criteria and enhancing the utility of databases such as FAERS are crucial.

There is a need for clinical tools for risk stratification to identify patients at higher risk of serotonin syndrome when prescribed linezolid. These tools can incorporate factors such as patient history, concurrent medications, and genetic predispositions. Large-scale prospective clinical trials and cohort studies are needed to better understand the incidence, risk factors, and outcomes of serotonin syndrome in patients treated with linezolid. These studies should aim to provide more robust data to guide clinical decision-making. Furthermore, the creation and dissemination of comprehensive clinical guidelines for the management of patients taking linezolid, particularly those taking serotonergic medications, is essential. These guidelines should include recommendations for monitoring, dose adjustment, and alternative treatment options.

Implementing education and awareness programs targeted at healthcare providers can improve their understanding of serotonin syndrome, as well as its risks and management strategies. This includes continuing medical education modules, workshops, and informational materials. Exploring pharmacogenomic approaches to predict individual patient responses to linezolid and the risk of developing serotonin syndrome is another promising area of research. Identifying genetic markers associated with increased susceptibility could lead to personalized medical strategies.

Finally, it is critical to investigate alternative therapies and novel antibiotics with a lower risk of inducing serotonin syndrome. This could involve the development and clinical testing of new antimicrobial agents that do not inhibit monoamine oxidase or otherwise interfere with serotonergic pathways. By addressing these future directions, the medical community can enhance the safety and efficacy of linezolid, ultimately improving patient outcomes and reducing the incidence of serotonin syndrome.

Conclusion

Linezolid is a crucial antibiotic for treating serious gram-positive bacterial infections, including those caused by MRSA. However, its association with serotonin syndrome, a potentially life-threatening condition, requires careful consideration in clinical practice. Owing to its mild inhibition of monoamine oxidase, linezolid can induce serotonin syndrome when used concurrently with other serotonergic medications such as SSRIs, SNRIs, and MAOIs. Understanding the pharmacological mechanisms underlying these interactions is vital. The Hunter Serotonin Toxicity Criteria represent a practical and accurate diagnostic tool, especially in emergency settings, and

these criteria are preferred to the less specific Sternbach criteria. The incidence of serotonin syndrome associated with linezolid, although relatively low, is clinically significant. This review has underscored the importance of vigilant monitoring and risk assessment when prescribing linezolid, particularly for patients receiving serotonergic agents. Future research should focus on enhancing pharmacovigilance, exploring underlying mechanisms, and developing clinical guidelines and risk stratification tools. Additionally, education programs for healthcare providers and the exploration of alternative therapies with lower risks for inducing serotonin syndrome are crucial. Addressing these issues can improve the safety profile of linezolid, ensuring its continued efficacy in treating severe bacterial infections while minimizing the risk of serotonin syndrome. This balanced approach will enhance patient outcomes and contribute to the effective management of infections in clinical settings.

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Data availability statement

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

Declaration of conflicting interest

I declare no conflicts of interest.

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