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CASE REPORT

Linezolid Associated Serotonin Syndrome Presenting as Persistent Fever in an Elderly Woman with Dementia, Diabetes and Chronic Lacunar Infarcts: A Case Report

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Abstract:

***Background and Objectives*:** Linezolid, a reversible non-selective monoamine oxidase inhibitor, is widely used for multidrug-resistant Gram-positive infections but can precipitate serotonin syndrome, particularly when combined with other serotonergic agents such as ondansetron. In critically ill patients, persistent fever is often presumed to be infectious, leading to unnecessary escalation of antimicrobial therapy. This report highlights linezolid-associated serotonin syndrome presenting as fever of unknown origin in an elderly ICU patient. ***Methods*:** A 75-year-old woman with dementia, psychosis, diabetes mellitus, and chronic lacunar infarcts was admitted with multidrug-resistant Escherichia coli urosepsis followed by MRSA pneumonia. During hospitalization, she was receiving ondansetron 8 mg twice daily, lorazepam 1 mg twice daily, and bromocriptine 2.5 mg once daily, without concurrent antipsychotic therapy. After 7 days of colistin and fosfomycin, antimicrobial treatment was changed to meropenem and linezolid. On the seventh day of linezolid therapy, she developed persistent high-grade fever, autonomic instability (tachycardia, labile blood pressure, diaphoresis), and neuromuscular hyperactivity (tremor, rigidity, hyperreflexia). Repeat cultures, inflammatory markers, and procalcitonin were negative. The patient fulfilled the Hunter Serotonin Toxicity Criteria, prompting suspicion of linezolid-associated serotonin syndrome. Linezolid was discontinued, while ondansetron and bromocriptine were continued. ***Results*:** Following withdrawal of linezolid, the patient's fever resolved within 3 days, with marked improvement in autonomic and neuromuscular manifestations. No alternative infectious sources were identified, supporting the diagnosis of linezolid-associated serotonin syndrome. ***Conclusion*:** Linezolid-associated serotonin syndrome should be considered in elderly ICU patients with persistent fever, autonomic instability, and neuromuscular abnormalities, particularly when concomitant serotonergic agents such as ondansetron are being administered. Early recognition using the Hunter Serotonin Toxicity Criteria and prompt withdrawal of the offending drug can prevent unnecessary diagnostic investigations and inappropriate escalation of antimicrobial therapy.

Keywords: Linezolid, Serotonin Syndrome, Ondansetron, Fever of Unknown Origin, Elderly, Critical Care.

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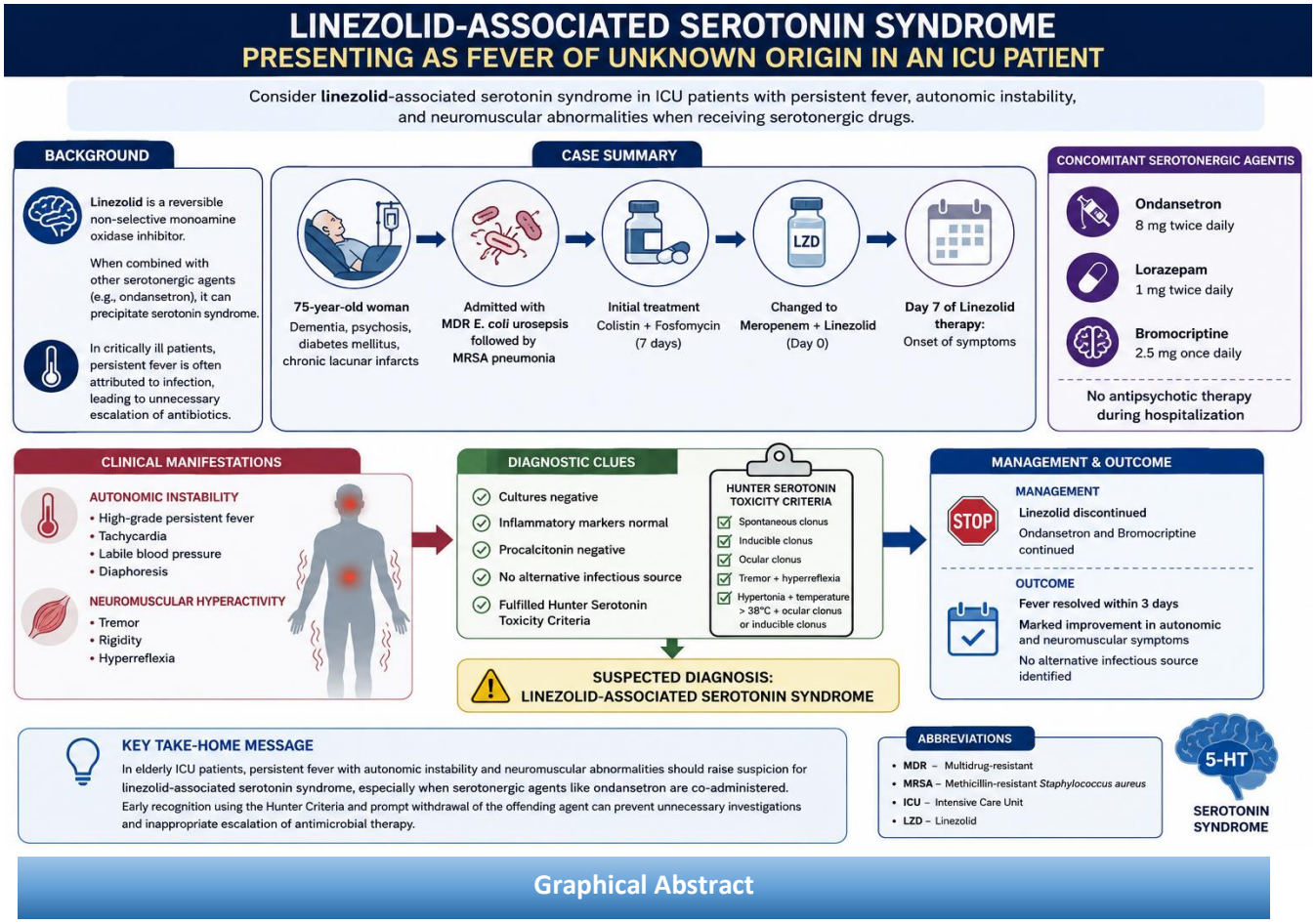

Graphical Abstract

1. Introduction:

Multidrug-resistant (MDR) infections are a major challenge in Indian intensive care units (ICUs), and linezolid is widely used for MDR Gram-positive infections such as methicillin-resistant Staphylococcus aureus (MRSA). Linezolid is a weak, reversible, non-selective inhibitor of monoamine oxidase A and B. By inhibiting serotonin breakdown, it can increase central serotonergic tone, particularly when combined with other serotonergic or dopaminergic agents. Ondansetron, although primarily a 5-HT_3 receptor antagonist, has serotonergic activity and is frequently implicated in ICU serotonin syndrome, especially in combination with linezolid. Serotonin syndrome in ICU is often under-diagnosed and may present atypically, with fever as a dominant feature, especially in elderly patients with cerebrovascular disease and dementia. We report a case of probable linezolid-induced serotonin syndrome presenting as persistent fever in an elderly woman with dementia, diabetes and chronic lacunar infarcts receiving ondansetron and bromocriptine.

2. Case Report:

A 75-year-old woman with a history of dementia, psychosis, type 2 diabetes mellitus, and chronic lacunar infarcts was admitted to the intensive care unit (ICU) with sepsis and respiratory failure. In April 2026, she developed extrapyramidal symptoms attributed to antipsychotic therapy, for which bromocriptine was initiated. In July 2026, she had been treated at another hospital for approximately 15 days for a suspected infection associated with altered sensorium before being transferred to our centre.

On admission to our ICU, she was afebrile and hemodynamically stable. Clinical examination revealed features of sepsis, with bilateral crepitations on chest auscultation. Urine culture grew multidrug-resistant Escherichia coli, while the respiratory specimen was positive for methicillin-resistant Staphylococcus aureus (MRSA). Blood cultures and other microbiological investigations were negative. Chest imaging demonstrated findings consistent with pneumonia. Based on the clinical, microbiological, and radiological findings, she was diagnosed with

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multidrug-resistant E. coli urosepsis with subsequent MRSA pneumonia.

During the ICU admission, she was not receiving any antipsychotic medications. Her concomitant medications included antimicrobial agents, ondansetron 8 mg twice daily, lorazepam 1 mg twice daily for agitation, and bromocriptine 2.5 mg once daily for previously documented extrapyramidal symptoms. She was not receiving selective serotonin reuptake inhibitors, tramadol, or other commonly recognized serotonergic medications.

Initial antimicrobial therapy consisted of colistin and fosfomycin, administered for seven days. In view of the documented MRSA pneumonia, intravenous linezolid was initiated at a dose of 600 mg twice daily. Meropenem was also administered for Gram-negative coverage in the setting of prolonged hospitalization and the previously documented multidrug-resistant infection. Linezolid was continued at the standard therapeutic dose for seven days.

On the seventh day of linezolid therapy, the patient developed persistent high-grade fever accompanied by autonomic instability and neuromuscular hyperactivity. She developed tachycardia, labile blood pressure, diaphoresis, tremor, hyperreflexia, and rigidity. In view of this acute clinical deterioration, an extensive evaluation for persistent or recurrent infection was undertaken. Repeat blood, urine, and respiratory cultures remained negative. Procalcitonin and C-reactive protein levels did not support an ongoing bacterial infectious process, and repeat imaging failed to identify a new focus of infection. Other potential causes of persistent fever, including catheter-related bloodstream infection, deep-vein thrombosis, pulmonary embolism, and antimicrobial-associated drug fever related to beta-lactam therapy or colistin, were considered but were not supported by the clinical course or investigations.

With no identifiable infectious source and a clear temporal association between the onset of symptoms and linezolid exposure, serotonin syndrome was suspected. The patient's advanced age, dementia, chronic cerebrovascular disease, and exposure to multiple centrally acting medications represented additional factors that could increase vulnerability to central nervous system drug toxicity. Of particular relevance, she was concurrently receiving ondansetron and bromocriptine. Although ondansetron is primarily a 5-HT_3 receptor antagonist and bromocriptine is a dopamine agonist, their concurrent administration with linezolid raised concern for an additive disturbance of monoaminergic neurotransmission.

The patient fulfilled the Hunter Serotonin Toxicity Criteria in the setting of linezolid exposure and the development of compatible neuromuscular and autonomic manifestations, including tremor, hyperreflexia, rigidity, and hyperthermia. Based on the clinical presentation and exclusion of alternative causes, linezolid was discontinued. Meropenem was continued to provide ongoing Gram-negative antimicrobial coverage. Ondansetron and bromocriptine were continued, while lorazepam was maintained at the pre-existing dose. Supportive treatment included antipyretic therapy, external cooling measures, and close monitoring of neurological and hemodynamic status. Cyproheptadine was not administered because the patient demonstrated clinical improvement following withdrawal of linezolid and supportive management.

The patient's fever resolved within three days of discontinuing linezolid, accompanied by gradual improvement in the autonomic and neuromuscular abnormalities. No new infectious focus was identified during this period. Her overall clinical condition subsequently improved, and she was transferred from the ICU to the ward in a stable condition.

The temporal association between linezolid administration and symptom onset, the presence of characteristic neuromuscular and autonomic manifestations, the absence of an alternative infectious source, fulfillment of the Hunter Serotonin Toxicity Criteria, and prompt clinical improvement following discontinuation of linezolid supported the diagnosis of linezolid-associated serotonin syndrome.

3. Discussion:

Linezolid is a reversible, non-selective inhibitor of monoamine oxidase (MAO)-A and MAO-B. Although its MAO-inhibitory activity is relatively weak, clinically relevant interactions may occur when linezolid is administered concurrently with drugs that influence serotonergic neurotransmission. Inhibition of monoamine metabolism can increase serotonergic activity within the central nervous system and, in susceptible individuals, may result in serotonin toxicity. Serotonin syndrome has been reported with linezolid in combination with several centrally acting medications, including antidepressants, tramadol, ondansetron, and other serotonergic agents. The onset is variable but generally occurs within the first few days to weeks of concomitant exposure, while clinical

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improvement commonly follows withdrawal of the offending medication over several days [1,2]. The temporal pattern observed in our patient was consistent with this pharmacological relationship.

Ondansetron presents a particularly relevant consideration in this context. Although it is principally recognized as a selective 5-HT_3 receptor antagonist, its potential contribution to serotonin toxicity when used alongside other serotonergic medications has been described. The combination of linezolid and ondansetron has therefore attracted attention in pharmacovigilance literature and drug-interaction databases, with recommendations ranging from close clinical surveillance to avoidance when suitable alternatives are available [3-5]. In the present case, the concurrent administration of these agents may have contributed to an increased susceptibility to serotonergic toxicity.

Bromocriptine introduces additional pharmacological consideration. As a dopamine receptor agonist, it influences central dopaminergic pathways and may potentially compound disturbances in central neurotransmission and autonomic regulation in the setting of MAO inhibition. Although the precise contribution of bromocriptine to the clinical syndrome cannot be established, its concomitant use may have increased the overall neurochemical burden in an elderly patient with pre-existing cerebrovascular pathology. Importantly, the development of toxicity in this setting does not necessarily require supratherapeutic dosing; pharmacodynamic interactions may become clinically important even when each individual medication is administered within its conventional therapeutic range.

Several patient-specific factors may also have lowered the threshold for neurological and autonomic toxicity. Advanced age, dementia, diabetes mellitus, and chronic lacunar infarcts represented significant underlying vulnerabilities in our patient. Pre-existing structural cerebral disease may alter neuronal reserve and increase susceptibility to centrally mediated adverse drug effects. These factors, together with polypharmacy and the simultaneous exposure to drugs affecting serotonergic and dopaminergic neurotransmission, may have created a clinical environment in which relatively modest pharmacological perturbations resulted in a pronounced systemic response.

The classical clinical spectrum of serotonin syndrome encompasses a triad of mental-status abnormalities, autonomic dysfunction, and neuromuscular hyperactivity. However, recognition can be considerably more difficult in critically ill patients. Sedation, mechanical ventilation, pre-existing neurological disease, impaired communication, and overlapping manifestations of severe infection may obscure characteristic findings such as agitation, clonus, hyperreflexia, or tremor. Consequently, hyperthermia may become the most conspicuous clinical feature. In such circumstances, persistent fever may initially be attributed to ongoing infection, antimicrobial treatment failure, or nonspecific drug fever, potentially delaying recognition of serotonin toxicity.

In our patient, the persistence of high-grade fever despite the absence of a convincing microbiological source, together with the temporal association with linezolid exposure and subsequent clinical improvement following withdrawal, strengthened the clinical suspicion of drug-induced serotonin toxicity. While the absence of a specific laboratory biomarker makes definitive confirmation difficult, serotonin syndrome remains primarily a clinical diagnosis, and the overall clinical course and response to withdrawal are important components of the diagnostic assessment.

This case underscores the importance of maintaining a high index of suspicion for serotonin syndrome in elderly and neurologically vulnerable patients receiving linezolid, particularly when other centrally acting medications such as ondansetron are administered concurrently. Recognition is especially important when persistent or otherwise unexplained fever develops in the intensive care setting. Prompt identification and discontinuation of the suspected offending agent may serve both diagnostic and therapeutic purposes and can prevent unnecessary escalation of antimicrobial therapy, additional investigations, and prolonged intensive care exposure.

Where clinically appropriate, alternative agents for the treatment of susceptible Gram-positive infections, such as vancomycin or daptomycin, may be considered in patients with substantial risk for clinically significant drug interactions. When linezolid remains the most appropriate antimicrobial option, careful review of the patient's medication profile and avoidance of unnecessary serotonergic or centrally acting drugs should be considered. Close clinical surveillance for early manifestations—including unexplained fever, altered mental status, tremor, hyperreflexia, clonus, agitation, diaphoresis, and autonomic instability—may facilitate earlier recognition.

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This report has several limitations. Serum serotonin concentrations were not measured, as such testing is neither routinely available nor routinely required for the clinical diagnosis of serotonin syndrome. Furthermore, given the simultaneous exposure to multiple centrally acting medications and the absence of a definitive biochemical test, a causal relationship with linezolid cannot be established with absolute certainty. The diagnosis should therefore be regarded as probable rather than unequivocal. Finally, this represents a single case, and the observations cannot be generalised to all patients receiving linezolid or ondansetron. Nevertheless, the case highlights an important and potentially under-recognized adverse drug interaction that should remain within the differential diagnosis of otherwise unexplained fever in critically ill patients.

4. Conclusion:

Linezolid-associated serotonin syndrome should be included in the differential diagnosis of persistent or otherwise unexplained fever in elderly critically ill patients, particularly those with underlying cerebrovascular disease and concomitant exposure to ondansetron or other centrally acting medications. Early recognition and prompt discontinuation of linezolid may result in rapid clinical improvement and help prevent unnecessary escalation of antimicrobial therapy and prolonged intensive care management.

5. Declarations:

Conflict of Interest: Authors report no conflict of interest.

Financial Support and Sponsorship: Nil.

Data Availability Statement: The data supporting the findings of this case report are contained within the article. Additional clinical information is not publicly available because of patient privacy and confidentiality considerations.

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Authors' Contributions: All authors contributed to the conception and design of the case report, acquisition and interpretation of clinical data, and preparation of the manuscript. All authors critically reviewed the manuscript for important intellectual content, approved the final version, and agreed to be accountable for all aspects of the work.

Ethical Approval and Consent to Participate (Human Ethics): Formal ethical approval was not required for this case report in accordance with the institutional policy governing the reporting of individual clinical cases.

Consent (Declaration of Patient's consent): Authors certify that they have obtained written informed consent for publication of the patient's clinical information. They have been informed regarding the purpose of publication and the measures taken to maintain the patient's privacy and confidentiality.

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