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SEROTONIN SYNDROME FOLLOWING LINEZOLID AND SERTRALINE CO-ADMINISTRATION: A CASE REPORT

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Abstract

Linezolid is an oxazolidinone antibiotic that also inhibits monoamine oxidase, and sertraline is a widely prescribed selective serotonin reuptake inhibitor. Used together they can produce serotonin syndrome, a predictable but sometimes overlooked drug toxicity. This narrative review summarises published case reports, cohort studies and reviews on the pharmacology of the interaction, its reported frequency, clinical recognition and management, and strategies for prevention. It describes no individual patient and presents no new data. The literature indicates that severe cases are uncommon, that most reported events are mild to moderate and resolve after stopping the drugs, and that the true incidence is uncertain because studies differ in design and reporting.

Single-drug overdoses and dose escalations can also cause it. The severity ranges widely. Many patients have a mild form with tremor, diarrhoea and restlessness that settles within a day or so of stopping the offending drug, and

1. INTRODUCTION

Serotonin syndrome, also called serotonin toxicity, is a condition caused by excess serotonergic activity in the central nervous system and periphery. It is not an allergic or idiosyncratic reaction but a predictable, dose-related result of drugs that raise serotonin in the synapse. Typical features are altered mental state, neuromuscular excitation and autonomic instability, and in severe cases hyperthermia, rigidity and death [1, 2, 3]. Most cases follow a combination of two or more serotonergic drugs, which is why the interaction between linezolid and an antidepressant is a textbook example.

some may never reach medical attention. A smaller group develop clonus, agitation and fever, and a very few develop temperatures above 41 °C with rigidity, which is a medical emergency [1, 2, 4]. Onset within hours of a change in dose is characteristic.

Linezolid, the first oxazolidinone antibacterial, became an important option for infections caused by resistant Gram-positive organisms, including meticillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci, and later for drug-resistant tuberculosis [5, 6, 7, 8]. Sertraline, meanwhile, is among the most commonly prescribed antidepressants. Because depression and anxiety are common in hospital patients, a person taking sertraline who develops a serious bacterial infection is hardly a rare event, and clinicians repeatedly face the question of whether the antibiotic can safely be given [9, 10]. Prescribers' awareness of the problem has grown, but practical difficulty remains. The warning in a product label is easily lost in a long list, and a patient admitted to hospital with sepsis may be taking antidepressants that are not carried forward onto the drug chart. Antibiotic stewardship teams often recommend linezolid for resistant infections, sometimes without being told the full psychiatric history [11, 12]. Both drugs are commonly started in primary care, so patients arrive in hospital with a history that ward staff may not have.

The aim of this review is to describe what the published literature shows about serotonin syndrome following the combination of linezolid and sertraline. It covers the mechanism of the interaction, the case reports and larger studies that estimate its frequency, the recognition and treatment of the syndrome, and sensible ways to prevent it. The principal reports are gathered in table 1, and fig. 1 shows how they divide by theme. The article is a narrative synthesis of published sources. It does not describe any individual patient, reports no new data, and treats published case reports as a description of what can happen and not a measure of how often it does. Titles that promise a case report in this area can be misleading, because a single case, however well described, cannot establish how often an interaction occurs. This review therefore uses cases to illustrate presentation and management and relies on cohorts and pharmacovigilance for frequency, as set out in table 1. The balance of the evidence by theme is shown in fig. 1.

A note on language. 'Serotonin syndrome' and 'serotonin toxicity' are used interchangeably here, although the second is preferred by toxicologists because it describes a spectrum from mild to life-threatening and not a single all-or-nothing syndrome [2, 13]. Serotonin syndrome is also the subject of misinformation in both directions; some clinicians regard the linezolid interaction as a rare theoretical risk, while others regard it as an absolute contraindication [11, 14].

2. MECHANISM OF THE INTERACTION

Serotonin (5-hydroxytryptamine) is released from presynaptic neurones, acts on a family of receptors, and is cleared by the serotonin transporter, which takes it back into the cell, and by monoamine oxidase A, which breaks it down. Sertraline blocks the transporter, increasing the amount of serotonin in the synaptic cleft [15, 16]. At therapeutic doses this effect is the basis of its antidepressant action. By itself it seldom causes toxicity, which is why the syndrome mainly appears when a second drug adds to the effect. Serotonin itself is found in much larger amounts in the gut and platelets than in the brain, and peripheral effects such as increased bowel motility explain the diarrhoea so often seen. The drug acts on both central and peripheral systems, which accounts for the mixture of mental, motor and autonomic features of the toxic state [17, 18]. Binding is selective for the transporter at usual doses, although sertraline also has weaker effects on dopamine uptake and on sigma receptors that are not thought to matter for toxicity [15, 16].

Table 1: Selected published evidence on linezolid, serotonergic antidepressants and serotonin syndrome

Source or topic	Reported finding or feature	Ref.
MAO inhibition by linezolid tyramine pressor studies	Weak, reversible, non-selective inhibition at therapeutic doses with modest pressor effects.	[19, 20]

Source or topic	Reported finding or feature	Ref.
Classical MAO inhibitors combination rules	Irreversible inhibition strongly potentiates serotonin; washout periods are required before serotonergic drugs.	[13, 21]
Early case report citalopram and linezolid	Serotonin syndrome described after adding linezolid to an SSRI.	[22]
Post-marketing review serotonin toxicity	Most reports involved an SSRI, with onset commonly within days of starting linezolid.	[23]
Retrospective survey co-exposed patients	Few probable cases among many patients taking linezolid with serotonergic drugs.	[14, 24]
Cohort comparison SSRI versus no SSRI	Low incidence in both groups, with no clear excess among co-exposed patients.	[25]
Pharmacovigilance analysis spontaneous reports	Signal strongest with multiple serotonergic drugs; incidence cannot be derived.	[26]
Hunter criteria diagnostic rules	Decision rules based on clonus, tremor, hyperreflexia and hypertonia outperform older criteria.	[2, 27]
Cyproheptadine case reports	Used for moderate cases not settling with supportive care; controlled evidence is lacking.	[28, 29]
Fatal cases systematic review	Deaths linked to multiple drugs, delayed recognition and complications such as rhabdomyolysis.	[4]
FDA safety communication 2011	Avoid linezolid with serotonergic psychiatric drugs unless urgent, then monitor closely.	[12]

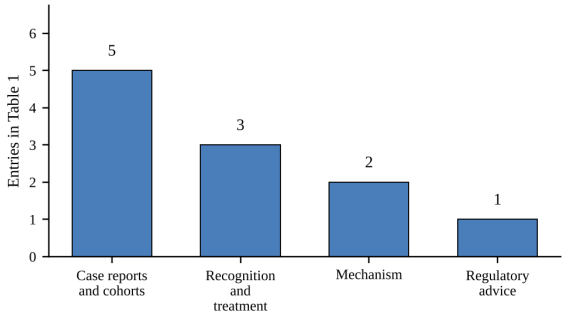


Fig. 1: Number of entries in table 1 by theme

Linezolid adds in a second way. Its antibacterial action comes from binding to the 23S ribosomal RNA of the 50S subunit and preventing formation of the initiation complex for bacterial protein synthesis [5, 30]. Separately, laboratory work and clinical pharmacology studies showed that linezolid is a weak, reversible and non-selective inhibitor of monoamine oxidase, the enzyme that breaks down serotonin and other amines [19, 20]. Tyramine pressor studies in healthy volunteers found only a modest effect at therapeutic doses, but the effect was sufficient to make interactions with serotonergic drugs a recognised risk [20]. Selectivity data explain why the effect of the antibiotic is modest. Studies in healthy volunteers showed that linezolid at the standard dose produced limited changes in the pressor response to tyramine, and that co-administration with pseudoephedrine produced a small increase in blood pressure, a pattern consistent with weak inhibition of the enzyme [19, 20]. Dietary tyramine restrictions are accordingly relaxed compared with classical inhibitors, although advice to avoid very large amounts is still given.

Put together, the two drugs act on opposite ends of the pathway: the antidepressant raises the amount of serotonin released into the synapse and keeps it there, while the antibiotic slows its breakdown. The result is more serotonin acting at postsynaptic receptors. Animal and human evidence suggests that stimulation of 5-HT_{2A} receptors is central to the severe form, with contributions from 5-HT_{1A} and other receptor subtypes, and that hyperthermia reflects excessive muscle activity as well as central effects [13, 17, 18]. What remains uncertain is why some patients, but not most, react. Individual susceptibility may reflect dose, renal function, genetic variation in transporters and receptors, and the presence of other drugs that add to the effect. Authors who have reviewed the data acknowledge that the mechanistic explanation is better established than the factors that predict who will be affected [13, 18]. Text-book descriptions of the clinical picture usually rest on observations of overdoses of single agents.

Classical monoamine oxidase inhibitors such as phenelzine and tranylcypromine are irreversible and strongly potentiate serotonin, so combinations with serotonin reuptake

inhibitors are contraindicated and carry washout requirements of several weeks [13, 21]. Linezolid is weaker and reversible, so its interactions are less predictable. Some reviewers describe the compound as a monoamine oxidase inhibitor in disguise, which is a useful warning for practitioners who do not think of an antibiotic in that category [10, 21]. The regulatory distinction between a drug that inhibits monoamine oxidase and one that does not is blurred by linezolid. It was developed as an antibiotic, and its monoamine oxidase action was found during preclinical and early clinical studies, so labels carry its warnings in the interaction section and not in the contraindications of the older inhibitors [12, 20].

Pharmacokinetic factors may add to the risk. Sertraline has a half-life of about a day and an active metabolite, desmethylsertraline, with a longer half-life, so serotonergic effects persist for days after the last dose [16]. Linezolid is eliminated more quickly, mostly by non-enzymatic oxidation, with a half-life of a few hours, and accumulates in people with renal impairment [16, 31]. This difference matters when planning interruption or switching, since stopping the antidepressant for a short antibiotic course does not clear its effect. Other antibiotics are occasionally discussed in this context, but the evidence is much thinner than for linezolid and none has a comparable body of case reports [5, 23].

3. PUBLISHED CASES AND REPORTED FREQUENCY

Individual case reports appeared soon after linezolid reached the market. One early report described serotonin syndrome in a patient who received linezolid after citalopram, which prompted wider attention [22]. Later series gathered cases submitted to the manufacturer and the regulator, and a review of post-marketing data found that most reports involved a selective serotonin reuptake inhibitor or another serotonergic drug, with onset commonly within a few days of starting linezolid [23, 24]. Sertraline was among the antidepressants named, though cases with citalopram, escitalopram, paroxetine and venlafaxine were also described. The time course described in these reports was fairly consistent. Symptoms usually began within one to a few days of adding linezolid, and resolution generally followed within one to three days of stopping one or both drugs. A few patients needed intensive care, and deaths have been reported, usually in the presence of other serotonergic drugs or serious illness [4, 23, 32]. Those early reports were important mainly because they were specific about the sequence of drugs, which later series often could not reconstruct.

Interpreting these reports requires care. Case series are subject to reporting bias, since unusual and severe events are more likely to be published, and the denominator of patients who took the combination without trouble is invisible. Diagnoses in older reports were also made without standardised criteria, so some cases may have been other conditions such as neuroleptic malignant syndrome, anticholinergic toxicity or sepsis-related delirium [27, 32, 33]. The reports tell us that the interaction is real; they do not tell us how often it occurs. Another source of uncertainty is the definition of exposure. Some studies counted any overlap between the drugs, including a single dose of the antidepressant in the same admission, while others required both drugs to be given on the same day. These choices change denominators by large factors, and the lack of a standard makes pooling studies difficult [14, 25].

Cohort studies gave a more reassuring picture. A retrospective survey of patients who received linezolid while on serotonergic drugs found a small number of cases of probable serotonin syndrome among many co-exposed patients [14]. A chart review at a large centre came to a similar conclusion and described mild events [24]. A later comparison of patients given linezolid with and without serotonin reuptake inhibitors found a low incidence in both groups, with no clear excess in the co-exposed group, although confidence intervals were wide [25]. Put simply, these studies suggest that the absolute risk is low. The variation in the comparison groups also matters. If patients on antidepressants are sicker and receive linezolid for longer, the apparent risk could be inflated, while clinicians who avoid the combination in the highest-risk patients could

deflate it. Confounding of this kind affects every observational comparison in this area, and none has been fully resolved by statistical adjustment [25, 26].

Pharmacovigilance analysis points the same way, with caveats. A disproportionality analysis of spontaneous reports found that linezolid was associated with serotonin syndrome reports more often than other antibiotics, and that the signal was strongest with several serotonergic agents together or at higher doses of the serotonergic partner [26]. Because the method compares reports and not patients, it cannot give incidence, and stimulated reporting after a regulatory warning may inflate numbers [12, 26]. The relevance of dose is an open question. Most reports describe standard linezolid doses of 600 mg twice daily, and sertraline doses have ranged from low to high, but the available data do not allow a dose-response relationship to be drawn with confidence. Linezolid exposure rises in renal impairment, which could contribute, although this has not been shown directly for serotonin toxicity [26, 31]. The practical value of these results is in guiding vigilance and not in granting permission.

Regulators responded. In 2011 the United States Food and Drug Administration issued a safety communication advising that linezolid should generally not be given to patients taking serotonergic psychiatric medicines, with exceptions for urgent, life-threatening infections when no alternative exists, in which case the antidepressant should be stopped and the patient monitored closely for two weeks or until 24 hours after the last linezolid dose, whichever comes first [12]. Product labels in other countries carry similar advice, though wording varies [11, 12]. Practical advice drawn from this evidence appears in several reviews. Their recommendations include avoiding the combination when possible, ensuring that the benefit outweighs the risk when it is used, informing the patient, and monitoring closely during the first days of therapy, when most events begin [11, 34]. Product information also reminds prescribers that the interaction is not limited to antidepressants, as opioids, buspirone and some migraine drugs are included.

Reviews of published cases also record who is affected. Many of the described patients were elderly, had renal impairment or were on several serotonergic drugs, including opioids such as tramadol, meperidine and methadone, as well as triptans and lithium [11, 21, 35, 36]. Where an antidepressant dose was recently increased, or where linezolid was used for longer than a few days, the risk seemed greater. A patient on sertraline alone at a moderate dose seems to be at lower risk than one on a high dose with several other agents [11, 24]. Clinicians in tuberculosis programmes face a version of the problem that differs from hospital practice, because linezolid is given for months and not days. Reports from that setting describe the combination with antidepressants more rarely, but the long exposure means vigilance is needed, and some programmes review psychiatric medications as part of the baseline assessment [8, 37].

4. RECOGNITION AND MANAGEMENT

Diagnosis rests on history and examination, since no laboratory test confirms it. Sternbach's original criteria were widely used, but the Hunter Serotonin Toxicity Criteria, derived from a large series of overdoses, have better sensitivity and specificity and are simpler to apply [27, 33]. In the presence of a serotonergic drug, the Hunter rules ask for any of spontaneous clonus, inducible clonus with agitation or sweating, ocular clonus with agitation or sweating, tremor with hyperreflexia, or hypertonia with temperature above 38 °C and ocular or inducible clonus [2, 27]. In practice, clonus is the sign that carries most weight. Spontaneous or inducible clonus in a patient on serotonergic drugs makes the diagnosis likely, and ocular clonus, slow horizontal eye movements, is highly suggestive. Examining for clonus takes a few seconds, but is often missed unless the clinician has the interaction in mind [2, 27, 38]. Using a rule rather than gestalt also reduces the chance of labelling any febrile, shaky patient with the syndrome.

Clinical signs fall into three groups. Neuromuscular findings include tremor,

hyperreflexia, clonus (especially in the lower limbs) and rigidity. Autonomic findings include fever, sweating, tachycardia, labile blood pressure, diarrhoea and dilated pupils. Mental-state changes range from restlessness and anxiety to agitation, confusion and coma [1, 3, 38]. Onset is usually rapid, within hours of a new drug or a dose increase, and in a majority of reported cases within a day, which is a useful clue [1, 32, 38]. Laboratory tests are used to exclude other conditions and to detect complications. Creatine kinase, electrolytes, renal function, liver enzymes, coagulation tests and blood gases show rhabdomyolysis, acidosis and organ injury, and cultures may be needed to look for infection. Serum serotonin levels are not useful in the acute setting [2, 3, 29]. Lower-limb clonus is easily elicited by sudden dorsiflexion of the ankle.

The differential diagnosis matters because treatments differ. Neuroleptic malignant syndrome evolves over days, with bradyreflexia and lead-pipe rigidity rather than clonus. Anticholinergic toxicity produces dry skin and reduced bowel sounds, in contrast with the sweating and hyperactive bowel of serotonin toxicity. Malignant hyperthermia follows anaesthetic agents, and sepsis, withdrawal states and thyrotoxicosis can all mimic parts of the picture [2, 3, 29]. In an infected patient on linezolid, sepsis and the syndrome may coexist, which complicates the assessment. Timing helps with diagnosis. Neuromuscular signs that appear within hours of a dose increase or the start of linezolid fit serotonin toxicity better than a picture that developed slowly over a week. Recording the sequence of drug starts and changes on admission is therefore valuable, and pharmacy medication histories can supply it [1, 2, 32].

Management begins with stopping every serotonergic drug, including linezolid and sertraline. Supportive care follows: oxygen, intravenous fluids, continuous cardiac monitoring and correction of vital signs. Mild cases usually improve within one or two days after withdrawal of the offending drugs, in line with the half-lives of the agents involved [1, 2, 29]. Benzodiazepines control agitation and muscle activity, and avoiding physical restraints is advised because isometric contraction raises temperature and lactic acidosis [2, 3]. The expected course is short. After removal of the drugs, most patients improve in 24 hours, although those who have taken longer-acting agents may take longer. For linezolid, which is cleared quickly, recovery tends to be quick, whereas persistent sertraline and its metabolite may prolong the picture a little [16, 29]. Patients who have required intensive support need follow-up for muscle and renal complications. Hydration and cooling are often enough in the mild cases that make up most of the literature.

Cyproheptadine, a first-generation antihistamine with 5-HT_{2A} antagonist properties, is the antidote most often recommended for moderate cases that do not settle with supportive care, given orally or crushed through a nasogastric tube [28, 29]. Evidence for it is limited to case reports and small series, so its benefit has not been proved in controlled trials [2, 28]. Chlorpromazine has been used parenterally, although it can cause hypotension and lower the seizure threshold. Antipyretics are not effective against the temperature rise, since it derives from muscle activity [2, 3]. Decisions about the antibiotic after an episode need care. The infection still needs treatment, so another agent without serotonergic effects is normally substituted. Restarting the antidepressant should be left until symptoms have resolved and, ideally, until any linezolid has been cleared, with psychiatric review to avoid relapse [2, 11, 29]. Dose, route and tolerability should be reviewed daily in the first week.

Severe cases with temperature above 41 °C need sedation, paralysis with a non-depolarising agent, and intubation with active cooling. Succinylcholine should be avoided because of the risk of hyperkalaemia in rhabdomyolysis. A systematic review of fatal cases found that death was often linked to combinations of drugs, delays in recognition and complications such as rhabdomyolysis, disseminated intravascular coagulation and multi-organ failure [4, 39]. Such fatalities are rare compared with the number of patients exposed to serotonergic drugs [4]. Pharmacology teaching has begun

to use serotonin syndrome as a model of predictable toxicity. It illustrates that an interaction can be foreseen from mechanism alone, and that recognising it depends on clinical examination more than on investigation [3, 17].

5. PREVENTION AND PRACTICE

The sensible first question is whether linezolid is the right antibiotic for a patient taking sertraline. Alternatives with activity against resistant Gram-positive organisms, such as vancomycin, daptomycin and others, may be suitable depending on the site and organism, and guidelines on skin and soft tissue infection and on MRSA treatment give options [6, 7]. When a non-serotonergic alternative exists and works equally well, choosing it avoids the interaction altogether. Where the combination cannot be avoided, a practical plan helps. Use the lowest effective doses, avoid adding further serotonergic drugs such as tramadol, ondansetron or triptans for the duration, limit linezolid to the shortest effective course, and arrange observation for several days [11, 35, 36]. In practice, the choice is often made jointly by the infection team, the psychiatrist and the pharmacist, and documented in the notes.

There will be cases where linezolid is the best or only option, for example in drug-resistant tuberculosis, where regimens including linezolid have achieved high rates of favourable outcome in highly resistant disease [8, 37]. Here the decision is individual. Some clinicians stop the antidepressant before the antibiotic and wait out the washout period when the infection allows it; others continue the antidepressant with close observation, particularly when the patient is stable on a modest dose and stopping would risk relapse or discontinuation symptoms [10, 11, 24, 34]. Hospital policy can support this plan. Antimicrobial stewardship teams, clinical pharmacists and psychiatry liaison services can agree a local protocol that sets out when linezolid is permitted in patients on antidepressants and how they are to be monitored. Audit of such protocols could provide the local data that the published literature lacks [11, 12, 25]. Where the antidepressant is needed to keep the patient well, dose reduction rather than withdrawal is sometimes tried, although supporting data are anecdotal.

The washout question has no clean answer. The regulatory advice to withdraw the antidepressant for two weeks before linezolid applies when the infection can wait, but it is unrealistic for most hospital infections, and sertraline's long-lived metabolite means the pharmacological effect lingers [12, 16]. Abrupt withdrawal also carries its own risks, including discontinuation symptoms and relapse of depression. In practice, risk is judged by dose, duration of linezolid, other serotonergic drugs on the chart and the patient's renal function [11, 24, 25]. Special groups need extra thought. Older people tend to take many medicines, have lower renal clearance, and may present with confusion that is easily attributed to infection. Patients with renal failure accumulate linezolid metabolites and may have higher exposure, so close observation is warranted [11, 26, 31]. A written plan to restart the antidepressant is part of the same process.

Pharmacists have a natural role. Screening prescriptions for the combination, checking the full medicine list for opioids, triptans, lithium, St John's wort, ondansetron and other serotonergic agents, and raising a flag when a patient on an antidepressant is prescribed linezolid can prevent harm [11, 36]. Electronic prescribing alerts are helpful if they are specific; indiscriminate alerts are ignored. Patients who go home on a combination should be told what symptoms to report, namely shaking, sweating, agitation, diarrhoea and fever, and who to call [29, 39]. There is also the matter of self-medication. Over-the-counter products such as dextromethorphan, and herbal preparations such as St John's wort, are serotonergic, and patients rarely mention them. Asking directly about these products, and about recreational drugs, belongs in the medicines history of anyone starting linezolid [13, 19, 29].

Education also covers the prescriber's side. Infectious disease teams and psychiatrists seldom share notes, so a patient may be seen by one team that does not know the other's drugs. Joint review at the bedside, with a short written plan for monitoring, is cheap

and has few downsides. A common plan is to review the patient daily for neuromuscular signs, record temperature, and prescribe no new serotonergic drug during the course [11, 29, 34]. Documentation should record that the interaction was considered, the reasoning behind the decision, the monitoring plan and the information given to the patient. Such records help the next clinician, who may see the same patient with a different infection and need to make a similar choice [11, 39].

6. LIMITATIONS AND FUTURE DIRECTIONS

The evidence base has well-known weaknesses. It consists chiefly of case reports, retrospective chart reviews and spontaneous reports, with no randomised trial of the combination, and with differing definitions of the outcome from study to study. Many reports predate the Hunter criteria. Dose, duration and timing are inconsistently recorded, and the identities of co-medications are often incomplete, so the contribution of sertraline specifically, as opposed to antidepressants in general, is hard to extract [14, 23, 25, 27]. Publication bias is a further limit. Cases of unremarkable co-prescription are not written up, so the published record over-represents adverse outcomes, and reports that do appear tend to come from centres with an interest in the problem. Cohort studies partly correct this, though each has its own constraints on size and follow-up [14, 23, 25]. Reviewers of the topic have made the same point.

Better data could come from large linked health-record studies with clearly defined outcomes, ideally using validated criteria and capturing both exposures and the doses of each drug. Population pharmacokinetic work might show whether linezolid exposure, which varies between patients and rises in renal failure, predicts toxicity, and genetic factors affecting sertraline metabolism could be examined in the same way [16, 26, 31]. Until then, clinical judgement remains the main tool, supported by the principle that a predictable interaction can be managed by awareness and monitoring. Educational and policy work should also be evaluated. Alerts, protocols and pharmacist review are widely recommended, but few studies have tested whether they reduce events or simply add to the work. Evaluations of such interventions, even in modest before-and-after designs, would be useful to the many hospitals that use linezolid [11, 12].

A last caution concerns generalisation. Most of the data come from adults in hospitals in high-income countries, and the picture for children, for people on multiple long-term psychiatric drugs, and for low-resource settings where linezolid is used for tuberculosis is much less clear [8, 37]. Evidence on other drugs with monoamine oxidase effects is limited, and experience with linezolid cannot be assumed to apply to them.

7. CONCLUSION

The published literature leaves little doubt that linezolid and sertraline can interact to cause serotonin syndrome. The mechanism is understood: sertraline raises synaptic serotonin and linezolid, a weak reversible inhibitor of monoamine oxidase, slows its breakdown [15, 19, 20]. Case reports show that the event can happen, usually within days of starting the antibiotic, yet larger cohort studies suggest that serious toxicity is uncommon among co-exposed patients and that most episodes are mild and resolve after the drugs are stopped [14, 23, 25].

For practice, the message is awareness without alarm. If an equally effective non-serotonergic antibiotic exists, use it. If linezolid is needed, as it often is in resistant infections and tuberculosis, review the whole medication list, keep doses of serotonergic drugs stable, monitor for tremor, clonus, agitation and fever, and stop all serotonergic agents promptly if the syndrome is suspected [8, 12, 27]. Supportive care, benzodiazepines and, where needed, cyproheptadine usually bring recovery [2, 28, 29]. Better quality data would sharpen the estimates of risk.

8. ABBREVIATIONS

5-HT-5-Hydroxytryptamine (serotonin), FDA-US Food and Drug Administration,
MAO-Monoamine oxidase,
MRSA-Meticillin-resistant Staphylococcus aureus, NMS-Neuroleptic malignant syndrome,
SSRI-Selective serotonin reuptake inhibitor,
TB-Tuberculosis, VRE-Vancomycin-resistant enterococci

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10. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

11. CONFLICT OF INTERESTS

Declared none

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