



SEROTONIN SYNDROME AND LINEZOLID

Summary and Recommendations

- Serotonin toxicity associated with linezolid appears to be rare and unpredictable.
- Given its activity against resistant gram-positives, oral formulation, and generic availability, linezolid therapy may be preferred in many scenarios
- In most cases, use of linezolid does not warrant discontinuation of concomitant serotonergic agents, and the risks of discontinuation may outweigh potential benefits.
- Linezolid use is contraindicated in patients taking any MAOI or within two weeks of taking an MAOI ([Table](#)). Linezolid use in patients taking other agents that increase serotonin levels ([Table](#)) is not contraindicated. However, linezolid should be used with caution in patients taking multiple serotonergic agents based on inherent risk of serotonin syndrome with multiple agents and the known weak MAOI mechanism of linezolid.
- Patients and providers should be informed of the signs and symptoms of serotonin toxicity. If serotonin toxicity is suspected, linezolid and other serotonergic agents should be promptly discontinued.

Contraindicated with Linezolid

Monoamine oxidase inhibitor antidepressants:

Isocarboxazide, Phenelzine, Selegiline transdermal, Tranylcypromine

Agents with significant serotonergic potential (compelling mechanistic serotonergic activity)

Selective Serotonin Reuptake Inhibitors:

Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline

Tricyclic Antidepressants:

Amitriptyline, Clomipramine, Imipramine, Nortriptyline

Other Antidepressants:

Desvenlafaxine, Duloxetine, Venlafaxine, Vilazodone, Vortioxetine

Others:

Buspirone, Fentanyl, Methadone, Mepiridine, St. John's wort

Drugs of Abuse:

LSD, MDMA (Ecstasy), Mescaline

Agents noted in case reports but not confidently responsible due to lack of significant potential serotonergic effects (*not comprehensive*)

Serotonin 5-HT_{1B, 1D} Receptor Agonists (e.g., sumatriptan)

Selective 5-HT₃ Receptor Antagonists (e.g., ondansetron)

Atypical antipsychotics (e.g., olanzapine)

Anti-Parkinson's agents (e.g., carbidopa and levodopa)

Miscellaneous anti-depressants:

Bupropion, Mirtazapine, Trazodone

Miscellaneous:

Cocaine, Codeine, Dextroamphetamine, Lithium, Methamphetamine, Tramadol

Serotonin toxicity associated with linezolid appears to be rare and largely idiosyncratic. In addition, given its activity against resistant gram-positives, oral formulation, and generic availability, linezolid therapy may be preferred in many scenarios. The following are recommendations based on the best available evidence at this time:

- Linezolid use is contraindicated in patients taking any MAOI or within two weeks of taking an MAOI
- Linezolid use in patients taking other agents that increase serotonin levels (serotonergic) is not contraindicated. However, linezolid should be used with caution in patients taking multiple serotonergic agents based on inherent risk of serotonin syndrome with multiple agents and the known weak MAOI mechanism of linezolid.
 - o Note: Serotonin antagonists (e.g., ondansetron, second generation antipsychotics) do not increase serotonin levels are not 'serotonergic'.
 - o Risk of serotonin syndrome is not dose-related and antidepressant medication doses should not be empirically reduced when initiating linezolid.
- For inpatients, linezolid may be utilized for patients on concomitant serotonergic agents as deemed necessary and in consultation with Infectious Diseases and/or the Antimicrobial Stewardship Team; primary services should be educated to be mindful of the risk and signs/symptoms of serotonin toxicity so that events may be promptly identified. For patients on chronic antidepressant treatment who require an interruption in medication, consider consulting psychiatry consult service.
- For outpatients, linezolid may be utilized in conjunction with other serotonergic agents, with appropriateness judged on a case-by-case basis. For example, an older adult patient with dementia who lives alone and is on a multiple serotonergic agents would be less suitable for linezolid administration than a patient on PRN amitriptyline who has consistent support.
- In general, use of linezolid does not warrant discontinuation of concomitant serotonergic agents. However, if the patient takes multiple serotonergic agents, or discontinuation of agents is warranted for another reason (i.e., no current indication), the original prescriber of the psychotropic medication may be contacted for input on necessity.
- Careful discussion of the risks and benefits of combination treatment or discontinuation of serotonergic agents should be discussed with the patient/caregiver and documented in the medical record. Potential consequences of discontinuation of antidepressant medication can result in a variety of symptoms, including withdrawal (which may also mimic serotonin syndrome), a reoccurrence of depression or anxiety, suicidal ideation, or death by suicide and risks of discontinuation may outweigh potential benefit.
- In all cases, if serotonin toxicity is suspected, linezolid and other serotonergic agents should be promptly discontinued. Need for additional care is dependent on the clinical scenario. For mild cases, supportive care and benzodiazepines may be sufficient. For more severe cases, administration of 5-HT_{2A} antagonists, such as cyproheptadine may be necessary.

Supportive Information:

Serotonin syndrome results from a drug-induced excess of serotonin in the central nervous system. The severity of the toxicity is dependent on the degree of increase in serotonin. Linezolid is a weak, reversible inhibitor of monoamine oxidase (MAO). The degree of inhibition is sufficiently weak that linezolid alone, even in the case of an overdose, cannot produce serotonin syndrome. The diagnosis of serotonin syndrome (also termed "serotonin toxicity"), as applied to cases involving linezolid, has been variably defined, but the following was suggested by Lawrence and Gillman ([Clin Infect Dis 2006](#)). Serotonin toxicity involving linezolid:

Linezolid + concurrent administration of ≥ 1 other drug known to increase serotonin concentrations in the CNS ([Table](#)) + serotonin toxicity, as defined by the modified Hunter Serotonin Toxicity Criteria.

Modified Hunter Serotonin Toxicity Criteria:

≥ 1 of the following:

- Clonus, seizure, myoclonus, ataxia, incoordination, jaw-trismus, rigidity, shivering, rigors, or nystagmus.
- Tremor or twitching and hyperreflexia

If symptoms only include infection-related symptoms of shivering, rigors or seizure (in context of CNS infection), the Hunter criteria may falsely identify serotonin toxicity.

A literature search reveals the following findings:

1. A review of serotonin syndrome associated with linezolid identified 32 documented cases in the literature, which includes case reports/series, clinical trials, and queries of post-marketing data from the FDA ([Woytowish Ann Pharmacotherapy 2013](#)). Upon application of diagnostic criteria, 11 of the 32 cases did not meet criteria (evaluated by the Hunter Criteria as well as another published definition- Sternbach’s criteria). There were very few consistencies noted throughout the cases:
 - a. Mean age: 50.9 years (range 4-85)
 - b. Female: 20/32 (62.5%)
 - c. 22/32 (69%) involved an SSRI. 16/32 (50%) cases involved ≥ 2 concomitant serotonergic agents
 - d. Onset of symptoms: Median time 60 hours (range 30 minutes to 21 days)
 - e. Medical management was applied in 5 cases; 3 patients died (1 due to severe lactic acidosis that led to cardiac arrest, 1 due to cardiopulmonary arrest due to myoclonus, 1 due to cerebral hemorrhage 1 month after discontinuation of linezolid)

2. There were no contraindicated medications in initial licensing clinical trials, allowing for a robust assessment of the risk for serotonergic toxicity with linezolid with concomitant serotonergic agents. In one assessment of clinical trials by Butterfield, ~41% of 5,426 enrolled patients received linezolid concomitantly with a serotonergic agent, with 303 (5.6%) receiving an SSRI, and 10% and 7% receiving two or three concomitant agents, respectively. No patients were reported by investigators in the trials to have adverse events contributed by serotonin toxicity. When retrospectively applying Sternbach and Hunter Serotonin Toxicity Criteria to all adverse effect reports in the database, of patients receiving at least one serotonergic agent, 12 (0.54%) vs. 4 (0.19%) patients receiving linezolid versus comparator agents, respectively, met criteria for serotonin syndrome. No patients met both criteria. Only one patient meeting criteria was reported to have a serious adverse event, although the investigators did not consider the event related to the study medication. There was 1 (0.03%) patient who met criteria in patients taking linezolid without a serotonergic agent versus 1 (0.08%), 3 (0.55%), and 5 (1.29%) patients taking linezolid plus one, two, or >2 serotonergic agents, respectively ([Butterfield JAC 2011](#)). A similar analysis retrospectively identified adverse events from RCTs that could potentially be attributed to MAO inhibition. There was no difference between linezolid and comparators. The only noted symptoms of MAOI interaction among patients taking linezolid were hypertension (0.3%), hyperthermia (0.9%), and palpitations (0.2%). Investigators noted similar frequencies of these symptoms in patients taking comparator therapies (which did not have MAO inhibitory properties) ([Rubinstein AAC 2003](#)).

3. A retrospective review at the Mayo Clinic of 72 patients who received linezolid and an SSRI or venlafaxine within 14 days of each other (or concurrently) identified 2 patients as having a high probability of having serotonin toxicity. In both, symptoms reversed rapidly upon discontinuation of serotonergic agent(s). It was noted in this study that the Sternbach serotonin syndrome criteria appeared overly sensitive in patients with infection ([Taylor CID 2006](#)). An observational, matched-cohort study was conducted at the Upstate New York Veterans Affairs network to determine the comparative risk of serotonin toxicity with linezolid vs. vancomycin. Of 251 matched pairs of patients (received SSRIs in similar proportions), serotonin toxicity was identified (by chart review) in fewer patients receiving linezolid than vancomycin ([Lodise AAC 2013](#)).

Antimicrobial Subcommittee Approval: N/A	Originated: Unknown
P&T Approval: 3/21/23	Last Revised: 03/2023
Revision History:	

The recommendations in this guide are meant to serve as treatment guidelines for use at Michigan Medicine facilities. If you are an individual experiencing a medical emergency, call 911 immediately. These guidelines should not replace a provider’s professional medical advice based on clinical judgment, or be used in lieu of an Infectious Diseases consultation when necessary. As a result of ongoing research, practice guidelines may from time to time change. The authors of these guidelines have made all attempts to ensure the accuracy based on current information, however, due to ongoing research, users of these guidelines are strongly encouraged to confirm the information contained within them through an independent source.

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