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SEROTONIN SYNDROME AND LINEZOLID

Recommendations: 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, there are distinct scenarios where linezolid therapy may be preferred. 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 on other serotoninergic agents is not absolutely contraindicated, but should be used with caution
- 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 as well as Psychiatry, when deemed appropriate to help determine the risk of discontinuing the psychotropic medication; 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 outpatients, linezolid should be utilized in conjunction with other serotonergic agents more cautiously, with appropriateness judged on a case-by-case basis. For example, an elderly patient with dementia who lives alone and is on a high-dose SSRI would be less suitable for linezolid administration than a patient on tramadol who has consistent support.
- In all cases, an effort should be made to determine if concomitant serotonergic agents are necessary, and if not, to taper/discontinue as appropriate. Consideration should be given to contacting the original prescriber of the psychotropic medication 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, a reoccurrence of depression or anxiety, suicidal ideation, or completed suicide.
- 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-HT2A antagonists, such 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 (Appendix 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

A literature search reveals the following findings:

1. The most recent 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. Of course, such an analysis cannot be considered comprehensive, as it is likely a significant number of cases are not reported (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. This review highlights use with linezolid and serotonergic medications as NOT contraindicated; rather, there is a "need to carefully balance the risk/benefit ratio in this situation."
3. In Phase 3 and 4 clinical trials, ~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 to have serotonin toxicity. When different criteria for identification of toxicity were utilized, 12 (0.54%) vs. 4 (0.19%) patients receiving linezolid versus comparator agents, respectively, met criteria (Butterfield JAC 2011).
4. 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) (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).

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Drugs with serotonergic potential (NOTE: List should not be considered to be all-inclusive

Contraindicated in Linezolid Prescribing Information	Warning/Precaution in Linezolid Prescribing Information	Other agents with serotonergic potential
Monoamine oxidase inhibitor antidepressants Isocarboxazide Moclobemide Phenelzine Tranylcypromine Selegiline (high dose)	*Selective Serotonin Reuptake Inhibitors* Fluoxetine Sertraline Citalopram Escitalopram Fluvoxamine Paroxetine	*Analgesics* Fentanyl Codeine Tramadol Pentazocine Dextropropoxyphene
	Tricyclic Antidepressants Amitriptyline Clomipramine Desipramine Doxepine Imipramine Nortryptyline	*Anti-Parkinsons* Amantadine Bromocriptine Levodopa Selegiline
	Serotonin Receptor Agonists Naratriptan Rizatriptan Sumatriptan Zolmitriptan	*Atypical Antipsychotics* Clozapine Olanzapine Risperidone Ziprasidone Quetiapine
	Others Meperidine Bupropion Buspirone	*Antidepressants* Vilazodone Venlafaxine Desvenlafaxine Vortioxetine Duloxetine Mirtazapine Nefazodone Trazodone
		Anti-emetics Dolasetron Granisetron Ondansetron Droperidol Metoclopramide

Miscellaneous other agents with serotonergic potential		
Cocaine LSD MDMA (Ecstasy) Mescaline Methamphetamine	Carbamazepine Valproate Dextromethorphan Diphenhydramine Chlorpheniramine Brompheniramine	Dihydroergotamine Dextroamphetamine Phentermine Sibutramine Lithium Reserpine St. John's wort Tetrabenazine

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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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