Linezolid and Serotonin Syndrome SBAR

Situation: Linezolid has potent gram-positive activity and is generically available in IV/PO formulations lending to its position as a first-line treatment option for MRSA pneumonia (PNA) and skin and soft tissue infections (SSTI). EPIC order sets (SSTI/PNA) are being updated accordingly. A review of the approach to management of drug-drug interactions (DDIs) with serotonergic agents is warranted to promote best practice to mitigate the potential risk of Serotonin Syndrome (SS).

Assessment/Recommendation: **Serotonin syndrome in patients receiving one additional serotonergic agent is rare (<1%), with a 5-fold increased risk identified in patients on multiple serotonergic agents**.[1,25]

- A framework for risk vs benefit assessment to initiate linezolid is provided below
  - Coadministration within 14 days of an MAO-I is strictly contraindicated (red)
  - Receipt of agent(s) with significant serotonergic potential (yellow) should not preclude linezolid initiation in the inpatient setting where monitoring is available
    - Risks and benefits of linezolid plus > 1 agent with significant serotonergic potential should be discussed with the provider and documented in the medical record
  - Coadministration with an agent that has limited serotonergic potential (green) should generally be safe
  - The number of interacting serotonergic agents and individualized clinical picture should be part of the risk assessment (i.e. ability of the patient and/or caregiver to recognize the s/sx of serotonin syndrome)
- Antidepressants discontinuation is NOT routinely recommended when linezolid is initiated[14]
  - Does not mitigate risk for SS due to long anti-depressant half-life (requires two-week wash out period)
    - May precipitate withdrawal symptoms that overlap with presentation of SS
  - Consider consulting Psychiatry if antidepressant discontinuation/interruption is necessary
- Patients initiated on linezolid should be able to comprehend the signs and symptoms of SS (especially for outpatient use)
  - *Signs of serotonin syndrome*: mental status changes (confusion, hyperactivity, memory problems), muscle twitching, excessive sweating, shivering or shaking, diarrhea, trouble with coordination and/or fever[5]
- If SS is suspected, **linezolid and other serotonergic agents should be immediately discontinued**. Additional management should be tailored to the clinical situation.
  - Mild to moderate cases may be treated with supportive care and benzodiazepines
  - Severe cases may require administration of serotonin (5HT2A) antagonists like cyproheptadine
- Tedizolid is a reversible MAO-I *in vitro* with much lower receptor affinity vs linezolid and lacks CNS penetration making it a reasonable last line alternative to linezolid where risk of SS precludes use.
  - Consider tedizolid 200 mg IV/PO daily as an alternative last line agent where appropriate/feasible (ID restricted)
    - Note: Lacks urinary/CNS penetration. Average wholesale cost is ~$400-500/day and may be prohibitive.
- Modification to DDI alerting in Epic requires changes to the First Databank (FDB) database for all Epic users
  - Inquire with SSMPC/FDB if changes to Epic alerting are feasible for agents with lower serotonergic potential

Contraindicated (within 14 days)	**MAO inhibitors*:** isocarboxazid, phenelzine, selegiline, tranylcypromine, rasagiline
Agents with significant serotonergic potential - Linezolid initiation is acceptable with one interacting medication in this category - Use of linezolid plus >1 agent w/ sig serotonergic potential requires risk vs benefit discussion and documentation in the medical record	**A review of post-marketing reporting found citalopram, escitalopram, and methadone to be higher risk for causing linezolid associated serotonin syndrome[7]** **Serotonin Specific Re-uptake Inhibitors*** (SSRIs) • citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline **Serotonin and norepinephrine reuptake inhibitors*** (SNRIs) • duloxetine, venlafaxine, desvenlafaxine **Tricyclic Antidepressants*** (TCAs) • amitriptyline, imipramine, nortriptyline, doxepin **Others**: buspirone, fentanyl, meperidine, methadone, mirtazapine, tramadol, St John's Wort vortioxetine **Illicit drugs**: LSD, MDMA, cocaine, methamphetamines
Agents noted in case reports but not confidently responsible due to lack of significant potential serotonergic effects (Lack of case reports and unlikely to cause serotonin syndrome)	**Triptans* (5-HT1 agonist):** sumatriptan, rizatriptan, zolmitriptan, almotriptan, naratriptan **5-HT3 antagonists*:** ondansetron, granisetron, palonosetron **Stimulants*:** dextroamphetamine, methylphenidate **Anti-Parkinson's:** carbidopa and levodopa **Others**: bupropion, codeine, lithium, morphine, trazodone, hydromorphone **Antipsychotics*:** Few case reports documented; additionally neuroleptic malignant syndrome can be mistaken for serotonin syndrome

Table is adapted from University of Michigan Serotonin Syndrome and Linezolid document Serotonin Syndrome with Linezolid, Accessed 11.26.24
*Class effect, list may not be comprehensive

Linezolid and Serotonin Syndrome SBAR

Background:

- SS is associated with excessive serotonergic activity in the CNS and presents with a spectrum of clinical findings ranging from mild to life threatening symptoms[17]
    - Classic tetrad of findings: mental status changes, autonomic hyperactivity and neuromuscular abnormalities
- Linezolid has weak nonselective monoamine oxidase inhibitory (MAO-I) effects which can increase risk of SS when co-administered with other serotonergic agents[1]
    - Time to onset ranges from <24 hours to weeks
    - A dose dependent relationship has not been established[24]
- Manufacturer prescribing information outlines warnings when linezolid is used with serotonergic agents[2]
    - Use within 2 weeks of taking an MAO-I is strictly contraindicated
    - Concomitant use of SSRIs, tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans), bupropion, buspirone, or opioids (including meperidine) is not recommended unless clinically necessary
        - An impractical minimum 2-week washout period for antidepressants is recommended[3]
    - In urgent situations, it is recommended to discontinue serotonergic antidepressants upon linezolid initiation and monitor for signs and symptoms of SS
        - Abrupt discontinuation may precipitate significant withdrawal symptoms (occurring in ~20% of patients)[15]
- EPIC flags linezolid and serotonergic DDIs with a "high" or "very high risk" warning face up to the prescriber/pharmacist
- **Literature evaluation demonstrates the overall incidence of SS is rare and risk is dependent on the number and serotonergic activity of the interacting agents.**[1,25]

Linezolid and Antidepressants (SSRI, SNRI, TCAs)

- A 2023 meta-analysis (SanFilippo et al) found a 1.78-fold increased risk of SS associated with concomitant use of linezolid and one serotonergic agent versus a 5-fold increased risk with linezolid and >1 serotonergic agents[1]
- A 2023 retrospective cohort study (Kufel et al) evaluated 1743 patients who received at least one dose of linezolid with or without a serotonergic agent found that the incidence of SS was 0.06% and 0% based on Sternbach and Hunter Criteria, respectively.[24]
- A 2023 publication in Clinical Infectious Diseases (McCreary et al) declared linezolid avoidance in patients receiving SSRI's to be a myth owing to the rare incidence of SS and acceptable risk/benefit profile. Patient monitoring is advised.[18]
- A 2022 population based, retrospective cohort study (Bai et al) included 215 patients that were prescribed linezolid and antidepressants (SSRI, SNRI, TCA). Serotonin syndrome occurred in < 0.5% in the antidepressant group which was not significantly different from the cohort without antidepressants[4]
- A 2012 meta-analysis (Butterfield et al) of 20 Phase III and IV linezolid vs comparator controlled clinical studies found that 41% of the linezolid group received at least one concomitant serotonergic agent [23% one agent, 10% two agents, and 7% three agents]. There was no significant difference in serotonin toxicity between groups. Those who received >2 concomitant agents had higher proportions of meeting Sternbach Criteria or Hunter Serotonin Toxicity Criteria; however, this was notable for both treatment and comparator groups.

Linezolid and Opioids

- A 2024 retrospective review (Huang et al) of 194 encounters of patients on linezolid and methadone, buprenorphine, and/or dextroamphetamine identified only one definitive case of SS with resolution of symptoms after discontinuation.[8]
- A 2022 cross-sectional analysis (Traver et al) of 494 encounters revealed that two possible cases of SS occurred in patients administered linezolid and methadone for more than 8 days and in setting of multiple serotonergic agents[20]
- A 2022 retrospective study (Mitwally et al) of 106 patients who received linezolid and an opioid agent found that morphine and fentanyl were most commonly prescribed and only one patient met Hunter Criteria while on linezolid and fentanyl. The spontaneous myoclonus appeared post cardiac arrest (unlikely related to the DDI). The author concluded the incidence of SS among patients who received concomitant opioids and linezolid was very low and use was likely safe.

Linezolid and other Serotonergic Agents

- There has been one case report of possible SS with linezolid and carbidopa/levodopa but leaves room for interpretation due to the patient originally presenting in an outpatient setting and uncertainty if carbidopa-levodopa was a precipitating factor based on past medical history.[21]
- Atypical antipsychotics and anti-Parkinson's medications rarely cause serotonin syndrome[9, 10]
    - Furthermore, neuroleptic malignant syndrome has been occasionally mistaken for serotonin syndrome[11]
- Triptans and 5HT-3 antagonists have very low to no risk of serotonin syndrome[12, 13]

Linezolid and Serotonin Syndrome SBAR

Linezolid and MAOIs

Linezolid use with any MAOI or within two weeks of a MAOI is **contraindicated**. Combination of two MAOIs or an MAOI and another serotonergic drug carries the greatest risk of serotonin toxicity.

Linezolid and Antidepressants

SanFilippo et al. (2023) performed a meta-analysis that evaluated the incidences of serotonin toxicity in patients treated with linezolid and concomitant use of serotonergic agent vs linezolid alone. Four studies and 6025 patients were included in the comparison between linezolid vs linezolid plus serotonergic agent. Four studies and 2501 patients were included in the comparison between linezolid plus one serotonergic agent vs linezolid plus >1 serotonergic agent. The Hunter Serotonin Toxicity Criteria was used for diagnosis for serotonin toxicity excluding one study. Analysis revealed a 1.78-fold increased risk of serotonin toxicity associated with concomitant use of linezolid and a serotonergic agent (OR 1.78 [95% CI 1.04-3.02]). Additionally, the concomitant use of linezolid with more than one serotonergic agent resulted in 5-fold increased risk of serotonin toxicity compared to the use of a single serotonergic agent (OR 5.18 [95% CI 1.05-25.49]). Notably, studies where no serotonin toxicity occurred in either treatment group were excluded from this analysis which can cause overestimation of the association between linezolid and serotonergic agents. Also, due to the small number of outcomes and limited studies included in the analysis, there is risk of imprecision of estimates. The authors concluded that linezolid can be used safely in patients on a single serotonergic agent, but cautions use with multiple serotonergic agents.[1]

Kufel et al. (2023) performed a single-center, retrospective cohort study that evaluated 1743 patients who received at least one dose of linezolid with or without one or more concurrent serotonergic agent. Hunter Criteria and Sternbach Criteria were both utilized to identify serotonin toxicity. Serotonin toxicity was ruled out if patient did not met 3 or more of Sternbach Criteria or any of Hunter Criteria. It was noted that Hunter Criteria was found to be more sensitive (84% vs 75%) and specific (97% vs 96%) compared to Sternbach Criteria. The most common serotonergic agent administered with linezolid were ondansetron, SSRIs, and antipsychotics. Possible serotonin toxicity was identified in 2 out of 1743 (0.1%) patients. Patient A received linezolid with two serotonergic agents (escitalopram and trazodone); however, did not result in linezolid discontinuation since the patient did not meet the full criteria (met 2 of Sternbach Criteria). Patient B received linezolid with three serotonergic agents (duloxetine, vilazodone, and metoclopramide) and was suspected of serotonin toxicity sixteen-days post-linezolid discontinuation. Patient B did meet 3 of Sternbach Criteria, but did not meet Hunter Criteria which led to the discontinuation of all serotonergic agents. The authors concluded that linezolid with or without concurrent serotonergic agent was exceedingly rare (0.06% based off Sternbach and 0% based off of Hunter Criteria), even among patients who received multiple and high-dose serotonergic agents.[24]

Bai et al. (2022) performed a population-based, retrospective cohort study that included 1134 patients aged $\geq$ 65 years that were prescribed linezolid of which 215 were also taking antidepressants. The antidepressant group consisted of 103 (47.9%) SSRI, 36 (16.7%) SNRI, 15 (7%) TCA, 7 (3.3%) norepinephrine and dopamine reuptake inhibitor, 0 MAOIs, and 54 (25.1%) other antidepressants. The Sternbach Criteria or Hunter Criteria were utilized for diagnosis of serotonin syndrome. In the propensity score-matched cohort analysis, risk of serotonin syndrome was lower in the antidepressant group with an adjusted risk difference of 1.2% [95% CI -2.9-0.5]. There was an observed risk of serotonin syndrome at less than 0.5% due to antidepressants with a number needed to harm of 200. The authors concluded that antidepressants did not significantly increase risk of serotonin syndrome in patients taking linezolid and should not be an absolute contraindication.[4]

Butterfield et al. (2012) performed an analysis to evaluate serotonin toxicity with concomitant use of linezolid or comparators and serotonergic agents from 20 Phase III and IV comparator-controlled clinical trials. Reported adverse events were evaluated retrospectively for serotonin toxicity utilizing Sternbach Criteria and Hunter Serotonin Toxicity Criteria. 2208 out of 5426 patients receiving linezolid had at least one concomitant serotonergic agent [23% one agent, 10% two agents, and 7% three agents]. Some classes of serotonergic agents included were 5.6% SSRI, 2.8% TCA, 0.1% SNRI, 0.1% MAOI and 22.4% analgesics. Among the patients who received at least one serotonergic agent with linezolid vs comparator, there was no notable difference in serotonin toxicity. Those who received more than two concomitant agents had higher proportions of meeting Sternbach Criteria or Hunter Serotonin Toxicity Criteria; however, this was notable for both treatment groups. 13 (0.24%) patients who received linezolid vs 6 (0.12%) patients who received comparator met Sternbach Criteria or Hunter Serotonin Toxicity Criteria. Only one patient meeting the criteria was reported to have experienced serious adverse events (myoclonus) but was not considered to be related to linezolid.[15]

Linezolid and Serotonin Syndrome SBAR

Gatti et al. (2021) conducted a review of post-marketing reports of linezolid related SS to identify most likely causative agents and investigate the relationship with serotonergic agent PK/PD. Overall, 11,429 reports of SS were found, 669 (5.9%) of which mentioning linezolid as suspect agent. Ninety-nine percent of reports were serious (i.e., resulting in death, hospitalization, or life-threatening event), and death was reported in 41 cases (18 with citalopram co-administration).

Single DDI was reported in 366 cases (54.7%), being linezolid-citalopram (N = 69; 10.3%) and linezolid-fentanyl (46; 6.9%) the most frequent, while multiple DDIs were reported in 179 cases (26.8%), being linezolid-citalopram-tramadol (23; 3.4%) the predominant. In 124 reports (18.5%), no concomitant serotonergic medications were recorded.

Citalopram and methadone showed respectively the highest proportion of SS reports (0.28%) and the lowest mean number of DDIs(1.41). Citalopram, escitalopram, and methadone emerged as red (i.e., alert)-zone medications: they exhibited high lipophilicity and large VD (proxies of excellent central nervous system penetration) coupled with high potency.

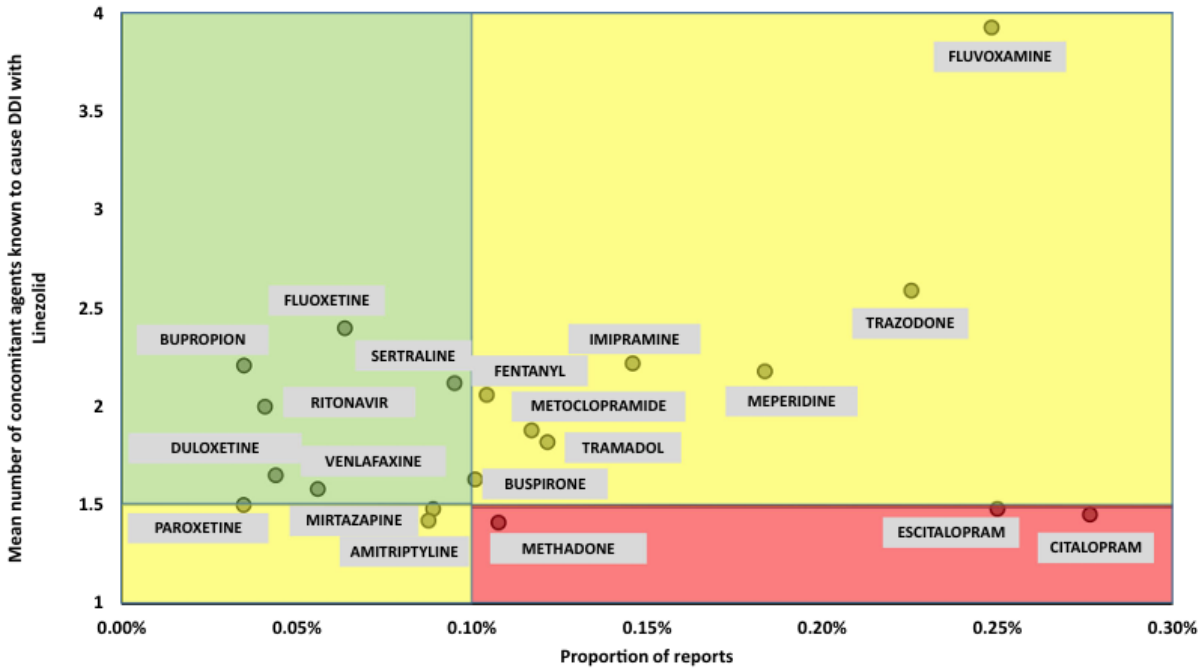

Fig. 2 Scatterplot showing the relationship between the proportion of SS reports (on *x*-axis) and the mean number of DDIs (on *y*-axis) for each serotonergic agent. Threshold values of ≥ 0.1% and ≤ 1.5 were respectively selected for proportion of SS reports and mean number of DDIs, identifying three different SS risk zones (red-zone, high-risk medications; yellow-zone, intermediate-risk medications; green-zone, low-risk medications)

Taylor et al. (2006) performed a retrospective chart review of 72 in-patients who received linezolid and an SSRI or venlafaxine concomitantly or within 14 days of each other. 52 (76%) patients received concomitant therapy while 20 (28%) patients received linezolid and an SSRI within 14 days. The Sternbach criteria and Boyer algorithm were used to identify clinical presentations of serotonin syndrome. Patients were considered to have a high probability of serotonin if they met >3 Sternbach clinical criteria or any of Boyer criteria with no clear alternative explanation or symptom reversal after discontinuation of serotonergic agent. Four patients met clinical criteria for serotonin syndrome. Of the four, only two patients had a high probability of serotonin syndrome with rapid reversely of symptoms upon discontinuation of serotonergic agent and other two patients with low probability continued with concomitant therapy of linezolid and an SSRI with no progression of symptoms. It was noted that the Sternbach criteria appeared to be overly sensitive in patients being treated for infection and that the Boyer algorithm may be more specific for the diagnosis of serotonin syndrome. The total incidence of high-probability serotonin syndrome was 2.8% with resolution within 24-48 hours upon discontinuation. The authors concluded that linezolid can be used concomitantly with SSRIs without a 14-day washout period with careful monitoring for signs and symptoms of serotonin syndrome.[19]

Linezolid and Serotonin Syndrome SBAR

Lawrence et al. (2006) evaluated linezolid-associated reports of serotonin syndrome from post-marketing voluntary adverse events from the Food and Drug Administration between November 1, 1997 through September 25, 2003. The most common drug classes received concomitantly with linezolid were SSRIs (61%), TCAs (14%), and atypical antidepressants (9%). A total of 29 cases were classified as serotonin toxicity due to linezolid use. Twenty-six out of 29 were described as serotonin toxicity by the reporter, but only 3 cases met Hunter Criteria. Notably, Sternbach criteria was not utilized in this study. Overall, incidences of serotonin toxicity could not be determined based on the study design.[22]

Linezolid and Opioids

Huang et al. (2024) performed a single-center, retrospective review of 194 unique encounters to evaluate the risk of serotonin syndrome associated with linezolid used concomitantly with methadone, buprenorphine, and/or dextroamphetamine. The Hunter Criteria was used to assess for possible and confirmed serotonin syndrome. One encounter met criteria for confirmed serotonin syndrome and two other encounters met criteria for possible serotonin syndrome. The confirmed serotonin syndrome patient received linezolid while on methadone and developed clonus of right leg after 72 hours of concomitant therapy. The symptoms resolved once linezolid was discontinued and was considered definitive serotonin syndrome. The first possible case was a patient who received linezolid while on buprenorphine, bupropion, and positive for amphetamines. It was unclear if the patient's clinical presentation was due to illicit substance use or serotonin syndrome. The second possible case involved a patient on linezolid and methadone concerning for seizure activity. Consulting neurology and infectious disease had low concerns for serotonin syndrome, but discontinued linezolid out of caution. The author concludes that linezolid may be given safely with methadone, buprenorphine, and/or dextroamphetamine.[8]

Traver et al. (2022) performed a retrospective cross-sectional analysis of 494 unique encounters who were administered linezolid and methadone and/or buprenorphine and risk of serotonin toxicity. A subgroup of 106 encounters was analyzed for prolonged overlap ($\geq$ 3 days). Diagnosis of serotonin toxicity was divided into possible and definite based on confirmation by the clinical team and the Hunter Criteria was applied to both. There were no definite cases of serotonin toxicity identified among the 494 encounters, but there were two possible cases of serotonin toxicity among the subgroup of prolonged co-administration. The first possible case had a 48.5-day overlap and the second possible case had an 8-day overlap. OF note, in both possible cases, the patients were being administered 3 other serotonergic agents as well and neither case met Hunter Criteria. The author concluded that possible serotonin toxicity only occurred in patients administered linezolid and methadone for more than 8 days and in setting of multiple serotonergic agents.[20]

Mitwally et al. (2022) performed a retrospective observational study of 106 patients who received linezolid and a concomitant opioid agent. Morphine and fentanyl were the most prescribed opioid and serotonin syndrome was defined accordingly to Hunter Criteria. Among the study patients, only one patient met Hunter Criteria while on linezolid and fentanyl. However, the patient's spontaneous myoclonus appeared post cardiac arrest which made the serotonin toxicity associated between linezolid and opioid interaction unlikely. The author concluded that the incidence of serotonin syndrome among patients who received concomitant opioids and linezolid was very low and use was likely safe.[23]

Linezolid and other Serotonergic Agents

Orlova et al. (2017) performed a retrospective chart review of 19,017 patients who were prescribed triptans and SSRI or SNRI. 17 cases had confirmed suspicion of serotonin syndrome. Out of 17 cases, only two met the criteria for serotonin syndrome, however, some symptoms began before triptans were ingested. Of note, most of the 17 cases identified were also taking numerous other medications concurrently. There were no cases of life-threatening serotonin syndrome identified or where triptans were unequivocally the main cause. The authors concluded that patients taking concomitant triptans and SSRI or SNRI do not need to forgo treatment of one condition to treat the other.[13]

Pettit et al. (2016) evaluated a case report of an 89-year-old female patient taking linezolid for treatment of a VRE bacteremia and carbidopa-levodopa for Parkinson's Disease. The patient had a past medical history of COPD, sick sinus syndrome, atrial fibrillation on rivaroxaban, hypertension, CVA 5 months prior, and ischemic colitis. She presented to the emergency department after experiencing seizure-like activity and was noted to have been taking linezolid for 8 days. Two days following the initial seizure symptoms, the patient exhibited clonus on physical examination. Patient had met both Hunter and Sternberg Criteria. The patient's symptoms persisted until 48 hours following discontinuation of linezolid. Neurology was consulted and determined CVA was unlikely and work up of other causes were unyielding. Based on clinical presentation, onset of symptoms, resolution of symptoms following

discontinuation of linezolid, and no other known etiology; it was determined that the patient experienced serotonin syndrome from the concomitant use of linezolid and carbidopa-levodopa. Some limitations of this case report are that the patient originally presented with symptoms in the outpatient setting and it is uncertain if carbidopa-levodopa was a precipitating factor.[21]

References:

1. SanFilippo S, Turgeon J, Michaud V, Nahass RG, Brunetti L. The Association of Serotonin Toxicity with Combination Linezolid-Serotonergic Agent Therapy: A Systematic Review and Meta-Analysis. Pharmacy (Basel). 2023 Nov 20;11(6):182. doi: 10.3390/pharmacy11060182. PMID: 37987392; PMCID: PMC10661260.
2. Zyvox (linezolid) [prescribing information]. New York, NY: Pharmacia and Upjohn; June 2024.
3. Center for Drug Evaluation and Research. "CNS Reactions Possible When Linezolid given to Patients Taking Psyc..." U.S. Food and Drug Administration, FDA, www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-serious-cns-reactions-possible-when-linezolid-zyvox-given-patients#ref. Accessed 18 Oct. 2024.
4. Bai AD, McKenna S, Wise H, Loeb M, Gill SS. Association of Linezolid With Risk of Serotonin Syndrome in Patients Receiving Antidepressants. JAMA Netw Open. 2022;5(12):e2247426. doi:10.1001/jamanetworkopen.2022.47426
5. Foong AL, Grindrod KA, Patel T, Kellar J. Demystifying serotonin syndrome (or serotonin toxicity). Can Fam Physician. 2018 Oct;64(10):720-727. PMID: 30315014; PMCID: PMC6184959.
6. Chiew A, Buckley, N. The serotonin toxidrome: shortfalls of current diagnostic criteria for related syndromes. Clin Toxicol (Phila). 2022;60(2):143-158.
7. Gatti M Raschi E, DePonti F et al. Serotonin syndrome by drug interactions with linezolid: clues from pharmacovigilance-pharmacokinetic/pharmacodynamic analysis. Eur J Clin Pharmacol. 2021. PMID: 32901348
8. Huang J, Edrees H, Lee G. A Case Series on Serotonin Syndrome from Concomitant use of linezolid With Methadone, Buprenorphine, and/or Dextroamphetamine. Journal of Pharmacy Practice. 2024;37(3):780-785. doi:10.1177/08971900231182772
9. Miyamatsu Y, Tanizaki R. Serotonin Syndrome Triggered by Increasing the Dose of Quetiapine. Clin Pract Cases Emerg Med. 2021 Aug;5(3):365-366. doi: 10.5811/cpcem.2021.5.52505. PMID: 34437050; PMCID: PMC8373192.
10. Kushwaha S, Panda AK, Malhotra HS, Kaur M. Serotonin syndrome following levodopa treatment in diffuse Lewy body disease. BMJ Case Rep. 2014 Sep 22;2014:bcr2013201375. doi: 10.1136/bcr-2013-201375. PMID: 25246451; PMCID: PMC4173194.
11. Nemet M, Andrijević A, Nedeljkov Đ, Andrić V, Gavrilović S. A Case Report on Serotonin Syndrome in a Patient With Parkinson's Disease: Diagnostic and Management Challenges. Cureus. 2023 Mar 28;15(3):e36780. doi: 10.7759/cureus.36780. PMID: 37123809; PMCID: PMC10145624.
12. Rojas-Fernandez CH. Can 5-HT3 Antagonists Really Contribute to Serotonin Toxicity? A Call for Clarity and Pharmacological Law and Order. Drugs Real World Outcomes. 2014 Dec;1(1):3-5. doi: 10.1007/s40801-014-0004-3. PMID: 27747475; PMCID: PMC4883185.
13. Orlova Y, Rizzoli P, Loder E. Association of Coprescription of Triptan Antimigraine Drugs and Selective Serotonin Reuptake Inhibitor or Selective Norepinephrine Reuptake Inhibitor Antidepressants With Serotonin Syndrome. JAMA Neurol. 2018 May 1;75(5):566-572. doi: 10.1001/jamaneurol.2017.5144. PMID: 29482205; PMCID: PMC5885255.
14. Gabriel M, Sharma V. Antidepressant discontinuation syndrome. CMAJ. 2017 May 29;189(21):E747. doi: 10.1503/cmaj.160991. PMID: 28554948; PMCID: PMC5449237.
15. Butterfield J, Lawrence K, Reisman A, et al. Comparison of serotonin toxicity with concomitant use of either linezolid or comparators and serotonergic agents: an analysis of Phase III and IV randomized clinical trial data. J Antimicrob Chemother. 2012;67(2):494-502.
16. Lodise TP, Patel N, Tristani L et al. Comparative evaluation of serotonin toxicity among veterans affairs patients receiving linezolid and vancomycin. Antimicrob Agents Chemother. 2013 ;57(12):5901-11.
17. Boyer EW. Shannon M. The Serotonin Syndrome. N Engl J Med. 2005; 17;352(11):1112-20.
18. McCreary EK, Johnson MD, Jones TM, et al. Antibiotic Myths for the Infectious Diseases Clinician. Clin Infect Dis. 2023;77:1120-1125.
19. Taylor JJ, Wilson JW, Estes LL. Linezolid and serotonergic drug interactions: a retrospective survey. *Clin Infect Dis*. 2006;43(2):180-187.
20. Traver EC, Heil EL, Schmalzle SA. A Cross-sectional Analysis of Linezolid in Combination with Methadone or Buprenorphine as a Cause of Serotonin Toxicity. *Open Forum Infect Dis*. 2022;9(7):ofac331. Published 2022 Jul 1. doi:10.1093/ofid/ofac331
21. Pettit NN, Alonso V, Wojcik E, Anyanwu EC, Ebara L, Benoit JL. Possible serotonin syndrome with carbidopa-levodopa and linezolid. *J Clin Pharm Ther*. 2016;41(1):101-103. doi:10.1111/jcpt.12352
22. Lawrence KR, Adra M, Gillman PK. Serotonin toxicity associated with the use of linezolid: a review of postmarketing data. *Clin Infect Dis*. 2006;42(11):1578-1583. doi:10.1086/503839
23. Mitwally H, Saad MO, Alkhiyami D, Fahmi AM, Mahmoud S, Hmoud EA, Enany RE, Younis H, Mohammed S, Rouf PA, Thomas B, Hail MA. Risk of serotonin syndrome in acutely ill patients receiving linezolid and opioids concomitantly: a retrospective cohort study. IJID Reg. 2022 Sep 24;5:137-140. doi: 10.1016/j.ijregi.2022.09.008. PMID: 36324824; PMCID: PMC9618969.
24. Kufel WD, Parsels KA, Blaine BE, Steele JM, Seabury RW, Asiago-Reddy EA. Real-world evaluation of linezolid-associated serotonin toxicity with and without concurrent serotonergic agents. *Int J Antimicrob Agents*. 2023;62(1):106843. doi:10.1016/j.ijantimicag.2023.106843
25. University of Michigan Serotonin Syndrome and Linezolid Serotonin Syndrome with Linezolid, Accessed 11.26.24