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## In the Literature

### Can Linezolid be Safely Used in Patients Receiving Serotonergic Drugs?

Butterfield JM, Lawrence KR, 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; 67:494–502.

Linezolid is a nonselective weak reversible inhibitor of monoamine oxidase (MAO) with greater affinity for MAO-B ( $K_i$  0.71  $\mu$ M) than for MAO-A ( $K_i$  56  $\mu$ M). The former is mostly responsible for oxidation of benzylamine, dopamine, and  $\beta$ -phenylethylamine, whereas the latter primarily oxidizes epinephrine, norepinephrine, and serotonin. Tyramine is metabolized by both. As a consequence of its inhibitory activity, linezolid has the potential for causing serotonin toxicity in patients also receiving potentially interacting drugs.

Lawrence et al reviewed spontaneous reports to the US Food and Drug Administration (FDA) from 1997 through 2003 of serotonin toxicity in linezolid recipients [1]. They identified 29 cases that met their case definition, the majority of which were being treated with serotonin reuptake inhibitors (SSRIs). Only 3 of these, however, met a standardized set of criteria (modified Hunter Serotonin Toxicity Criteria). Most other reports of serotonin toxicity in patients receiving linezolid consist only of case reports or small case series that allow neither a determination of the incidence of this complication, nor comparison to a control group.

Butterfield et al have attempted to address this deficiency by examining the locked databases of 20 phase III and IV comparator-controlled clinical trials evaluating the relative efficacy of linezolid in the treatment of a variety of infections. The comparators were all  $\beta$ -lactam or glycopeptide antibiotics. Of the 10 484 patients enrolled in these trials, 4265 (40.7%) were receiving at least 1 serotonergic drug and are the subject of the analysis.

There were no investigator-initiated reports of serotonin toxicity. The presence of serotonin toxicity was also determined by the investigators in a treatment-blinded review, using standardized criteria (Sternbach Criteria and the Hunter Serotonin Toxicity Criteria). Of the 2208 patients receiving linezolid who also received at least 1 serotonergic medication, 9 (0.41%) met the Sternbach criteria, and among comparator recipients, 3 (0.15%) of the 2057 met them (risk ratio, 2.79; 95% confidence interval: .76–10.31). Among patients also receiving serotonergic agents, the Hunter Serotonin Toxicity Criteria were met by 3 (0.14%) linezolid recipients and 1 (0.05%) of recipient of a comparator (risk ratio, 2.79; 95% confidence interval, .29–26.85). No patient met both sets of criteria.

Thus, the incidence of apparent serotonin toxicity among patients also receiving serotonergic agents, although numerically greater, did not significantly differ between patients receiving linezolid and those receiving a comparator antibiotic. Nonetheless, some degree of risk does exist and must be considered by the clinician. The FDA has, over the years, published cautions such as: "Unless patients are carefully observed for signs and/or symptoms of serotonin syndrome, ZYVOX should not be administered to patients with carcinoid syndrome and/or patients taking any of

the following medications: SSRIs, tricyclic antidepressants, serotonin 5-HT<sub>1</sub> receptor agonists (triptans), meperidine, and buspirone" [2]. Although the FDA warns that linezolid should generally not be given to patients taking serotonergic drugs, it states the following: "However, there are some conditions that may be life-threatening or require urgent treatment with linezolid such as when:

- Linezolid is used to treat vancomycin-resistant *Enterococcus faecium* (VRE) infections.
- Linezolid is used to treat infections such as nosocomial pneumonia and complicated skin and skin structure infections, including cases caused by methicillin-resistant *Staphylococcus aureus* (MRSA)."

Another consideration for the clinician is that serotonergic medications possess highly variable risk, something that cannot be teased out from the article reviewed here. The variability is acknowledged by the FDA in its recent warnings in which they have attempted stratification, with the drugs in the following table having the greatest risk [3]:

Serotonergic psychiatric drugs implicated in the adverse event reporting system cases of serotonin syndrome with linezolid

### 1. Selective Serotonin Reuptake Inhibitors

Generic Name	Found in Brand Names
Paroxetine	Paxil, Paxil CR
Fluvoxamine	Luvox, Luvox CR
Fluoxetine	Prozac, Symbyax
Sertraline	Zoloft
Citalopram	Celexa
Escitalopram	Lexapro
vilazodone*	Viibryd

\*Although the US Food and Drug Administration has not received cases of serotonin syndrome to date involving vilazodone, the pharmacology of this drug places it in the selective serotonin reuptake inhibitor (SSRI) category and suggests that it possesses a risk comparable to that of the SSRIs.

### 2. Serotonin Norepinephrine Reuptake Inhibitors

Generic Name	Found in Brand Names
Venlafaxine	Effexor, Effexor XR
Desvenlafaxine	Pristiq
Duloxetine	Cymbalta

It should be further noted that discontinuing these agents at the time of initiating linezolid therapy does not solve the problem, at least with regard to SSRIs. Rapid discontinuation of an SSRI may lead to severe withdrawal symptoms. In addition, members of this class of drugs have prolonged elimination half-lives and complete elimination may take weeks.

Thus, the use of linezolid with serotonergic agents comes down to a confluence of the available data and expert clinical judgment. The clinician must balance the limited, but existent, risk with the potential benefits of treatment with linezolid relative to treatment with alternative antibiotics.

### References

1. Lawrence KR, Adra M, Gillman PK. Serotonin toxicity associated with the use of linezolid: a review of postmarketing data. *Clin Infect Dis* 2006; 42:1578–83.
2. FDA. Zyxol (linezolid): drug safety communication - serious CNS reactions possible when given to patients taking certain psychiatric medications. Available at: [http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm265479.htm?utm\\_campaign=Google2&utm\\_source=fdaSearch&utm\\_medium=website&utm\\_term=linezolid&utm\\_content=2](http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm265479.htm?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=linezolid&utm_content=2). Accessed 30 May 2012.
3. FDA. Drug safety communication: updated information about the drug interaction between linezolid (Zyxol) and serotonergic psychiatric medications. Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm276251.htm>. Accessed 30 May 2012.