Linezolid: general information

World Health Organization
REGIONAL OFFICE FOR Europe

Elmira Gurbanova, MD, PhD, mSTR VMC Coordinator

- Joint TB, HIV and Viral Hepatitis Programme, Division of Country Health Programmes

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LINEZOLID

- Bactericidal activity against MTB
- Inhibits bacterial protein synthesis through binding to rRNA.
- It also binds to human mitochondria and inhibits protein synthesis, which is the mechanism of toxicity in clinical use.
- Introduced in 1996.
- Approved by the US Food and Drug Administration in 2000.
- Recommended by WHO for TB treatment in 2006

Hashemian SMR, et al. 2018.

EFFECTIVENESS FOR M/XDR-TB

- Patients who received linezolid-containing regimens were more likely to achieve treatment success (aOR, 3.4; 95% CI, 2.6–4.5) and to have a lower rate of death (aOR, 0.3; 95% CI, 0.2–0.3) than those who did not receive linezolid.
- The combination of bedaquiline and linezolid was associated with an aOR of 2.7 (95% CI, 1.5–4.9) for success versus failure/relapse, and of 0.3 (95% CI, 0.2–0.4) for death versus success/failure/relapse.

ATS/CDC/ERS/IDSA [Nahid 2019]

ADVERSE EFFECTS WHEN USED FOR INDICATIONS OTHER THAN M/XDR-TB (FDA-APPROVED FOR<=28 DAYS)

- >10%:
  - Diarrhea (8% to 11%)
  - Decreased white blood cells (≤2%), decreased platelet count (≤10%)
- 1% to 10%:
  - Headache (6% to 9%), dizziness (2% to 3%), vertigo (1%)
  - Skin rash (1%-2%), pruritus (≤1%)
  - Increased amylase (≤2%), increased lactate dehydrogenase (≤2%)
  - Vomiting (3% - 9%), nausea (2% - 7%), increased serum lipase (<1%), abdominal pain (≤2%), oral candidiasis (≤2%)
  - Vulvovaginal candidiasis (adults: 1% to 2%)
  - Anemia (≤2%), decreased neutrophils (≤1%), eosinophilia (≤2%)
  - Increased serum ALT (2% -10%), increased serum bilirubin (<1%), increased serum AST (2% -5%), increased serum alkaline phosphatase (≤4%)
  - Fungal infection (≤2%)
  - Increased blood urea nitrogen (≤2%), increased serum creatinine (≤2%)

UpToDate.2020. Linezolid: Drug information

ADVERSE EFFECTS WHEN USED FOR M/XDR-TB

- Rates are significantly higher than those observed in patients receiving linezolid for other indications! 58.9% experienced adverse events attributed to linezolid
- Of those, 68.4% required linezolid treatment interruption or dosage reduction.
- The main adverse events were:
  - Anaemia (38.1%)
  - Peripheral neuropathy (47.1%)
  - Gastro–intestinal disorders (16.7%)
  - Optic neuritis (13.2%)
  - Thrombocytopenia (11.8%).

Sotgiu G. et al, 2012

- Hematological toxicity can occur quickly after starting treatment and can involve any cell line.
- Neurotoxicity, including optic neuritis and peripheral neuropathy, occur later, usually after 12 to 20 weeks of treatment.

ATS/CDC/ERS/IDSA [Nahid 2019]

EXPERIENCE OF GEORGIA

- Exclusion criteria: baseline Hb 9.0 g/dl, platelets , 100x109/L, WBC 4.0 x109/L, absolute neutrophil count 1.5x109/L, baseline moderate-to-severe peripheral/optic neuropathy, concomitant medications with myelosuppression effect, MAO (monoamine oxidase) inhibitors, and serotonergic antidepressants.
- WHO-recommended aDSM applied.
- Pyridoxine 50 mg/day, higher dosing determined by CS (50 mg pyridoxine for every 250 mg of CS).
- Total -100 patients, the median duration of LZD use - 503 days.
- 95% achieved culture conversion and 79% patients had a successful treatment outcomes.
- LZD-associated adverse events occurred in 12 (12%) patients (cytopenia – 4%, peripheral neuropathy - 8%), leading to:
  - discontinuation in 4 (2 each due to peripheral neuropathy and cytopenias), and
  - dose reduction to 300 mg/day in 6 cases (4 due to peripheral neuropathy and 2 for cytopenias).

Mikiashvili L, et al. 2020

SEROTONIN SYNDROME

- Potentially life-threatening condition associated with increased serotonergic activity in the CNS.
- Incidence: 1,1% on combination therapy (linezolid + SSRIs), 0.4% on monotherapy. *(Karkow D, et al.2017)*
- Symptoms: agitation, confusion, hallucinations, hyper-reflexia, myoclonus, shivering, and tachycardia.
- Serotonin syndrome can occur with therapeutic medication use, overdose, or as the result of additive or synergistic effects due to drug interaction(s) or carcinoid syndrome.
- Diet high in tyramine-containing foods (such as cheese, red wine, cured meats, soy sauce, and fermented foods).

UpToDate.2020. Serotonin syndrome (Serotonin toxicity)

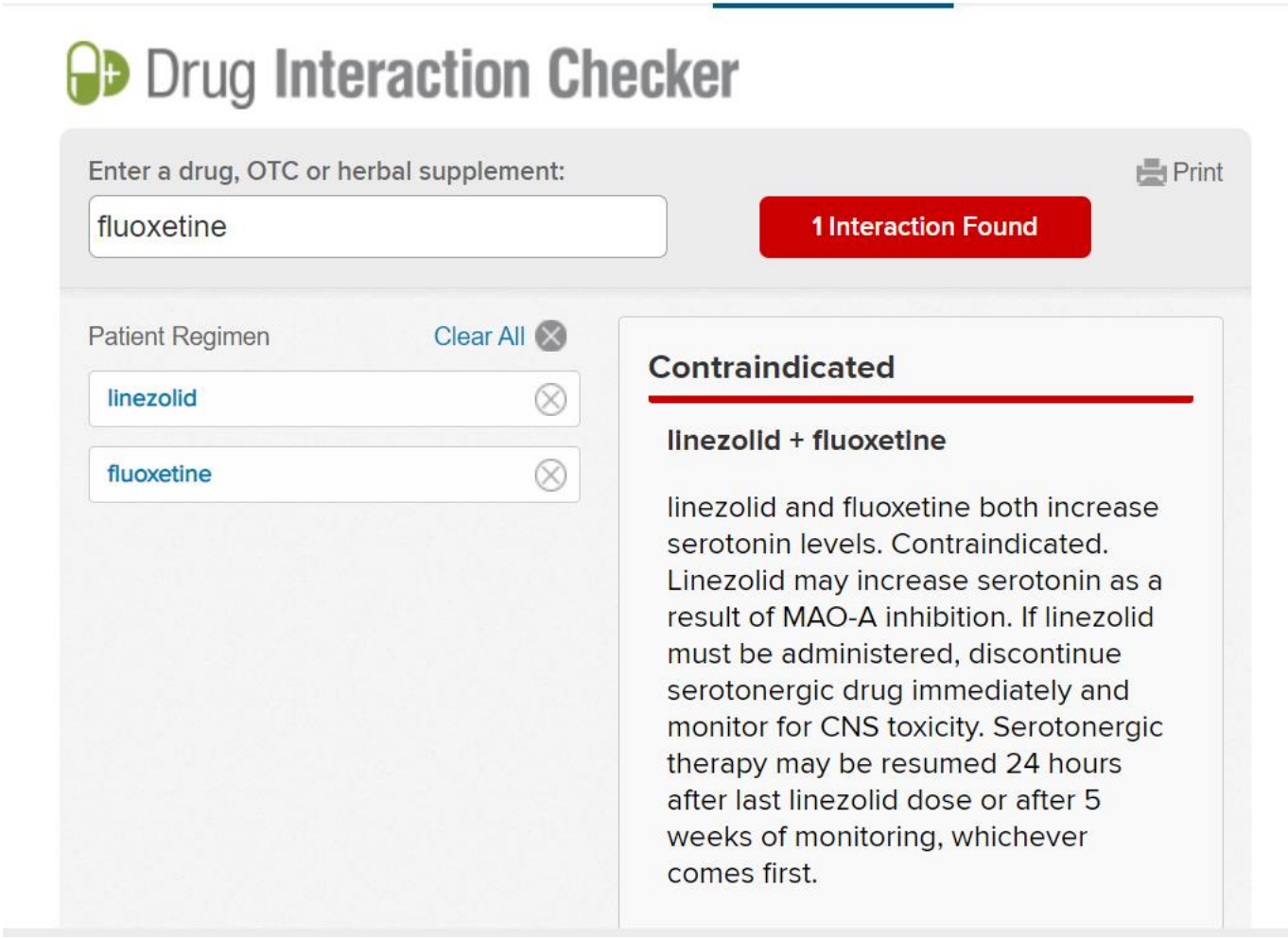
Examples of agents that can precipitate serotonin syndrome

Mechanism	Agent involved
Increases serotonin formation	Tryptophan, oxitriptan*
Increases release of serotonin	Amphetamines (including dextroamphetamine, methamphetamine)
	MDMA (ecstasy)
	Amphetamine derivatives (including fenfluramine, dexfenfluramine, phentermine)
	Cocaine
	Mirtazapine
Impairs serotonin reuptake from the synaptic cleft into the presynaptic neuron	Cocaine
	MDMA (ecstasy)
	Meperidine
	Tramadol
	Pentazocine
	Dextromethorphan
	Selective serotonin reuptake inhibitors (SSRIs; citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline)
	Serotonin-norepinephrine reuptake inhibitors (SNRIs; desvenlafaxine, duloxetine, levomilnacipran, milnacipran, and venlafaxine)
	Sibutramine
	Bupropion¶
	Serotonin modulators (nefazodone, trazodone, vilazodone, and vortioxetine)
	Cyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline, trimipramine)
	St. John's wort (*Hypericum perforatum*)
	5-HT3 receptor antagonists (dolasetron, granisetron, ondansetron, palonosetron)
	Cyclobenzaprine
	Methylphenidate, dexmethylphenidate

Selective serotonin reuptake inhibitors and tricyclic antidepressants should be

Inhibits serotonin metabolism by inhibition of monoamine oxidase (MAO)	MAO inhibitors, nonselective (isocarboxazid, linezolid, phenelzine, Syrian rue [*Peganum harmala*, harmine], and tranylcypromine)
	MAO-A inhibitors[Δ] (methylene blue, moclobemide)
	MAO-B inhibitors[Δ] (rasagiline, safinamide, and selegiline)
Direct serotonin receptor agonist	Buspirone
	Triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan)
	Ergot derivatives (including dihydroergotamine, ergotamine, methylergonovine)
	Fentanyl
	Lysergic acid diethylamide (LSD)
	Lasmiditan
	Lorcaserin[◇]
	Metaxalone
Increases sensitivity of postsynaptic serotonin receptor	Lithium

Data courtesy of authors with additional data from: Boyer EW, Shannon M. The serotonin syndrome. NEJM 2005; 352:1112; Finberg JPM and Rabey JM. Inhibitors of MAO-A and MAO-B in psychiatry and neurology. Front. Pharmacol. 2016; 7:340; and Lexicomp Online. Copyright © 1978-2020 Lexicomp, Inc.



https://reference.medscape.com/drug-interactionchecker

PHARMACOKINETICS

- Linezolid is very well absorbed orally with a bioavailability of 100%.
- The presence of food does not affect its absorption.
- Co-administration with antacids like magnesium hydroxide and aluminum hydroxide had no effect on the oral absorption.
- Plasma concentrations of linezolid in elderly patients, and patients with mild-to-moderate hepatic damage or mild-to-chronic renal failure were similar to those obtained in healthy or young volunteers.
- Plasma half-life ranges from 3.4 to 7.4 h.

ADMINISTRATION AND DOSE REDUCTION

- Oral 600 mg once daily as part of an appropriate combination regimen including pyridoxine. *(WHO 2019; ATS/CDC/ERS/IDSA [Nahid 2019]; Ahmad 2018)*
- There are insufficient data regarding the effectiveness of initiating treatment with doses <600 mg daily to recommend lower doses.
- Lowering the dose from daily 600 mg to 300 mg after culture conversion reduced toxicity. (*Lee M, et al. 2012*)
- Vitamin B6 given at 50 mg/day may have an impact on anaemia but did not prevent linezolid-induced thrombocytopenia or leucopenia. (Y*oussef S, et al. 2008)*
- Some reports on Vitamin B6 decreasing peripheral neuropathy.

USE IN RENAL AND HEPATIC IMPAIRMENT

- Mild to severe impairment: No dosage adjustment necessary. The two primary metabolites accumulate in patients with renal impairment, but the clinical significance is unknown; use with caution. (Cattaneo 2016; Gervasoni 2015; Pea 2017).
- Dialyzable (~30% removed during 3-hour dialysis session): No dosage adjustment necessary; administer after hemodialysis on dialysis days.
- Mild to moderate hepatic impairment (Child-Pugh class A or B): No dosage adjustment necessary.

Thank you!

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Marmorvej 51
Copenhagen Ø
Denmark

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