Cardiorespiratory Effects of Coadministration of *Oral* Olanzapine and Lorazepam

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Background

- **Agitation** poses a significant safety risk to both patients and healthcare providers.
- **Olanzapine and lorazepam coadministration** is one of the strategies used to manage agitation in patients with known psychiatric disorder.
- In **2005**, after reports of **29 fatalities** associated with (IM) olanzapine in combination with benzodiazepines, the **FDA issued a warning** against this practice.
- **Several studies** conducted after this warning have provided **conflicting results– failing to establish** a **causal relationship** between the coadministration of olanzapine and benzodiazepines and serious adverse effects.
- In **2023,** The **American Association for Emergency Psychiatry (AAEP)** updated its recommendations for the **assessment and management of agitation**, which included the **coadministration of oral olanzapine and lorazepam**, as outlined in the table below**:**

For primary psychiatric agitation or undifferentiated agitation with prominent psychosis	
Medication and dose	**olanzapine**, 5 mg-10 mg (**PO**, ODT or IM); risperidone, 2 mg (PO, ODT or liquid); ziprasidone, 10 mg-20 mg (IM); haloperidol, 2 mg-10 mg (PO or IM); droperidol, 5 mg-10 mg (IM)
Comments	Add **lorazepam** 1 mg–2 mg **if** haloperidol or **monotherapy ineffective**; risk of **respiratory depression** for IM olanzapine and benzodiazepine

- The **(IM) olanzapine** product insert, updated in **July 2024**, maintains the **FDA warning**: *"Concomitant administration of intramuscular olanzapine and parenteral benzodiazepine is not recommended due to the potential for excessive sedation and cardiorespiratory depression."*
- This warning **does not explicitly extend** to the oral coadministration of these medications.
- At our institution:
  - Physicians are advised against administering these medications in injectable form **within six hours** of each other.
  - **No specific guidance** exists regarding their **oral coadministration**.

Objective

This retrospective study aims to investigate the **cardiorespiratory effects** of ***oral*** **olanzapine and lorazepam coadministration**.

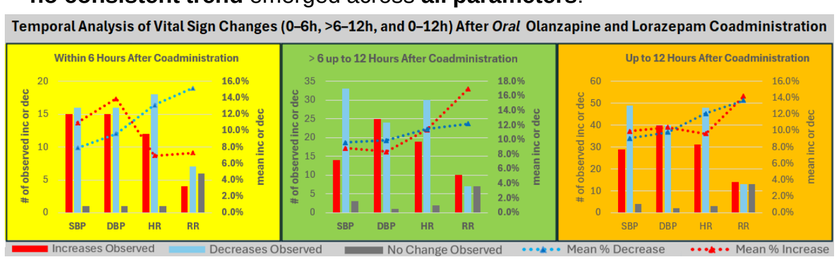
Methods:

- This study was conducted as part of a **quality improvement project** assessing whether the FDA warning on (IM) olanzapine and lorazepam should be extended to **oral coadministration**.
- Patients were identified through an **EPIC search** at our institution, covering a **one-month period** (August 1–31, 2024).
- To capture clinically relevant effects:
  - Only included patients who:
    - ✓ Received **olanzapine and lorazepam within 6 hours** of each other, as **oral olanzapine peaks at 6 hours**.
    - ✓ Had **vitals recorded within 12 hours** post-coadministration, as oral lorazepam has a 12-hour half-life.
  - Stratified **vital sign measurements** into two timeframes:
    - ✓ **0–6 hours:** Aligning with peak plasma concentrations of oral olanzapine (~6 hours).
    - ✓ **6–12 hours:** Capturing potential prolonged effects.
    - ✓ **0–12 hours:** Providing an overall assessment of vital sign trends across the entire study period.
- **Baseline vitals** were defined as the measurement taken before and closest to the administration of the **second medication**.
- **Directional changes** (increase or decrease) in heart rate (HR), respiratory rate (RR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were **evaluated**.
- A total of **82 instances** of oral coadministration within a **6-hour timeframe,** with vitals recorded over the following 12 hours, were analyzed across **27 patients** (15 males, 12 females), aged **19–85 years** (μ = 45.6, SD = 20.5).
- **Demographics:** Caucasian: 70.4%, African American: 25.9%, Hispanic: 3.7%.

Results:

Our findings showed mixed results:

- While **decreases** in vitals were **more frequent** than increases overall **(n=228** vs. **302)**, the **degree of change** was **variable**, and **no consistent trend** emerged across **all parameters**:



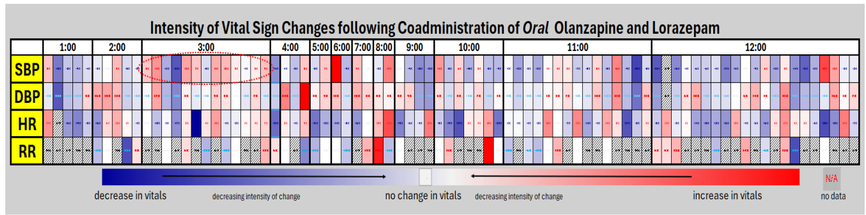
Results

- **Statistically significant decreases** in **HR** (p=0.03) and **RR** (p=0.04) were noted within **6 hours** post-coadministration, with **no significant changes** observed after 6 hours:

Observed Changes in Vitals from the *Oral* Coadministration of Olanzapine and Lorazepam

	Within 6 hours				> 6 up to 12 hours				Up to 12 hours after coadministration			
Parameter	**SBP**	**DBP**	**HR**	**RR**	**SBP**	**DBP**	**HR**	**RR**	**SBP**	**DBP**	**HR**	**RR**
Increases Observed	15	15	12	4	14	25	19	10	29	40	31	14
Decreases observed	**16**	**16**	**18**	**7**	33	24	30	**7**	49	40	48	**14**
No change observed	1	1	1	6	3	1	2	7	4	2	3	13
Mean % increase	**11%**	**14%**	7%	**7%**	9%	8%	**11%**	**17%**	**10%**	**10%**	10%	**14%**
Mean % decrease	8%	10%	**13%**	15%	**10%**	**10%**	**11%**	12%	9%	**10%**	**12%**	**14%**
***p*- value**	p = 0.12	p = 0.12	p **= 0.03**	p **= 0.04**	p = 0.35	p = 0.19	p = 0.48	p = 0.20	p = 0.28	p = 0.37	p = 0.1	p = 0.45

- In contrast to the coadministration warning, systolic blood pressure **(SBP) increases** were **more frequent** at **3 hours**, suggesting **time-dependent effect** (n=9, μ=8% vs n=4, μ=8%, ***p*<0.05**):



- Although **4 instances** of **MAP decreases** exceeded **20%** and **1 HR** fell **below 60 bpm**, **no fatalities** were observed.

Conclusion:

- **Decreases in vital signs** (**SBP, DBP, HR, RR**) were more frequent than increases across various time points. However, only **HR** and **RR** within **6 hours** showed **statistical significance**, while **all other changes were not significant.**
- While the results do not establish a direct causal relationship, the **observed reductions** in **HR** and **RR** raise considerations regarding **potential cardiorespiratory effects**.
- **Additionally, SBP increases** observed at 3 hours suggest a time-dependent effect, **contrasting with** the FDA **warning** on intramuscular coadministration. This may warrant further investigation.
- **Clinically**, despite **isolated** instances of **notable MAP and HR reductions**, **no fatalities** occurred after oral coadministration. The absence of severe adverse events suggests that while vital sign changes were observed, their clinical impact remains unclear.
- Given the retrospective nature of this study, its sample size, and the high standard deviation in age, **larger retrospective** and **prospective studies** are needed to more accurately characterize the safety profile of this combination and assess whether current institutional guidance should be expanded to oral formulations.