Taking side effects seriously – management of nausea and vomiting

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Conflict of Interest Disclosure Statement

- Neither I, nor my spouse/partner have financial or other relationships with any commercial interest organizations within the past 12 months.
- I will be discussing off-label use of olanzapine for treatment of nausea, based on data from randomized controlled trials and meta-analyses.

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Adverse drug reactions are expensive for patients and programs:

432 patients with HIV/TB in Thailand (adjusted U.S. dollars)

Severity of adverse event	Direct medical costs, mean (SD)	Direct non-medical costs, mean (SD)	Indirect costs, mean (SD)	Total
Mild	16 (45)	69 (74)	106 (250)	**$191**
Moderate	355 (855)	179 (293)	226 (334)	**$759**
Severe	1392 (3385)	684 (195)	1,396 (1,820)	**$5,555**

- Direct medical – “costs related to public health facilities and out-of-pocket payments by patients”
- Direct non-medical – “transportation, meal, accommodation, and caregiver time loss”
- Indirect – “patient time lost due to morbidity or mortality”

Rochanathimoke O, et al. ClinicoEconomics and Outcomes Research 2022:14 587–599

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Adverse drug reactions are a common cause of missed doses:

174 adult patients on RIPE in Latvia (treated from 2015-2022)

- 13.5% of all doses were missed
- 21% of the missed doses were due to ADRs
- 54 patients (31%) missed doses due to ADRs
- Hepatotoxicity caused long gaps in treatment (median 15 days)

Dixon E, et al. Br J Clin Pharmacol 2025;91:3461-70

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Adverse drug reactions: the most common cause of treatment interruption (Malaysia, 2024)

16% of patients (475/2953) interrupted TB treatment

Reason	N	%
Adverse drug reaction	**253**	**53%**
Reason not stated	**149**	**31%**
Logistics (e.g., transportation)	47	10%
Personal issues (e.g., finance)	34	7%
Traveling	26	6%
Other	69	15%

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Oh AL, et al. Top Med Int Health 2024; 24: 434-45

Treatment interruptions increased treatment changes, prolongation and loss to follow-up (Malaysia, 2024)

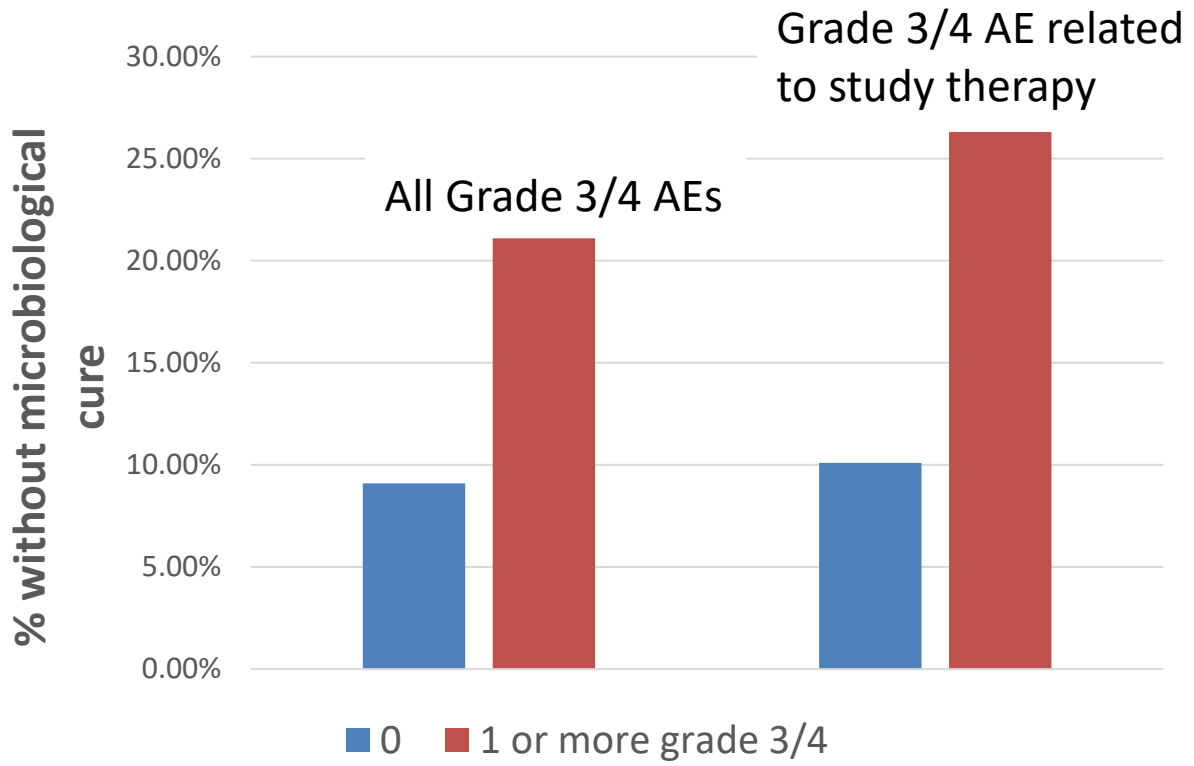
Consequence	No interruption or interruptions < 2 weeks (n = 2478)	Interruption > 2 weeks (n = 475)
Change in meds	**5%** (122)	**48%** (227)
Treatment duration, median	**194 days**	**247 days**
Loss to follow-up	**0**	**13.5%** (64)

Oh AL, et al. Top Med Int Health 2024; 24: 434-45

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Adverse drug reactions and TB treatment outcomes: ReMox clinical trial



- **Adj OR 3.1 [**1.6–6.1], p < 0.001) for failure/relapse
- Adverse events associated with **36% of all primary endpoints** in HRZE arm of the trial
- Similar results in multiple cohort studies
- **Side effects are a leading cause of poor TB treatment outcomes**

Tweed et al. BMC Infectious Diseases (2018) 18:317
https://doi.org/10.1186/s12879-018-3230-6

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Summary – impacts of adverse drug reactions during TB treatment

- ↓ quality of life for patients
- ↑ costs for patients and programs (e.g., clinic visits, lab tests)
- ↑ missed doses
- ↑ interruptions/changes in treatment, prolonged treatment
- ↑ in not completing treatment
- ↑ failure, recurrence, death during treatment
- It's not just grade 3/4 adverse events; grade 1-2 increase poor treatment outcomes

Side effects are a major barrier to TB cure – we won't improve outcomes without improving the safety and tolerability of treatment

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Cohort studies of nausea/vomiting in adults being treated for active TB

Cohort	N	% reporting N/V	Comments
Prospective, adults in China (1)	4,304	**3.7%**	55% of patients with N/V had treatment changed
Prospective, adults in Korea (2)	410	**31%**	QOL lower in those with side effects Risk factor – older age
Retrospective, adults in Korea (3)	2,478	**2.2%**	Endpoint – change in therapy Risk factors – older age
Retrospective, adults in BC (4)	1,061	**10%**	Risk factors – older age, female, use of PZA

1. Lv X, et al. PLOS One; 2013: e65037, 2. Choi J, et al. Pharmacoepidemiol Drug Saf. 2022; 31: 1153-63
3. Kwon B, et al. PLOS One; 2020: 15(7): e0236109. 4. Marra F, et al. Int J Tuberc Lung Dis 2007; 11: 863-75

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Cohort studies of nausea/vomiting in children being treated for active TB

Cohort	N	% reporting N/V	Comments
Retrospective, active TB, Pakistan (1)	508	**7%**	Risk factors – female, retreatment for TB (14% had any GI event)
Retrospective, active TB, Uzbekistan (2)	302	**28%**	Any GI adverse event
Meta-analysis, active TB (3)	5,021	**14%**	Any GI adverse event

1. Laghari M, et al. Int J Mycobacteriol 2020: 9: 281-8 2. Abdusalmova M, et al. In J Env Res Pub Health 2021; 18: 7574
3. Prodanuk M, et al. Clin Infect Dis 2025

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Recommendations for management of nausea in international and prominent national guidelines

Guidelines	Recommendations for managing treatment-related nausea/vomiting
US (IDSA/ CDC/ATS)	"The optimum approach to management of…nausea with tuberculosis drugs is not clear…may take the medications at bedtime…can be treated with antacids [preferred to taking with food]…Some experts report success with proton pump inhibitors for reducing gastrointestinal upset". (2016)
WHO	None
EU	None
MSF	**Detailed recommendations, including drug, dose, dosing in children**

No recommendations for managing nausea in current guidelines from UK, Canada, and Australia

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Burman W, et al. eClinicalMedicine 2025;82: 103148

Summary: nausea/vomiting in patients being treated for TB

- Wide range in reported frequencies
  - Differences in criteria (e.g., only those who changed therapy)
  - Prospective vs. retrospective studies
  - Few studies used Patient-Reported Outcomes
  - Age of the cohort
- Common in treatment of active TB (10-50%)
- Decreases patient QOL, leads to treatment delays, regimen changes, and worse overall treatment outcomes
- Few recommendations for management in widely-used treatment guidelines

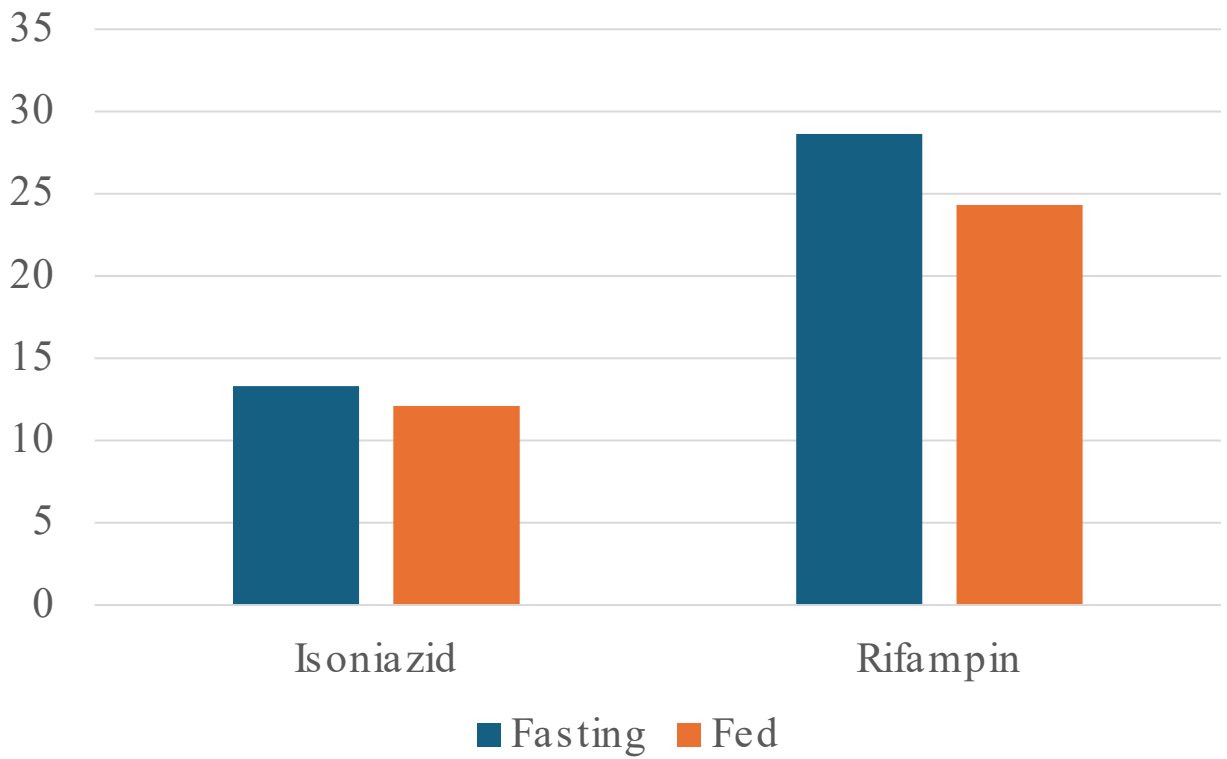
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31-year-old woman with pulmonary TB

- Started RIPE for Xpert+, RIF-susc. pulmonary TB
- Vomited after 1st dose, several episodes of post-dose nausea/vomiting during the 1st week of treatment
- Medications held, in the clinic for evaluation
- PMH – from Ethiopia, no other meds , infertility for 2 years
  - ROS – continued cough causing nausea
- BP – 114/74, P – 117, weight decreased 0.4 kg
- Abdominal exam - normal
- ALT normal

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Effect of food on total exposure (AUC) of isoniazid and rifampin



<u>Dosing with food</u>

- ↓ levels of INH and RIF, but the impact is small (10-18%)
- ↑ levels of RPT
- I recommend trying meds with food, ***for mild nausea*** (no data on effectiveness)

<u>Dosing at bedtime</u>

- No data

<u>Medications</u> – no data on:

- Antacid or PPI, ***for nausea***
- Standard anti-emetics in TB patients

Requena-Mendez A, et al. J Antimicrob Chemother 2019; 74: 416–24

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Use existing data: TB treatment regimen changes to consider in the patient with nausea/vomiting

- Discontinuation of PZA – most common cause of N/V
- Temporary discontinuation of all meds, followed by sequential re-challenge (consider graded dose escalation)
- Twice-daily dosing
  - Small study (61/arm), trend toward ↓adverse events

    Chuchottaworn C, et al. J Med Assoc Thai 2012; 95 (Suppl. 8): S1-S5
- Split dosing – 2 meds (RE) on one day, followed by the other 2 meds (IP) on alternate days
  - GI AEs: Split - **3%** (28/822) vs. daily - **7%** (29/418), p = 0.01
  - Favorable outcome at 5 years: Split – 91%, 93% vs. daily – 90%

    Santha T et al. Trop Med Int Health. 2004;9(5):551–8

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Use data from other fields of medicine: management of nausea/vomiting

- PubMed search (2/26) – treatment of nausea/vomiting
  - Randomized trials – 16,649
  - Meta-analyses – 3,390
- Major fields: cancer chemotherapy, radiation therapy, post-operative management, acute N/V
- Lessons across these fields
  - Prevention is more effective than treatment of nausea/vomiting
  - Preventing nausea improves treatment outcomes (cancer chemotherapy)
  - At least 5 drug classes are effective anti-emetics
  - Adding a new drug class more effective than higher doses of initial drug class

Summary of anti-emetic drug classes, for patients being treated for TB

Drug class (example)	Efficacy	Toler-ability	Comments on side effects	RIF effects	Cost
5 HT-3 inhibitors (odansetron)	**+++**	**+++**	**Headache, constipation, QT (high-dose IV)**	**65% ↓**	**$**
Dopamine antagonists					
Metoclopramide	++	++	Sedation, movement disorder, weight gain	50% ↓	$
Prochlorperazine	++	++	Sedation, movement disorder, weight gain	No effect	$
Olanzapine	+++	++	Sedation, movement disorder, weight gain, QT	50% ↓	$
Antihistamines (hydroxyzine)	+	+++	Sedation	No effect	$
NK-1 inhibitors (aprepitant)	++++	++++	Few side effects	> 80% ↓	$$$$
Corticosteroids	+++	++	Insomnia, many with chronic use	50% ↓	$

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Recommendations for treatment of nausea/vomiting from other fields of medicine

	Initial drug of choice	Dose of oral ondansetron
Acute nausea/vomiting (ED)	No clear winner for efficacy, ondansetron often used	4-8 mg (thrice-daily)
Cancer chemo (oral therapy)	Ondansetron *	8 mg (daily or BID) or 24 mg single dose
Radiation therapy	Ondansetron	8 mg (daily or BID)
Post-operative nausea/vomiting	No clear winner for efficacy, ondansetron often used	8-16 mg (single dose)

* Or other member of this drug class (5HT3 receptor blockers); ondansetron is cheapest

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Tolerability, safety of ondansetron

- Side effects – mild headache, constipation
- QT prolongation – high-dose IV bolus (> 16 mg, equivalent > 32 mg of an oral dose)
- When to do ECG to assess QT interval
  - Use of another drug that prolongs QT (fluoroquinolone, bedaquiline, olanzapine)
  - Known QT prolongation
  - Known hypokalemia, hypomagnesemia
  - Bradycardia, heart failure

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Practical points about using ondansetron in patients being treated for TB

- Special populations
  - Children - licensed in children of all ages
  - Pregnancy – not approved for routine use, but extensive published experience
  - Lactation – no concerns
  - Renal disease – no issues; liver disease – no data in severe liver disease
- Dosing: 4-16 mg (1-2 times per day); my usual initial dose with RIF/RPT: 8 mg once or twice-daily
- Oral dissolving tablet – useful for baseline nausea or concern about taking pills
- Use early – don't wait for anticipatory nausea to develop
- No routine EKG needed

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Managing inadequate response to ondansetron: data from other fields of medicine

- Data from cancer chemotherapy and post-operative nausea/vomiting
  - Adding new drug class is better than switching
  - Most effective 2nd drug is olanzapine

- Practicalities of giving olanzapine
  - Rifampin interaction – 50% decrease in blood levels
  - Dose – 5-10 mg daily (I favor 10 mg in patients on RIF)
  - Side effects – QT prolongation, weight gain
  - Cost – $ (generic drug)

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Managing anticipatory nausea/vomiting

- Avoid, if at all possible – early, aggressive management of nausea, consideration of prophylaxis in high-risk patients
- Consider temporary discontinuation of TB therapy, then graded dose-escalation re-challenge with prophylactic ondansetron
- Consider pre-dose benzodiazepine
- In refractory cases – gastric tube

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Summary

1. Always test for hepatotoxicity presenting with nausea
2. Define the GI syndrome – nausea/vomiting vs. reflux/ gastritis vs. other
3. Early medical treatment – avoid anticipatory nausea/vomiting
4. Don’t underdose ondansetron
5. Remember drug-drug interactions
    1. RIF/RPT ↓: omeprazole (90%), ondansetron (65%), olanzapine (48%)
    2. Antacids – ↓ FQ absorption
6. Inadequate response – re-evaluate for other cause, add new drug class (olanzapine)

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- History/exam
  - Non-prescription meds/vitamins/supplements
  - Alcohol and marijuana
  - Look for non-TB meds/products that may cause nausea/vomiting (NSAIDs, etc.)
  - Exam for jaundice, abdominal findings, neurological findings

- Labs
  - ❑ AST, ALT, bilirubin, alkaline phosphatase
  - ❑ Consider Basic Metabolic Panel + magnesium level
  - ❑ B-HCG in anyone who could become pregnant

- Consider other medical causes of nausea/vomiting
  - Adrenal insufficiency
  - IRIS (particularly in patients with HIV with recent start of antiretroviral therapy)
  - *H. pylori* related conditions (gastritis, peptic ulcer disease)

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Management of GI symptoms – initial treatment

Primary symptom is reflux or gastritis

- Famotidine (40 mg twice-daily); 0.5-1mg/kg for children 12yo and under, maximum 20-40mg); also consider recommending *H. pylori* testing in coordination with primary care provider

Primary symptoms is nausea/vomiting

- Ondansetron 8 mg once or twice-daily (if the patients is being treated with rifampin or rifapentine) for 12 years and above; 4-8 mg for children 4-11 years old.

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Management of GI symptoms – inadequate response to initial therapy

Primary symptom is reflux or gastritis

- Pantoprazole 40 mg daily. Omeprazole should not be used in a patient on rifampin or rifapentine as these agents decrease its levels by ~90%.

Primary symptom is Nausea and vomiting

- *Addition* of olanzapine 5-10 mg daily (or twice-daily) for adults and 0.1 to 0.14 mg/kg/dose once or twice daily for children.

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Should we use prophylaxis for nausea in selected patients being treated for TB?

- No data
- Clear lesson from chemotherapy, radiation therapy, post-operative care – prevention is better than treatment
- Reasonable to consider in selected cases
  - I use ondansetron (4-8 mg)

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