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Pharmacology of emerging drugs for the treatment of multi-drug resistant tuberculosis

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ABSTRACT

Mycobacterium tuberculosis (TB) remains the leading cause of infection-related mortality worldwide. Drug resistance, need for multiple antimycobacterial agents, prolonged treatment courses, and medication-related side effects are complicating factors to TB cure. The introduction of treatment regimens containing the novel agents bedaquiline, pretomanid, and linezolid, with or without moxifloxacin (BPaL-M or BPaL, respectively) have substantially reduced TB-related morbidity and mortality and are associated with favorable rates of treatment completion and cure. This review summarizes key information on the pharmacology and treatment principles for moxifloxacin, bedaquiline, delamanid, pretomanid, linezolid, and tedizolid in the treatment of multi-drug resistant TB, with recommendations provided to address and attenuate common adverse effects during treatment.

1. Introduction

Worldwide, *Mycobacterium tuberculosis* (MTB) remains one of the most prevalent infectious pathogens, with tuberculosis (TB) the 2nd leading cause of infectious mortality in 2022 behind COVID-19 [1]. Global incidence of TB, multidrug-resistant TB (MDR-TB), and TB-associated mortality have steadily increased since 2020, likely a result of the COVID-19 pandemic's effect on TB detection and treatment [2]. Most commonly a pulmonary infection, TB can also cause disseminated disease, with possibility for meningitis and multi-organ involvement, and without appropriate treatment, active TB results in substantial morbidity and mortality.

American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America (ATS/CDC/IDSA) clinical practice guidelines for non-cavitary, drug-susceptible pulmonary TB recommend a standard phased approach to therapy [3]. Therapy begins with 4 drugs (rifampin (RIF), isoniazid (INH), pyrazinamide (PZA), and ethambutol (EMB)) during the first 8 weeks of the "intensive phase" of treatment. Subsequently, dual therapy of RIF and INH comprise the "continuation phase" for an additional 18 weeks, with RIF and INH considered the "backbone" of standard TB therapy. Clinical data and the pharmacology of agents for drug susceptible TB are provided in detail in several comprehensive reviews [4–7].

Drug-resistant TB is defined by resistance to at least one first-line anti-TB drug, while MDR-TB carries resistance to both core first-line drugs, RIF and INH. Extensively drug-resistant TB (XDR-TB) is a subcategory of MDR-TB where, in addition to having resistance to RIF and INH, MTB isolates are also resistant to fluoroquinolones and at least one aminoglycoside. The World Health Organization (WHO) and ATS/CDC/European Respiratory Society (ERS)/IDSA provide drug-resistant TB therapy recommendations, with discussion on novel oral antitubercular agents: moxifloxacin (MXF), linezolid (LZD), bedaquiline (BDQ), pretomanid, and delamanid [3,8]. Several of these agents may be used in combination, with or without MXF (BPaL-M or BPaL, respectively). TB treatment with multiple novel antimicrobial agents, long durations of therapy, potential drug interactions, and adverse drug events associated with therapy necessitate an understanding of these emerging approaches to pharmacologic management of MDR-TB infection. Our review will focus on the pharmacology of these new agents, addressing pharmacokinetics, dosing considerations, metabolism, drug-drug interactions, and adverse effects of these therapies in the treatment of TB, with a brief discussion on mitigation strategies for select adverse effects. Additional emerging antimycobacterial agents can be found using the WHO's.

"TB Research Tracker" or The Working Group for New TB Drugs' "Clinical Pipeline" web page [9,10].

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2. General treatment principles

MDR-TB is a complex disease that requires an interdisciplinary team for timely diagnosis, prompt initiation of an effective treatment regimen, and assurance of ongoing adherence and tolerability to the prescribed antimicrobial program. In consultation with a TB expert, careful treatment selection should be based on a multitude of factors: susceptibility results of individual MTB isolates (when possible) or knowledge of local susceptibility patterns, availability/accessibility of TB agents, and patient-specific characteristics (e.g., drug tolerability, site of infection, comorbidities, drug-drug interactions).

MDR-TB treatment has evolved over the previous two decades [11]. Historically, the treatment landscape of MDR-TB emphasized injectable-based regimens for an extended treatment course of up to 18 months or longer. These regimens were problematic given the challenges pertaining to parenteral routes of administration, medication toxicity profiles, patient dissatisfaction, and high cost of treatment and monitoring. The continued unmet needs of MDR-TB therapy and rising incidence worldwide lent urgency to discover effective and safer therapeutic alternatives. From repurposing of antibiotics (e.g., clofazimine and linezolid) to the discovery and synthesis of novel agents (e.g., bedaquiline, delamanid, and pretomanid), MDR-TB treatment guidance gradually shifted to deemphasize injectable-based regimens with better or comparable cure rates with shorter treatment courses [12]. By 2019, the treatment landscape of MDR-TB significantly progressed to include an all-oral, extended duration (18–20 months) treatment option, in addition to the injectable-based shorter regimen for 9–12 months recommended in 2016 [3]. Preferred oral agents for MDR-TB include novel fluoroquinolones (moxifloxacin, levofloxacin), bedaquiline, oxazolidinones (linezolid, tedizolid), and clofazimine, which are preferred over second-line IV injectables (e.g., amikacin, capreomycin) due to enhanced convenience of oral administration and favorable tolerability.

Despite the treatment advantages in 2019 guidelines, continued effort to evaluate a shorter course, all-oral medication regimen was needed. Three recent landmark studies, Nix-TB, ZeNix, and TB-PRACTECAL provide the foundation for recommendations in the updated 2022 WHO consolidated guidelines for MDR-TB infection [13–15]. Based on superior treatment success rates, decreased incidence of death and lower medication adverse events compared to historical standard of care, 6–9-month treatment regimens with BPaL and BPaL-M are the most recent breakthrough in MDR-TB treatment.

While BPaL and BPaL-M offer notable advancements in MDR-TB treatment, challenges remain with evolving drug resistance and medication toxicities associated with complex and relatively long durations of these regimens. Understanding of the pharmacology of emerging drugs for the treatment of MDR-TB, commonly encountered adverse events, and suggested management strategies are imperative to successful use and completion of therapy. These concepts are reviewed herein, with subsequent sections discussing specific emerging antitubercular therapy and summative categorical tables provided for reader reference. Given their unique development for MDR-TB treatment, we comment on development histories for bedaquiline and the nitroimidazole agents. Table 1 highlights dosing, mechanism of action, and common drug interactions for our covered medications, with Tables 2 and 3 outlining common adverse events and select mitigation strategies, respectively. Recommended monitoring parameters for these therapies are provided in Table 4.

Table 1
Antitubercular medication characteristics: usual dose, antimicrobial mechanism of action, expected drug-drug interactions.

Medication	Dose	Mechanism of Action	Drug Interactions affecting antimicrobial	Drug Interactions affecting other drugs
Bedaquiline	Oral: 400 mg once daily x 14 days, then 200 mg three times weekly[i]	Inhibition of proton transfer chain of mycobacterial ATP synthase	• CYP3A4 inhibitors will increase bedaquiline exposure • CYP3A4 inducers will decrease bedaquiline exposure	• Additive potential for QT prolongation with other agents that lengthen QT interval
Moxifloxacin	IV or Oral: 400 mg once daily	Inhibition of bacterial topoisomerase II and IV	• Polyvalent cations impair absorption during oral coadministration • Rifampin may decrease moxifloxacin exposure	• Additive potential for QT prolongation with other agents that lengthen QT interval • Increased risk of tendinopathy/rupture with systemic corticosteroids
Nitroimidazoles				
Delamanid	Oral: 100 mg twice dailyc	Aerobic: Activated by MTB with subsequent inhibition of mycolic acid cell wall biosynthesis Anaerobic: nitroreductase chemical reduction leads to damaging reactive nitrogen intermediates within bacilli	• Delamanid exposure was decreased with rifampin[ii] • ≥ Moderate CYP3A4 inducers will decrease pretomanid exposure	• No significant CYP induction/inhibition/ transporter interactions anticipated • Pretomanid inhibits OAT3 which may increase serum exposure of OAT3 substrates (i.e. methotrexate)
Pretomanid	Oral: 200 mg once daily[iii]			
Oxazolidinones				
Linezolid	IV or Oral: 600 mg once daily	Inhibition of bacterial protein synthesis by binding to bacterial 23 s ribosomal RNA and preventing formation of 70 s complex, disrupting translation	• PgP inducers (i.e. rifampin) can decrease linezolid exposure • PgP inhibitors (i.e. amiodarone, clarithromycin) can increase linezolid exposure	• Inhibition of MAO-A and MAO-B may increase risk of serotonin syndrome with concomitant use of serotonergic drugs (SSRIs, SNRIs, TCAs, MAOIs, serotonergic opioids) and may amplify adrenergic effects of sympathomimetics • Linezolid can increase INR when added to stable warfarin regimen
Tedizolid	IV or Oral: 200 mg once daily	Inhibition of bacterial protein synthesis by binding to 50 s subunit of bacterial ribosome	• No significant interactions anticipated	• Tedizolid inhibits BCRP and can increase exposure of BCRP substrates

ATP=adenosine triphosphate; BCRP=breast cancer resistance protein drug transporter; CYP=cytochrome p450; IV=intravenous; MAO-A=monoamine oxidase A; MAO-B monoamine oxidase B; MAOI=monoamine oxidase inhibitor; MTB=*Mycobacterium tuberculosis*; OAT3 = organic anion transporter 3; RNA=ribonucleic acid; PgP=P-glycoprotein; SNRI=serotonin and norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant.
[i] At least 48 h between doses.
[ii] Rifampin co-administration decreased delamanid exposure due to pill burden related malabsorption (see text for description).
[iii] Should be administered with food.

Table 2
. Adverse effect rates[i] for antitubercular agents in select landmark MDR TB treatment trials.

Medication	AEs/ DC	Treatment	Comparator
Moxifloxacin[ii]	Nausea	29.8 %	11.5 %
	QTc prolongation[iii]	1 %	0 %
	Liver-related TEAE	4.2 %	2.9 %
	Arthralgia/tendonitis	8.6 %	13.9 %
	Drug DC or Death (any reason)	7.7 %	9.8 %
Bedaquiline[iv]	Nausea	11.5 %	40.7 %
	QTc prolongationc	0 %	14 %
	Liver-related TEAE	2.9 %	11.0 %
Delamanid[v]	Nausea[vi]	3.7 %	3.8 %
	Vomitingf	6.2 %	1.3 %
	Insomniaf	8.1 %	5.6 %
	QTc prolongationf	6.2 %	1.3 %
	DC of DLM/placebo due to TEAEf	2.5 %	2.5 %
Pretomanid[vii]	Headache	4.4 %	9.9 %
	GI disorders	25.6 %	27.5 %
	Liver-related TEAE	25.6 %	26.4 %
	Skin/subcutaneous tissue disorders	27.8 %	30.7 %
	Any PTM-related TEAE	47.8 %	49.4 %
	DC PTM due for TEAE	4.4 %	3.3 %
Linezolidg	Peripheral neuropathy[viii]	20 %	34.1 %
	Optic neuropathy/neuritis	0 %	4.4 %
	Myelosuppression	4.4 %	18.7 %
	Any LZD-related TEAE	51.1 %	61.5 %
	Reduce dose/interrupt LZD	7.8 %	25.2 %
	TEAE leading to DC of LZD	5.6 %	6.6 %

AE=adverse effect; DC=discontinuation; DLM=delamanid; GI=gastrointestinal; LZD=linezolid; MXF=moxifloxacin; OBR=optimized background regimen; PTM=pretomanid; SOC=standard of care; TEAE=treatment-emergent adverse effect; QTc = corrected QT interval; WHO=World Health Organization

[i]Adverse effect rates attributable to the indicated drug are specified as such (when investigator-determined attributable adverse effects for the target medication were reported for the clinical trial). Otherwise, adverse effect rates are those listed for the study arm/regimen for which the target agent was included with comparator arm information provided.

[ii]Treatment = **MXF 400 mg daily** + (PTM+BDQ+LZD); Comparator = PTM+BDQ+LZD; PTM+BDQ+LZD=PTM 200 mg daily, BDQ (400 mg daily x 2 weeks, then 200 mg thrice weekly x 22 weeks) + LZD (600 mg daily x 16 weeks, then 300 mg daily x 8 weeks) (Nyang'wa et al., 2022).

[iii] ≥ Grade 3 severity.

[iv] Treatment = **BDQ (400 mg daily x 2 weeks, then 200 mg thrice weekly for 22 weeks)** + PTM 200 mg daily + LZD (600 mg daily x 16 weeks, then 300 mg daily x 8 weeks); Comparator = Variable SOC regimens per local and WHO guidelines (Nyang'wa et al., 2022).

[v]Treatment = **DLM 100 mg twice daily** + OBR; Comparator: Placebo + OBR (Gler et al., 2012).

[vi]Investigator-determined to be attributable to DLM or Placebo.

[viii]Treatment = **600 mg linezolid arms** (from Zenix trial); Comparator = **1200 mg linezolid arms** (from Zenix trial). Both had additional background regimen including PTM 200 mg daily + BDQ (200 mg daily x 8 weeks, then 100 mg daily for 18 weeks) (Conradie et al., 2022).

[viii]Includes descriptions reported as peripheral neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, parasthesia, neuropathy peripheral, and hypoaesthesia.

3. Emerging medications

3.1. Moxifloxacin

3.1.1. Mechanism of action

Moxifloxacin (Avelox®) is a novel generation, fluoroquinolone class antibiotic that inhibits bacterial topoisomerase II (also known as DNA gyrase) and topoisomerase IV, disrupting DNA replication, repair, recombination, and transposition [16]. It exhibits potent, bactericidal activity against many mycobacterial species, including MTB. The lowest concentrations of antibiotic that inhibit 90 % of examined isolates (MIC_{90}) for MTB are generally several-fold lower for moxifloxacin than other in-class agents (ciprofloxacin, levofloxacin), making moxifloxacin the preferred fluoroquinolone in MDR-TB [17]. In MTB, phenotypic resistance to fluoroquinolones is associated with mutations in the quinolone resistance-determining region of DNA subunits A (gyrA) and B (gyrB), which encode the bacterial type II DNA topoisomerase [18]. Mutations in these areas confer elevated MICs, with MICs above the WHO/Clinical and Laboratory Standards Institute (CLSI) critical concentration of 0.5 mcg/mL (Middlebrook 7H11/7H10 medium) conferring reduced activity at standard dosing [19]. Given the enhanced bactericidal activity of moxifloxacin, it may retain activity even in isolates with demonstrated resistance to other quinolones [20]. Additional advantages of moxifloxacin include a higher degree of Central Nervous System (CNS) penetration compared to in-class alternatives and availability of a single tablet, once daily dosing regimen [16,21,22].

3.1.2. Pharmacokinetic-Pharmacodynamic (PK-PD) considerations

Moxifloxacin is available as an oral tablet and intravenous solution. Oral moxifloxacin is highly bioavailable (90 %) and is well-absorbed by the gastrointestinal tract, independent of the presence or absence of food. Peak (C_{max}) concentrations typically reach 4.5 (±0.5) mcg/mL at a median of 3 h post-oral dose administration (T_{max}), with similar C_{max} and area-under-the-curve (AUC) values compared to IV administration [16]. Moxifloxacin demonstrates linear absorption, with plasma drug concentrations increasing proportionally with dose increases. For patients with swallowing difficulties, the tablets may be crushed and suspended in water for immediate administration [23]. Moxifloxacin is widely distributed to most body tissues, including bronchial mucosa, alveolar macrophages, and epithelial lining fluid, with drug concentrations in these tissues exceeding plasma drug concentrations. Peak cerebrospinal fluid (CSF) concentrations and total drug exposure measured by AUC are approximately 50 % and 75 % of those obtained in plasma, respectively, with standard dosing [21]. Moxifloxacin has no known Phase 1/Cytochrome *P*-450 system metabolism, nor does it induce, inhibit, or otherwise affect this drug metabolism system. Approximately 50 % of the dose is hepatically metabolized via sulfate and glucuronide conjugation (phase II metabolism). Elimination of unchanged drug (approximately 45 % of each dose) occurs through both urine and feces, while metabolites are excreted via urine (glucuronide conjugates) or feces (sulfate conjugates) [16].

Table 3
. Mitigation Strategies for Common Adverse Drug Events Associated with TB drug therapy.

Adverse Drug Event	Management/Monitoring
Gastrointestinal Distress (n/v/d)	• Administer antibiotics with food (during or after meal) • Administering antibiotics at different time of day (i.e. evening to mitigate disturbance of ADLs) • Avoidance of irritating foods (greasy, spicy, salty, acidic) or drinks (coffee/tea) • Avoidance of sugar substitutes, alcohol, smoking • Addition of probiotics, yogurt, kefir • Slow introduction of fiber-containing foods • Antiemetics, acid-suppressing agents – consider PRN use or scheduled "pre-treatment" dosing • PRN usage of peppermint lozenges, ginger candies
QT prolongation	• Minimization/avoidance of additional QT prolonging medications • Correct electrolyte abnormalities (Ca^{2+}, Mg^{2+}, K^{+}) • Correct underlying predisposing factors (i.e. hypothyroidism)
Hepatotoxicity	• Avoid alcohol, acetaminophen, and other hepatotoxins • Liver monitoring lab abnormalities (asymptomatic) • ALT/AST<5x ULN: repeat labs within 48–72 hrs • ALT/AST 5-8x ULN on multiple assessments: consider therapy discontinuation • ALT/AST>8x ULN: consider therapy discontinuation • Any ALT/AST elevation with total bilirubin > 2x ULN: consider therapy discontinuation • Liver monitoring lab abnormalities (symptomatic) • Urgent, in-person evaluation by a clinician, with follow-up, testing, and investigation for alternative causes • Consider therapy discontinuation if no alternative etiology found
Peripheral Neuropathy	• Limit linezolid starting dose to 600 mg daily • Consider linezolid TDM with dose reductions to achieve trough target levels < 2 mcg/mL • Physical exam including monofilament testing

ADL=activities of daily living; ALT=alanine aminotransferase; AST=aspartate aminotransferase; n/v/d = nausea, vomiting, and/or diarrhea; PRN=as needed; TDM=therapeutic drug monitoring; ULN=upper limit of normal.

3.1.3. Dosing considerations

Moxifloxacin labeled dosing is 400 mg orally or IV once daily. No dosage adjustments are provided for any degree of renal or hepatic impairment due to its cytochrome P450-independent metabolism and elimination pathways; however, caution is warranted in patients with impaired hepatic function, whom may have baseline metabolic disturbances that may predispose to an increased risk of QT prolongation [24]. Increased doses are not needed for obesity [25], however, increased doses of 800 mg should be considered for those with CNS involvement/TB meningitis to ensure adequate drug concentrations at the site of infection [21,26,27].

3.1.4. Adverse effects

Moxifloxacin has few agent-specific side effects, and its adverse effect profile is reflective of the fluoroquinolone class. All agents in this class carry Food and Drug Administration (FDA) boxed warnings for tendinitis/tendon rupture, peripheral neuropathy, CNS-related side effects, including altered mentation, seizures and psychiatric effects, and worsening of myasthenia gravis. Despite a greater degree of CSF penetration, incidence of CNS-related side effects appears no higher compared to alternative fluoroquinolones (1–2 %) [28]. Additional, commonly-encountered safety considerations include nausea (7 %), diarrhea (5 %), and abnormalities in blood glucose in patients with diabetes (16 %) [29,30]. Severe drug effects, less commonly reported, include tendon rupture (3.2 cases/1,000 patient treatment years), aortic aneurysm and dissection (1 case/9,747 treatment courses), and severe hepatotoxicity (<0.1 %) [28,30,31]. Compared to other fluoroquinolones, risk of QT prolongation may be increased (mean change from baseline: moxifloxacin 16.34 to 17.83 ms, levofloxacin 3.53 to 4.88 ms, ciprofloxacin 2.27 to 4.93 ms), while risk of tendon rupture may be lower with moxifloxacin (Odds Ratio [95 % Confidence Interval] 17.23 (12.22–24.32), 76.38 (69.64–83.78), and 56.49 (51.14–62.40) for moxifloxacin, levofloxacin, and ciprofloxacin, respectively) [32–34].

3.1.5. Drug-Drug interactions

Moxifloxacin has minimal metabolic or transport-related drug interactions and most interactions are fluoroquinolone class related rather than agent-specific. Like all fluoroquinolones, moxifloxacin absorption is impaired by coadministration with polyvalent cation-containing medications. Oral moxifloxacin should be administered at least 4 h before or 8 h after products containing magnesium, aluminum, iron, or zinc, including antacids, sucralfate, and multivitamins [16]. QT prolonging potential is additive when combined with other medications known to prolong the QT interval and may lead to Torsades de Pointes in severe cases. Concurrent therapy with systemic corticosteroids may increase risk of tendinopathies and tendon rupture [16,35,36]. Pharmacokinetic studies in combination with rifampin are conflicting, with some studies demonstrating reduced moxifloxacin concentrations, while others have not noted a statistically significant difference [27,37–39]. Available guideline recommendations note a possible reduction in moxifloxacin exposure when combined with rifampin, but the clinical significance of this in individual patients is unknown and no formal dose adjustments are recommended [3].

3.2. Bedaquiline

3.2.1. Mechanism of action

Bedaquiline is a diarylquinoline antibiotic that inhibits the proton transfer chain of mycobacterial ATP (adenosine 5′-triphosphate) synthase, ultimately preventing ATP generation in Mycobacterium species [40]. Both metabolically active and dormant MTB isolates utilize ATP synthase, providing bactericidal activity initially, with potent sterilization effect during extended treatment [41,42]. Bedaquiline has a selectivity index > 20000 for mycobacterial ATP synthase compared to eukaryotic mitochondrial ATP synthase [42–44].

3.2.2. Pharmacokinetic-Pharmacodynamic (PK-PD) considerations

In a PK/PD study with murine models, bedaquiline bactericidal activity was most strongly correlated with total weekly drug exposure (AUC), suggesting that AUC/MIC is the PK/PD target most associated with efficacy [45]. Currently, CLSI does not publish a bedaquiline MIC breakpoint standard for MTB. However, laboratory observations of preclinical and clinical isolates suggest that bedaquiline is considered susceptible with a MIC≤0.5 mcg/mL (agar method) or MIC≤0.25 mcg/mL (Resasurin microtiter assay method) [46]. Furthermore, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) has established a susceptibility breakpoint for MIC≤0.25 mcg/mL (Middlebrook 7H11/7H10 medium) for bedaquiline against MTB.

Bedaquiline is a well-absorbed oral drug, with absorption optimized when taken with food (bioavailability up to 95 %). C_{max} and AUC

Table 4
. Safety and monitoring parameters[a] for antitubercular medications during MDR TB treatment.

Medication	Laboratory/Procedural monitoring and timeframe	Clinical Assessments
Moxifloxacin	ECG (baseline, 2, 12, 24 weeks) Liver toxicity monitoring: AST, ALT, Alk Phos, Bili (baseline, 2 weeks, then monthly)	Monitor for nausea, vomiting, abdominal pain, joint pain, headache
Bedaquiline	ECG (baseline, 2, 12, 24 weeks) Liver toxicity monitoring: AST, ALT, Alk Phos, Bili (baseline, 2 weeks, then monthly)	Monitor for nausea, vomiting, abdominal pain, poor appetite, joint pain, headache, chest pain/hemoptysis
Pretomanid	ECG (baseline, 2, 12, 24 weeks)[b] Liver toxicity monitoring: AST, ALT, Alk Phos, Bili (baseline, 2 weeks, then monthly)	Monitor for headache, rash, nausea, vomiting, abdominal pain
Delamanid	ECG (baseline and monthly) Liver toxicity monitoring: AST, ALT, Alk Phos, Bili (baseline, 2 weeks, then monthly)	Monitor for nausea, vomiting, abdominal pain, insomnia
Tedizolid	CBC with differential (baseline, then monthly) Monofilament test (monthly)	Monitor for signs/symptoms of peripheral neuropathy (tingling, pain, numbness of hands/feet), GI upset (nausea/vomiting/diarrhea), optic neuropathy (visual disturbances/color indiscrimination)
Linezolid	CBC with differential (baseline, weekly x 8 weeks, then monthly) Visual evaluation: Baseline fundoscopic exam, visual acuity assessment monthly, color discrimination (Ishihara) assessment monthly Monofilament test (monthly)	Monitor for signs/symptoms of peripheral neuropathy (tingling, pain, numbness of hands/feet), GI upset (nausea/vomiting/diarrhea), optic neuropathy (visual disturbances/color indiscrimination), and lactic acidosis (nausea/vomiting, myopathy, fatigue, confusion, tachypnea)

AST=aspartate aminotransferase, ALT=alanine aminotransferase, Alk Phos = alkaline phosphatase, Bili = bilirubin, GI=gastrointestinal, MDR=multi-drug resistant.
[a] Consensus author recommendations for medication safety monitoring, considering medication package insert information, consensus TB guidelines, and CDC provisional guidance while presuming resource availability for safety evaluations/assessments. Individual patient case details and clinician evaluation should always dictate specific monitoring.
[b] If used without BDQ, an ECG at baseline and 2–4 weeks is reasonable.

increase proportionally with increasing doses, with T_{max} obtainment approximately 5 h post oral dose administration. Bedaquiline is highly protein-bound (>99.9 %) and distributes widely in the body with a mean volume of distribution of 164 L, but with limited CNS penetration. Given the wide distribution of bedaquiline, the long half-life of 4 to 5 months is thought to be associated with the slow release of bedaquiline and its metabolites from peripheral tissues [40].

3.2.3. Dosing considerations

Bedaquiline is available as a 20 mg or 100 mg tablet. The 100 mg tablet should be swallowed whole, while the 20 mg tablet is a scored tablet and can be dispersed in water or crushed for patients unable to take intact tablet by mouth [40]. Bedaquiline's long serum half-life results in the need for less than daily dosing frequencies, after an initial 2-week "loading period". This loading period is utilized to obtain therapeutic drug concentrations more rapidly. The standard dosing regimen initiates treatment with 400 mg once daily for 2 weeks (loading period), followed by 200 mg 3 times weekly with doses spaced ≥ 48 h apart (maintenance period). In the case of missed doses, the manufacturer provides guidance on dose resumption whether the missed dose occurs during the first 2 weeks of therapy (loading) or from week 3 onward (maintenance). If a dose is missed during the first 2 weeks, do not make up the missed dose, and continue the usual dosing schedule. From week 3 onward, if a dose is missed, administer the missed dose as soon as possible, and resume the 3 times a week schedule; the total weekly dose should not exceed 600 mg.

There is no dose adjustment required for any degree of impaired renal or hepatic function. However, caution in patients with end-stage renal disease (ESRD) and severe hepatic impairment (e.g., Child-Pugh Class C) should be used given lack of study data in these populations. Serum drug level assessment of bedaquiline can be considered for patients with ESRD, as drug concentrations may be increased due to alterations in drug absorption, distribution, and metabolism secondary to pathophysiologic changes in these PK parameters associated with severe renal dysfunction [47].

3.2.4. Metabolism/Elimination

Bedaquiline is primarily metabolized in the liver by CYP3A4 into an active N-desmethyl metabolite (M2) with the majority of drug excreted in the feces (<0.001 % urinary excretion) [40]. Although active, the M2 metabolite displays 4 to 6 times less activity against MTB compared to its parent compound. After peak drug concentrations are achieved, bedaquiline concentrations decline tri-exponentially. The mean terminal half-life of both bedaquiline and its M2 metabolite is approximately 5–6 months, likely reflective of redistribution from saturated peripheral tissues [40]. Minimal inter-patient variability is seen in bedaquiline pharmacokinetics, with no clinically relevant differences noted based on age, sex, or HIV serostatus. Black patients were noted to have higher bedaquiline clearance of up to 52 %, resulting in mean AUCs of about 34 % lower compared to other races in a population pharmacokinetic analysis [48], however, the clinical significance of this is unknown and no dose adjustment is currently recommended [43].

3.2.5. Adverse effects

Bedaquiline has an FDA boxed warning for increased mortality and QT prolongation. Increased mortality was seen with the bedaquiline treatment group compared to placebo (13 % vs 2 %) by week 120 in a phase IIb trial [49]. The increased mortality in the bedaquiline treatment group remains unclear due to variabilities in cause of death in this trial. One death occurred during the 24 weeks of bedaquiline treatment, and the remaining deaths (n = 9) were observed after treatment completion, with a median time to death of 329 days after the last dose of bedaquiline. The imbalance in deaths remains unexplained as there is no obvious pattern observed in the phase IIb trial; additionally, a 2015 post-marketing pharmacovigilance study has not shown excess mortality with treatment of bedaquiline [50]. Bedaquiline carries a QT prolongation boxed warning, with degree of QT prolongation correlated with M2 metabolite concentrations [40]. Risk of QT prolongation is heightened in patients on additional drug therapies known to prolong the QT interval (e.g., clofazimine, fluoroquinolones). During phase 2 evaluation, mean increases in QTc from baseline were higher for bedaquiline (15.4 ms increase) compared to placebo (3.3 ms increase) at 24 weeks. After bedaquiline discontinuation, the mean QTc value was similar between the two groups by week 60 [49]. CDC provisional guidance recommends a baseline ECG along with ECGs at 2, 12, and 24 weeks after starting bedaquiline. Baseline serum potassium, calcium, and magnesium are also recommended with correction for electrolyte abnormalities. Other notable adverse effects in the placebo-controlled

trial include arthralgia (37 % vs 27 %), nausea (41 % vs 37 %), and headaches (29 % vs 22 %) for bedaquiline and placebo-treated recipients, respectively. The incidence of grade 3 to 4 liver-related treatment emergent adverse events (TEAE) was numerically higher in bedaquiline recipients compared to placebo (AST 11.5 % vs 4.9 %, ALT 7.7 % vs 2.5 %, GGT 9.0 % vs 3.7 %) [49].

3.2.6. Drug-Drug interactions

Bedaquiline primarily undergoes hepatic metabolism, most predominantly via CYP3A4 (major substrate), though CYP2C19 and CYP2C8 contribute to a lower extent (minor substrate) based on laboratory assessment. Consequently, strong CYP3A4 inducers and inhibitors should be avoided to reduce the risk of decreased and increased exposures of bedaquiline, respectively. If prolonged co-administration (>14 days) with a strong CYP3A4 inhibitor is unavoidable, serial ECGs should be followed closely and serum drug level monitoring of bedaquiline should be considered, if possible, recognizing that drug will accumulate with repeated dosing given the large distribution and prolonged terminal half-life of the drug. Bedaquiline's target average plasma concentration is 0.6 mcg/mL based on murine models [43,45]. Additionally, concomitant QTc prolonging agents taken with bedaquiline should be carefully monitored given the potential additive QTc prolongation.

3.3. Nitroimidazoles

3.3.1. Mechanism of action

Delamanid and pretomanid share antibacterial effect against replicating MTB in oxygen-rich, aerobic conditions while also providing bactericidal activity against hypoxic non-replicating MTB in anaerobic conditions [51,52]. Both are prodrugs requiring activation by MTB for antimicrobial activity [52–54], with microbial activation selectively targeting MTB and no 'cross-activation' within human or mammalian cells expected [55]. When acting on replicating MTB bacilli in an aerobic environment, delamanid and pretomanid inhibit steps within mycolic acid cell wall biosynthesis [52,53,56,57]. The mechanism, however, for bactericidal activity of non-replicating bacilli in the anaerobic environment differs. Delamanid and pretomanid are chemically reduced (via the rv3547 nitroreductase enzyme) [53,57] leading to reactive nitrogen intermediates and nitric oxide release within MTB, effectively delivering a chemical "bomb" inside these dormant mycobacteria. The reactive nitrogen species are believed to impair ATP homeostasis, inactivate mycobacterial enzymes, and damage nucleic acids [58].

3.3.2. Pharmacokinetic-Pharmacodynamic (PK-PD) considerations

Dose optimization and development of novel antitubercular therapy seeks enhanced antimicrobial effect while minimizing toxicity and adverse effects. Testing multitudes of dosing programs in large clinical trials is generally not feasible, so pharmacometric modeling [59] helps optimize dosing platforms for clinical trial evaluation. Such modeling, using clinical trial data, serum drug level assessments, and early PK evaluations has helped inform the PK/PD profiles of the antitubercular nitroimidazoles, delamanid and pretomanid.

3.3.2.1. Delamanid. Delamanid follows a two-compartment pharmacokinetic model with both first-order absorption and elimination [60], though dose increases above 100 mg do not result in proportional exposure profiles, which may be attributable to dose-limited absorption [60–62]. Food significantly enhances absorption of delamanid, a standard meal increasing oral bioavailability 2.7 times that of a fasted state [63]. T_{max} is between 4–5 h [62] and produces a mean C_{max} range of 400–414 ng/mL and 588–611 ng/mL with twice daily mealtime administration of 100 mg and 200 mg doses, respectively [61]. Delamanid's elimination half-life is 38 h [61], but inactive metabolite half-lives are significantly longer due to extensive tissue binding and slow return to plasma [64].

PK/PD evaluation of delamanid in a murine model of TB infection highlighted the $AUC_{0\text{-}24}$/MIC (ratio comparing area under the concentration time curve in 24 h to the MTB isolate MIC) as the PK/PD parameter that best predicted microbiologic efficacy [65]. The cumulative fraction of response (CFR) is the proportion of patients that would attain the PK/PD target at a given dosing regimen for a given MIC distribution. Using parameters from two MDR-TB clinical trials, a delamanid dose of 100 mg twice daily generated a CFR>95 %, with CFR ranging 89–96 % for a dose of 200 mg daily. Though CFRs were mildly reduced, delamanid dosed at 200 mg daily suggested potential for lower QT interval prolongation [65]. Using Monte Carlo simulation, Liu determined a PK/PD-derived (specifically $AUC_{0\text{-}24}$/MIC) susceptibility breakpoint for delamanid 100 mg twice daily dose at an MIC of 0.016 mcg/mL [66].

3.3.2.2. Pretomanid. Pretomanid follows a one-compartment kinetic model, reflects saturable first-order absorption, and demonstrates first-order elimination [67] with a median steady-state elimination half-life of 18 h (range 10—–30 h) [68]. Poorly soluble in water [69], pretomanid's absolute bioavailability may approximate 50–60 % [70], with saturable absorption likely related to tablet dissolution properties and/or drug solubility [71]. Food increases oral tablet absorption, with a 1,000-calorie, high-fat meal (~150 kcal protein, 250 kcal carbohydrate, 600 kcal fat) yielding a 76 % C_{max} increase along with an AUC increase of 88 % [71], justifying advice to take pretomanid with food [72]. T_{max} for a 200 mg dose ranges between 4 h (fasted) and 5 h (fed) [71], with median steady-state C_{max} in a population PK model (compiled using PK data from 14 studies) of 3.2 mcg/mL for 200 mg dose given daily with food [68].

Pretomanid demonstrates time-dependent antimicrobial effect on MTB, with $T_f > MIC$ (time that free/unbound drug in blood remains greater than the MIC) correlating best with bactericidal activity in murine TB models [73]. Exhibiting a long half-life in humans, pretomanid attained near-maximal bactericidal effects for daily dose groups ranging from 200 to 1200 mg [73,74]. The plateau of antimicrobial effect with pretomanid dose-escalation and the comparable bactericidal activity for daily doses of ≥200 mg per day in smear-positive adult TB patients confirmed the predictive value of $T_f > MIC$ in humans.

3.3.3. Dosing considerations

Delamanid is approved in Europe as 100 mg given twice daily, taken with food to optimize absorption, carrying clinical trial data to support safety and efficacy of this approach [63]. With a longer half-life than pretomanid, considering a single daily dosing scheme for delamanid may be reasonable. In fact, after an initial two-month intensive phase of 200 mg twice daily, delamanid 200 mg once daily has been used clinically, and PK-PD analysis suggests this a reasonable dosing approach with favorable CFR and AUC/MIC target attainment. Nevertheless, lower relative absorption of higher doses has contributed to lower overall AUCs reported for 200 mg once daily [65] vs 100 mg twice daily [61] due to saturable absorption.

Pretomanid in adults is approved at 200 mg once daily, taken with food to optimize absorption, with this dosing scheme validated in randomized clinical trials [72]. Pretomanid's long half-life supports once daily dosing while diminished absorption from higher doses and limited incremental increase in probability of target attainment (PTA) restrict justification for empiric dose-escalation. Doses lower than 200 mg daily may not be as effective. Monte Carlo simulations using PTA from murine models, while accounting for food intake variability, protein binding, and MTB MIC ranges, demonstrated more favorable PTA for 200 mg pretomanid daily when compared to 100 mg daily [67].

3.3.4. Metabolism/Elimination

Delamanid drug clearance occurs via metabolism of parent drug to

multiple metabolites that do not possess MTB activity, with the majority excreted via fecal elimination (only 3 % recovered in the urine) [75]. Albumin degrades delamanid (parent drug) to it's primary M1 metabolite (DM-6705), with minimal contribution from hepatic microsomal enzymes. Subsequent further metabolism of M1 occurs via three pathways: (1) initial hydroxylation of the oxazole moiety via CYP1A1, CYP3A4, CYP2D6, and CYP2E1, (2) hydrolysis and deamination of the oxazole amine component, and (3) hydrolytic cleavage of the oxazole ring [64,76]. With metabolism primarily driven by delamanid conversion to M1 (which is impacted little in the setting of circulating albumin) and the presence of multiple pathways for M1 degradation, the potential for significant drug interactions is minimal [64].

Pretomanid undergoes multiple pathways for metabolism including both phase 1 (oxidation, reduction of the nitro group, oxidative deamination, oxidative cleavage) and phase 2 (glucuronidation and glycine conjugation), with no single pathway considered primary nor major [77]. Based on *in vitro* analysis, CYP3A4 could account for up to 20 % of pretomanid biotransformation, while CYP2C9, CYP2C19, and CYP2D6 are minimally involved [77]. Ultimately, bodily drug removal appears modestly split between urine and fecal routes, with radiolabel recovery assessments showing 53 % renal drug recovery (only 1 % unchanged parent drug) and 38 % fecal recovery [77].

3.3.5. Drug-Drug interactions

Delamanid's metabolism, marked by initial albumin biotransformation followed by multiple subsequent degradation pathways, including several CYP isoenzymes, limits the potential for drug effect on delamanid exposure [64]. Additionally, delamanid does not inhibit nor induce CYP450 enzymes [78], nor is it a substrate or inhibitor of clinically relevant drug transporters [53,63]. *In vivo* assessment confirmed that neither CYP3A4 induction nor inhibition contributes significantly to systemic delamanid exposure [79]. During co-administration with rifampin, delamanid exposure was reduced (45 % AUC reduction), but the overall decrease resulted from limited delamanid absorption in the setting of 15 coadministered tablets, not due to changes in delamanid clearance. The lack of effect on delamanid clearance was reflected in both concentration–time profile analysis and metabolite ratio assessments, where significantly different results should have been seen if CYP3A4 induction was contributing to decreased delamanid exposure [79]. Eliciting no appreciable effect on delamanid exposure, the less potent CYP3A inducer efavirenz confirmed lack of 3A4 induction effect on delamanid clearance [79]. Potent CYP3A4 inhibition with lopinavir/ritonavir also lacked relevant delamanid exposure effect (25 % AUC increase) [79].

Pretomanid has multiple metabolic pathways, which would suggest a minimal change in pretomanid exposure due to the inhibition of CYP450 enzymes. However, the minor role of CYP3A4 in pretomanid biotransformation [77] warranted closer evaluation. PK data confirmed that CYP3A4 inhibition does not increase pretomanid drug concentrations, though CYP3A4 induction decreases pretomanid exposure. In a rat model, darunavir (a CYP3A4 inhibitor) showed decreased pretomanid exposure (AUC) due to increased pretomanid clearance [80]. In healthy subjects, rifampin 600 mg daily, efavirenz 600 mg daily, and lopinavir-ritonavir (LPV/r) 400 mg-100 mg twice daily all decreased pretomanid exposure (AUC) by 66 %, 35 %, and 17 %, respectively, by increasing pretomanid clearance [81]. It is suspected that decreased pretomanid exposure seen with protease inhibitors that inhibit CYP3A4 likely relates to alternative effects of enzyme induction (i.e. glucuronidation), though more importantly, the data confirms lack of increased pretomanid exposure when combined with a significant CYP3A4 inhibitor. In summary, a degree of moderate (or higher) CYP3A4 induction will decrease pretomanid exposure, while CYP3A4 inhibition is not expected to have significant effect.

At clinically used doses, currently available data suggests pretomanid has limited effect on drug metabolizing and transport systems, though administration of organic anion transporter-3 (OAT3) substrates warrants close monitoring. Pretomanid does not significantly affect CYP3A4 substrates [77,81]. Additionally, *in vitro* evaluation suggests pretomanid is not a substrate for nor does pretomanid affect activity of clinically relevant drug transport systems, except for OAT3 (significant inhibition) and the MATE2-K transporter (very low inhibition potential) [77]. Until clinical drug interaction studies provide more guidance, OAT3 substrates (such as methotrexate) should be considered for lower dosing, closely monitored for toxicity, and/or have serum levels assessed when combined with pretomanid.

3.3.6. Adverse effects

Delamanid is well-tolerated in most patients with MDR-TB. Combined with an optimized background regimen (OBR), delamanid's adverse effect profile consists primarily of gastrointestinal symptoms, insomnia, and QTc prolongation, though severe treatment-related complications and discontinuation rates are minimal. Preclinical animal data suggests delamanid is not expected to be genotoxic, carcinogenic, teratogenic, nor affect fertility [75]. TEAEs were common in Study 204 (≥89 %) when delamanid was used with an OBR for MDR-TB, though most individual drug events were comparable to the placebo group, the majority of mild-moderate severity, and only 3.1 % of patients stopped delamanid due to adverse events [61]. When evaluating adverse effects, investigators attributed higher rates of nausea/vomiting (8.7 %, 28/321 vs 5 %, 8/160) and insomnia (10 %, 32/321 vs 5.6 %, 9/160) to delamanid when compared to placebo [61]. QT prolongation was also significantly increased from placebo (3.8 %) in both the 100 mg (9.9 %) and 200 mg (13.1 %) delamanid groups, importantly noting a dose–response relationship, though no clinical manifestations (syncope or arrhythmias) occurred [61]. Time-averaged QTc assessment show progressive QTc increase from day 1 to 56 of delamanid therapy, with mean changes of 12 ms (10 – 15 ms) and 15 ms (12 – 17 ms) for the 100 and 200 mg twice daily doses, respectively [75]. The QTc effect peaks at 8 weeks of therapy, steadily reverses after treatment discontinuation, and resolves within 4 weeks after cessation [82]. A favorable tolerability profile overall, providers should be aware of delamanid's potential to contribute to gastrointestinal upset, prolong the QT interval, and potentially affect sleep.

Pretomanid is generally well tolerated with limited toxicity in short-term monotherapy evaluation, though combined use with other TB agents can influence the toxicity profile, noting more frequent GI symptoms and hepatic toxicity with combination TB treatment. During 2 weeks of pretomanid monotherapy (for daily doses of 50 – 1200 mg), no serious drug-attributable adverse effects occurred [74,83]. Analysis from different clinical trials with different drug combinations complicates the ability to isolate pretomanid's individual contribution to the adverse effect profile. Notwithstanding, pooled trial data identified the following TEAEs associated with pretomanid: gastrointestinal symptoms (28.4 %), hepatic disorders (25.5 %), elevated transaminases (19.2 %), skin/subcutaneous disorders (16.6 %) and headache (11 %) [84]. Only gastrointestinal symptom incidence correlated with higher systemic drug exposure, though most GI symptoms were mild-moderate severity (grade 3 = 5/474; grade 4 = 0) [84].

Hepatic toxicity attributable to pretomanid alone is low, though additional TB therapy used with pretomanid appears to exacerbate effect on the liver. Initial pretomanid monotherapy for two weeks lacked any discontinuations due to AST/ALT increase or hepatic issues [83]. When combining pretomanid with BDQ, PZA, and MXF+PZA for 2 weeks, 1 of 15 patients from each group stopped therapy due to ALT increases [85]. Furthermore, when compiling liver toxicity (defined as any one of the following: ALT (or AST) > 5x ULN; alkaline phosphatase (ALP) > 2x ULN; ALT (or AST) > 3x ULN+total bilirubin > 2x ULN) rates from phase 1–3 studies, toxicity with PTM alone is low (2.2 %), though pretomanid combination regimens were higher (5.6—11.7 %), supporting hepatotoxicity enhancement or attribution to other drugs in the regimen [86].

Other notable pretomanid effects (increased SCr, increased QT, lens

disorders, and effects on male fertility) do not appear clinically significant after evaluation of currently available data. Pretomanid increases serum creatinine, with a degree of effect dependent on pretomanid serum concentration [87]. However, the creatinine increase is not attributable to a change in GFR, but rather inhibition of tubular creatinine secretion which reverses on drug cessation [88]. During early analysis of daily dosing (doses 50–200 mg) no drug-attributable clinically significant QT changes occurred, though QTc change correlated with plasma levels (9.3 ms change for concentration of 1022 ng/mL, the mean concentration for 200 mg dose of pretomanid) [83]. A later QT study did not show any clinically meaningful QTc increase from pretomanid [77]. When rats were exposed to pretomanid levels 1.5–2 times human exposure, toxicology evaluation suggested possible association of lens disorders and testicular toxicity. However, slit-lamp examinations in Nix-TB did not identify any cases of cataracts [13,77] and normal sex hormone levels were seen in phase 2/3 trials [77]. A current study is underway to better evaluate pretomanid's effect on male reproductive safety [89].

3.4. Oxazolidinones

3.4.1. Mechanism of action

Linezolid (Zyvox©) and tedizolid (Sivextro©) are synthetic amphiphilic drugs in the oxazolidinone class that block bacterial ribosomal protein synthesis by binding to the bacterial 23S ribosomal RNA of the 50S bacterial ribosomal subunit thereby preventing the formation of a functional 70S initiation complex [90–92]. In patients with cavitary pulmonary TB, these agents penetrate into tuberculosis lesions, TB-infected alveolar macrophages, and have early bactericidal activity against rapidly dividing tubercle bacilli [91–93]. A phase 2, prospective, randomized, open-label controlled trial comparing the bactericidal activity of tedizolid with linezolid and standard treatment for tuberculosis (quadruple therapy: isoniazid, rifampicin, ethambutol, pyrazinamide) is currently recruiting participants [94].

3.4.2. Pharmacokinetic-Pharmacodynamic (PK-PD) considerations

The efficacy of linezolid has been correlated with AUC/MIC with a proposed target of at least 100 to prevent the development of TB resistance in the presence of a companion TB drug [95]. Oral linezolid is 100 % bioavailable and is rapidly and completely absorbed within 1–2 h of administration (T_{max}) [91,96]. Food may slow or delay absorption, but has little effect on the overall bioavailability [91]. Linezolid plasma protein binding is 31 % (range 4–32 %) and concentration-dependent [97]. In healthy adults, the steady state volume of distribution is 36.1——47.3 L with ready distribution to well-perfused tissues and low penetration into adipose tissue [91,98–100]. Linezolid lung tissue concentrations are comparable to serum concentrations, while CSF drug levels represent 60–70 % of that found in blood [101–106].

Tedizolid phosphate is rapidly absorbed with T_{max} 1-hour post-administration, with immediate conversion of the tedizolid phosphate prodrug to active form (tedizolid) by serum phosphatases. Tedizolid phosphate has an absolute bioavailability of 91 % with a steady state 24-hour AUC of 30 mcg*hr/mL for a 200 mg oral dose taken once daily [107,108]. Serum protein binding ranges from 75 – 90 % and the volume of distribution is 67——80 L [109].

3.4.3. Dosing considerations and adverse effects

3.4.3.1. Linezolid. Diarrhea is the most frequently reported adverse effect with linezolid (8——11 % of patients) and can occur at any time during therapy [99]. Long-term, treatment and dose-limiting side effects of linezolid include myelosuppression, as well as peripheral and optic neuropathy. The incidence of these increases with total cumulative drug exposure, with higher risk of myelosuppression seen after 14 days of use and higher risk of neuropathies seen after 28 days of therapy, when used as monotherapy at approved 600 mg twice daily dosing [110–114].

Linezolid dosing for bacterial infections is standardized at 600 mg twice daily (oral or intravenously), while the dose for TB has been variable, ranging from 300 – 1200 mg per day (in single daily doses or divided twice daily) [115]. Dose variability has been attributed to the drug's narrow therapeutic window and the long durations needed for treatment of MDR-TB, creating a delicate balance between efficacy and toxicity [116]. In the Nix-TB trial, 90 % of patients with XDR or MDR-TB had favorable outcome with BPaL for 26 weeks, but hematologic (myelosuppression in 48 % of patients) and neurologic (peripheral neuropathy in 81 % of patients) adverse events with linezolid were high. Investigators changed linezolid dose during the study from 600 mg twice daily to 1200 mg once daily to lessen clinical toxicity [13]. Subsequently, patients in the ZeNix trial with XDR or pre-XDR-TB were assigned linezolid 1200 mg once daily or 600 mg once daily (for either 9 or 26 weeks) with 26 weeks of bedaquiline and pretomanid. The overall risk–benefit ratio favored the lower daily dose of linezolid 600 mg given for 26 weeks duration. Linezolid at 600 mg daily compared to 1200 mg daily (26 week duration) had lower adverse events (peripheral neuropathy 24 % vs 38 %, myelosuppression 2 % vs 22 %, 0 % vs 9 % optic neuropathy, respectively) and fewer dose modifications (13 % vs 51 %, respectively). The 600 mg daily (26 week) treatment arm also had higher favorable treatment outcomes (91 %) and better microbiologic outcomes than the 9-week linezolid groups [14]. Currently, the US CDC recommends an initial dose of linezolid 600 mg once daily for BPaL [117]. No dose adjustments are recommended for any degree of hepatic or renal impairment, however, incidence of thrombocytopenia is increased in patients with severe hepatic impairment (Child-Pugh Class C) and in patients with severe renal impairment (CrCl $<$ 40 mL/min), likely reflective of drug accumulation [118–123].

Given the long TB treatment duration and narrow therapeutic index of linezolid, therapeutic drug monitoring has been advised by WHO when the dose is at the upper or lower end of the dosing range [124]. Both linezolid AUC/MIC and trough (C_{min}) monitoring methods have been studied for TB. Monitoring C_{min} is useful for surveillance of linezolid toxicity and often the more practical approach [91]. When linezolid C_{min} is $>$ 7.5 mcg/mL, thrombocytopenia incidence is significantly higher [125]. The suggested trough targets include $<$ 2 mcg/mL, 2–8 mcg/mL, 3.6–8.2 mcg/mL, or 2–7 mcg/mL from various sources, depending on dosing frequency and indication [126–129]. For TB, trough targets $<$ 2 mcg/mL may limit side effects associated with long-term usage. The relationship between linezolid exposure and other adverse effects such as neuropathy and lactic acidosis is less clear. Proponents of linezolid AUC/MIC monitoring purport that it allows for flexibility to aim for lower or higher overall exposures based on MICs, improving the likelihood of treatment efficacy. The suggested minimum AUC:MIC ratio is 100–119 with slight variation depending on the infection site [91,130]. Linezolid drug levels should be obtained at steady state, usually by the third day of therapy (after 4–5 half-lives), and proportional dose modifications applied when adjustments are indicated [126,128]. For a more comprehensive discussion of Therapeutic Drug Monitoring (TDM) for linezolid and other emerging therapies for MDR TB, we direct the reader to the review by Drs. Maranchick and Peloquin [131].

3.4.3.2. Tedizolid. The standard dose of tedizolid is 200 mg oral or IV once daily for bacterial infections [109]. While the optimal dose for TB treatment is unknown at this time, longer term use of tedizolid 200 mg once daily for non-tuberculosis mycobacterium was reported in at least two cases [132,133]. Tedizolid is thought to have an improved drug interaction and adverse effect profile (similar types, but less frequent/severe) compared to linezolid. A multicenter retrospective study of patients using tedizolid for $>$ 6 days reported 9 of 81 patients (11.1 %) experienced a probable tedizolid associated adverse effect. Two patients (2.5 %) developed GI disturbance, 1 (1.2 %) anemia, and 6

thrombocytopenia (7.4 %) after a median (IQR) duration of treatment of 26.5 (17.0 to 58.5) days with 4 (5 %) tedizolid discontinuations due to AEs [134]. The authors concluded that tedizolid was well tolerated and had lower GI and hematologic toxicity than linezolid, including those with history of linezolid associated toxicity. Of note, none of the patients in this study received tedizolid for TB [134]. More *in vitro* and clinical outcomes data is needed on tedizolid use for TB.

3.4.4. Metabolism/Elimination

The majority of the linezolid dose circulates as parent drug, with the minority hepatically metabolized via oxidation of the morpholine ring into two inactive carboxylic acid metabolites, hydroxyethyl glycine and aminoethoxyacetic acid [98]. Linezolid is approximately 35 % renally eliminated as unchanged drug with about 10 % fecal excretion as metabolites [91,99]. A small degree of nonlinearity in clearance has been observed, with a 30 % decrease in clearance after a fivefold increase in dose [135]. The elimination half-life is relatively short at 3 to 7 h in adults, resulting in need for at least once daily dosing regimens [136].

The tedizolid phosphate prodrug is rapidly and readily dephosphorylated by serum phosphatases to the active form. Tedizolid has no known cytochrome P450 metabolism, but undergoes conjugation (phase II metabolism) by sulfotransferase isoforms SULT1A1, SULT1A2, and SULT2A1. Over 82 % of tedizolid is excreted as unchanged drug in the feces, the remainder (18 %) is eliminated renally as metabolite with < 3 % as unchanged tedizolid in the urine [109].

3.4.5. Drug-Drug interactions

Linezolid is a weak, reversible, nonselective inhibitor of monoamine oxidase, leading to risk of serotonin syndrome when combined with other serotonergic agents. Risk from linezolid alone is generally considered low, but increases with the number of concomitant serotonergic agents and their serotonergic potential [137–139]. Linezolid also raises norepinephrine levels, thus co-administration with pseudoephedrine and bronchodilators could increase risk of adrenergic effects, i.e. elevated blood pressure [140]. Cytochrome P450 does not play a major role in linezolid drug interactions, however, linezolid is affected by p-glycoprotein inducers (i.e. rifampin and levothyroxine may decrease linezolid concentrations) and inhibitors (i.e. amiodarone, amlodipine, clarithromycin, omeprazole, and pantoprazole may increase linezolid concentrations) [140]. Though the mechanism is not fully elucidated, PT/INR may increase with linezolid addition to warfarin. Titration of warfarin dose with monitoring of PT/INR monitoring is recommended during and after linezolid use [141,142].

Tedizolid has some overlap in drug interaction potential when compared to linezolid, but is considered more favorable overall. Both the prodrug tedizolid phosphate, and tedizolid were found to be weak, reversible inhibitors of monoamine oxidase A and B with negligible effect on blood pressure in the presence of tyramine [143]. Despite the *in vitro* concerns of monoamine oxidase inhibition, human and animal models did not yield signals worrisome for severe adrenergic or serotonergic toxicity at therapeutic tedizolid exposure [143]. Notwithstanding, subjects in phase 3 trials on serotonergic agents were excluded, limiting confirmation of the clinical safety when used in combination [109]. Tedizolid is not significantly metabolized via phase 1 hepatic oxidation (including CYP enzymes), limiting potential for inhibitors or inducers to impact tedizolid exposure. Tedizolid increased the AUC of rosuvastatin by 70 %, believed due to inhibition of BCRP. Other than inhibition of BCRP, however, tedizolid is not expected to have any effect on clinically relevant drug transporters [109].

4. Management of common adverse effects

Management of antimicrobial adverse drug events/side effects is a common and expected reality when treating mycobacterial infections. Toxicities are more likely to occur due to the use of multiple antimicrobial agents simultaneously for prolonged treatment durations. To maximize tolerability and identify the causative agent among the antimicrobial regimen, many experts recommend a sequential and incremental introduction of antitubercular agents after holding therapy for toxicity. Reintroduction generally involves starting one medication at a time, at relatively low doses, with slow, upward titration of doses to "target" dosing. Suggested management and monitoring strategies for common adverse effects are detailed below and summarized in Table 3.

4.1. Gastrointestinal distress

Gastrointestinal adverse effects often arise from a disruption of the usual gut microbiota when exposed to antimicrobials. In some studies, the reported incidence of antibiotic-associated diarrhea (AAD) is as high as 35 %, with an increased likelihood occurring in patients receiving multiple antimicrobial agents, fluoroquinolone or oxazolidinone antibiotics, and those of older age [144–147]. Additional risk factors include other underlying gastrointestinal illnesses, drugs that alter bowel motility, and recent surgery [148]. The importance of gastrointestinal-related adverse events in the treatment of MDR-TB should not be understated as it is a significant cause of patient morbidity and may be a primary barrier to patient willingness to complete the prolonged MDR-TB treatment regimen.

Supportive measures are often employed to mitigate GI-related side effects and may include a combination of dietary modifications, addition of probiotic supplements, and anti-diarrheal, antacid, and/or anti-nausea medications, dependent on the presenting symptom(s) [149,150]. Generally, a "bland" diet, avoidance of greasy, spicy, salty, acidic foods, dairy (lactose-containing) products, non-digestible sugar substitutes, alcohol, or other irritating substances is advised to limit additional stressors on the digestive system. Slow introduction of fiber-containing foods may serve as a "binding" agent to absorb excess fluid in the colon and add bulk to stools, slowing GI-transit time. Probiotic supplements or foods containing live bacterial cultures (yogurt, kefir) may be helpful for the management of antibiotic-associated diarrhea [151].

In addition to supportive care, modifications to antimicrobial administration techniques should also be considered. Antibiotics that may be administered without regard to food (i.e. absorption is not impacted significantly by the presence or absence of food) should generally be trialed with food to limit GI distress, such as the case with all agents found in BPaL/M [117]. Food in the stomach may limit direct chemical contact with the stomach/intestinal lining and mitigate GI upset. Additionally, taking medication with a full glass of water may enhance tablet dissolution and speed absorption, further limiting chemical irritation of the stomach lining. However, if antibiotic administration with a meal is found to irritate the GI tract and disrupt meals, administration on an empty stomach may be trialed to ascertain what is most tolerable for individual patients. Additionally, the time of day of medication administration may affect response to GI symptoms. Many experts may recommend taking the majority of the antibiotic regimen in the evening initially. If nausea/GI distress were noticed, it would likely have less impact or noticeability during the hours of sleep versus daytime hours when trying to perform activities of daily living [124]. Other patient-specific variables, such as daily work schedules, dietary restrictions, meal schedules, and administration time of other medications, must also be factored in to design a medication administration regimen that can be administered on a consistent basis to minimize antimicrobial-related side effects and optimize the likelihood of treatment course completion.

4.2. QT prolongation

Both moxifloxacin and bedaquiline have potential to cause cardiac conduction delays, namely, prolongation of the QT interval, through blockage of voltage-gated potassium channels, particularly the rapid component of the delayed rectifier potassium current I(Kr) [32].

Prolonged QT causes premature action potentials during the late phases of depolarization and can increase the risk of developing ventricular arrhythmias, including ventricular fibrillation. Heart rate may affect QT interval interpretation, with tachycardia causing artificial prolongation. To correct for variations in heart rate, the heart-rate corrected QT interval (QTc interval) is often used for medication monitoring. Additional cardiac abnormalities that may affect QT interval interpretation are both right and left bundle branch blockade, whereby manual calculation of the QT interval is most accurate. Normal QTc values are generally < 450 ms for men and < 460 ms for women. QTc values above these thresholds, but < 500 ms are considered "prolonged". Values > 500 ms are considered "highly abnormal" as the risk of developing torsade de pointes incrementally increases with increasing QTc. In addition to the absolute QTc value, the change from baseline can also be used to estimate risk of severity. As QTc measurements > 500 ms have been described as a risk factor for a proarrhythmic event, so to have changes of > 30 ms and > 60 ms from baseline [152,153].

After initiation of either bedaquiline or moxifloxacin, a QTc increase of 10–15 ms may be expected. The extent of increase is thought to be more prominent with an increasing number of concomitant QT-prolonging medications, although a significant difference in absolute QTc or the number of patients with prolonged QTc interval in head-to-head randomized trials with separate cohorts of patients treated with BPaL, with and without moxifloxacin (BPaL-M) was not seen [15]. The composite incidence of QTc interval increases > 60 ms from baseline or QTc > 500 ms was 1–2 % of recipients receiving BPaL or BPaL-M in phase 3 trials [13–15].

While the risk of severe QTc interval prolongation leading to serious adverse events or requiring drug discontinuation are relatively low, consequences of unmonitored therapy may be fatal. As such, the CDC has published provisional guidance for the safe use of bedaquiline in treatment of MDR-TB [47]. Recommendations include ECGs at baseline, after the initial 2-week titration, and again at 12 and 24 weeks after starting treatment, at a minimum. Patients receiving additional QT interval-prolonging medications (including fluoroquinolones or clofazimine) or with health conditions that predispose to long QT (including congenital long QT syndrome, decompensated heart failure, or underlying bradyarrhythmias) should be monitored more frequently (i.e. weekly). Baseline potassium, magnesium, calcium, TSH, and other modifiable laboratory risk factors should be obtained and corrected, if abnormal, to minimize risk. These should be followed at regularly scheduled intervals throughout treatment. Management of prolonged QT depends on the absolute QTc, extent of increase from previous baseline, and presence of related cardiac symptoms. If QTc prolongation above the normal limit, but < 500 ms, is detected during therapy, monitor ECG frequently to confirm QTc return to baseline and correct underlying lab abnormalities, if present. Discontinue therapy (and all other QT prolonging drugs) if patient develops confirmed QTc interval of > 500 ms or > 60 ms from baseline (confirmed by repeat ECG), ventricular arrhythmia, or other symptoms related to prolonged QTc.

4.3. Hepatotoxicity

Hepatotoxicity has been associated with BPaL and BPaL-M regimens. While differing definitions of hepatoxicity were used in the major randomized controlled trials, incidence of transaminitis (ALT or AST>3x ULN) occurred in roughly 10 % of participants, while incidence of "serious" liver-related adverse events is reported in 2–4 % of participants [13–15]. The incidence of these findings was more significant in persons living with HIV compared to HIV-negative subjects, likely related to a combination of antiretroviral medications, additional hepatotoxic agents, and other underlying comorbidities.

While receiving BPaL or BPaL-M, patients should be counseled to minimize or eliminate additional hepatotoxic substances, including, but not limited to, alcohol, acetaminophen, and non-prescribed herbal supplements. CDC Guidelines recommend baseline, 2-week, and then monthly assessment of AST, ALT, ALP, and serum bilirubin throughout the duration of these regimens [117]. More frequent monitoring may be considered if elevations in these labs occur or if clinical symptoms, such as recurrent nausea/vomiting, fatigue, jaundice, dark urine, or abdominal pain occur. Urgency of intervention is dictated by the degree of lab abnormality and presence or absence of symptoms. Asymptomatic elevations of mild-moderate severity can be repeated within 48–72 h. Symptomatic elevations should prompt urgent, in-person evaluation by a clinician, with follow-up, testing, and investigation for alternative causes as recommended in American Thoracic Society (ATS) guidelines [154], with disruption in therapy. General ATS guidance recommends therapy disruption if ALT>5x ULN or > 3x ULN with accompanied symptoms. CDC guidance provides more specific recommendations related to BPaL, with severe laboratory elevations (ALT/AST>8x ULN on a single measurement, ALT/AST>5x ULN on repeat measurements > 2 weeks, or AST/ALT elevations accompanied with total bilirubin > 2x ULN) prompting therapy discontinuation [117].

4.4. Peripheral neuropathy

Peripheral neuropathy was the most commonly reported drug-related adverse event and the most frequently cited reason for linezolid treatment interruption in the Nix-TB and ZeNix trials [13,14]. In the Nix-TB trial, linezolid was initiated at a dose of 1200 mg day for at least 4 weeks. In Nix-TB, 80 % of patients reported peripheral neuropathy, with over 50 % of these classified as "moderate to severe". Most cases resolved after treatment completion, although not all cases were reversible. In ZeNix, patients were randomized to 4 cohorts in a 1:1:1:1 ration based on differing daily linezolid doses (1200 mg or 600 mg) and durations (26 weeks or 9 weeks). Both the incidence and severity of linezolid-associated peripheral neuropathy was higher in patients receiving higher daily doses (1200 mg) and longer durations (26 weeks) [14].

Initial linezolid dosing should be limited to 600 mg daily to limit potential for neuropathy and other linezolid-related adverse effects [117]. If symptoms arise, treatment interruption and/or dose reduction to 300 mg daily should be considered. Linezolid TDM may be considered for dose optimization and to limit mitochondrial-related toxicities, including neuropathy. Generally, dosing is guided to a target trough level < 2 mcg/mL. Discussion of TDM for Linezolid and other emerging therapies for MDR TB is reviewed in detail by Maranchick and Peloquin [131].

All patients receiving linezolid as part of BPaL or BpaL-M should be assessed at baseline and routinely monitored while on therapy for symptoms including tingling, burning, freezing, numbness, or itching of the upper and lower extremities (usually first developing in the fingers and toes before progressing proximally). Monofilament testing monthly during extended courses may help identify symptoms early and should also be included in the physical examination of any patient reporting new onset of symptoms or worsening from baseline [117].

5. Conclusion

Moxifloxacin, bedaquiline, the nitroimidazoles (pretomanid/delamanid), and the oxazolidinones (linezolid/tedizolid) together have become welcome tools for treating drug-resistant TB, shortening the treatment course and providing less burdensome and less toxic treatment than earlier treatment paradigms. Moxifloxacin heralds potent TB microbiologic effect, impressive bioavailability, and extensive distribution, though long duration therapy requires close monitoring for QT prolongation and neuropsychiatric effect, with attention to the possibility of tendonitis/rupture. Bedaquiline's selectivity for mycobacterial ATP synthase, along with excellent absorption, extensive distribution, and a long half-life (months), provides value in extensive and long-lasting therapeutic exposure, even after patients cease oral therapy. Notwithstanding, QT prolongation occurs, agents that induce or inhibit

3A4 require caution with use, and monitoring for liver toxicity is important. The nitroimidazoles, pretomanid and delamanid, represent unique gems of chemical engineering that produced novel TB treatment with activity in both active and latent mycobacterial growth phases. Both require food during administration for optimal exposure, and multiple metabolic pathways limit their potential for drug interaction, though CYP3A4 inducers can decrease exposure of pretomanid. Well tolerated overall and in comparison, with historical MDR TB treatments, both are associated with gastrointestinal adverse effects and rarity of liver toxicity, and QT effects should be monitored. Linezolid's excellent microbiologic activity against TB can be offset by its mitochondrial toxicity (myelosuppression, neuropathy) during long TB treatment duration, though individualization of dosing schemes and TDM approaches are evolving to optimize use. Otherwise, linezolid is associated with mild GI upset and carries mild inhibitory effects on monoamine oxidase that require evaluation of interacting psychiatric medications and adrenergic stimulants, though usually mitigation allows linezolid incorporation into TB therapy. Tedizolid, though limited in clinical data, may afford a more tolerable agent with more favorable toxicity and interaction profile. Notwithstanding the inherent management needed for these emerging therapies and the required awareness of drug specific effects during long-duration antimicrobial treatment, these emerging therapies for TB have become valuable implements for clinicians, upgraded the therapeutic index of MDR TB treatment overall, and have enhanced treatment of what remains one of our world's most challenging infectious diseases.

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CRediT authorship contribution statement

Tanner M. Johnson: Writing – review & editing, Writing – original draft, Visualization, Project administration, Conceptualization. **Christina G. Rivera:** Writing – review & editing, Writing – original draft, Conceptualization. **Grace Lee:** Writing – review & editing, Writing – original draft, Conceptualization. **John D. Zeuli:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Conceptualization.

Declaration of competing interest

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