The effects of bedaquiline, delamanid, and pretomanid on QT interval prolongation among patients with tuberculosis: A systematic review and meta-analysis

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ABSTRACT

INTRODUCTION Certain anti-tuberculosis drugs, i.e. bedaquiline (BDQ), pretomanid (Pa), and delamanid (DLM) have been shown to prolong corrected QT interval (QTc), which can be fatal. We aimed to estimate the incidence and risk of QTc prolongation among tuberculosis patients receiving either BDQ, DLM, or Pa alone or in combination.

METHODS This meta-analysis systematically explored seven electronic databases (Clinicaltrials.gov, Cochrane CENTRAL, Embase, PROQUEST, PubMed, ScienceDirect, and SinoMed). Studies considered eligible if they were randomized clinical trials (RCTs) or non-randomized clinical trials (NRCTs) assessing QTc interval prolongation in patients receiving BDQ, DLM, and/or Pa, non-clinical trial study designs and studies of non-tuberculous mycobacterial infection were excluded. Risk of bias was assessed using the Delphi list for the RCTs and the Newcastle–Ottawa Scale for the NRCTs. Main outcomes were the incidence and risks compared to standard of care (SOC) of grades 3 and 4 QTc prolongation and the mean change of QTc interval (milliseconds). Limitations include inadequate subgroup analysis for potentially important and relevant confounders, variability in the period of drug administration, follow-up duration, as well as the incorporation of NRCTs.

RESULTS Eighteen trials were eligible out of 1184 retrieved records. Combination therapy was associated with higher incidence of grade ≥3 QTc prolongation (BDQ+DLM 25.0%; BDQ+Pa 7.3%) compared with single-drug use (DLM 3.1%; BDQ 2.6%; Pa 5.1%; SOC 3.4%). Compared to SOC, DLM receiving arms significantly increased the risk of QTc prolongation (RR=2.27; 95% CI: 1.21–4.24). In contrast, no significant difference in the risk of prolonged QTc interval was found with either BDQ alone (RR=1.03; 95% CI: 0.82–1.29) or BDQ+Pa (RR=0.31; 95% CI: 0.05–1.85).

CONCLUSIONS In comparison to standard treatment, the incidence of QTc was significantly higher when BDQ, DLM, or Pa were administered in combination, but not when used alone. These findings highlight the need for periodic ECG follow-up when these drugs are prescribed in combination.

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INTRODUCTION

The emergence of drug-resistant tuberculosis (DR-TB) strains that are refractory to the standard combination therapy is a worldwide concern[1]. Little progress was made with anti-TB agents for 40 years prior to the 2010s[2]. Only rifapentine (a long-acting rifamycin) was introduced in 1998[3]. The effectiveness of the available therapy against resistant strains during this time was limited. Recently, however, three new anti-TB drugs have been introduced: bedaquiline (BDQ) in 2012, delamanid (DLM) in 2014, and pretomanid (Pa) in 2019[4,5]. They are now part of the treatment regimen (for 6 or 9 months or longer) to treat multi-drug-resistant tuberculosis (MDR-TB)[6].

In addition to the standard of care, BDQ, DLM, and Pa are often used individually or in combination, and despite the encouraging evidence of the use of these drugs on DR-TB strains, they have been linked to cardiotoxic risks, specifically an effect on corrected QT interval (QTc). A cohort study reported that QTc prolongation was the most frequent treatment emergent adverse event (TEAE) (1.5%) among patients who received BDQ, leading to either discontinuation of the medication or withdrawal[7]. A systematic review reported that Pa was also associated with QTc prolongation, and the risk was even higher when combined with BDQ[8]. Li et

al.[9] studied concentration-QTc modeling on Pa alone and on the combination BDQ-Pa-linezolid (BPaL) regimen and found a mean change in QTc of 9.1 milliseconds (ms) and 13.6 ms, respectively. Similar concerns about QTc interval prolongation were also raised in several studies that assessed the safety of DLM-containing regimens[10,11]. Contrary evidence of no association between these drugs and QTc change also exists[12,13]. A trial from Motta et al.[13] reported differences in QTc prolongation across different BDQ and Pa combinations; however, none of them was considered clinically significant. The findings among the different aforementioned reviews highlight the need for a comprehensive systematic review and meta-analysis to quantify the incidence and the comparative risk of QTc prolongation upon using these drugs, both individually and in combination, to guide the need for clinical monitoring and ensure patient safety.

A limitation of the available studies is that they did not specify the cardiotoxicity or the risk of QTc prolongation that comes with the use of these drug[8,14-21]. Understanding the impact of these agents specifically on QTc can benefit both physicians and patients in making informed decisions and can allow physicians to adequately predict, assess, and monitor the cardiac risks following their administration. To our knowledge, no prior meta-analysis has systematically compared the incidence and relative risk of QTc prolongation associated with BDQ, DLM, and Pa, whether used alone or in combination. This study was therefore designed to fill this gap and provide clinicians with a more comprehensive, quantitative assessment of cardiotoxicity risks.

METHODS
Study protocol and registration

This meta-analysis complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol (PROSPERO: CRD42024553530).

Search strategy and study selection
We systematically searched seven electronic databases: ClinicalTrials.gov, Cochrane CENTRAL, Embase, ProQuest, PubMed/MEDLINE, ScienceDirect, and SinoMed. The search combined population terms ('tuberculosis' OR 'TB') with intervention terms ('bedaquiline' OR 'delamanid' OR 'pretomanid'). Two authors (MJ and IS) conducted the database searches, and four reviewers (AS, RH, IS, MJ) independently screened records, removed duplicates, and assessed eligibility for potential researches published up until December 2024. References of included studies were also screened for additional relevant records. No restrictions on publication date or language were applied.

Eligibility criteria
To be included, a study had to be: 1) a randomized controlled trial (RCT) or non-randomized controlled trial (NRCT); 2) participants diagnosed with TB; 3) an intervention arm that used any of the novel drugs (i.e. BDQ, DLM, or Pa); and 4)

reported outcomes relevant to QTc changes. Exclusion criteria included non-clinical trial study designs and studies of non-tuberculous mycobacterial infection.

Data extraction
A predefined Google Sheet was developed by MJ and IS prior to the data extraction process, which was performed by seven authors (MJ, IS, MFA, SA, YS, AS, RH). The data extracted included the following variables: trial registry codes, principal author's name, year of publication, trial design, blinding status, country of study, sample size, genders, participants' mean age, resistance profiles (i.e. rifampicin-resistant TB [RR-TB], multidrug-resistant TB [MDR-TB], pre-extensively drug-resistant TB [pre-XDR-TB], and extensively drug-resistant TB [XDR-TB]), and the HIV status. Data on the administered novel anti-TB regimens, doses, and durations were also recorded. Other anti-TB agents included in the regimens were also noted. Data on the QTc, including mean changes and the proportion of patients with prolonged QTc following therapies, were recorded.

Quality assessment
The quality of each included study was assessed independently by nine authors (CJ, IS, MFA, SA, YS, AS, RH, MAC, HI) using the Delphi Risk of Bias Tool for Clinical Trials[22]. The tool assesses the following methodological domains: 1) randomization, 2) allocation concealment, 3) baseline similarity, 4) specification of eligibility criteria, 5) blinding (i.e. assessors, care providers and patients), 6) estimates and measures of variability presentation, and 7) the inclusion of intention-to-treat analysis[22]. Each methodologic criterion scored 1 if 'yes', and 0 if either 'no' or 'don't know', with 9 being the highest possible overall score[23]. The assessment of NRCTs was done using the Newcastle Ottawa Scale (NOS)[24], which assesses three main domains: 1) selection (i.e. sample representativeness, non-respondents, exposure measurement); 2) comparability (i.e. controlling for confounding factors); and 3) outcome (i.e. outcome assessment method, statistical analysis). A study with a cumulative NOS score of ≥7 is considered good quality.

Outcome definitions
The outcome of interest was QTc prolongation following the addition of bedaquiline, pretomanid, and/or delamanid to the usual standard of care. The QTc was corrected using the Fridericia formula[25]. The QTc prolongation grading was done in accordance with the National Cancer Institute's Common Terminology of Clinical Adverse Events (NCI-CTCAE)[26]. Concerning our study: grade 3 QTc prolongation is a QTc of >501 ms or a change of >60 ms from baseline; grade 4 is defined as a QTc of >501 ms in addition to associated arrhythmias, i.e. torsades de pointes (TdP), polymorphic ventricular tachycardia (VT), or severe arrhythmias. The outcomes of interest included: 1) the incidence of grade 3

QTc and grade 4 QTc prolongation among patients receiving novel anti-TB agents; 2) the risk ratio (RR) for developing a prolonged QTc among patients receiving anti-TB agents compared to patients in the control arms; and 3) and the mean change of QTc (ms) following the use of novel anti-TB agents, which is defined as the average change in QTc interval compared to their baseline values.

Statistical analysis

Data analysis and plot synthesis were done using OpenMeta[Analyst] software, Brown University. The overall incidence of grade 3 QTc prolongation was calculated and estimated by taking absolute numbers reported by each study, followed by proportion single-arm meta-analysis. The binary outcome, i.e. risk of QTc prolongation compared to the standard of care (SOC), was reported as RR. The continuous outcome, i.e. the mean change of QTc during the follow-up period was reported as mean difference (in ms). A random-effects analysis model was selected for all analyses due to considerable between-study variability. Subgroup analyses were performed for all outcomes based on the novel anti-TB drugs administered. The I^2 statistic was used to assess heterogeneity, with a score of >75% regarded as highly heterogeneous. A $p<0.05$ was considered significant at a two-tailed 95% confidence interval (CI).

RESULTS

Literature search results

A total of 1184 studies were initially identified from seven electronic databases: PubMed/MEDLINE (n=522), Embase (n=200), Cochrane CENTRAL (n=148), ScienceDirect (n=141), Clinicaltrials.gov (n=75), PROQUEST (n=54), and SinoMed (n=44) (Figure 1). Following the initial removal of duplicate records (n=319), titles and abstracts were

Figure 1. PRISMA flowchart of selection of studies
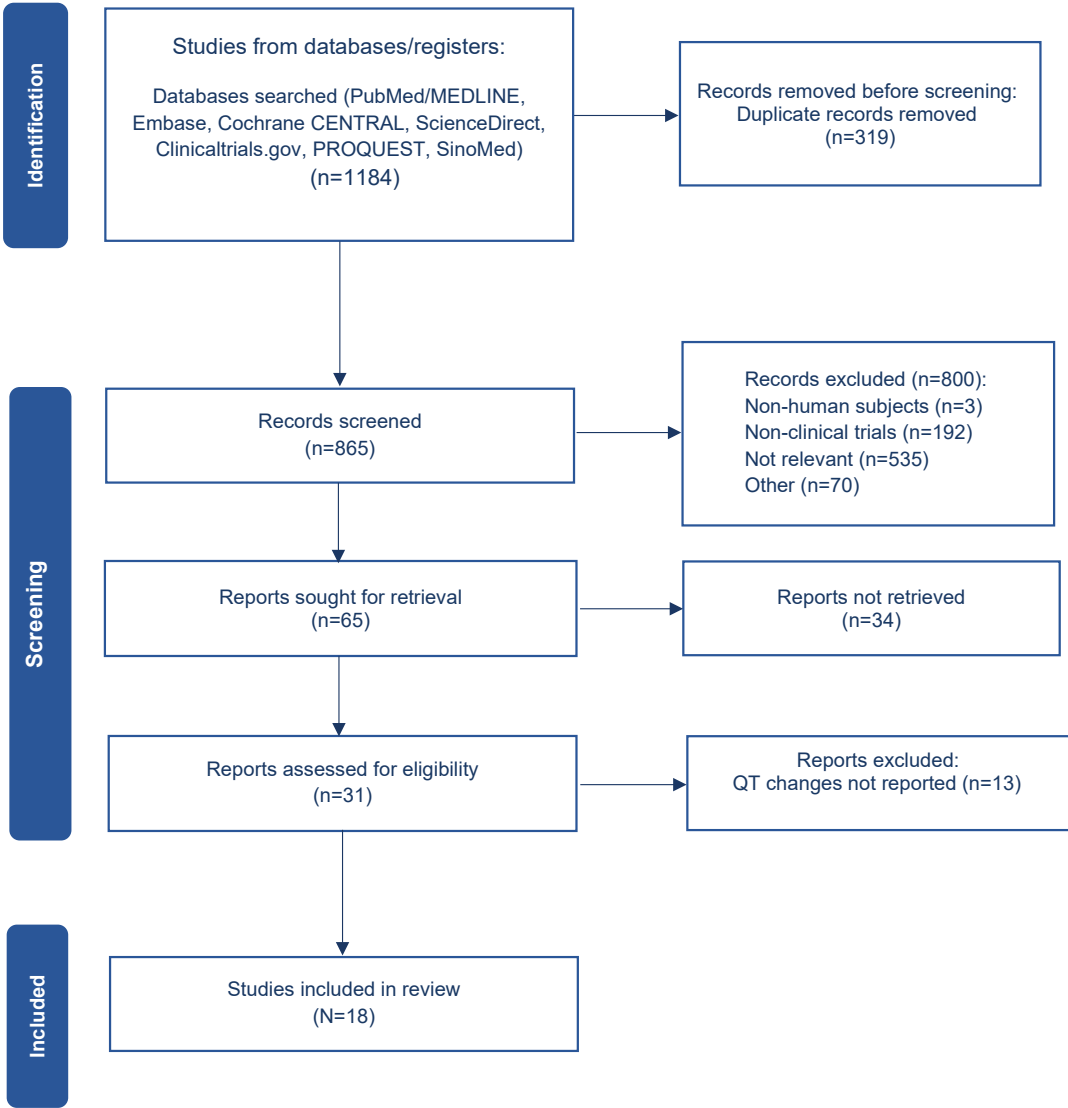
screened, and 800 additional records were excluded for the following reasons: irrelevant records (n=535), literature reviews (n=122), observational studies (n=56), systematic reviews (n=13), non-human subjects (n=3), and other (n=70). Of the remaining 65 reports that were eligible for full-text review, 34 were excluded due to full-text unavailability, and 13 were excluded for not reporting QTc changes. Among the excluded articles Diacon et al.[27] and Goodal el al.[28] were originally included in the initial review but not in the current one as they did not report QTc changes. A total of 18 clinical trials were ultimately selected for qualitative and quantitative analysis.

Overview of trials

Characteristics of included trials

The key characteristics of the included trials (n=18) are detailed in Table 1. The trials were published between 2012 and 2023 across multiple countries, including China, Egypt, Japan, Peru, South Africa, and the United States, among others. The pooled sample size was 3790 participants; the studies ranged from 6 patients[29] to 552 patients[30]. The majority of participants in the trials were men (2494), which was approximately double the total number of women (1296). Ten of the 18 trials were phase II[29,31-39], three trials were phase II/III[30,40,41], two trials were phase III[42], only one trial was phase I/II[28,43] and two trials did not specify what phase they were[44,45]. Four studies were double-blinded[31,32,38,40,42]. Five trials investigated BDQ in comparison to SOC[32,38,41,45]; three trials examined DLM in comparison to SOC[28,31,40,42], and one trial investigated Pa compared to SOC[33]. Three trials compared a combination therapy of BDQ and Pa against SOC[30,35,39]. One trial compared BDQ with DLM[37]. Four trials that assessed BDQ had no control arm (i.e. one arm design)[29,34,36,44]. The remaining one trial by Garcia-Prats et al.[43] assessed the safety and efficacy of DLM in a pediatric population. Follow-up durations varied across the trials.

Intervention characteristics

The regimen of BDQ was largely similar across the trials, i.e. 400 mg once daily for 2 weeks, followed by 200 mg three times a week[29,30,32,34,36-38,41,44,45] (Table 2). However, Tweed et. al.[35] prescribed a different dosing strategy with 200 mg of BDQ once daily for 8 weeks. Cevik et al.[39] also used 200 mg of BDQ once daily for up to 8 weeks followed by a decrease to 100 mg daily for up to 18 weeks. Most studies on DLM prescribed 100 mg twice a day for various durations up to 9 months[31,37,40,42,43]. However, three studies were dose-ranging studies comparing the 100 mg dose to a higher dose of 200 mg[31,42,43]. Lower doses were used in one study investigating a pediatric population by Garcia-Prats et al.[43] where the dose ranged from 10 mg for infants to 2-year-olds to 100 mg for the older subgroup (aged 12–17 years). For Pa dosing, most studies prescribed 200 mg once daily for between 8 weeks and 26 weeks[30,33,35,39,44]. However, Dawson et al.[33] compared the 100 mg of Pa with 200 mg dose once daily.

TB resistance profile and HIV coinfection status

TB resistance profiles are summarized in Supplementary file Table 1. The TB resistance profiles were reported as follows: MDR-TB (n=1507), RR-TB (n=1348), pre-XDR-TB (n=347), and XDR-TB (n=153). Of the pooled sample, 604 TB patients (15%) were also infected with HIV.

Quality of studies

The methodological quality of the trials is summarized in both Supplementary file Table 2 (for RCTs) and Supplementary file Table 3 (for NRCTs). For RCT studies, two studies received the highest score of 8 out of 9[38,42], while two studies had the lowest quality score of 3 out of 9[33,35]. Regarding NRCTs, four studies[34,43-45] scored ≥7, i.e. were good-quality studies, whereas one trial[29] scored 5, which is regarded as fair quality.

Outcome analysis

Incidence of grades 3 and 4 QTc prolongation

The pooled incidence of grade 3 QTc prolongation varied across regimens (Table 3). Combination therapies, particularly BDQ+DLM, showed the highest rates, while single-drug regimens generally had incidences ≤5% and were comparable to SOC. Grade 4 events were rare, with only four cases reported across three studies, two in BDQ arms and two in SOC arms. Compared with SOC, DLM monotherapy significantly increased the risk of QTc prolongation, whereas BDQ and BDQ+Pa did not (Figure 2).

Only three of the eighteen studies reported an incidence of grade 4 QTc interval prolongation[28,29,43]; two cases of grade 4 QTc interval prolongation were reported from two BDQ receiving arms[28,29] and two other cases were reported from SOC receiving arms[28]. The Garcia-Prats et al.[43] dose-increasing trial did not report any grade 4 QTc interval prolongation in any of DLM-receiving arms.

Relative risk of prolonged QTc interval compared to SOC

Among reporting studies (n=9), DLM-receiving arms were associated with a significant risk of QTc interval prolongation compared to SOC (RR=2.27; 95% CI: 1.21 – 4.24) (Figure 2). No significant difference in the risk of prolonged QTc interval was found with either BDQ alone (RR=1.03; 95% CI: 0.82–1.29) or in combination with Pa (RR=0.31; 95% CI: 0.05– 1.85).

Mean change of QTc interval

Details on the mean change of QTc interval were provided by five studies[30,32,33,36,37] (Table 4). Diacon et al.[32] found a considerable increase in the mean QTc interval in those receiving BDQ compared to SOC (15.4 vs 3.3 ms). Dooley et al.[37] also reported a similar value of 12.3 ms (95% CI: 7.8–16.7) among those receiving BDQ. Meanwhile, Vasilyeva et al.[36] only reported a 1.4 ms increase in QTc interval. Regarding DLM, Dooley et al.[37] reported an increase of 8.6 ms (95% CI: 4.0–13.1) among DLM-only recipients; when

Table 1. Baseline characteristics of the included trials

Authors Year	Study design, phase, blinding	Countries	Arms	Sample size (n)		Sex (n)		Age (years)
				Total	Each arm	M	F	Median (IQR) or Mean (SD)
Gler et al.[31] 2012	RCT, II, double-blinded	Philippines, Peru, Latvia, Estonia, China, Japan, Korea, Egypt, and the United States	DLM 100 mg BID	402	141	91	50	36 (19–63)
			DLM 200 mg BID		136	95	41	33 (18–63)
			SOC		125	89	36	35 (18–63)
Diacon et al.[32] 2014	RCT, IIb, double–blinded	Brazil, India, Latvia, Peru, Philippines, Russia, South Africa, and Thailand	BDQ	132	66	45	21	32 (18–63)
			SOC		66	40	26	34 (18–57)
Dawson et al.[33] 2015	RCT, IIb, open label	South Africa and Tanzania.	Pa 100 mg	2027	60	38	22	29.5 (11)
			Pa 200 mg		62	40	22	30.9 (9)
			SOC		59	41	18	30.4 (10)
			Pa 200 mg (DR-TB)		26	16	10	32.4 (10)
Pym et al.[34] 2016	Single arm, II, open label	China, South Korea, Philippines, Thailand, Estonia, Latvia, Russia, Turkey, Ukraine, Peru and South Africa	BDQ	233	233	150	83	32 (18–68)
Tsuyuguchi et al.[29] 2019	Single arm, II, open label	Japan	BDQ	6	6	3	3	45.5 (25–73)
Tweed et al.[35] 2019	RCT, IIb, open label	South Africa, Tanzania, Uganda	BloadPaZ	240	59	45	14	35.1 (13.0)
			B200PaZ		60	48	12	33.9 (10.5)
			SOC		61	46	15	33.3 (8.6)
			BPaMZ		60	43	17	34.0 (12.7)
Vasilyeva et al.[26] 2019	Single arm, II, open label	Russia and Lithuania.	BDQ	57	57	24	33	28 (18–61)
von Groote-Bidlingmaier et al.[42] 2019	RCT, III, double blind	Estonia, Latvia, Lithuania, Moldova, Peru, the Philippines, and South Africa	DLM	327	226	162	64	32 (18–64)
			SOC		101	76	25	31 (18–68)
Conradie et al.[44] 2020	Single arm, II, open label	South Africa	BDQ	109	109	57	52	35 (17–60)
Dooley et al.[37] 2021	RCT, II, open-label	South Africa, Peru	BDQ	84	28	22	6	34.5 (21–48)
			DLM		28	21	7	32 (19–56)
			BDQ-DLM		28	20	8	34 (19–49)

Table 1. Continued

Authors Year	Study design, phase, blinding	Countries	Arms	Sample size (n)		Sex (n)		Age (years)
				Total	Each arm	M	F	Median (IQR) or Mean (SD)
Fu et al.[45] 2021	NRCT open-label	China	SOC	103	68	50	18	36 (29–50.25)
			BDQ		35	25	10	32 (25–48)
Esmail et al.[41] 2022	RCT, II/III, open-label	South Africa	BDQ	93	49	34	15	37 (31–43)
			SOC		44	28	16	36 (29–46.5)
Garcia-Prats et al.[43] 2022	RCT, I/II, open label	Philippines and South Africa	12–17 years (DLM 100 mg)	37	7	4	3	15.5 (13.3–17.5)
			6–11 years (DLM 50 mg)		6	2	4	9.55 (7.3–11.4)
			3–5 years (DLM 25 mg)		12	6	6	4.35 (3.1–5.9)
			0–2 years (DLM 5–10 mg)		12	6	6	1.65 (0.7–2.5)
Goodall et al.[28] 2022	RCT, III, open label	Ethiopia, Georgia, India, Moldova, Mongolia, South Africa, and Uganda	BDQ oral	644	196	124	72	32.5 (26.3–41.9)
			SOC		187	115	72	
			BDQ 6 mo		134	81	53	
			SOC 6 mo		127	77	50	
Mok et al.[40] 2022	RCT, II/III, open label	South Korea	DLM	168	79	53	26	49 (39–57)
			SOC		89	63	26	46 (34–60)
Nyang'wa et al.[30] 2022	RCT, II/III, open-label	Belarus, South Africa, and Uzbekistan	SOC	552	152	96	56	37 (18–71)
			BPaL		123	65	58	35 (15–72)
			BPaLM		151	85	66	35 (17–71)
			BPaLC		126	84	42	32 (15–67)
Yao et al.[38] 2023	RCT, II, double-blinded	China	BDQ	68	34	18	16	46 (13)
			BDQ		34	19	15	43 (14)
Cevik et al.[39] 2024	RCT, IIC, open-label	Philippines, Tanzania, Brazil, South Africa, Uganda, Malaysia, Georgia, Russia	SOC	455	153	118	35	34 (26–46)
			BPaMZ (DS-TB)		150	112	38	35 (25–45)
			BPaMZ (DR-TB)		152	94	58	35 (26–47)
Total				**3790**		**2494**	**1296**	

B200PaZ: 200 mg BDQ plus pretomanid and pyrazinamide. BDQ: bedaquiline. BID: twice daily. BloadPaZ: BDQ loading dose plus pretomanid and pyrazinamide. BPaL: bedaquiline, pretomanid, and linezolid. BPaLC: bedaquiline, pretomanid, linezolid, and clofazimine. BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin. BPaMZ: bedaquiline, pretomanid, moxifloxacin and pyrazinamide. DLM: delamanid. DR-TB: drug-resistant tuberculosis. DS-TB: drug-sensitive tuberculosis. NRCT: non-randomized controlled trial. Pa: pretomanid. RCT: randomized controlled trial. SOC: standard of care.

Table 2. Bedaquiline, delamanid, and/or pretomanid dosing and accompanying regimens in the included studies

Author, year, registry	Arms	Intervention						Other anti-TB regimens	Tx Dur (week)	Follow-up (week)
		Bedaquiline (BDQ)		Delamanid (DLM)		Pretomanid (Pa)				
		Yes/No	Dosing regimen	Yes/No	Dosing regimen	Yes/No	Dosing regimen			
Gler et al.[31] 2012	DLM 100 mg BID	No	NA	Yes	100 mg BID (8 w)	No	NA	Ame/ Cm, Flq	12	weekly
	DLM 200 mg BID	No	NA	Yes	200 mg BID (8 w)	No	NA	Ame / Cm, Flq	12	weekly
	SOC	No	NA	No	NA	No	NA	Ame / Cm, Flq	12	weekly
Diacon et al.[32] 2014	BDQ	Yes	400 mg qd (2 w), then 200 mg tiw (22 w)	No	NA	No	NA	Ame, Flq, Eto / Pto, Z, E, Cs / Trd, PAS, Cm, Amx/ Clv, S	24	24, 72, 120
	SOC	No	NA	No	NA	No	NA			
Dawson et al.[33] 2015	Pa 100 mg	No	NA	No	NA	Yes	100 mg (8 w)	400 mg Mfx + 1500 mg Z	8	days 1, 2, 3, then once weekly for 8 weeks, followed by once every 10 days for 20 weeks
	Pa 200 mg	No	NA	No	NA	Yes	200 mg (8 w)	400 mg Mfx + 1500 mg Z		
	SOC	No	NA	No	NA	No		75 mg H, 150 mg R, 400 mg Z, 275 mg E		
	Pa 200 mg (DR-TB)	No	NA	No	NA	Yes	200 mg (8 w)	400 mg Mfx, 1500 mg Z	8	8, 20 weeks
Pym et al.[34] 2016	BDQ	Yes	400 mg qd (2 w), then 200 mg tiw (22 w)	No	NA	No	NA	Ofl, Lfx, Z, Ame, Cs, E, Pto	24	2, 4, 8, 12, 16, 20, 24, 36, 48, 60, 72, 84, 96
Tsuyuguchi et al.[29] 2019	BDQ	Yes	400 mg qd (2 w), then 200 mg tiw (22 w)	No	NA	No	NA	Lfx, S / Lzd, Kan / E, Cs, PAS / Z	24	2, 22, 24, 102, 126
Tweed et al.[35] 2019	BloadPaZ	Yes	400 mg qd (2 w), then 200 mg tiw (22 w)	No	NA	Yes	200 mg qd (8 w)	Z	8	weekly, 8 times
	B200PaZ	Yes	200 mg qd (8 w)	No	NA	Yes	200 mg qd (8 w)	Z	8	weekly, 8 times
	SOC	No	NA	No	NA	No	NA	H, R, Z, E	8	weekly, 8 times
	BPaMZ	Yes	200 mg qd (8 w)	No	NA	Yes	200 mg qd (8 w)	Mfx	8	weekly, 8 times
Vasilyeva et al.[26] 2019	BDQ	Yes	400 mg qd (2 w), then 200 mg tiw (22 w)	No	NA	No	NA	Flq, Lfx, Mfx, PAS, Z, Cm, Lzd, Trd, Cs	24	2, 4, 12,24, 28, 48, 72, 96, 120

Table 2. Continued

Author, year, registry	Arms	Intervention						Other anti-TB regimens	Tx Dur (week)	Follow-up (week)
		Bedaquiline (BDQ)		Delamanid (DLM)		Pretomanid (Pa)				
		Yes/No	Dosing regimen	Yes/No	Dosing regimen	Yes/No	Dosing regimen			
von Groote-Bidlingmaier et al.[42] 2019	DLM	No	NA	Yes	100 mg BID (2 m), then 200 mg qd (4 m)	No	NA	NA	26	8, 26, 78, 104, 130
	SOC	No	NA	No		No	NA	NA		
Conradie et al.[44] 2020	BDQ	Yes	400 mg qd (2 w), then 200 mg tiw (22 w)	No	NA	Yes	200 mg qd (26 w)	Lzd	26	1 to 16, 20, 26,
Dooley et al.[37] 2021	BDQ	Yes	400 mg qd (2 w), then 200 mg tiw (22 w)	No	NA	No	NA	Cm, Cs, E, Eto, Z, Lfx, H, Trd, Kan, Lzd	24	Every 2 weeks till week 30
	DLM	No	NA	Yes	100 mg BID (24 w)	No	NA			
	BDQ-DLM	Yes	400 mg qd (2 w), then 200 mg tiw (22 w)	Yes	100 mg BID (24 w)	No	NA			
Fu et al.[45] 2021	SOC	No	NA	No	NA	No	NA	Lzd, Flq, Cs, Cfz, Z, E /Pto	36-48	12, 24, 36
	BDQ	Yes	400 mg qd (2 w), then 200 mg tiw	No	NA	No	NA	Lzd, Flq, Cs, Cfz, Z, E		
Esmail et al.[41] 2022	BDQ	Yes	400 mg qd (2 w), then 200 mg tiw	No	NA	No	NA	Lfx, Lzd, Z + high-dose H / Eto / Trd	24-36	1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 48, 72, 96, 120, 144
	SOC	No	NA	No	NA	No	NA	Kan, Mfx, Cfz, Z + high-dose H / Eto / Trd	108-124	
Garcia-Prats et al.[43] 2022	12-17 years (DLM 100 mg)	No	NA	Yes	100 mg (6 m)	No	NA	Cm, Lfx, Cs, Pto, Z, E, PAS	24	96
	6-11 years (DLM 50 mg)	No	NA	Yes	50mg (6 m)	No	NA	Cm, Lfx, Cs, Pto, Z, E, PAS, H	24	
	3-5 years (DLM 25 mg)	No	NA	Yes	25 mg (6 m)	No	NA	Cm, Lfx, Cs, Pto, Z, E, PAS, H, Cfz	24	
	0-2 years (DLM 5-10 mg)	No	NA	Yes	10 mg (6 m)	No	NA	Cm, Lfx, Cs, Pto, Z, E, PAS, H, Cfz, Lzd	24	

Table 2. Continued

Author, year, registry	Arms	Intervention						Other anti-TB regimens	Tx Dur (week)	Follow-up (week)
		Bedaquiline (BDQ)		Delamanid (DLM)		Pretomanid (Pa)				
		Yes/No	Dosing regimen	Yes/No	Dosing regimen	Yes/No	Dosing regimen			
Goodall et al.[28] 2022	BDQ oral	Yes	NM	NM	NA	No	NA	Lfx, Cfz, E, Z, H, Pto	56	1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 60, 68, 76
	BDQ 6 mo	Yes	NM	NM	NA	No	NA	Cfz, Z, Lfx, then H + Kan	36	
	SOC	No	NM	NM	NA	No	NA	Mfx, Cfz, E, Z, Kan, H, Pto	56	
Mok et al.[40] 2022	DLM	No	NA	Yes	100 mg BID (9 m)	No	NA	Lzd, Lfx, Z	36	1, 2, 4, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 60, 68, 76, 84, 92, 100, 104
	SOC	No	NA	No	NA	No	NA	H, R, Z, E		
Nyang'wa et al.[30] 2022	SOC	No	NA	No	NA	No	NA	Lzd, Mfx, Cfz	24	1, 2, 6, 10, 14, 18, 24, 72, 108
	BPaL	Yes	400 mg qd (2 w), then 200 mg tiw (22 w)	No	NA	Yes	200 mg qd (24 w)			
	BPaLM	Yes	400 mg qd (2 w), then 200 mg tiw (22 w)	No	NA	Yes	200 mg qd (24 w)			
	BPaLC	Yes	400 mg qd (2 w), then 200 mg tiw (22 w)	No	NA	Yes	200 mg qd (24 w)			
Yao et al.[38] 2023	BDQ	Yes	400 mg qd (2 w), then 200 mg tiw (22 w)	No	NA	No	NA	Lfx, Lzd, Cs, Cfz	72	Every week that is a multiple of 12 up to week 72
	BDQ	Yes	400 mg qd (2 w), then 200 mg tiw (22 w)	No	NA	No	NA	Lfx, Lzd, Cs, Pto		
Cevik et al.[39] 2024	SOC	No	NA	No	NA	No	NA	H, R, Z, E,	26	4, 6, 8, 12, 17, 26, 52, 104
	BPaMZ (DS-TB)	Yes	200 mg qd (8 w), then 100 mg qd (17 w)	No	NA	No	200 mg qd (17 w)	Mfx, Z, H, R, E	17	
	BPaMZ (DR-TB)	Yes	200 mg qd (8 w), then 100 mg qd (18 w)	No	NA	Yes	200 mg qd (26 w)	Mfx, Z, H, R, E	26	

Ame: aminoglycoside. Amx/Clv: amoxicillin/clavulanate. B200PaZ: 200 mg BDQ plus pretomanid and pyrazinamide. BID: twice daily. BloadPaZ: BDQ loading dose plus pretomanid and pyrazinamide. BPaL: bedaquiline, pretomanid, and linezolid. BPaLC: bedaquiline, pretomanid, linezolid, and clofazimine. BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin. BPaMZ: bedaquiline, pretomanid, moxifloxacin and pyrazinamide. Cfz: clofazimine; Cm: capreomycin. Cs: cycloserine. DR-TB: drug-resistant tuberculosis. DS-TB: drug-sensitive tuberculosis. E: ethambutol. Eto: ethionamide. Flq: fluoroquinolone. H: isoniazid. Kan: kanamycin. Lfx: levofloxacin. Lzd: linezolid. Mfx: moxifloxacin. NA: not applicable. OBR: optimized background regimen. Ofl: ofloxacin. PAS: para-aminosalicylic acid. Pto: prothionamide. qd: quaque die (once a day); R: rifampicin; S: streptomycin; tiw: three times a week. Trd: terizidone; Tx Dur: treatment duration; Z: pyrazinamide.

Table 3. Grade 3 QTc changes

Study Year Drug(s)	Grade 3 QTc	Sample size (n)	Est	Lower	Upper	Weight in the subgroup	Overall weight
Subgroup BDQ							
Diacon, 2014, BDQ	1	79	1.3	0	5.4	11.072	3.349
Pym, 2016, BDQ	2	233	0.9	0	2.6	14.231	3.945
Tsuyuguchi, 2019, BDQ	4	6	66.7	23.6	98.7	2.316	0.937
Dooley, 2021, BDQ	4	28	14.3	3.3	30.1	6.910	2.338
Fu, 2021, BDQ MDR-TB	1	34	2.9	0	12.2	7.694	2.578
Fu, 2021, BDQ Pre-XDR-TB	1	24	4.2	0	17.0	6.307	2.212
Esmail, 2022, BDQ	0	49	1.0	0	6.5	9.278	2.960
Goodall, 2022, BDQ	7	196	3.6	1.4	6.7	13.847	3.878
Goodall, 2022, BDQ 6 months	4	134	3.0	0.6	6.7	12.839	3.695
Yao, 2023, BDQ 1	1	34	2.9	0	12.2	7.694	2.578
Yao, 2023, BDQ 2	0	34	1.4	0	9.2	7.813	2.608
BDQ (p=0.002, I^2=63.86%)	25	851	2.6	0.6	5.5		
Subgroup DLM							
Dooley, 2021, DLM	0	28	1.7	0	11.0	19.667	2.412
Garcia-Prats, 2022, DLM 100 mg	1	7	14.3	0	51.7	5.000	1.047
Garcia-Prats, 2022, DLM 50 mg	0	6	6.5	0	41.1	5.000	1.047
Garcia-Prats, 2022, DLM 25 mg	0	12	3.6	0	23.5	9.000	1.580
Garcia-Prats, 2022, DLM 5–10 mg	1	12	8.3	0	32.4	8.333	1.503
Mok, 2022, DLM	4	79	5.1	1.1	11.2	53.000	3.349
DLM (p=0.777, I^2=0%)	6	144	3.1	0.3	7.6		
Subgroup Pa							
Dawson, 2015, Pa 100 mg	2	60	3.3	0.1	9.8	40.468	3.124
Dawson, 2015, Pa 200 mg	4	62	6.5	1.4	14.2	41.806	3.153
Dawson, 2015, Pa 200 mg (DR-TB)	2	26	7.7	0.1	21.8	17.726	2.297
Pa (p=0.609, I^2=0%)	8	148	5.1	1.8	9.6		
Subgroup SOC							
Diacon, 2014, SOC	0	81	0.6	0	4.0	11.075	3.377
Dawson, 2015, SOC	0	59	0.8	0	5.4	9.488	3.124
Tweed, 2019, SOC	1	61	1.6	0	6.9	9.572	3.139
Fu, 2021, SOC	4	46	8.7	1.9	18.9	8.167	2.881
Esmail, 2022, SoC	1	44	2.3	0	9.5	7.952	2.838
Goodall, 2022, SOC	12	187	6.4	3.3	10.4	14.916	3.858
Goodall, 2022, SOC	8	127	6.3	2.6	11.3	13.220	3.665
Mok, 2022, SOC	0	89	0.6	0	3.6	11.544	3.445
Cevik, 2024, SOC	11	153	7.2	3.6	11.9	14.067	3.765
SOC (p=0.018, I^2=56.7%)	37	847	3.4	1.6	5.8		

Table 3. Continued

Study Year Drug(s)	Grade 3 QTc	Sample size (n)	Est	Lower	Upper	Weight in the subgroup	Overall weight
Subgroups BDQ + Pa							
Tweed, 2019, BloadPaZ	0	59	0.8	0	5.4	19.245	3.124
Tweed, 2019, B200PaZ	3	60	5.0	0.6	12.3	19.245	3.124
Tweed, 2019, BPaMZ	0	60	0.8	0	5.3	19.292	3.139
Cevik, 2024, BPaMZ 4 months	28	150	18.7	12.8	25.3	21.100	3.755
Cevik, 2024, BPaMZ 6 months	28	152	18.4	12.6	25	21.118	3.762
BDQ + Pa (p=0.001, I²=89.82)	59	481	7.3	1.4	16.8		
Subgroup BDQ + DLM							
Dooley, 2021, BDQ + DLM	7	28	25.0	9.0	41.0		2.375
BDQ + DLM	7	28	-	-	-		
Overall (p=0.001, I²=74.98)	142	2499	4.2	2.4	6.3		

B200PaZ: 200 mg BDQ plus pretomanid and pyrazinamide. BDQ: bedaquiline. BloadPaZ: BDQ loading dose plus pretomanid and pyrazinamide BPaMZ: bedaquiline, pretomanid, moxifloxacin and pyrazinamide. DLM: delamanid. DR: drug-resistant tuberculosis. DS: drug-sensitive tuberculosis. MDR-TB: multidrug resistant TB. Pa: pretomanid. Pre-XDR-TB: pre-extensively drug resistant TB. SOC: standard of care. TB: tuberculosis. Est: estimate.

Figure 2. Forest plot of the relative risk of overall QTc interval prolongation
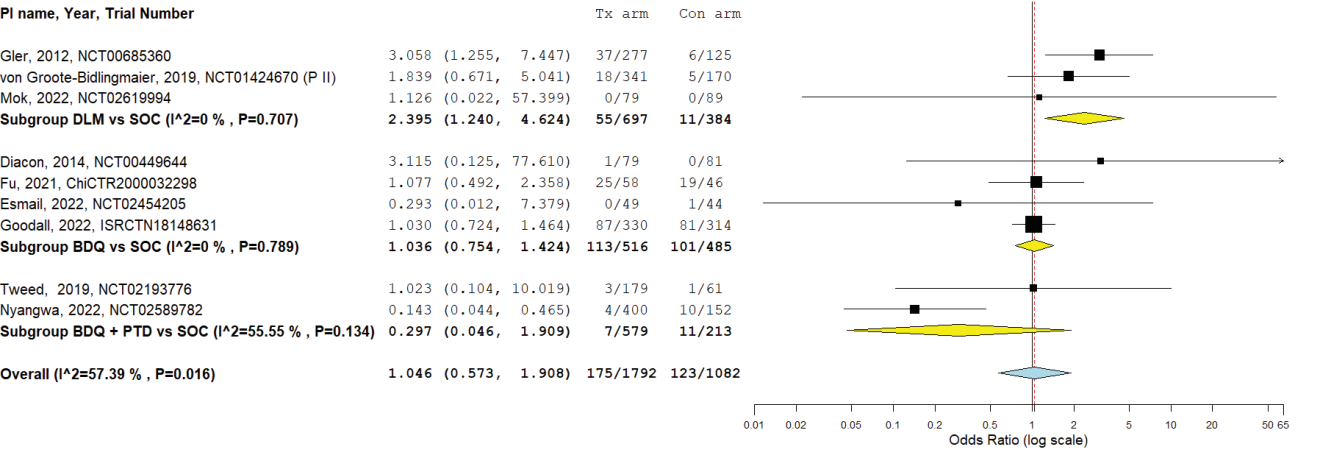
combined with BDQ, there was a considerable two-fold rise in the QTc interval (20.7ms; 95% CI: 16.1–25.3). Among those receiving Pa, Dawson et al.[33] reported a mean QTc interval increase of 11.1 ms with the 100 mg dose and 17.1 ms with the 200 mg dose, which were higher than the SOC (6.5 ms). Interestingly, Nyang'wa et al.[30] was the only study to find a decrease in the QTc interval; compared to the SOC at a 24-week follow-up, the combination regimens of BPaLM, BPaLC, and BPaL decreased -18.1, -5.4, and -20.0 ms, respectively. Pooled analyses were not performed due to lack of sufficient data and differences in interventions.

Publication bias assessment
The funnel plot in Figure 3 depicts a visually symmetrical distribution of studies. Egger's regression test demonstrated a low risk of publication bias (p=0.812).

Heterogeneity analysis between studies
The pooled analyses of overall QTc prolongation incidence showed a relatively high heterogeneity (I²=74.98%) (p=0.001). Each study had different regimens incorporating one or more of the novel drugs BDQ, DLM or Pa, as well as variations in the duration of the treatment, background regimen, and sample size. Further subgroup analyses revealed high heterogeneity among the BDQ+Pa subgroups (I²=89.82%) and moderate heterogeneity among the BDQ (I²=63.86%) and SOC (I²=56.7%) subgroups. The remaining subgroups (i.e. BDQ+DLM, DLM, and Pa subgroups) had very

Table 4. Mean post-treatment change of QTc interval in reporting studies

Author Year	Drugs of concern	Study arms	Sample size (n)	Mean change of QTc (milliseconds)	
				Mean	95% CI
Diacon, 2014	BDQ	BDQ	79	15.4	NA
	SOC	SOC	81	3.3	NA
Dawson, 2015	Pa	Pa 100 mg	60	11.1	5.7–16.5
	Pa	Pa 200 mg	62	17.1	15.1–20.4
	SOC	SOC	59	6.5	8.0–14.3
	Pa	Pa 200 mg (DR-TB)	26	11.1	5.7–16.5
Vasilyeva, 2019	BDQ	BDQ	57	1.4	NA
Dooley, 2021	BDQ	BDQ	28	12.3	7.8–16.7
	DLM	DLM	28	8.6	4.0–13.1
	BDQ + DLM	BDQ-DLM	28	20.7	16.1–25.3
Nyang'wa, 2022	SOC	SOC	152	0[a]	0
	BDQ + Pa	BPaL	123	-20[b]	-25.1–14.9
	BDQ + Pa	BPaLM	151	-18.1[b]	-23.4 – -12.8
	BDQ + Pa	BPaLC	126	-5.4[b]	-10.3 – -0.6

[a] Reference value compared to intervention arms. [b] Mean difference compared to SOC. BDQ: bedaquiline. BPaL: bedaquiline, pretomanid, and linezolid. BPaLC: bedaquiline, pretomanid, linezolid, and clofazimine. BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin. DLM: delamanid. NA: not applicable. Pa: pretomanid. SOC: standard of care.

Figure 3. Funnel plot of the publication bias (p=0.812)
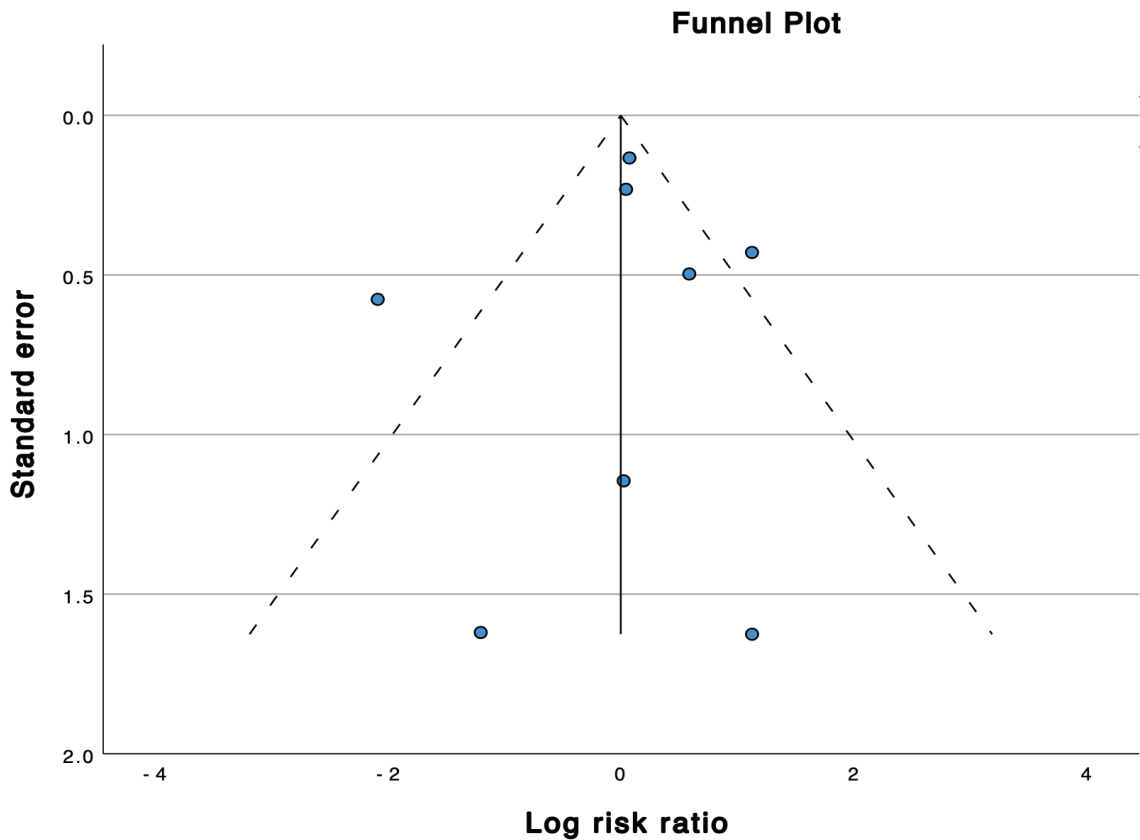
low heterogeneity (I²=0%) due to the low number of studies for each subgroup (between 1 and 2 studies).

DISCUSSION

Since the discovery of the first antibiotic, penicillin by Alexander Fleming, the treatment of infections was revolutionized; however, their effectiveness had a rapid decline due to the wide spread of antibiotic-resistant strains, creating the need for strict usage of antibiotics and continuous search for new treatment alternatives[46-48]. Due to increased resistance profiles the pharmacotherapeutic strategy for DR-TB treatment continues to evolve. The latest update to the WHO Consolidated Guidelines on Tuberculosis[49] has given two new recommendations for DR-TB treatment: 1) a 6-month BPaLM regimen for patients with RR-TB, MDR-TB, and pre-XDR-TB; and 2) a 9-month all-oral regimen in patients with MDR/RR-TB in whom fluoroquinolones resistance (i.e. pre-XDR-TB) has been excluded. Concerning this recommendation, determining the effect that novel anti-TB agents have on the QTc interval is particularly relevant for understanding the cardiac and arrhythmogenic risks to DR-TB patients.

This study aimed to evaluate the impacts that BDQ, DLM, and Pa – individually or in combination – have on the incidence and risk of QTc interval prolongation, as well as the mean change of QTc interval, based on published clinical trials. We found that, when added to the SOC, BDQ, DLM, and Pa when used individually, had incidence rates of 2.6%, 3.1%, and 5.1%, respectively, which are comparable to the SOC (3.4%). When it comes to the relative risk, only DLM-receiving arms showed significant risk of QTc interval prolongation compared to the controls (RR=2.27; 95% CI: 1.21–4.24).

Our pooled analyses estimated that when used alone, the drugs posed an insignificant difference in the risk of prolonged QTc compared to SOC. This correlates with a previous systematic review on BDQ-containing regimens which reported a relatively low incidence of QTc prolongation[50]. Moreover, the risk of serious dysrhythmias and grade 4 prolongation is generally considered low; in our study, the incidence of grade 4 prolongation among patients receiving BDQ-containing regimens was reported in only 2 cases[51-54]. However, a scoping review found a higher incidence of prolonged QTc with BDQ+DLM-containing regimens[10]. Although it was suggested that Pa may not be associated with an increase in QTc, the possibility of its effect on QTc length when combined with other drugs (BDQ, clofazimine, and fluoroquinolones) still mandates periodic QTc monitoring. Our findings suggest that the effects of combining ≥2 agents may produce exponential rather than additive effects on the incidence of QTc prolongation, i.e. BDQ+DLM (25% [9.0–41.0]) and BDQ+Pa (7.3% [1.4–16.8]). This is particularly relevant considering the 2022 World Health Organization updates that want to standardize the implementation of BPaL/BPaLM regimens in the clinical

setting.

With regard to the mean QTc change, the trends indicate that BDQ mildly increased the mean QTc; Diacon et al.[32] and Dooley et al.[37] reported a mean QTc change of 15.4 and 12.3 ms, respectively. Although DLM produced a smaller rise in the mean post-treatment QTc (8.6 ms), the combination of DLM-BDQ may produce a higher QTc (20.7 ms). A systematic review by Simanjuntak et al.[50] showed that pooled data from both interventional and observational studies reported a mean QTc change ranging from 11 to 52.5 ms following BDQ treatment. In contrast, a study among healthy volunteers found that neither a single administration of 400 mg nor 1000 mg of Pa was associated with any clinical QTc prolongation[55]. When co-administered with moxifloxacin (400 mg), Pa's pharmacokinetics were consistent, and the individually corrected QTc effects were attributed to moxifloxacin alone[55]. Regarding the BPaL regimen, Li et al.[55] predicted a 13.6 ms (90% CI upper limit: 15.0 ms) mean QTcN change, which was different from the reported trial by Nyang'wa et al.[30] that did not produce a higher QTc compared to baseline. These inconsistencies with regard to the evidence of mean QTc change following BPaL regimen administration should be further investigated.

BDQ's association with a higher risk of prolonged QTc may be explained by its primary metabolite, N-desmethyl metabolite (M2). M2 has been linked to a higher risk of toxicity, including prolonged QTc, secondary to cellular phospholipids accumulation[56]. Serum M2 concentration was constant during BDQ administration, which might explain why prolonged QTc occurred following BDQ discontinuation. Furthermore, the risk of prolonged QTc also appears to be associated with other anti-TB drugs, including clofazimine, fluoroquinolones, and Pa[56]. Our study found a similar trend, in which the combination of BDQ with either DLM or Pa was linked to a higher incidence of prolonged QTc. The Nix-TB study (NCT02333799) reported that at the estimated mean M2 concentration of 0.25 µg/mL, the mean QTcN increased 4.5 ms[9,44], which was further increased by the addition of Pa. The mean steady-state secular-trend QTcN was predicted to be 9.6 ms for the 200 mg dose[9]. The metabolite of DLM, DM-6705, has a similar mechanism to M2, which results in prolonged QTc due to its inhibition of the rapidly activating delayed rectifier potassium channels (iKR) in the cardiomyocytes[37]. Both DM-6705 and M2 have long half-lives, resulting in the maximal QTc effect of approximately 5–8 weeks and 24 weeks, respectively[34].

Our findings highlight that the risk of clinically significant QTc prolongation is greatest with combination regimens, particularly BDQ+DLM and, to a less extent, BDQ+Pa. Therefore, we recommend that clinicians adopt a structured monitoring strategy: a baseline ECG should always be obtained, with correction of any electrolyte abnormalities and careful review of concomitant QT-prolonging medications. For single-agent regimens (BDQ, DLM, or Pa), monthly ECG monitoring after a baseline and a 2-week follow-up is

generally sufficient, as QTc changes with monotherapy are uncommon and typically mild. In contrast, for combination regimens, closer early surveillance is warranted, with weekly ECGs during the first 2–4 weeks followed by checks at weeks 6 and 8, then monthly if stable. This schedule reflects the pharmacokinetic profiles of BDQ and DLM, whose active metabolites (M2 and DM-6705) accumulate slowly and can exert maximal QTc effects several weeks into therapy; hence, early and mid-course monitoring helps detect progressive prolongation before it becomes clinically significant. A QTc ≥500 ms or an increase ≥60 ms from baseline should prompt immediate evaluation, correction of reversible factors, and consideration of drug interruption or substitution. These measures provide a balance between patient safety and treatment feasibility, ensuring that potent novel regimens can be used effectively while minimizing arrhythmogenic risk.

Strengths and limitations

This study, to the best of our knowledge, represents the first meta-analysis to assess the effects of the three anti-TB agents (BDQ, DLM, and Pa, alone or in combination) on the QTc interval. The findings in this study exhaustively addressed the incidence and risk of QTc interval prolongation as well as the mean change of QTc interval in each BDQ-, DLM-, and/or Pa-containing regimen pooled from published clinical trials. This study is important since the three studied agents were integrated into the WHO Group A (BDQ, linezolid, and levofloxacin/moxifloxacin) and Group C (DLM, ethambutol, pyrazinamide, and imipenem/meropenem) regimens for treating MDR-TB in 2019, as well as the BPaL/BPaLM regimens for treating DR-TB in 2022[6,57]. This study further supports the WHO recommendation to use electrocardiographic screening during the administration of the anti-TB agents, especially for at-risk populations[58].

There were some limitations in our study. These include inadequate subgroup analysis for potentially important and relevant confounders, such as treatment adherence, serum drug level, baseline QTc interval, drug resistance profile, and cardiovascular comorbidities. Furthermore, optimized background regimens (OBR) are another important confounding factor as they may also play a role in influencing the QTc interval. As observed in our study, the combination of BDQ with either DLM or Pa increased the incidence of QTc interval prolongation compared to individual drugs alone; the same trends may be observed with other select OBR in combination with any of those agents. These limitations should be the subject for future studies. Another notable limitation is the variability in the period of drug administration, follow-up duration, adjunctive OBR, as well as the incorporation of NRCTs, which amplify the risk of confounding. Furthermore, none of the included studies reported body temperature in relation to QTc prolongation. Knowing that it is biologically plausible for fever and hypothermia to independently increase arrhythmic risk, this remains an unaddressed factor and warrants investigation in future trials.

CONCLUSIONS

While BDQ, DLM, or Pa when used individually did not increase the incidence of QTc prolongation compared with SOC, combining two or more of these agents substantially amplified the risk. This finding carries clear clinical implications: routine ECG monitoring must be considered essential, for all patients treated with a combination of these novel anti-TB agents. baseline and follow-up ECGs to detect early QTc changes must be considered. Equally important, the use of multiple QTc-prolonging drugs should be avoided whenever possible; such combinations should be reserved only for circumstances where therapeutic benefits clearly outweigh the potential for life-threatening arrhythmias.

CONFLICTS OF INTEREST

FUNDING

ETHICAL APPROVAL AND INFORMED CONSENT

Ethical approval and informed consent were not required for this study.

DATA AVAILABILITY

The data supporting this research are available from the authors on reasonable request.

AUTHORS' CONTRIBUTIONS

MCJ: conceptualization. MCJ and IS: methodology, project administration. MCJ: software. NS: validation. MCJ, IS and YS: database searching. MCJ, IS, YS, AS and AU: reports screening. MCJ, IS, MFSA, SA, YS, AS, RH, MAC and HI: quality. MCJ, IS, MFSA, SA, YS, AS and RH: data extraction. IS: data analysis. MCJ, IS, MFSA, SA and MAC: writing of original draft. MCJ and NS: writing, reviewing and editing of the manuscript. MCJ: visualization. NS: supervision. All authors have read and approved the final version of the manuscript.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer reviewed.

REFERENCES

1. World Health Organization. Department for HIV, Tuberculosis, Hepatitis and Sexually Transmitted Infections. World Health Organization. Accessed September 4, 2025. https://www.who.int/teams/global-tuberculosis-programme/diagnosis-treatment/treatment-of-drug-resistant-tb/types-of-tb-drug-resistance
2. Mahajan R. Bedaquiline: First FDA-approved tuberculosis

drug in 40 years. Int J Appl Basic Med Res. 2013;3(1):1-2. doi:10.4103/2229-516X.112228

3. Roehr B. FDA approves rifapentine for the treatment of pulmonary tuberculosis…. Food and Drug Administration. J Int Assoc Physicians AIDS Care. 1998;4(8):19-25. Accessed September 4, 2025. https://pubmed.ncbi.nlm.nih.gov/11365728/

4. Ryan NJ, Lo JH. Delamanid: First global approval. Drugs. 2014;74(9):1041-1045. doi:10.1007/s40265-014-0241-5

5. U.S. Food and Drug Administration. Drug Trials Snapshots. Accessed September 4, 2025. https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots

6. Vanino E, Granozzi B, Akkerman OW, et al. Update of drug-resistant tuberculosis treatment guidelines: A turning point. Int J Infect Dis. 2023;(130 suppl 1):S12-S5. doi:10.1016/j.ijid.2023.03.013

7. Pai H, Ndjeka N, Mbuagbaw L, et al. Bedaquiline safety, efficacy, utilization and emergence of resistance following treatment of multidrug-resistant tuberculosis patients in South Africa: A retrospective cohort analysis. BMC Infect Dis. 2022;22(1):870. doi:10.1186/s12879-022-07861-x

8. Gils T, Lynen L, de Jong BC, Van Deun A, Decroo T. Pretomanid for tuberculosis: A systematic review. Clin Microbiol Infect. 2022;28(1):31-42. doi:10.1016/j.cmi.2021.08.007

9. Li H, Salinger DH, Everitt D, Li M, et al. Long-term effects on QT prolongation of pretomanid alone and in combinations in patients with tuberculosis. Antimicrob Agents Chemother. 2019;63(10). doi:10.1128/AAC.00445-19

10. Putra ON, Yulistiani Y, Soedarsono S. Scoping review: QT interval prolongation in regimen containing bedaquiline and delamanid in patients with drug-resistant tuberculosis. Int J Mycobacteriol. 2022;11(4):349-355. doi:10.4103/ijmy.ijmy_178_22

11. Auchynka V, Kumar AMV, Hurevich H, et al. Effectiveness and cardiovascular safety of delamanid-containing regimens in adults with multidrug-resistant or extensively drug-resistant tuberculosis: A nationwide cohort study from Belarus, 2016-18. Monaldi Arch Chest Dis. 2021;91(1). doi:10.4081/monaldi.2021.1647

12. Gavras N, Schluger NW. QT Prolongation associated with administration of Bedaquiline, a novel anti-tuberculosis drug. Cardiol Rev. 2024. doi:10.1097/CRD.0000000000000790

13. Motta I, Cusinato M, Ludman AJ, et al. How much should we still worry about QTc prolongation in rifampicin-resistant tuberculosis? ECG findings from TB-PRACTECAL clinical trial. Antimicrob Agents Chemother. 2024;68(7):e0053624. doi:10.1128/aac.00536-24

14. Rehman O, Fatima E, Ali A, Akram U, Nashwan A, Yunus F. Efficacy and safety of bedaquiline containing regimens in patients of drug-resistant tuberculosis: An updated systematic review and meta-analysis. J Clin Tuberc Other Mycobact Dis. 2024;34:100405. doi:10.1016/j.jctube.2023.100405

15. Jihwaprani MC, Sun Y, Rizky WC, Sula I, Saquib N. Establishing the safety and efficacy of Bedaquiline-containing regimen for the treatment of drug-resistant tuberculosis: A systematic

16. Ahmed SH, Haider H, Moeed A, et al. Efficacy and safety of bedaquiline and delamanid in the treatment of drug-resistant tuberculosis in adults: A systematic review and meta-analysis. Indian J Tuberc. 2024;71(1):79-88. doi:10.1016/j.ijtb.2023.05.005

17. Holmgaard FB, Guglielmetti L, Lillebaek T, Andersen AB, Wejse C, Dahl VN. Efficacy and tolerability of concomitant use of Bedaquiline and Delamanid for multidrug- and extensively drug-resistant tuberculosis: A systematic review and meta-analysis. Clin Infect Dis. 2023;76(7):1328-1337. doi:10.1093/cid/ciac876

18. Nasiri MJ, Zangiabadian M, Arabpour E, et al. Delamanid-containing regimens and multidrug-resistant tuberculosis: A systematic review and meta-analysis. Int J Infect Dis. 2022;124 Suppl 1(Suppl 1):S90-S103. doi:10.1016/j.ijid.2022.02.043

19. D'Ambrosio L, Centis R, Tiberi S, et al. Delamanid and bedaquiline to treat multidrug-resistant and extensively drug-resistant tuberculosis in children: A systematic review. J Thorac Dis. 2017;9(7):2093-2101. doi:10.21037/jtd.2017.06.16

20. Al Omar MFS, Alchikhsuliman IEM, Awad SM, Rajab N, Alawi YM, Mohamed Ibrahim LY, et al. Hepatic Safety of Bedaquiline, Delamanid, and Pretomanid: A Systematic Review and Meta-analysis. International Journal of Mycobacteriology 2025. doi:10.4103/ijmy.ijmy_97_25

21. Sun Y, Sula I, Jihwaprani MC, Saquib N. Radiological Resolution of Pulmonary Lesions among Drug-resistant Tuberculosis Patients following Bedaquiline-containing Regimen Therapy: A Meta-analysis of Randomized Clinical Trials. International Journal of Mycobacteriology. 2025. doi:10.4103/ijmy.ijmy_174_25

22. Verhagen AP, de Vet HC, de Bie RA, et al. The Delphi list: A criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. J Clin Epidemiol. 1998;51(12):1235-1241. doi:10.1016/s0895-4356(98)00131-0

23. Berger VW, Alperson SY. A general framework for the evaluation of clinical trial quality. Rev Recent Clin Trials. 2009;4(2):79-88. doi:10.2174/157488709788186021

24. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25(9):603-605. doi:10.1007/s10654-010-9491-z

25. Phan DQ, Silka MJ, Lan YT, Chang RK. Comparison of formulas for calculation of the corrected QT interval in infants and young children. J Pediatr. 2015;166(4):960-964. doi:10.1016/j.jpeds.2014.12.037

26. National Cancer Institute. Common Terminology Criteria for Adverse Events v3.0 (CTCAE). National Cancer Institute; 2006. Accessed September 4, 2025. https://dctd.cancer.gov/research/ctep-trials/for-sites/adverse-events/ctcae-v3.pdf

27. Diacon AH, Donald PR, Pym A, et al. Randomized pilot trial

of eight weeks of bedaquiline (TMC207) treatment for multidrug-resistant tuberculosis: Long-term outcome, tolerability, and effect on emergence of drug resistance. Antimicrob Agents Chemother. 2012;56(6):3271-3276. doi:10.1128/AAC.06126-11

28. Goodall RL, Meredith SK, Nunn AJ, et al. Evaluation of two short standardised regimens for the treatment of rifampicin-resistant tuberculosis (STREAM stage 2): An open-label, multicentre, randomised, non-inferiority trial. Lancet. 2022;400(10366):1858-1868. doi:10.1016/S0140-6736(22)02078-5

29. Tsuyuguchi K, Sasaki Y, Mitarai S, Kurosawa K, Saito Y, Koh T. Safety, efficacy, and pharmacokinetics of bedaquiline in Japanese patients with pulmonary multidrug-resistant tuberculosis: An interim analysis of an open-label, phase 2 study. Respir Investig. 2019;57(4):345-353. doi:10.1016/j.resinv.2019.01.001

30. Nyang'wa BT, Berry C, Kazounis E, et al. A 24-week, all-oral regimen for Rifampin-resistant tuberculosis. N Engl J Med. 2022;387(25):2331-2343. doi:10.1056/NEJMoa2117166

31. Gler MT, Skripconoka V, Sanchez-Garavito E, et al. Delamanid for multidrug-resistant pulmonary tuberculosis. N Engl J Med. 2012;366(23):2151-2160. doi:10.1056/NEJMoa1112433

32. Diacon AH, Pym A, Grobusch MP, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. N Engl J Med. 2014;371(8):723-732. doi:10.1056/NEJMoa1313865

33. Dawson R, Diacon AH, Everitt D, et al. Efficiency and safety of the combination of moxifloxacin, pretomanid (PA-824), and pyrazinamide during the first 8 weeks of antituberculosis treatment: A phase 2b, open-label, partly randomised trial in patients with drug-susceptible or drug-resistant pulmonary tuberculosis. Lancet. 2015;385(9979):1738-1747. doi:10.1016/S0140-6736(14)62002-X

34. Pym AS, Diacon AH, Tang SJ, et al. Bedaquiline in the treatment of multidrug- and extensively drug-resistant tuberculosis. Eur Respir J. 2016;47(2):564-574. doi:10.1183/13993003.00724-2015

35. Tweed CD, Dawson R, Burger DA, et al. Bedaquiline, moxifloxacin, pretomanid, and pyrazinamide during the first 8 weeks of treatment of patients with drug-susceptible or drug-resistant pulmonary tuberculosis: A multicentre, open-label, partially randomised, phase 2b trial. Lancet Respir Med. 2019;7(12):1048-1058. doi:10.1016/S2213-2600(19)30366-2

36. Vasilyeva I, Mariandyshev A, Kazennyy B, et al. Early access to bedaquiline for extensively drug-resistant (XDR) and pre-XDR tuberculosis. Eur Respir J. 2019;54(1):1802208. doi:10.1183/13993003.02208-2018

37. Dooley K, Rosenkranz S, Conradie F, et al. QT effects of bedaquiline, delamanid, or both in patients with rifampicin-resistant tuberculosis: A phase 2, open-label, randomised, controlled trial. Lancet Infect Dis. 2021;21(7):975–983. doi:10.1016/S1473-3099(20)30770-2

38. Yao G, Zhu M, Nie Q, et al. Improved outcomes following addition of bedaquiline and clofazimine to a treatment regimen for multidrug-resistant tuberculosis. J Int Med Res. 2023;51(1):3000605221148416. doi:10.1177/03000605221148416

39. Cevik M, Thompson LC, Upton C, et al. Bedaquiline-pretomanid-moxifloxacin-pyrazinamide for drug-sensitive and drug-resistant pulmonary tuberculosis treatment: A phase 2c, open-label, multicentre, partially randomised controlled trial. Lancet Infect Dis. 2024;24(9):1003-1014. doi:10.1016/S1473-3099(24)00223-8

40. Mok J, Lee M, Kim DK, et al. 9 months of delamanid, linezolid, levofloxacin, and pyrazinamide versus conventional therapy for treatment of fluoroquinolone-sensitive multidrug-resistant tuberculosis (MDR-END): A multicentre, randomised, open-label phase 2/3 non-inferiority trial in South Korea. Lancet. 2022;400(10362):1522-1530. doi:10.1016/S0140-6736(22)01883-9

41. Esmail A, Oelofse S, Lombard C, et al. An all-oral 6-month regimen for multidrug-resistant tuberculosis: A multicenter, randomized controlled clinical trial (the NExT Study). Am J Respir Crit Care Med. 2022;205(10):1214-1227. doi:10.1164/rccm.202107-1779OC

42. von Groote-Bidlingmaier F, Patientia R, Sanchez E, et al. Efficacy and safety of delamanid in combination with an optimised background regimen for treatment of multidrug-resistant tuberculosis: A multicentre, randomised, double-blind, placebo-controlled, parallel group phase 3 trial. Lancet Respir Med. 2019;7(3):249-259. doi:10.1016/S2213-2600(18)30426-0

43. Garcia-Prats AJ, Frias M, van der Laan L, et al. Delamanid added to an optimized background regimen in children with multidrug-resistant tuberculosis: Results of a Phase I/II Clinical Trial. Antimicrob Agents Chemother. 2022;66(5):e0214421. doi:10.1128/aac.02144-21

44. Conradie F, Diacon AH, Ngubane N, et al. Treatment of highly drug-resistant pulmonary tuberculosis. N Engl J Med. 2020;382(10):893-902. doi:10.1056/NEJMoa1901814

45. Fu L, Weng T, Sun F, et al. Insignificant difference in culture conversion between bedaquiline-containing and bedaquiline-free all-oral short regimens for multidrug-resistant tuberculosis. Int J Infect Dis. 2021;111:138-147. doi:10.1016/j.ijid.2021.08.055

46. Lobanovska M, Pilla G. Penicillin's discovery and antibiotic resistance: Lessons for the future? Yale J Biol Med. 2017;90(1):135-145. Accessed September 4, 2025. https://pubmed.ncbi.nlm.nih.gov/28356901/

47. Sula I, Alreshidi MA, Alnasr N, Hassaneen AM, Saquib N. Urinary tract infections in the Kingdom of Saudi Arabia, a review. Microorganisms. 2023;11(4):952. doi:10.3390/microorganisms11040952

48. Jihwaprani MC, Sula I, Coha D, et al. Bacterial profile and antimicrobial susceptibility patterns of common neonatal sepsis pathogens in Gulf Cooperation Council countries: A systematic review and meta-analysis. Qatar Med J. 2024;2024(4):62. doi:10.5339/qmj.2024.62

49. World Health Organization. WHO consolidated guidelines

on tuberculosis: Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update. World Health Organization; 2022. Accessed September 4, 2025. https://www.who.int/publications/i/item/9789240063129

50. Simanjuntak A, Aulia R, Banjarnahor D, Harianja R, Yovi I. Bedaquiline effect towards QT interval in drug resistant tuberculosis (DR-TB): A systematic review. Siriraj Medical Journal. 2023;75(9):638-645. doi:10.33192/smj.v75i9.263683

51. Märtson AG, Burch G, Ghimire S, Alffenaar JC, Peloquin CA. Therapeutic drug monitoring in patients with tuberculosis and concurrent medical problems. Expert Opin Drug Metab Toxicol. 2021;17(1):23-39. doi:10.1080/17425255.2021.1836158

52. Tiberi S, Munoz-Torrico M, Duarte R, Dalcolmo M, D'Ambrosio L, Migliori GB. New drugs and perspectives for new anti-tuberculosis regimens. Pulmonology. 2018;24(2):86-98. doi:10.1016/j.rppnen.2017.10.009

53. Ignatius EH, Dooley KE. New drugs for the treatment of tuberculosis. Clin Chest Med. 2019;40(4):811-827. doi:10.1016/j.ccm.2019.08.001

54. Peloquin CA, Davies GR. The treatment of tuberculosis. Clin Pharmacol Ther. 2021;110(6):1455-1466. doi:10.1002/cpt.2261

55. Li M, Saviolakis GA, El-Amin W, et al. Phase 1 Study of the effects of the tuberculosis treatment pretomanid, alone and in combination With moxifloxacin, on the QTc interval in healthy volunteers. Clin Pharmacol Drug Dev. 2021;10(6):634-646. doi:10.1002/cpdd.898

56. Li J, Yang G, Cai Q, et al. Safety, efficacy, and serum concentration monitoring of bedaquiline in Chinese patients with multidrug-resistant tuberculosis. Int J Infect Dis. 2021;110:179-186. doi:10.1016/j.ijid.2021.07.038

57. World Health Organization. WHO consolidated guidelines on drug-resistant tuberculosis treatment. World Health Organization; 2019. Accessed September 4, 2025. https://www.ncbi.nlm.nih.gov/books/NBK539517/pdf/Bookshelf_NBK539517.pdf

58. Van Beek JG, Mushkudiani NA, Steyerberg EW, et al. Prognostic value of admission laboratory parameters in traumatic brain injury: Results from the IMPACT study. J Neurotrauma. 2007;24(2):315-328. doi:10.1089/neu.2006.0034