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REVIEW ARTICLE

A Scoping Review of the Clinical Pharmacokinetics of Bedaquiline

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Abstract
Tuberculosis continues to be a major infectious disease burden worldwide. Increasing drug resistance to first-line agents is making treatment more difficult. Bedaquiline is an orally administered drug active against *Mycobacterium tuberculosis* and is indicated for patients with confirmed multi-drug-resistant tuberculosis. This review aims to identify published literature reporting on the pharmacokinetics of bedaquiline, with a focus on key factors and drug interactions that may affect its use. Findings identified multiple areas for future study. First, exposure–response relationships should be further developed to determine the best ways to monitor both efficacy and safety. Second, dosing may be optimized through greater understanding of specific factors that may influence observed concentrations, including patient demographics and comorbidities. Finally, firm guidance for co-administration of bedaquiline with other drugs known to induce or inhibit cytochrome P450 enzymes is urgently required.

Key Points

Bedaquiline is greatly influenced by cytochrome P450 inducers and inhibitors with more research urgently needed to ensure safe co-administration with commonly used agents.

Exposure–response relationships suggest potential future roles for drug monitoring.

1 Introduction

Tuberculosis (TB) is a major infectious disease caused by the bacteria *Mycobacterium tuberculosis* that affects populations worldwide. The World Health Organization reports 10 million new cases of TB each year with 1.5 million people dying from TB-related disease [1]. As such, it is the leading most fatal infectious disease, the leading cause of death in patients co-infected with human immunodeficiency virus (HIV), and a major contributor to antimicrobial resistance [1]. Tuberculosis has a major economic impact, especially with its highest burden in low-income and middle-income countries [2]. Strengthening global TB control efforts may therefore reduce disease burden and result in health and economic benefits to many health systems worldwide [3].

Tuberculosis is treated with combination regimens of active medications in order to minimize acquired drug resistance and improve efficacy [4]. Duration of treatment may vary depending on clinical presentation and disease progression, tolerance of medications, and presence of drug resistance. There are different types of TB, which are classified based on drug susceptibility: drug-susceptible, multi-drug-resistant TB (MDR TB), and extensively drug-resistant TB (XDR TB) [1, 5]. Multi-drug-resistant TB occurs when the bacteria are resistant to at least two of the first-line agents (isoniazid and rifampin) and XDR TB occurs when the bacteria are resistant to isoniazid, rifampin, any fluoroquinolone, and either bedaquiline or linezolid (or both). Because of the increasing incidence of both MDR TB and XDR TB worldwide, much work has been undertaken to develop new alternatives with efficacy against TB that can be incorporated into combination regimens [6].

Bedaquiline fumarate is a newer anti-tubercular drug that is approved for use by the US Food and Drug Administration for use against MDR TB [7]. It is given in combination with other MDR-TB indicated agents and typically provided for a 6-month duration. It is administered orally and

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follows a recommended dosage regimen of 400 mg daily for weeks 1–2 and then 200 mg three times per week for weeks 3 through 24 (total weekly dose of 600 mg) [8]. Because of its extensive half-life (4–5 months), it is recommended to consider discontinuing bedaquiline in the presence of active disease before discontinuation of other active drugs, in order to avoid resistance occurring as a result of exposure to low drug concentrations [8]. The use of bedaquiline as a therapeutic alternative for MDR TB has demonstrated good efficacy and clinical success. The incidence of adverse effects is common, however, and should be monitored [8]. Of note, bedaquiline may cause more severe cardiotoxicity, hepatotoxicity, and should be used with caution in patients with extensive renal impairment. Case report data suggest bedaquiline may be administered via a nasogastric tube [9].

Bedaquiline is well absorbed and reaches its maximum plasma concentration in approximately 4–6 h from administration [10]. Exposure increases proportionally with doses administered within therapeutic dosing ranges. It is highly bound to plasma proteins (> 99.9%) and is extensively distributed to tissues. Bedaquiline is hepatically metabolized, primarily by cytochrome 450 (CYP) 3A4 with additional involvement from CYP2C8 and CYP2C19 [11]. M2 is an active metabolite but demonstrates activity to approximately fivefold less than the parent compound. The concurrent use of other drugs that affect these pathways (i.e., inhibit or induce enzyme activity) may result in clinically important drug interactions that could require avoidance of concomitant therapy, dosage reductions or increases, or more extensive clinical or laboratory monitoring. It is primarily eliminated in the feces and has a long terminal half-life of approximately 164 days (154 days for M2) [10]. Penetration into the cerebrospinal fluid is thought to be low [12].

Given a recent increase in the literature describing the pharmacokinetics of bedaquiline and the uncertainty surrounding the implications of its pharmacokinetics on clinical outcomes such as drug interactions, a greater understanding of the research published to date is needed. The aim of this review was to identify and summarize the available literature pertaining to the pharmacokinetics of bedaquiline and factors known to influence its disposition.

2 Data Sources

This was a scoping review of published literature that followed methods outlined by Munn et al. [13]. A scoping review was chosen to gain a comprehensive understanding of the topic but without intentions to answer a specific question. A title/abstract search of the online databases PubMed and EMBASE was conducted up to September 2021. Combinations of keywords used included 'bedaquiline,' 'pharmacokinetics,' 'drug disposition,' and 'drug metabolism'. No limits were placed on the search. References of identified studies were manually searched for articles not identified by the electronic search. Identified articles were included in the review if they reported bedaquiline pharmacokinetic data reported in humans or used previously published data to undertake population pharmacokinetic modeling. Reviews, animal studies, and studies completed in vitro were excluded. Studies published in languages other than English were also excluded. Information extracted from each study included title, authors, year of publication, aim, population, methods (including dosing, if applicable), and pharmacokinetic results. Data were then synthesized according to study type and factors reported to influence the pharmacokinetic parameters of bedaquiline. The search, screening of articles, and decisions on inclusion were completed twice, 2 weeks apart, by the same investigator.

3 Results

The results of the literature search are presented in Fig. 1. A total of 16 articles met inclusion for the review and are summarized below. Study characteristics are presented in Table 1.

3.1 Population Pharmacokinetics and the Influence of Co-variates

One study combined available data from phase I and II trials to determine the population pharmacokinetics of bedaquiline [14]. Pharmacokinetic data from a total of 480 patients were used to determine pharmacokinetics using a nonlinear mixed-effects modeling approach. Results described the pharmacokinetics as a four-compartment distribution model with dual zero order input. A long terminal half-life was observed and this was attributed to tissue compartment redistribution. Apparent clearance was estimated to be 2.78 L/h and increased by approximately 50% in black patients. Authors state that there were no observed differences in clinical effectiveness and thus this finding may be clinically insignificant. Apparent volume of distribution was estimated to be 164 L and decreased by approximately 15% in female patients. The pharmacokinetic parameters determined by this study suggest that bedaquiline concentrations remain fairly stable over the treatment period, especially when considering the dosage alteration after 2 weeks of treatment initiation. Using the model developed by McLeay et al., Salinger et al. explored differing dosing regimens to make dosing consistent with other TB drugs as a daily dosed medication [15]. Findings showed that bedaquiline provided as 200 mg daily for 2 months, followed by 100 mg daily for the remaining 4 months, may offer similar exposures to the

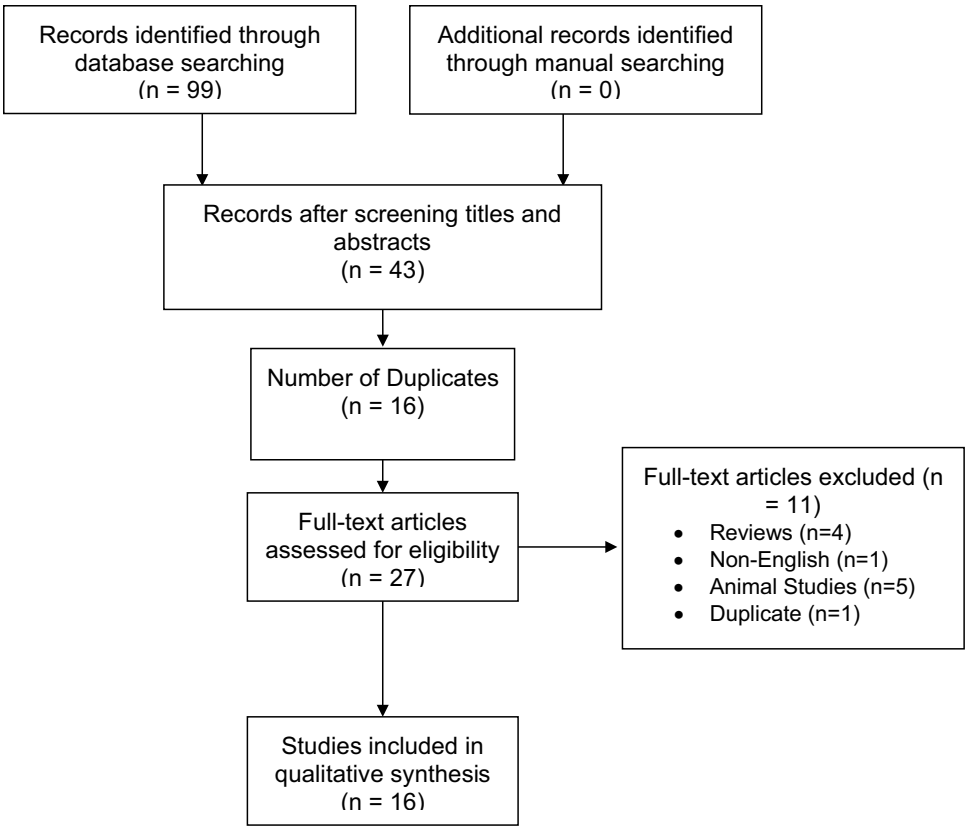

Fig. 1 Flow diagram outlining the scoping review process

initially approved dosing regimen and is now being studied in clinical trials.

Svensson et al. published a population pharmacokinetic study to describe the effect of time varying albumin and weight on the pharmacokinetics of bedaquiline and M2 in 335 patients with MDR TB [16]. It was found that three-compartment and one-compartment models best described the disposition of bedaquiline and M2, respectively. Authors found both body weight and albumin significantly influenced bedaquiline and M2 disposition, as well as the other covariates of age and race. Alghamdi et al. conducted a pharmacokinetic study that also assessed covariates influencing bedaquiline exposure [17]. A total of 63 patients received bedaquiline from Tbilisi, Georgia. Authors found for each 10-kg increase in weight, bedaquiline minimum concentration dropped by 0.12 mg/L ($p = 0.0011$). Male sex produced a higher bedaquiline minimum concentration (0.79 vs 0.39 mg/L, $p = 0.0001$) and area under the curve from 0 to 24 h (33.0 vs 21.3 mg/L, $p = 0.0203$).

3.2 Exposure–Response Modeling

Two studies were identified that assessed the exposure–response relationship for bedaquiline and clinical outcomes. Svensson and Karlsson investigated the exposure–response relationship of bedaquiline [18]. Data were obtained from a phase IIb trial and analyzed using nonlinear mixed-effects methodology. A model was developed with three linked components: a longitudinal representation of mycobacterial load in patients, a model describing the probability of bacterial presence in a sputum sample, and a time-to-event model describing time to positivity in a mycobacterial growth indicator tube system. Authors found that individual bedaquiline exposure significantly affected decreases in mycobacterial load. Findings showed that those patients not achieving sputum culture conversion were fewer with increasing bedaquiline exposures. Tanneau et al. completed a study to validate the model described above and further investigate the exposure–response relationship with bedaquiline [19]. Findings confirmed higher bedaquiline concentrations were associated with faster bacterial load decreases. In other words, the exposure differences observed with the standard dosing regimen were associated with different expected treatment responses. Authors concluded that the model could be suitable to investigate altered dosing regimens to optimize treatment for both MDR TB and XDR TB.

3.3 Drug–Drug Interactions with Rifamycins

Four studies were identified that investigated interactions between bedaquiline and rifamycin compounds. Rifampin and rifapentine are known CYP enzyme inducers and when

Table 1 Characteristics of studies included in the review

Study/year	Aim	Population	Methods	Relevant outcomes
McLeay/2014 [14]	To develop a population PK model for bedaquiline	Observations from $n = 111$ healthy volunteers, $n = 369$ patients	Non-linear mixed-effects modeling	Population PK model accounting for covariates
Salinger/2019 [15]	To explore daily dosing regimens of bedaquiline	Same as [14]	Simulation study using non-linear mixed-effects modeling	Population PK data according to different daily dosing regimens
Svensson/2016 [16]	To describe the pharmacokinetics of bedaquiline and M2	$n = 335$ patients with MDR TB	Non-linear mixed-effects modeling	Population PK model accounting for covariates (specifically weight and albumin)
Alghamdi/2021 [17]	To evaluate the pharmacokinetics of bedaquiline, delamanid, and clofazimine	$n = 99$ patients with MDR TB	Prospective cohort PK study	PK parameters accounting for covariates
Svensson/2017 [18]	To investigate the utility of a mycobacterial load on characterizing an exposure–response relationship	Culture data obtained from a previous RCT in patients with MDR TB	Secondary data analysis based on RCT data	Bedaquiline exposures considering mycobacterial load and other patient characteristics
Tanneau/2020 [19]	To externally evaluate a relationship between bacterial load and bedaquiline exposure	Data obtained from a previous clinical study in patients with drug-resistant TB	Secondary data analysis based on previous study data	Bedaquiline exposures considering mycobacterial load and other patient characteristics
Svensson/2015 [20]	To predict the effect of repeated doses of rifampicin or rifapentine on bedaquiline and M2 pharmacokinetics	$n = 32$ healthy volunteers	Phase I, two-arm, open-label trial	PK parameters with and without coadministration of a rifamycin
Winter/2015 [21]	To assess the effects of rifapentine or rifampin on a bedaquiline or M2 after a single dose	$n = 32$ healthy volunteers	Phase I, open-label, two-period, single-sequence, drug interaction study	PK parameters with and without coadministration of a rifamycin
Healan/2018 [22]	To evaluate the safety, tolerability, and pharmacokinetics of bedaquiline when co-administered with a rifamycin	$n = 33$ healthy volunteers	Phase I, open-label, RCT	PK parameters with and without coadministration of a rifamycin
Healan/2019 [23]	To investigate the effect of rifabutin on generation and disposition of the metabolites of bedaquiline	$n = 33$ healthy volunteers	Secondary analysis of [22]	Concentrations and disposition parameters or M2 and M3
Dooley/2012 [24]	To evaluate the effects of efavirenz on the pharmacokinetics of bedaquiline and M2	$n = 33$ healthy volunteers	Phase I PK study	PK parameters with and without co-administration of efavirenz
Svensson/2013 [25]	To develop a population PK model and interaction with multiple dosing of efavirenz	$n = 35$ healthy volunteers	Two-period sequential PK study	Population PK model accounting for interaction with multiple dosing of efavirenz
Svensson/2014 [27]	To provide model estimates of the impact of antiretrovirals on the pharmacokinetics of bedaquiline and M2	$n = 16$ healthy volunteers (lopinavir/ritonavir), $n = 16$ patients with HIV-1 naïve to antiretroviral therapy starting a nevirapine-based regimen	Non-linear mixed-effects modeling	Population PK model and estimates accounting for antiretroviral use
Tsuyuguchi/2019 [28]	To evaluate the safety, efficacy, and pharmacokinetics of bedaquiline in patients with MDR TB	$n = 6$ patients with pulmonary MDR TB	Prospective cohort study	PK parameters for bedaquiline and M2

Table 1 (continued)

Study/year	Aim	Population	Methods	Relevant outcomes
Perrineau/2019 [29]	To evaluate plasma concentrations of bedaquiline during treatment and its elimination after discontinuation	$n = 13$ patients with MDR or XDR TB	Retrospective cohort study	PK parameters for bedaquiline and M2
Svensson/2018 [30]	To evaluate the relative bioavailability of suspended bedaquiline tablets compared to whole tablets	$n = 24$ healthy volunteers	Randomized, open-label, two-period cross-over study	Bioavailability estimates

HIV-1 human immunodeficiency virus type 1, *MDR* multidrug-resistant, *PK* pharmacokinetic, *RCT* randomized controlled trial, *TB* tuberculosis, *XDR* extensively drug-resistant

co-administered with bedaquiline, could decrease levels affecting efficacy. Svensson et al. collected data from a phase I study consisting of 32 patients who were provided with two doses of bedaquiline alone or together with multiple-dose rifampin or rifapentine [20]. Rifampin administration increased bedaquiline clearance by almost fivefold and rifapentine administration increased clearance by almost fourfold. It was also noted that clearance of M2 was similar in strength. Authors state that steady-state concentrations of bedaquiline could decrease up to 75–79% when co-administered with rifampin or rifapentine, and until safety data are available from altered dosing regimen studies, suggest that the combination of bedaquiline with these agents is not recommended.

Findings from Winter et al. align with those summarized above [21]. This study enrolled 32 healthy volunteers to assess drug interactions between bedaquiline and rifamycins. During the first phase, participants received a 400-mg dose of bedaquiline, followed by a 28-day washout period. In the second phase, participants received either rifapentine (600 mg) or rifampin (600 mg) daily for 21 days and also received a 400-mg dose of bedaquiline on day 10. Findings showed geometric mean ratios for maximum concentration (C_{max}) and area under the curve from time zero to infinity ($AUC_{0–inf}$) of bedaquiline to be 62.2% (90% confidence interval [CI] 53.4–72.5) and 44.5% (90% CI 40.1–49.4) when administered with rifapentine, respectively. Geometric mean ratios for C_{max} and $AUC_{0–inf}$ of bedaquiline were 60.2% (90% CI 52.0–69.8) and 47.3% (41.5–54.0) when administered with rifampin, respectively. Authors also conclude that co-administration of these agents should be avoided.

Healan et al. reported pharmacokinetic data pertaining to bedaquiline and M2 from an open-label randomized controlled trial designed to assess the safety and pharmacokinetics of co-administering rifamycins with bedaquiline in healthy volunteers [22, 23]. A total of 33 participants were randomized to receive one of two rifamycins (17 = rifabutin, 16 = rifampin). Participants were given an oral dose of 400 mg of bedaquiline on day 1. On day 29, a second 400-mg dose was given. Participants received a daily dose of a rifamycin (300 mg of rifabutin or 600 mg of rifampin) from days 20 to 41. Findings showed rifampin and steady state reduced exposure of bedaquiline by approximately 45% (47.7 mcg h/mL vs 26.3 mcg h/mL) and increased clearance of bedaquiline by approximately 24% (6.59–8.19 L/h). Rifabutin did not appear to have an impact on bedaquiline exposure [22]. Findings also showed increased C_{max} of M2 from day 1 to day 29 (48 ng/mL vs 79 ng/mL, $p < 0.0001$), and increased $AUC_{0–inf}$ (33,324 h ng/mL vs 21,635 h ng/mL, $p < 0.0001$) when bedaquiline was co-administered with rifabutin [23]. When co-administered with rifampin, M2 had an increased C_{max} (48 ng/mL vs 102 ng/mL, $p < 0.0001$), increased $AUC_{0–inf}$ (24.579 h ng/mL vs 9194

h ng/mL), decreased half-life (855 h vs 216 h, $p < 0.0001$), and increased apparent clearance (20 L/h vs 49 L/h, $p < 0.0001$). Authors state that although clinical implications are unknown, sustained increases in metabolites may expose patients to a greater risk of long-term side effects.

3.4 Drug–Drug Interactions with Antiretrovirals

Three articles were identified that investigated potential drug interactions between bedaquiline and antiretrovirals used to treat HIV. Dooley et al. investigated interactions with efavirenz in 33 healthy volunteers [24]. Participants received a single 400-mg dose of bedaquiline for baseline and then a second dose while receiving efavirenz dosed at steady state. Geometric mean ratios for bedaquiline with efavirenz vs bedaquiline alone were 0.82 (90% CI 0.75–0.89) for area under the curve up to 14 days and 1.0 (90% CI 0.88–1.13) for C_{max}. Authors conclude that any differences observed were likely not clinically significant. This study was followed up with model-based estimates in a subsequent study to characterize the effects of efavirenz on bedaquiline pharmacokinetics [25]. It was found that bedaquiline was best described by a three-compartment disposition model. M2 and M3 were described by two-compartment models. The model predicted steady-state concentrations of bedaquiline and M2 to be decreased by 52% when co-administered over greater lengths of time, as compared with single dosing. Simulations were conducted and identified potential dosage adjustments that could reduce the impact of this effect but with no clinical validation. Based on these studies, switching of efavirenz to other antiretrovirals (such as nevirapine) is recommended but there is recent controversy stating that switching to high pill burden regimens (i.e., nevirapine) may decrease adherence and compromise HIV treatment [26]. Further study is therefore needed to determine the best course of action for patients required to take both efavirenz and bedaquiline.

Svensson et al. investigated co-administration of lopinavir–ritonavir or nevirapine on bedaquiline exposures in healthy volunteers using company-sponsored drug interaction studies [27]. No significant findings were observed when nevirapine was co-administered with bedaquiline. Co-administration of lopinavir–ritonavir with bedaquiline decreased clearance of bedaquiline and M2 (35% and 58%, respectively) and increased exposures by twofold to threefold for each compound. Based on these results, nevirapine was suggested as a preferred antiretroviral to co-administer with bedaquiline in patients with HIV taking lopinavir-ritonavir requiring further study.

3.5 Other Pharmacokinetic Studies

Tsuyuguchi et al. reported interim results from a phase II study assessing the safety, efficacy, and pharmacokinetics of bedaquiline and M2 in Japanese patients ($n = 6$) with MDR TB [28]. Patients received 400 mg of bedaquiline daily for 2 weeks, followed by 200 mg three times a week. Authors found that plasma C_{max} for bedaquiline was achieved within 4–6 h of administration. Bedaquiline exposure was found to be slightly higher in Japanese patients, as compared with previously reported, global phase II studies. No major safety signals were associated with this increase.

Perrineau et al. investigated long-term pharmacokinetics of bedaquiline in 13 patients with MDR TB or XDR TB [29]. Authors found median plasma concentrations of bedaquiline and M2 were 1264 ng/mL (interquartile range 910–2244 ng/mL) and 252 ng/mL (interquartile range 134–290 ng/mL), respectively. All but one patient had plasma bedaquiline concentrations > 600 ng/mL. Of the three patients who discontinued treatment, bedaquiline remained detectable in only one after 200 days of discontinuation. Authors state the importance for monitoring for resistance development with such a long terminal half-life for bedaquiline.

Svensson et al. investigated the bioavailability of suspended bedaquiline tablets, as compared to whole tablets, in an attempt to find a more suitable dosage form for use in children [30]. A randomized, open-label, two-period, crossover study design was used and completed in 24 healthy adult volunteers. Authors found no statistically significant difference in the bioavailability of suspended tablets compared to whole tablets with a 95% CI of 94–108. The suspension was well tolerated. Authors state that administrating bedaquiline in this manner offers bioequivalence to whole tablets and is safe.

4 Discussion

This scoping review aimed to identify and summarize the existing published literature pertaining to the pharmacokinetics of bedaquiline. In doing so, numerous factors were identified for further consideration and each of these are described below. It should be noted, however, that significant effort has been made to characterize the pharmacokinetic profile of bedaquiline and these data have helped to provide a clear picture of the issues relevant for continued work.

Two of the key findings of the review were the documented exposure–response relationship for bedaquiline and the significant influence of covariates on pharmacokinetic parameters such as C_{max} and overall exposure [14–19]. These findings are interesting because they may lay the groundwork for future studies aiming to develop target ranges for potential therapeutic drug monitoring. Although not studied at this time, if treatment success is known to be affected by factors such as weight, albumin, sex, or age, therapeutic drug monitoring may have a role in ensuring dosing regimens provide adequate exposure to a

drug that results in optimal clinical outcomes. These relationships should therefore be continued to be studied, in order to better understand the feasibility and appropriateness of dose optimization using measured concentrations.

Another set of key findings related to the potential for drug–drug interactions between bedaquiline and other commonly co-administered drugs. The results pertaining to co-administration of bedaquline with rifamycins are strongly suggestive of avoiding concurrent dosing, whenever possible. This recommendation is based on the data showing markedly reduced plasma concentrations and the unknown safety effects of prolonged metabolite exposure (due to more extensive metabolism of the parent compound) [20–23]. As bedaquiline is currently reserved for MDR TB and XDR TB, co-administration with rifamycins should not be a problem as resistance would already be present for these agents and therefore use would not be recommended. That being said, clinicians should be aware of this important drug–drug interaction, for exceptional cases where bedaquiline could be considered in addition to regimens containing a rifamycin.

Findings relating to drug–drug interactions between bedaquiline and antiretrovirals were important yet controversial. Although current guidance suggests substituting efavirenz for nevirapine when patients required antiretrovirals in combination with anti-TB treatment, some clinicians believe this may threaten the efficacy of the antiretroviral regimen because of increased pill burdens and poor adherence [26]. Other antiretroviral options could be considered, such as the use of integrase strand transfer inhibitors. Special considerations may be needed for countries or settings where the availability of antiretrovirals is limited.

Another area for future research is to investigate the optimal dosing and withdrawal strategies to avoid the development of drug resistance in light of the long terminal half-life of bedaquiline. One study found that bedaquiline was still present in plasma after 200 days post-dosing [29]. The implications for development of resistance are unclear, especially with limited use in widespread populations to date. Future studies should be conducted to better understand the susceptibility of bedaquiline to resistance and how resistance may be minimized through optimization of drug withdrawal.

This review has limitations that should be acknowledged. First, this study was limited to human studies and did not include data from animals or in vitro studies. While some data may exist from these other sources, this review identifies literature gaps that require further study in humans. Second, the review was conducted by one investigator and despite completing all methods in duplicate may have resulted in some data being missed. Finally, TB is an evolving disease and new data may change the treatment strategies studied in the articles identified by this review in the coming years.

5 Conclusions

Bedaquiline is an important therapeutic option for the treatment of MDR and XDR TB. Although limited data exist pertaining to its pharmacokinetics, studies are beginning to shed light on important things to consider for future dosing and optimization of bedaquiline in both mainstream and special populations. Better characterization of the exposure–response relationship, along with greater understanding of actual and potential drug–drug interactions, should be the focus of future research in this area.

Declarations

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Consent to participate Not applicable.

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Availability of data and material Not applicable.

Code availability Not applicable.

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