REVIEW ARTICLE

Penetration levels and concentration of bedaquiline and clofazimine into the brain parenchyma compared with those in blood plasma: a systematic review and individual case report analysis

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ABSTRACT

The absence of a clear summary of the pharmacokinetic-pharmacodynamic (PK/PD) properties of bedaquiline (Bdq) and clofazimine (Cfz) has limited their use in treating tuberculosis meningitis. This study is the first to summarize the pharmacokinetics and pharmacodynamics of Bdq and Cfz in the cerebrospinal fluid (CSF) and serum. Despite the few reports and studies conducted, we need clear evidence of the PK/PD properties to believe why these drugs must be considered. The included studies report the PK/PD properties of Bedaquiline and or Clofazimine in the blood plasma and or in the brain parenchyma. We exclude non-English articles, papers from non-English speaking countries, and publications before 2000. In this systematic review, we searched articles from PubMed, Scopus, Web of Science, and Google Scholar for studies published from 2000 to Sept 20th, 2023 that assessed treatments and experiments including using bedaquiline "AND" "OR" clofazimine. We also reported studies that included animals in the experimental setting. The risk of Bias in the extracted data was independently assessed by the authors via the EQUATOR (Enhancing the Quality and Transparency of Health Research) study protocol and visualized with Robvis tools. We found nine studies that were suitable for our inclusion criteria. Among nine studies we reviewed, Bedaquiline has a better penetrating ability into the brain parenchyma and central nervous system (CNS) and yields a higher concentration than clofazimine. This study has limitations, including the use of a combination of both drugs where few reports are available. Moreover, further studies are needed to evaluate the efficacy of Bdq and Cfz in the treatment of TBM. All studies were carried out systematically following PRISMA (Preferred Reporting

Items for Systematic Reviews and Meta-Analyses) guidelines and were registered in the PROSPERO database CRD42023466389.

Key words:
tuberculosis, bedaquiline, clofazimine, pharmacokinetics and pharmacodynamics; brain parenchyma.

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INTRODUCTION

Tuberculosis meningitis (TBM) has become the leading fatal manifestation of tuberculosis disease[1–3]. TBM dominantly happens to those at the extremes of age, such as children in TB-endemic areas. Pathogenesis of TBM remains unclear and one theory mentioned how the progression of pulmonary TB is followed by hematogenous dissemination of the bacteria to the meninges and failure to prevent the formation of an area called 'Rich foci'[4]. The symptoms initially comprise subacute meningitis, confusion, neurological disorder, paralysis, and progressive coma[5]. The prevalence of TBM is between 1-5% among all TB cases and is around 20-50% risk of fatal infection in all ages. [6,7]

Studies have reported the evaluation of Bedaquiline (Bdq) and Clofazimine (Cfz) in the treatment of tuberculosis meningitis cases, several studies reported that both drugs have a poor penetration ability into the blood-brain barrier and blood-cerebrospinal fluid barrier, therefore, inclusion in the regimen would be ineffective. Nevertheless, we found a new study that reports the actual penetration level of Bedaquiline into the barrier and concluded the opposite. Multiple studies have reported successful treatment outcomes for tuberculosis meningitis patients with treatment including Bdq and/or Cfz-containing regimens. This study provides updated information and a comparison of the clinical use of both drugs Bedaquiline and/or Clofazimine in the treatment of tuberculosis meningitis. Moreover, the clinical outcomes from the previous studies are also included to better descriptively evaluate the progression of evaluation of the pharmacokinetics-pharmacodynamics between these drugs to help optimize the treatment.

There are three challenges in the treatment of TBM including (1) the dynamic changes in the pharmacokinetics-pharmacodynamics (PK/PD) of the drugs are poorly characterized in TBM which results in difficulty in choosing effecting regimens; (2) there are few drugs with good penetration levels into the blood-brain barrier (BBB) and the blood-cerebrospinal fluid barrier (BCSFB) into where bacilli reside; and (3) there is a lack of information about the mechanism interactions between types of bactericidal and the host inflammatory response. [8,9] Strategies to optimize TBM treatment have been developed based on intensified treatment and increased drug exposure in the central nervous system (CNS). Increasing exposure to poorly penetrating drugs combined with excellent penetration drugs may increase the survival rate of TBM patients and microbial killing activity. [10,11]

A recent debate over the ability of Bdq and Cfz to penetrate the BBB and the BCSFB has raised concerns about selecting effective regimens for TBM. The study provides significant information on the

pharmacokinetics and pharmacodynamics of newly proposed drugs Bdq for developing effective regimens for the treatment of TBM.

MATERIALS AND METHODS

Search strategy and selection criteria

In this systematic review and individual case report analysis, we included studies reporting the inclusion of Bdq and/or Cfz in the research in the form of the pharmacokinetics and pharmacodynamics properties related to their level of penetration across the barrier into the brain parenchyma and central nervous system. Treatment of TBM is categorized into three subgroups on the basis of their level of penetration level into the brain parenchyma: excellent; good; and poor. The excellent level indicates the potency of drugs in penetrating the CSF; the good level means the drugs can reach only inflamed meninges; meanwhile, the poor level indicates the inability of the drugs or their poor ability to penetrate the CSF. [12] The study also reviewed the treatment outcome for the inclusion of each drug in clinical and non-clinical settings. We excluded conference abstracts and book chapters or studies that did not report original data. Moreover, we analyzed individual case report data from PubMed, Scopus, and Google Scholar from the inception of each database until Sept 20, 2023, using the terminology of ("bedaquiline" OR "Bdq" OR "sirturo" OR "TMC207") AND ("clofazimine" OR "Cfz") AND ("tuberculosis meningitis" OR "TBM" OR "meninges") AND ("plasma" OR "CSF" OR "Cerebro") with language restrictions only in English and dates between 2000-2023. All studies and protocols were carried out systematically following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines from June to September 2023 and were registered in the PROSPERO database CRD42023466389. The risk of bias in the extracted data was independently assessed by the authors via the EQUATOR (Enhancing the Quality and Transparency of Health Research) study protocols and visualized with Robvis tools. The quality of each article was reviewed using the appropriate ROB assessment tool for RCT and the Newcastle-Ottawa Scale (NOS) for observational studies.

Data analysis

Data extracted from the observational study and case report included geographical origin, year of the study, number of subjects, type of study, subject population, method for diagnosing TBM, treatment (drug regimens, doses, duration, resistance level, and the output of the study), the pharmacokinetics of drugs (level of penetration across barriers, mean concentration), and the pharmacodynamics properties of the drugs (percentage of protein binding ability, and molecular action of the drugs). This systematic review is registered in the PROSPERO database (CRID42023466389). The primary aim was to determine the penetration level of each drug into the brain and the concentration level inside the CSF and plasma. The PRISMA Systematic review and bias assessment results are shown in Figure 1 of the PRISMA flowchart diagram and Figure 2 for the ROBVIS tool.

RESULTS

Among the 320 identified studies, 9 were eligible for review. Two studies utilized a Bdq-Cfz-containing regimen, four studies used Bdq with no Cfz-containing regimen, and three records used Cfz with no Bdq-containing regimen. Four articles were individual case reports, whereas, five articles were original and experimental studies. In this study, we

found that 1 of the 6 articles mentioned a Bdq-containing regimen contributing to the success of the TBM treatment, meanwhile, 3 reports included Cfz. On the basis of the level of penetration into the brain and CNS, 2 studies reported that Bdq has a good penetration level, meanwhile, no reported case or study supports the ability of Cfz to penetrate the brain parenchyma. Two studies were found to report poor to zero penetration levels and CSF concentration for Cfz in humans. The characteristics of the studies included in the review are shown in Table 1.

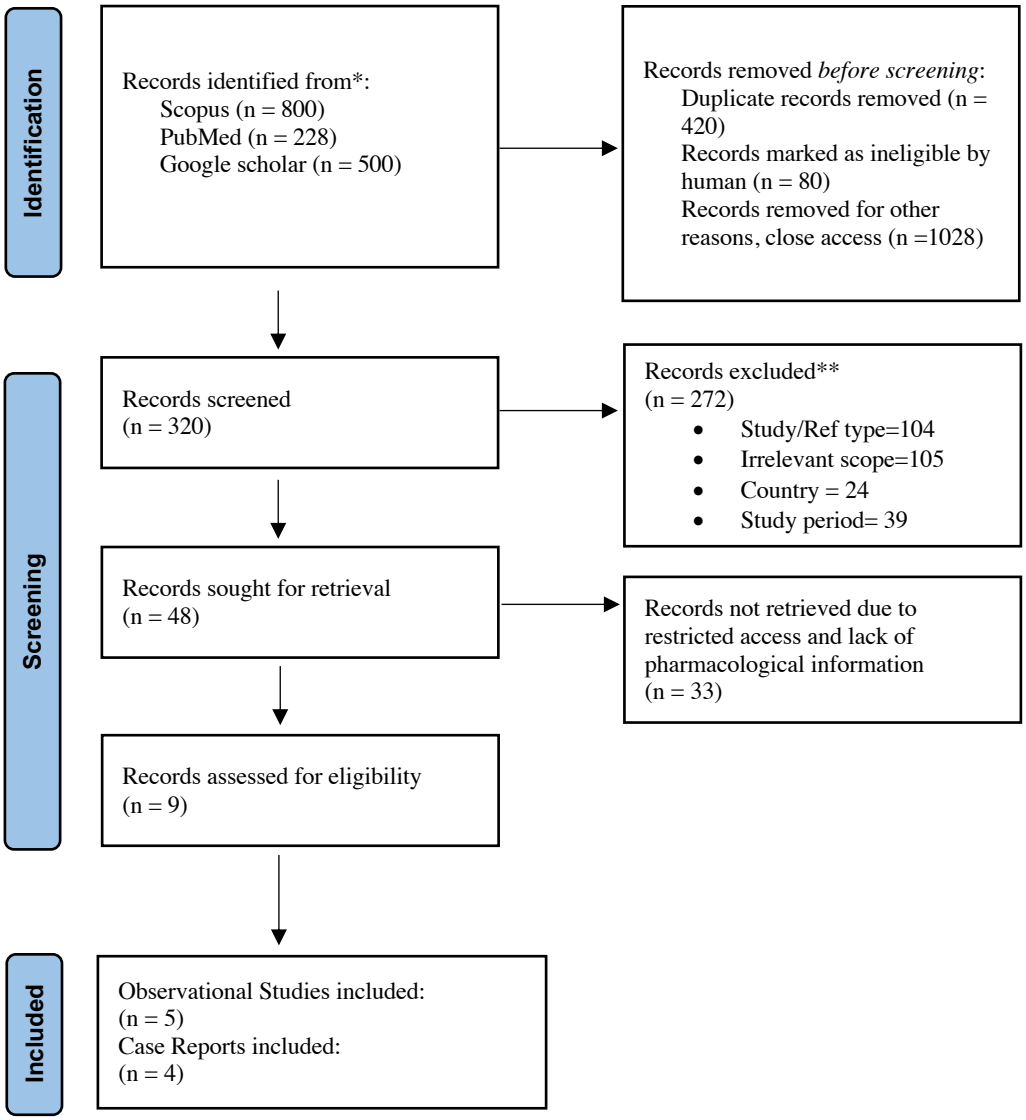

Figure 1. Article selection process based on the PRISMA systematic review flowchart

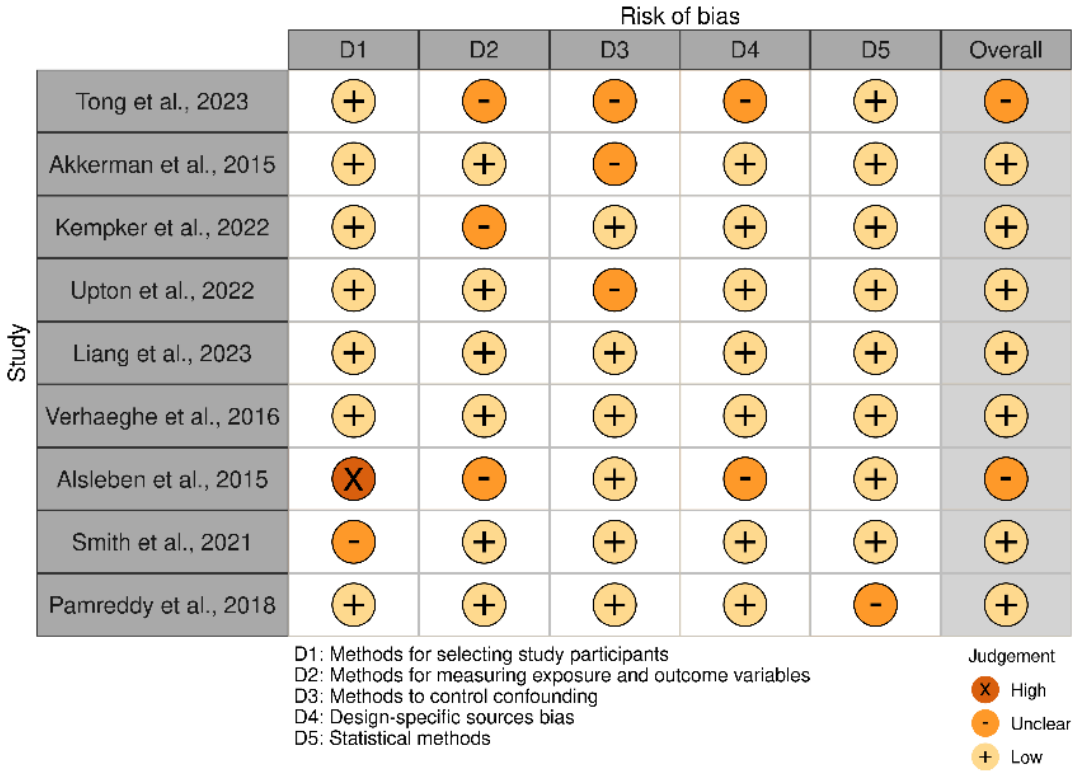

Figure 2. The risk of bias assessment

Table 1. Characteristics of the studies included in the literature review

No.	Author(s)	Type of study	Subject population	Method of verification
1	Tong et al, 2023[13]	Case report	MDR TBM in children	GeneXpert, CT scan, MRI, CSF extraction and biochemical analysis
2	Akkerman et al, 2015 [14]	Case report	MDR TB of the CNS in adult	CSF biochemical analysis
3	Kempker et al, 2022 [15]	Observational Study	MDR TBM in adult	Serum and CSF analysis
4	Upton et al, 2022 [16]	Observational study	TB RR in adult patients	Blood plasma analysis
5	Liang et al, 2023 [17]	Case report	MDR TBM in adult	CSF analysis
6	Verhaeghe et al, 2016 [18]	Observational Study	TBM in Human Studies	CSF analysis
7	Alsleben et al, 2015 [19]	Case report	Pre-XDR TBM in children	CSF analysis and X-ray Scan

No.	Author(s)	Type of study	Subject population	Method of verification
8	Smith et al, 2021[20]	Observational Study	TBM in adult human	Clinical outcome analysis
9	Pamreddy et al, 2018 [21]	Observational study	Animal study	LC-MS/MS and MALDI MS

LC-MS/MS: liquid chromatography-tandem mass spectrometry; MALDI MS: matrix-assisted laser desorption/ionization.

Currently, methods for diagnosing meningeal tuberculosis are limited. The urgency of addressing global health problems has arisen, particularly in the case of multidrug-resistant tuberculosis. Multidrug-resistant TBM rarely occurs, nevertheless, it is less likely to be cured. A previous report was the first in a clinical setting to increase the use of Cfz in treating MDR-TBM, and many thought that it had a lower penetration effect on the brain parenchyma and BBB[13]. Although the diagnosis of TBM relies on CSF and CT scans, it often causes pain and difficulty for patients. The World Health Organization (WHO) has recommended conventional and molecular-based diagnosis of TBM including CT scan, MRI, X-ray, CSF extraction, and GeneXpert. In animal studies, LC-MS/MS can be used to determine the concentration of drugs inside CSF and blood plasma[21]. Thus, this technique also played a significant role in deciding effective regimens and doses for certain types of populations.

Table 2. Characteristics of the treatments and the outcomes from the studies

No.	Author(s)	Drugs Regimens	Subject	Dose of the drug(s)	Duration of the treatment	Resistance level	Output of the treatment
1	Tong et al, 2023 [13]	Lzd, Cs, Z, Cfz, E, Pt	Human	Lzd (0,6 g/day); Cs (0,5 g/day); Cfz (0,1 g/day); Z (1,0 g/day); E (0,75 g/day); Pt (0,6 g/day);	19 months	MDR-TB (INH, RIF, Fluoroquinolones)	Cured
2	Akkerman et al, 2015 [14]	Bdq containing regimens	Human	Bdq 200 mg/ three times a week; others were not reported	11 weeks	MDR-TB	ongoing treatment
3	Kempker et al, 2022 [15]	Lzd, Cs, Bdq, Cfz, Dlm	Human	Lzd (600 mg/day); Cs (500 or 750 mg/day); Bdq (NR); Cfz (NR); Dlm (NR);	NR	5 MDR; 12 drugs susceptible to TB	ongoing treatment
4	Upton et al, 2022 [16]	Bdq containing regimens	Human	Bdq 14 days of 400 mg; followed with 200 mg 3 times/week	24 weeks	Resistant Rifampicin (RR) TB	ongoing treatment
5	Liang et al, 2023 [17]	Cfz containing regimens	Human	Inh (800 mg/day); Z (1500 mg/day); Cs (500 mg/day); Mfx (400 mg/day); Cfz(100 mg/day); Lzd (600 mg twice/day)	Observation on Day 10th	Pre-XDR TBM	ongoing treatment
6	Verhaeghe et al, 2016 [18]	Bdq containing regimen	Human	25 ng/mL of BDQ and its des-methyl metabolite	NR	MDR-TBM patients	Treatment success

No.	Author(s)	Drugs Regimens	Subject	Dose of the drug(s)	Duration of the treatment	Resistance level	Output of the treatment
7	Alsleben et al, 2015 [19]	Cfz containing regimen	Human	4 mg/kg of Cfz; 40 mg/kg Z; 25 mg/kg E; 20 mg/kg Eto; 20 mg/kg Amk, 20 mg/kg Ofx; 20 mg/kg Tzd; and 150 mg/kg; PAS given once daily	18 months	Pre-XDR (resistance to Amk, Ofx, E, and streptomycin)	Cured
8	Smith et al, 2021[20]	Bdq and Cfz-containing regimens	Human	In MDR-TB, 9 patients (82%) received Cfz 100 mg; 6 (55%) received Dlm 200 kg; and 4 (36%) received Bdq 400 mg (2 received both Dlm and Bdq)	486 days	Susceptible and MDR-TBM	Among 77 patients with TBM, 57 (74%) patients had a favorable outcome
9	Pamreddy et al, 2018 [21]	Bdq	Mice	25 mg/kg single dose of Bdq	Single dose injection	Healthy rodent (MaleSprague-Dawley)	Bdq has excellent potential to reach the CNS

NR: Not Reported; MDR: multidrug resistance; XDR: resistance to isoniazid, rifampicin, fluoroquinolone, and at least one additional group A drug); Inh: Isoniazid; Rif: Rifampicin; Bdq: bedaquiline; Cfz: clofazimine; Lzd: Linezolid; Cs: Cycloserine; Z: Pyrazinamide; E: Ethambutol; Pt: Protionamide; PAS: para-aminosalicylic acid; Mfx: Moxifloxacin; Tzd: Thiazolidinedione; Amk: Amikacin; Ofx: Ofloxacin; Eto: Ethionamide; Dlm: Delamanid; CNS: Central Nervous System.

Among the nine studies we reviewed in Table 2, one experimental study showed evidence based on animal experiments, whereas the others were based on human subjects. Bdq and Cfz have been reported previously to have a minimum permeability level and concentration inside the CSF and brain parenchyma but are maintained at high concentrations in the blood plasma. We found bias in the dose used in each study. We conducted a general descriptive analysis to report the actual data based on the available report. Bedaquiline has been reported to have excellent penetration into the mouse CNS, however, a Cfz-related animal study has not been reported.

Table 3. Pharmacokinetics of drugs in the plasma and CSF of the subjects in the studies

No.	Study	Level of penetration and Permeability into the Brain and CNS	Mean concentration (ng/ml)		
			Location	Bedaquiline	Clofazimine
1	Tong et al, 2023[13]	NR	Serum	NR	NR
			CSF	NR	NR
2	Akkerman et al, 2015 [14]	Bdq – (a poor ability to penetrate the CNS based on the given dose)	Serum	>0.5 mg/L after dosage	NR
			CSF	Undetectable (very low)	NR
3	Kempker et al, 2022 [15]	• Lzd (good) • Cs (good) • Bdq (poor) • Cfz (poor) • Dlm (poor)	Serum	0.9-1.50 (µg/mL) in 2-6 hours after dosage	0.85-0.86 (µg/mL) in 2-6 hours after dosage
			CSF	Undetectable	Undetectable
4	Upton et al, 2022 [16]	Bdq (Good - does penetrate the CNS, is measurable, and is found at concentrations similar to the estimated unbound fraction in plasma)	Plasma	>1000 ng/mL after 5 hours	NR
			CSF	• Cmax and Tmax for Bdq were 3.790 ng/mL and 5 hours • CSF concentrations are higher with inflamed meninges and often lessen as the inflammation recovers.	NR
5	Liang et al, 2023 [17]	• Cfz (poor) • Z (good) • Lzd (good) • Cs (good) • INH (poor) • Mfx (good)	Plasma	NR	Cmax: 0.35 mg/L
			CSF	NR	Cmax: 0 mg/L

No.	Study	Level of penetration and Permeability into the Brain and CNS	Mean concentration (ng/ml)		
			Location	Bedaquiline	Clofazimine
6	Verhaeghe et al, 2016 [18]	Bdq - (good, quantification using the addition of Tween-80 solution)	Plasma	NR	NR
			CSF	• Bdq without 0.2% Tween-80: 18.4% • M2 without 0.2% Tween-80: 18.4% • BDQ with 0.2% Tween-80: 86.8% • M2 with 0.2% Tween-80: 71.6%	NR
7	Alsleben et al, 2015 [19]	Cfz – (NR - included in a successful regiment)	Plasma	NR	NR
			CSF	NR	NR
8	Smith et al, 2021[20]	Bdq and Cfz - (NR - included in a successful regiment)	Plasma	NR	NR
			CSF	NR	NR
9.	Pamreddy et al 2018 [21]	Bdq has a wide distribution in the brain parenchyma	Plasma	Bdq Tmax (h)= 4.0 Cmax (ng/mL) = 910.00	NR
			CSF	Bdq Tmax (h)= 4.0 Cmax (ng/mL) = 134.97	NR

NR: Not Reported; MDR: multidrug resistance; XDR: resistance to isoniazid, rifampicin, fluoroquinolone, and at least one additional group A drug); Inh: Isoniazid; Rif: Rifampicin; Bdq: bedaquiline; Cfz: clofazimine; Lzd: Linezolid; Cs: Cycloserine; Z: Pyrazinamide; E: Ethambutol; Pt: Protionamide; PAS: para-aminosalicylic acid; Mfx: Moxifloxacin; Tzd: Thiazolidinedione; Amk: Amikacin; Ofx: Ofloxacin; Eto: Ethionamide; Dlm: Delamanid; CNS: Central Nervous System.

The pharmacokinetics of Bdq and Cfz in the plasma and CSF are shown in Table 3. Although the data are very limited, we aim to collect as much data as possible on the PK/PD of drugs in the plasma and CSF in both animal and human studies. Three studies reported that Bdq has good penetration and distribution through the brain parenchyma, whereas no studies have provided evidence that Cfz reaches high concentrations in the CSF or brain parenchyma.

Table 4. Pharmacokinetics and pharmacodynamic characteristics of anti-tuberculosis drugs used in studies

Drug(s)	Dose	Level of penetration across the barrier (BBB and BCSF)	CSF concentration	Molecular characteristic	Pharmacodynamic property	Free drug concentration in µg/ml, median (range)	Percentage of protein binding median (%)	Ref(s)
1st line drugs								
RIF	(10,20,30) mg/kg	Poor	0.125-1.06 mg/L	High plasma protein binding ability	Exposure or concentration-dependent	1.3 (0.4-2.4)	88.2	[22,23]
INH	(10-15) mg/kg daily	Excellent	NR	Low plasma protein binding ability	Exposure or concentration-dependent	2.6 (1.1-8.2)	13.8	[22,23]
Z	40 mg/kg once daily (max. 2000 mg daily)	Well / good	NR	Low plasma protein binding ability	Exposure-dependent	31.8 (23.9-54.0)	1.0	[22–24]
E	15 mg/kg (range 15–20 mg/kg)	Poor	NR	High plasma protein binding ability	Concentration-dependent	2.3 (0.8-6.0)	12.1	[23,25]
2nd line drugs:								

Drug(s)	Dose	Level of penetration across the barrier (BBB and BCSF)	CSF concentration	Molecular characteristic	Pharmacodynamic property	Free drug concentration in µg/ml, median (range)	Percentage of protein binding median (%)	Ref(s)
Fluoroquinolones (Mfx)	400 mg	Excellent	NR	Low plasma protein binding ability	Concentration-dependent	1.23	3.37	[24,26]
Repurposed drugs: Cs Eto	(10–15) mg/kg; max 1 g	Well / good	NR	Low plasma protein binding ability	Concentration-dependent	33.5	• Cycloserine (water-based: 0% protein binding) • Eto: 30%	[24,27]
Cfz	100 mg OD	Poor	0	high protein binding ability	Concentration-dependent	Below the MIC	Presumably 99	[28,29]
PAS	(200–300) mg/kg	Poor	NR	High plasma protein binding ability	Concentration-dependent	0.25 to 8	50-60	[24]
Lzd	600 mg	Excellent	CSF/Serum conc. ratios: 0.7-1.0	Low plasma protein binding ability	Exposure (Time)-dependent	10 to 20	31	[24]

New drugs

Drug(s)	Dose	Level of penetration across the barrier (BBB and BCSF)	CSF concentration	Molecular characteristic	Pharmacodynamic property	Free drug concentration in µg/ml, median (range)	Percentage of protein binding median (%)	Ref(s)
Dlm	100 mg twice daily	Poor	1.8	High plasma protein binding ability	Presumably Concentration-dependent	NR (Most likely, very low)	99	[30]
Pa	200 mg/day	NR-but PET imaging shows good distribution in the brain parenchyma (under evaluation)	NR	High plasma protein binding ability	Exposure (Time) - dependent	Above MIC	93	[29]
Bdq	Not determined-(study recommended 400 mg once daily for two weeks followed by 200 mg three times per week)	Poor-good (under evaluation)	(18.4-86.8) %	High plasma protein binding ability	Concentration-dependent	150	99.9	[18,29]

NR: Not Reported; MDR: multidrug resistance; XDR: resistance to isoniazid, rifampicin, fluoroquinolone, and at least one additional group A drug); Inh: Isoniazid; Rif: Rifampicin; Bdq: bedaquiline; Cfz: clofazimine; Lzd: Linezolid; Cs: Cycloserine; Z: Pyrazinamide; E: Ethambutol; Pt: Protionamide; Pa: Pretomanid; PAS: para-aminosalicylic acid; Mfx: Moxifloxacin; Tzd: Thiazolidinedione; Amk: Amikacin; Ofx: Ofloxacin; Eto: Ethionamide; Dlm: Delamanid; CNS: Central Nervous System; MIC: Minimum Inhibitory Concentration.

In this systematic study, we also compared the PK/PD interactions between Bdq and Cfz with other drugs shown in Table 4. Among the first and second-class drugs to treat pulmonary tuberculosis (PTB) and TBM, Lzd, Cs, and Mfx have good penetration performance into the BBB and across the brain parenchyma. The ability of the drug to reach the CNS depends on its plasma protein binding ability. The stronger the interactions are, the less likely it is to enter the CNS and the brain. We found an association between the plasma protein binding ability and the level of penetration of each drug into the brain and CNS. We observed that almost all drugs that have high plasma protein binding ability had poor penetration ability, except for Pa and Bdq. On the other hand, drugs with low plasma binding ability have good to excellent penetration ability. Although this study is limited in that it only descriptively analyzes the evidence, it provides preliminary findings for further research on the PK/PD of new drugs that are effective in combating

TBM. Although Bdq and Cfz have been reported to have almost 99% protein binding in the plasma, substantial evidence provides support for the inclusion of Bdq in the treatment of TBM because of its efficacy in treating PTB and MDR-TB. We encourage further research to evaluate the standardized effective doses of Bdq in future TBM studies.

DISCUSSION

Tuberculosis meningitis (TBM) has the potential to become the hardest infection to treat because of the limited number of options for drugs with excellent penetration and bacilli-killing activity. [31] Many of the baseline drugs showed a decrease in pharmacokinetic properties and lower treatment success. [32] We also found that a recent study reported methods to optimize TBM treatment, one of which was to increase drug exposure. In this review, we provide updated information related to the treatment of TBM with Bdq and/or Cfz, aiming to descriptively evaluate the PK/PD associated with the successful treatment in TBM patients. The two drugs share a similar action target, which is the respiratory system of *Mycobacterium tuberculosis* (MTB), and further studies are needed to assess the difference in the PK/PD of these drugs to propose a more effective drug composition. Current anti-TB treatments for TBM are based on those that are efficacious in treating pulmonary tuberculosis (PTB), bedaquiline and clofazimine being two of these drugs. [24]

Discussion of the optimization of treatment strategies in TBM care has led to the recommendation of an intensified treatment strategy. This means increasing the exposure of poorly penetrating drugs combined with excellent penetrating drugs to achieve greater bactericidal activity and a lower risk of drug resistance. A difficult case of pre-XDR TBM in children reported in a previous study revealed the potential efficacy of the inclusion of Bdq and Cfz in a therapeutic regimen to cure TBM. [19,20,33] Bdq has been reported to have poor penetration into the brain parenchyma and the CNS and was found at a low concentration in CSF, [14,29] however, the ability of Bdq to bind to the plasma protein does not affect its concentration inside the CSF and Bdq has the same concentration in the CSF as that in the plasma. [16,18] This review helps answer the question regarding the progress in the study of Bdq in TBM care. We found that Bdq could be metabolized into the second metabolite form named, M2, which could help further investigate whether this molecule plays a role in the inhibition of protein binding of the parental molecule in the plasma.

The PK/PD interaction with the host has a significant role in interpreting the

efficacy of the drug. Currently, we assume that drugs with high protein-binding ability will have a low penetration level and a lower concentration in the CSF, however, there is a potential exception for Bdq. [34,35] As a comparison, we also investigated the PK/PD for CFZ, and a continuous study and case report never reported a potentially higher penetration level of Cfz into the CSF due to its high protein binding ability with the plasma proteins. [22,30,36,37] Additionally, a recent study reported that encapsulating a molecular Cfz with nanoparticles increased its penetration and concentration levels. This was potentially attributable to the diminished molecular binding capacity. [38] Pharmacokinetic variability also depends on an individual's body mass and metabolic progression. [39,40]

The pharmacodynamic property of a drug is also a factor in the intensity of treatment. Increased dose and duration of the treatment could exacerbate drug exposure and concentration dependence. While there are limited studies that show that Cfz and Bdq can directly treat TBM, we have found a lot of studies that show that TBM can be successfully treated with a combination of Bdq and Cfz along with good penetrating drugs. This suggests that poorly penetrating drugs can help to reduce the risk of resistance and the spread of bacteria in the plasma.[5,13,41–43] Notably, Bdq and Cfz exhibit an exceptionally high protein-binding capacity compared to other drugs with lower penetration. [44] Additional value was added to the study for treating TBM in children with a successful outcome using a therapeutic regimen containing Bdq and/or Cfz. [13,24,45]

Further evaluation is needed to obtain more promising evidence for adding value to the potential inclusion of Bdq, Cfz, and other poorly penetrating drugs in the treatment of TBM. [46] Based on the findings of this study, Bdq may serve as an alternative medication for TBM treatment. The number of collected articles constrains the inclusion criteria of this systematic study. This review complements the previous reports by providing additional information. [35]

CONCLUSION

Our results indicate that a greater number of studies have investigated the potential for a higher level of bedaquiline to cross the brain-central nervous system barrier. Despite the advancements, no report has demonstrated any modifications to the suboptimal pharmacokinetics-pharmacodynamics characteristics of clofazimine.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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