EFFICACY AND ADVERSE OF EFFECTS MULTI-DRUG RESISTANT PULMONARY TUBERCULOSIS REGIMEN THERAPY: A SYSTEMATIC REVIEW FROM RANDOMIZED CONTROL TRIAL

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ABSTRACT

Multidrug-resistant tuberculosis (MDR-TB) remains a major challenge in global tuberculosis control due to low treatment success rates, long therapy durations, and a high risk of adverse effects. The development of new therapy regimens and additional strategies continues to be evaluated to improve treatment efficacy and safety. This systematic review aimed to evaluate the efficacy and adverse effects of treatment regimens for multidrug-resistant and rifampicin-resistant pulmonary tuberculosis based on evidence from randomized controlled trials (RCTs). This systematic literature review was conducted by examining four randomized controlled trials published between 2015 and 2025, namely the studies by Tang et al., Zhang et al., Ruan et al., and Nyang'wa et al. Articles were selected based on their relevance to the topic of efficacy and adverse effects of MDR-TB therapy regimens. Extracted data included culture conversion rates, treatment success, recovery time, and safety profiles. This review shows that innovations in MDR-TB therapy regimens, whether through the addition of new drugs, the use of adjuvant herbal therapies, or the development of short-course oral regimens—can enhance efficacy while improving treatment safety profiles. These findings support the implementation of new regimens as more effective and safer therapeutic alternatives, with the potential to improve patient adherence in MDR-TB management.

Keywords: Adverse effect; Efficacy; Multi drug resistant; Pulmonary tuberculosis; Randomized control trial; Regiment therapy; Systematic literature review

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INTRODUCTION

Multiple Drug-Resistant Tuberculosis (MDR-TB) is one of the public health problems in various countries and poses a significant challenge in tuberculosis disease control efforts. Globally, cases of multidrug-resistant tuberculosis (MDR-TB) are estimated to continue increasing year by year. MDR-TB is defined as tuberculosis caused by Mycobacterium tuberculosis bacteria that are resistant to at least two main first-line anti-TB drugs, namely isoniazid and rifampicin. Drug resistance occurs when patients with drug-sensitive TB receive inadequate or interrupted treatment, which triggers resistant bacteria and leads to drug resistance(Soedarsono, S., et al, 2020).

The clinical management of MDR-TB differs from the treatment of drug-sensitive TB. In drug-sensitive TB management, first-line treatment consists of a combination of four drugs for 2 months, followed by a combination of two drugs for 4 months, with dosages according to the World Health Organization (WHO) recommendations. In the management of MDR-TB, at least five types of drugs that remain effective are administered, including injectable drugs during the 6–8 month intensive phase, and the therapy must be given for 18–24 months (PDPI, 2021).

The management of MDR-TB is often associated with the occurrence of varying side effects, ranging from mild to severe. A rational approach in selecting anti-TB drugs (ATDs) prioritizes the use of drugs that have the potential to kill bacteria with low toxicity (Soedarsono, S., et al., 2020). This review journal was conducted to assess the efficacy and side effects of drug therapy regimens in patients with drug-resistant TB using a systematic review (SR). SR has a high level of evidence, as depicted in the evidence-based pyramid, and is a systematic method to summarize evidence related to research questions in a detailed and comprehensive manner, following the latest developments in evidence-based practice (Tawfik, G. M., et al, 2019).

MATERIALS AND METHODS

This systematic review was conducted following the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Screening was carried out using two databases: PubMed, Taylor & Francis, and Scopus, covering the years 2015 to 2025. The search was performed using a combination of keywords as shown in **Table 1.** The search focused on the efficacy of therapy regimens and side effects in patients with drug-resistant pulmonary tuberculosis.

The inclusion criteria for this review were as follows:

1. Population of patients with multidrug-resistant tuberculosis, regardless of age, gender, or geographic location
2. Articles published between 2015 and 2025
3. Studies employing randomized controlled trial methods
4. Studies including new therapy regimens for drug-resistant tuberculosis, including new drugs or innovative combination regimens
5. Articles published in English

The exclusion criteria for this review were:

1. Duplicate articles across the two databases
2. Studies focusing on monotherapy for drug-resistant tuberculosis
3. Study types without results, in vitro studies, and animal studies

Table 1. Keywords Title

Search engines	Keywords
PubMed	1. Multi drug pulmonary tuberculosis AND Regimen therapy
	2. Multi Multi drug pulmonary tuberculosis AND Regimen therapy AND adverse effect
Taylor and Franci	1. Multi drug pulmonary tuberculosis AND Regimen therapy AND Randomized control trial
	2. Multi Multi drug pulmonary tuberculosis AND Regimen therapy AND adverse effect AND Randomized control trial
Scopus	3. Multi drug pulmonary tuberculosis AND Regimen therapy AND Randomized control trial
	4. Multi Multi drug pulmonary tuberculosis AND Regimen therapy AND adverse effect AND Randomized control trial

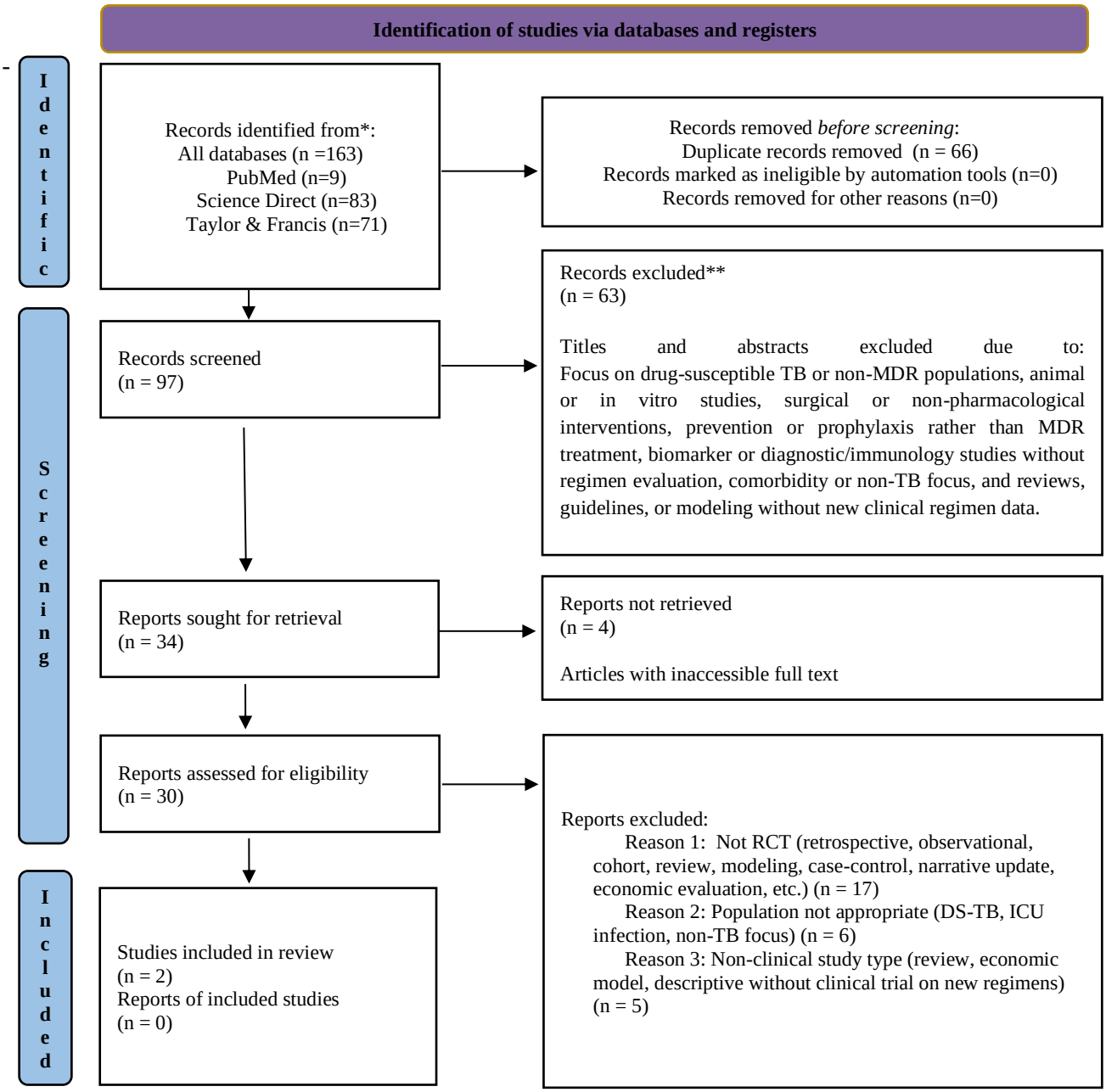

Figure 1. PRISMA flowchart of study selection.

RESULT

Study Characteristics

A total of 163 records were identified through the search strategy. Following title and abstract screening and the removal of duplicates, 66 articles remained for further assessment (Figure 1). After full-text evaluation and quality appraisal, only 2 distinct articles met the inclusion criteria.

The randomized controlled trial by Tang et al. (2015) was conducted across six tuberculosis specialty hospitals in China and enrolled 105 adults with sputum culture–positive multidrug-resistant (MDR) tuberculosis. Participants were randomized to receive either an individualized 21-month regimen incorporating clofazimine (n=53) or a control regimen without clofazimine (n=52). The mean age of participants was 42 years (range 18–64), and 71% were male. Baseline comorbidities included diabetes (20%), chronic obstructive pulmonary disease (10.5%), and bronchiectasis (23.8%).

The TB-PRACTECAL trial (Nyang'wa *et al*., 2023) was an open-label, multi-arm, multicenter phase 2b–3 non-inferiority trial conducted in Belarus, South Africa, and Uzbekistan. A total of 552 patients aged ≥15 years with rifampicin-resistant tuberculosis were randomized to receive standard care or one of several investigational regimens containing bedaquiline, pretomanid, and linezolid (BPaL), with or without clofazimine or moxifloxacin. The modified intention-to-treat population included 275 participants in stage two (137 in the standard care arm and 138 in the BPaLM arm). The median age across groups ranged from 34–38 years, with 51–66% male, and 25–32% were HIV-positive. Pulmonary cavities were present in 55–64% of participants, and 19–23% had baseline fluoroquinolone resistance.

MDR-TB Therapy Regimen

Clofazimine

One of the novel regimens evaluated for multidrug-resistant tuberculosis (MDR-TB) is clofazimine. In the study by Tang et al. (2015), clofazimine was not administered as monotherapy but was incorporated into the standard WHO-based MDR-TB regimen. This background regimen consisted of five drugs, including prothionamide, pyrazinamide, a fluoroquinolone, isoniazid aminosalicylate, and an aminoglycoside. Clofazimine was added at a daily oral dose of 100 mg for a treatment duration of 21 months.

In the TB-PRACTECAL trial (Nyang'wa et al., 2023), one of the investigational regimens evaluated was BPaLC, consisting of bedaquiline, pretomanid, linezolid (BPaL), and clofazimine. Clofazimine was administered orally at a dose of 100 mg once daily throughout the 24-week treatment course, in addition to the BPaL backbone. The inclusion of clofazimine aimed to enhance bactericidal activity and improve treatment outcomes compared with the standard BPaL regimen.

Moxifloxacin

In the TB-PRACTECAL trial, another investigational regimen assessed was BPaLM, which combined bedaquiline, pretomanid, linezolid, and moxifloxacin. Moxifloxacin was administered orally at a dose of 400 mg once daily for the entire 24-week treatment duration, added to the standard BPaL regimen.

DISCUSSION

In the study by Tang et al. (2015), the addition of clofazimine to individualized regimens for patients with multidrug-resistant tuberculosis (MDR-TB) demonstrated significant improvements in treatment success and earlier sputum culture conversion. However, adverse events were highly concentrated in dermatological manifestations. Nearly all patients receiving clofazimine experienced skin discoloration (94.3%), while almost half developed ichthyosis (47.2%). Although these events were not life-threatening and rarely led to treatment discontinuation, their ubiquity raises concerns regarding patient tolerability and adherence in long-term therapy. The findings underscore a trade-off between improved microbiological efficacy and

cosmetic side effects that may influence quality of life and willingness to continue therapy.

By contrast, the TB-PRACTECAL trial (Nyang'wa et al., 2024) evaluated shorter, all-oral regimens containing bedaquiline, pretomanid, and linezolid, with or without clofazimine or moxifloxacin, in patients with rifampicin-resistant TB. The regimen of bedaquiline–pretomanid–linezolid–moxifloxacin (BPaLM) demonstrated a markedly superior safety profile compared with conventional lengthy regimens. Serious adverse events (grade ≥3) were reported in only 23% of participants in the BPaLM group, compared with 48% in the standard care group. Importantly, treatment-related deaths occurred only in the standard regimen, while none were reported in the BPaLM arm. The most notable adverse effects within the BPaLM regimen were hepatotoxicity and peripheral neuropathy, predominantly associated with linezolid exposure, yet their frequency and severity were significantly lower than in the control arm.

When comparing the two studies, a key distinction emerges in the nature of adverse events. Clofazimine, though effective, was associated with nearly universal dermatological toxicity, raising long-term tolerability concerns despite a lack of life-threatening outcomes. In contrast, the BPaLM regimen reduced the incidence of severe or fatal adverse events, but retained risks of systemic toxicity such as neuropathy and hepatic dysfunction. These findings suggest that while clofazimine's toxicity is more cosmetic and tolerability-driven, the newer BPaLM regimen offers a safer alternative with reduced systemic harm, thereby shifting the balance towards regimens that optimize both efficacy and patient safety.

In the TB-PRACTECAL study published in The Lancet Respiratory Medicine (Nyang'wa et al., 2024), safety was one of the main focuses in evaluating the effectiveness of a short-course oral regimen based on bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaLM) compared to the standard long-term therapy for rifampicin-resistant pulmonary tuberculosis. The study results showed that the BPaLM regimen had a significantly better safety profile. Of the total 151 patients in the BPaLM group, only about 23% experienced severe adverse effects (grade ≥3) or serious adverse events, whereas in the standard therapy group, this figure reached approximately 48%. Additionally, treatment discontinuation due to adverse effects was lower in the BPaLM group. These findings indicate that the short-course oral regimen not only offers high efficacy but also provides a superior safety profile compared to conventional injectable-based and long-duration regimens.

Furthermore, in the study conducted by Tang et al. (2015) on the use of clofazimine as part of the therapy regimen in patients with multidrug-resistant pulmonary tuberculosis (MDR-TB), it was shown that the regimen had a good safety profile and was well tolerated by patients. The results demonstrated that clofazimine (Cfz) was effective against MDR-TB, as evidenced by a significantly higher sputum culture conversion rate in the Cfz group compared to the control group. Moreover, pulmonary cavity closure occurred faster in patients receiving Cfz. The treatment success rate was also higher in the Cfz group, at 73.6% compared to 53.8% in the control group. Additionally, during the treatment period, no significant differences were found in key clinical safety parameters between the clofazimine group and the standard group.

Moreover, the safety aspect related to the use of moxifloxacin (MOX) and gatifloxacin (GAT) in the initial therapy of drug-sensitive tuberculosis by Ruan et al. (2016) showed no significant differences between regimens containing MOX or GAT and the standard regimen regarding the incidence of death or serious adverse events. This analysis concluded that the use of MOX or GAT in initial therapy can be considered relatively safe compared to the standard regimen, as it does not significantly increase the risk of severe side effects.

The study conducted by Tang et al. (2015) assessed the use of adding clofazimine

to the MDR-TB treatment regimen. This study had a prospective, multicenter design with clinically relevant outcomes such as culture conversion, closure of pulmonary cavitations, and treatment success rates. The results showed that the addition of clofazimine provided statistically significant improvements and accelerated culture conversion and pulmonary cavitation closure. However, the study still used a relatively small sample size (n=105), experienced a high incidence of dermatological adverse effects (discoloration and ichthyosis), and the sample did not include populations with complex comorbidities. In addition, the study was conducted in China, which limits the generalizability of the results. This research indicates that clofazimine may be a potential component in MDR-TB regimens, but further studies with larger populations are needed to evaluate long-term efficacy and safety.

The study by Nyang'wa et al. (2024) evaluated the effectiveness of a short oral regimen based on BPaLM (bedaquiline, pretomanid, linezolid, moxifloxacin). This study had a phase IIb-III, multicenter, open-label design with a non-inferiority approach, which is highly relevant in TB therapy development. Conducted across countries with the highest TB burden such as Uzbekistan, Belarus, and South Africa, the study offers better geographic generalizability. The results showed that the 24-week BPaLM regimen had comparable or even superior effectiveness compared to the older standard of care (duration 36–80 weeks), while reducing the incidence of serious adverse effects (23% vs 48%). Although open-label design and a relatively wide non-inferiority margin (12%) may introduce potential bias, the study provides strong evidence that the short oral regimen can be a new alternative in resistant TB therapy. However, variability of results between countries and the need for long-term monitoring of relapse and resistance to new drugs (such as bedaquiline and pretomanid) remain aspects that require further investigation. This study offers an alternative TB treatment regimen that is shorter, safer, and easier to implement, but further research is necessary to test the sustainability of efficacy and resistance durability.

This systematic review evaluated two randomized controlled trials addressing multidrug-resistant tuberculosis (MDR-TB) management. Tang et al. (2015) demonstrated that clofazimine, when added to conventional long-term regimens, improved culture conversion and treatment success. However, its use was associated with notable adverse events, mainly skin pigmentation and gastrointestinal effects, highlighting the need for safety monitoring despite its therapeutic benefit.

On the other hand, the TB-PRACTECAL trial by Nyang'wa et al. (2023) showed that the all-oral BPaLM regimen (bedaquiline, pretomanid, linezolid, and moxifloxacin) provided higher efficacy with fewer severe adverse effects compared to standard prolonged regimens. This represents a significant step toward shorter, safer, and more tolerable MDR-TB treatment strategies.

Overall, the two trials illustrate complementary approaches: optimizing older agents like clofazimine versus adopting innovative short-course regimens. Both contribute to advancing MDR-TB therapy, balancing improved efficacy with manageable safety profiles.

In the discussion include theories that support or convey previous research (if any) for comparison and are written in Times New Roman font, font 12, space 1 and the size of the paper used is A4, with margins Top 1 ", Bottom 1", Left 0 , 75 "and Right 0.75" (in inches), or Top margin 2.54 cm, Bottom 2.54 cm, Left 1.90 cm and Right 1.90 cm (in centimeters). Images and photos must be clear and must include a proportional image or photo description. use page layout with columns Two

CONCLUSION

This systematic review highlights the evolving landscape of treatment regimens for multidrug-resistant and rifampicin-resistant tuberculosis. The evidence synthesized demonstrates that while the addition of

clofazimine improves microbiological outcomes and treatment success, its widespread dermatological toxicity poses challenges for long-term tolerability. Conversely, the TB-PRACTECAL trial establishes strong evidence for the BPaLM regimen, which combines bedaquiline, pretomanid, linezolid, and moxifloxacin, as a shorter, all-oral alternative with superior safety and efficacy compared to conventional lengthy regimens. Additional studies, including those evaluating fluoroquinolones and adjunctive therapies such as Bufei Jiedu Granules, further underscore the importance of balancing efficacy with safety to improve patient adherence and overall treatment outcomes. Collectively, these findings emphasize a paradigm shift toward shorter, safer, and more patient-centered regimens, while also highlighting the need for continued surveillance of long-term safety, relapse risk, and emerging drug resistance.

Conclusions are briefly explained and cover the aspects studied, make suggestions if any. Written in Times New Roman font, font 12, spacing 1 and the size of the paper used is A4, with a margin of Top 1 ", Bottom 1", Left 0.75 "and Right 0.75" (in inches), or Top margin 2.54 cm, Bottom 2.54 cm, Left 1.90 cm and Right 1.90 cm (in centimeters).

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