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Pharmacological Management of Tuberculosis, Challenges, and Potential Strategies

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Abstract: Tuberculosis (TB) is an infection caused by the pathogen *Mycobacterium tuberculosis*. The disease causes around 2 million deaths worldwide, and incidences of drug resistance only makes increases the number. The most vulnerable victims of TB infections are children and human immunodeficiency virus (HIV) patients. TB and HIV co-infections can be deadly in AIDS sufferers, as the immune system is not able to combat TB infections, hence worsening the infection. Common drugs to treat TB are available in the market, first-line drugs such as isoniazid and rifamycin are broad-spectrum drugs. Second-line antibiotics such as fluoroquinolones are also available. In this review, the mechanisms of action of TB drugs are briefly discussed, as wells as the respective resistant mechanisms of *M. tuberculosis* against these drugs. An updated treatment regime for TB management using bedaquiline, pretomanid and linezolid was also discussed, which shows 90% therapeutic efficacy against highly drug-resistant tuberculosis cases. Furthermore, novel strategies such as nanoparticle-conjugated TB drugs can improve drug delivery, TB drug efficiency while reducing side

effects. However, importance on patient compliance to the treatment regime is still the most crucial part of TB management, hence initiatives can be put to improve patient awareness and education.

Keywords: tuberculosis; *Mycobacterium tuberculosis*; drug resistance; antibiotics

1. Introduction

Tuberculosis (TB) is an infection caused by *Mycobacterium tuberculosis,* which can be contracted by breathing in tiny droplets from an infected person's cough or sneeze. TB is classified into pulmonary TB (PTB) and extrapulmonary TB (EPTB). PTB affects the lungs, while EPTB affects organs other than the lungs, such as abdomen, lymph nodes, pleura, joint, skin, bones, and meninges[1]. TB kills more than 2 million people annually, and the rise of drug-resistant *M. tuberculosis* has made the mortality toll from tuberculosis worse. According to estimations, children account for 10% of all TB cases worldwide[1]. During the HIV/acquired immune deficiency syndrome (HIV/AIDS) epidemic, a resurgence in TB infection was observed due to HIV and TB co-infections[1]. HIV has an impact on the immune system of the body, hastening the progression of TB from a non-threatening infection to a potentially fatal condition. Additionally, TB is one of the main causes of death among HIV-positive people. Furthermore, numerous researches conducted worldwide and in community-based studies from south India reported that diabetes has been demonstrated to be an independent risk factor for TB. Diabetes causes 20.8% of smear-positive TB and 14.8% of all TB cases. For TB to be effectively controlled, epidemiological knowledge is necessary[2].

The drugs available to treat TB inhibit the bacteria by targeting biological processes of *M. tuberculosis*, these include inhibiting synthesis of cell walls proteins or nucleic acids. However, the full mechanisms of action for several drugs preventing and treating *M. tuberculosis* infections are still elusive[3]. However, TB can be cured with a combination of first-line drugs taken daily for several months[4]. Most TB patients need to take TB medication for at least six months in order to be cured[5]. As *M. tuberculosis* bacilli are found in internal macrophages, necrotic granulomas, and huge cavities with liquid contents in TB disease, drugs are required to reach each of these compartments to exert its therapeutic effects[6].

In recent years, a number of fresh prospective antituberculosis drugs candidates with new mechanisms of action have successfully tested in clinical trials. Most likely, these substances could work against resistant strains[7]. Besides, both *in vitro* and *in vivo* preclinical models are leveraged to assess the clinical utility of new TB drugs and drug

combinations. These models vary both in their ability to assess efficacy relative to the shifting metabolic states of *M. tuberculosis* infection and in their ability to recapitulate human disease. Still, two models are proving to be highly informative. The mouse model of infection has been invaluable in selecting rank-ordered drug combinations, whereas the now-validated *in vitro* pharmacodynamic system has significantly improved our understanding of the pharmacokinetic drivers of treatment response in various growth and physiologic states[8].

This article examines the current potential of the first-line TB medications such as rifamycins, isoniazid, pyrazinamide, and ethambutol, as well as the fluoroquinolones to implement a real short-course TB regimen[9].furthermore, it gives a brief overview of the links between their structure and function, as well as their *in vitro* and *in vivo* activity, pharmacokinetics, mechanisms of action, and combinations.

2. Current TB Statistics

As of 2021, the WHO reported over 10 600 cases of TB, with roughly 4 800 cases in South-East Asia region. The number of deaths recorded was estimated to be around 1500 globally[10]. TB infections usually start from a reservoir, who is an infected person and is a source of infections. Patients with smear-positive sputum and culture-positive for TB are the most contagious reservoirs[11]. Transmission of pathogens occurs via aerosol produced when the infected person talks, coughs, or sings. However, TB-contaminated aerosol can be spread through other mechanisms including cutaneousmucosal, urogenital, transplacentarial and percutanial inoculation[11].

Once inhaled, *M. tuberculosis* enters the lungs and into the alveolar space. The bacteria are then spread through the lymphatic system to the lymph nodes in the lung, which forms the primary or Ghon complex. Conversion to tuberculin, which is used as a means of TB diagnosis, occurs during this time. As *M. tuberculosis* continue to spread, some individuals may experience acute and even fatal TB in the form of TB meningitis or disseminated TB[12]. Pleural inflammation can occur by interaction of the bacteria with sensitized CD4 T lymphocytes, which produces inflammatory cytokines, this results in severe chest pain[12].

3. Pharmacological Management

Treatment of TB utilizes antibiotics to kill *M. tuberculosis.* Nonetheless, developing a successful TB therapy is challenging due to the unique chemical and physical structure of the mycobacterial cell wall that obstructs drug entry and renders many antibiotics ineffective[13]. The antibiotics used to treat TB is classified into first-line and second-line antibiotics. The most efficient anti-tuberculosis medications are categorized as first-line.

Isoniazid, rifamycin, ethambutol, pyrazinamide, and streptomycin are among antibiotics in this group[14]. However, due to increasing incidence of antibiotic resistance, streptomycin is no longer considered as a first-line drug in the US (Nahid *et al*., 2016). The clinical efficacy of second-line anti-tuberculosis drugs is significantly lower than that of first-line drugs, and they are far more likely to result in severe adverse effects[14]. The examples of second-line anti-tuberculosis antibiotic include para-aminosalicylic acid (PAS), ethionamide, cycloserine, amikacin, capreomycin, and fluoroquinolones. The following table 1 summarises the types of antibiotics used to treat TB.

Table 1. Summary of drugs used to treat TB.

Drug	Classification	Mechanism of action	Reference
Isoniazid	First-line	Formation of reactive species that affect metabolic activities of *M. tuberculosis*	[14]
Rifamycin		Binding to RNA polymerase, inhibiting transcription	[15]
Pyrazinamide		Accumulation in tubercle bacilli, targets dormant *M. tuberculosis*	[16]
Ethambutol		Inhibition of RNA metabolism, phospholipid synthesis, transfer of mycolic acids to cell wall-linked arabinogalactan	[17]
Streptomycin	First/second-line	Targets bacterial ribosomes, causes misreading and inhibition of mRNA translation	[14]
Fluoroquinolones	Second-line	Targets DNA gyrase, prevents the migration of replication forks and transcription complexes	[18]

3.1 Administration of Drugs

To reduce the likelihood of the development of anti-tuberculosis antibiotic resistance, it is preferred to treat active TB using mixtures of multiple drugs[19]. The combination of isoniazid, rifampin, pyrazinamide, and ethambutol administering for the first two months of treatment is the medical standard for treating active TB. Isoniazid is used with pyridoxal phosphate during the early phase to prevent peripheral neuropathy. The final four months of active TB therapy consist of taking isoniazid along with rifampicin. After six months, a patient is thus deemed to be cleared of any *M. tuberculosis* infection[20].

Isoniazid is used to treat latent TB for three to nine months; however, this prolonged therapy often increases the risk of hepatotoxicity. It has been demonstrated that combining isoniazid with rifampicin for three to four months is an equally effective way to treat latent TB while reducing the risk of hepatotoxicity. To prevent the spread of active TB, latent TB must be treated[20,21]. Described below are known mechanisms of action of some antibiotics, while a clear understanding of the specific mechanisms of action of antibiotics is yet to be fully elucidated.

3.2 Isoniazid

Isoniazid interferes with nearly every metabolic pathway in *M. tuberculosis*. First by entering the bacteria via passive diffusion, followed by activation by *M. tuberculosis* catalase peroxidase enzyme (KatG), forming radical species such as reactive oxygen species and organic radicals[14], which have an impact on a variety of cellular targets. Furthermore, they are associated with the bactericidal effects of isoniazid, resulting in the inhibition of mycolic acid synthesis, phospholipid synthesis, DNA synthesis, and protein synthesis in addition to causing the build-up of soluble carbohydrate and phosphate esters[14]. It has been suggested that isoniazid blocks nicotinamide adenine dinucleotide (NAD) metabolism by incorporating itself into NAD to create pseudo-NAD, which is unable to serve as an electron acceptor in the respiratory chain. This biochemical process impedes numerous NAD functions, such as energy metabolism and DNA repair, where NAD is a cofactor for the DNA ligase required for the restoration of damaged DNA[14].

3.3 Rifamycin

Rifamycin, on the other hand, is known to be one of the most effective sterilizing drugs used in TB chemotherapy, as it continuously destroys tubercle bacilli throughout the whole course of treatment[16]. As a broad-spectrum antibiotic, it diffuses across *M. tuberculosis* cell membrane due to its lipophilicity, followed by binding to and halting the action of the DNA-dependent RNA polymerase of mycobacteria, thus inhibiting transcription and preventing the elongation of the RNA chain[15]. However, uncertainty exists about the precise mechanism by which this interaction kills mycobacteria[16].

3.4 Pyrazinamide

The potent sterilizing activity and treatment-shortening potential of pyrazinamide have been linked to the unique ability of the drug to target semi-dormant bacilli found in an acidic environment[22]. When added to rifampicin-containing regimens, it mostly kills persistent tubercle bacilli in the initial intense phase of chemotherapy, allowing the course of treatment to be reduced from nine to six months[14]. This action occurs when the drug enters the bacilli passively via an ATP-dependent transport system and accumulates due to an inefficient efflux system unique to *M. tuberculosis*[16]. In fact, the anti-tuberculosis activity of pyrazinamide has been linked to the disruption of the proton motive force needed for necessary membrane transport functions by pyrazinoic acid in acidic environments[16].

3.5 Ethambutol

The bactericidal effects of ethambutol against mycobacterial species, including *M. tuberculosis* infection, are the inhibition of RNA metabolism, phospholipid synthesis, transfer of mycolic acids to cell wall-linked arabinogalactan, spermidine synthesis, and an early step of glucose conversion into the constituent monosaccharides of cell wall

polysaccharides like arabinogalactose[17]. In addition, ethambutol could act as an arabinose mimic, blocking several processes that produce the key components of the bacterial cell wall[14]. Although most studies were conducted on *M. smegmatis*, Forbes *et al*. reported that ethambutol is active against *Mycobacterium* including isoniazid- and streptomycin-resistant *M. tuberculosis*[17].

3.6 Fluoroquinolones

Fluoroquinolones act by targeting DNA gyrase, which is a DNA topoisomerase in *M. tuberculosis*. DNA gyrase is composed of four subunits, two A and two B subunits, these subunits catalyse the supercoiling of DNA required in *in vivo* DNA replication[23]. The subunits are trapped on DNA as ternary complexes by fluoroquinolones, which prevents the migration of replication forks and transcription complexes[18]. Targeting DNA gyrase enables fluoroquinolones to act on Gram-negative bacteria, while DNA topoisomerase IV enables targeting of Gram-positive bacteria[24].

3.7 Streptomycin, Macrolides, and Aminoglycosides

Streptomycin, macrolides, and aminoglycosides exerts its effects on the bacterial ribosomes, which causes misreading of the genetic code. This in turn inhibits the initiation of mRNA translation[14,25]. However, due to increased incidences of drug resistance, the need for parenteral administration, significant side effects and the availability of better drugs, streptomycin usage as a first-line drug has declined in industrialized countries since the 1960s. Now ethambutol often replaces streptomycin in addition to isoniazid, rifampicin and pyrazinamide treatment regime during the initial phase of therapy. In some developing countries, streptomycin is still used for the initial 2 months of chemotherapy[14].

4. Current Issues with Pharmacological Management

Global tuberculosis pharmacological management is under threat due to developing drug resistance[26]. When the medications used to treat tuberculosis are improperly administered or managed, drug resistance to tuberculosis may develop. Misuse or poor management of tuberculosis drugs includes patients who did not receive a complete full course of tuberculosis treatment, improper treatment, such as the wrong length of time and dose, recommended by the healthcare professional, and others. Besides, drug resistance in tuberculosis is more typical among patients who do not take all of the tuberculosis drugs, do not take the tuberculosis drugs regularly, and others[27]. Table 2 below summarises the types of resistance observed in TB.

Table 2. Drug resistance in tuberculosis.

Type of Drug Resistance	Drug	Mechanism of Resistance	Reference
MDR-TB	Isoniazid	Mutations of *ahpC*, *inhA*, *katG*, *kasA* and *ndh* genes	[14]
	Rifampicin	Mutation in the RNA polymerase β subunit (*rpoB*) gene	[28]
XDR-TB	Amikacin, kanamycin, capreomycin	Mutations in the 16S ribosomal RNA (*rrs*), **hemolysin (***tlyA*), enhanced intracellular survival (*eis*) promoter and glucose-inhibited division gene B (*gidB*) genes	[29]
	Fluoroquinolones	Mutations in the quinolone resistance determining regions (QRDRs) of *gyrA*	[14]

4.1 Types of Drug Resistance in Tuberculosis

Historically, drug resistance in tuberculosis was divided into three categories: multidrug-resistant TB (MDR-TB), rifampicin-resistant TB (RR-TB), and extensively drug-resistant TB (XDR-TB)[26].

4.1.1 Multidrug-resistant tuberculosis

Multidrug-resistant TB (MDR-TB) is characterized as a *M. tuberculosis* infection that is resistant to both isoniazid and rifampicin, with or without resistance to alternative medicines[30]. Non-adherence to the recommended regimen, poor patient management, a subpar national program, or some combination of these three are the primary causes of MDR-TB[31]. MDR-TB is an increasing potential threat to TB control and has become a concern for human health on a global scale. According to the Global TB Report 2016, there were 21% of previously treated TB and 21% of newly diagnosed cases had MDR-TB[30]. In addition, MDR-TB is far more challenging to treat than a completely susceptible disease, necessitating costly second-line medications for at least eighteen months[31].

Drug resistance in TB occurs due to spontaneous mutation, unlike most bacteria with innate drug-resistance genes. Furthermore, TB gains resistance in the absence of drug pressure[32]. MDR-TB are typically tested using phenotypic assays, such as nitrate reductase assay, microscopic-observation drug susceptibility and thin-layer agar assays, or genotypic assays, such as polymerase chain reaction (PCR) and line probe assays[32].

4.1.2 Rifampicin-resistant tuberculosis

Rifampicin-resistant TB (RR-TB) is characterized by rifampicin resistance that has been identified by phenotypic or genotypic techniques, with or without the resistance to other first-line anti-tuberculosis drugs. RR-TB is a human-caused issue that is growing as a result of poor TB management and poses a danger to TB control. It is crucial to diagnose and suspect problems early. In 2015, around 580,000 cases of tuberculosis were predicted to be at least rifampicin-resistant globally[30].

4.1.3 Extensively drug-resistant tuberculosis

Extensively drug-resistant TB (XDR-TB) is referred to as MDR-TB strains that are resistant to second-line injectable drugs, such as amikacin, kanamycin, capreomycin, and fluoroquinolones[33]. Patients are left with far fewer effective treatment options, because XDR-TB is resistant to potent TB drugs. People who have HIV infection or other diseases that can compromise their immune systems should take special attention to XDR-TB. Once infected, these individuals have a higher likelihood of contracting tuberculosis, which increases their risk of death[27].

4.2 Mechanism of Drug Resistance in Isoniazid

Recent evidence and findings have started to challenge the critical role of isoniazid in the early stages of treating tuberculosis and its involvement in the effectiveness of long-term treatment[34]. According to one study, resistance rates were seen in both 6 months and continuous isoniazid groups. In the study, 164 patients who received isoniazid for 36 months had one occurrence of isoniazid resistance, whereas 327 patients who received it shorter duration of6 months had none. In addition, other investigations have shown the observed rate of resistant cases among confirmed tuberculosis cases are comparable to the hypothesized rate[35].

The molecular foundation of isoniazid resistance has seen significant advancement in recent years. Isoniazid resistance is linked to alkyl hydroperoxide reductase C (*ahpC*), inhibin subunit alpha (*inhA*), *M. tuberculosis* catalase-peroxidase (*katG*), β-ketoacyl-acyl carrier protein (*kasA*), and NADH dehydrogenase (*ndh*) mutations. It is a prodrug that needs the catalase-peroxidase enzyme expressed by the katG gene to be activated. By blocking the NADH-dependent enoyl-ACP reductase enzyme, which is encoded by inhA, activated isoniazid appears to interfere with the production of important mycolic acids[14].

Isoniazid resistance is anticipated to arise via various molecular mechanisms, only a subset of which have been completely described. Clinical *M. tuberculosis* isolates with isoniazid resistance exhibit 40 to 95% *katG* mutations, with 75 to 90% of these changes are found in different *katG* loci[36,37]. It is possible that *katG315* mutations are preferred, because they could reduce isoniazid activation without eliminating catalase-peroxidase activity,

which is a potential virulence factor. Besides, isoniazid resistance can arise from overexpression or alterations of its drug target *inhA*. It has reported that 8 to 20% of isoniazid-resistant *M. tuberculosis* isolates have mutations in the *inhA* promoter, while 0 to 5% have mutations in the *inhA* open reading frame (ORF)[38]. Furthermore, the mutation in the *ndh* gene has been reported to make *M. bovis* resistant to isoniazid and ethionamide. The *ndh* mutants altered NADH/NAD ratios are more likely to protect against isoniazid toxicity. Moreover, it has been shown that isoniazid resistance in clinical isolates is linked to mutations in at least 16 other genes. However, the functions of these genes in isoniazid resistance, are still unknown. Additionally, between 20 and 25% of isoniazid-resistant strains lack mutations in any of the known isoniazid resistance-related genes[14].

4.3 Mechanism of Drug Resistance in Ethambutol

Ethambutol has been reported to inhibit *M. tuberculosis* by preventing the synthesis of arabinogalactan[17]. The *embABC* gene cluster, which codes for the arabinotransferases that catalyze the polymerization of arabinose into arabinan, is necessary for the biosynthesis of arabinogalactan. Increasing evidence has shown that the toxic effects of ethambutol on mycobacteria are caused by the inhibition of *embABC* encoded proteins. Mutations in *embABC* is also a major factor in promoting ethambutol resistance in both *M. smegmatis* and M. *tuberculosis*[14]. Shi *et al*. (2007) demonstrated that clinical strains of *M. tuberculosis* associated with ethambutol resistance and mutations in *embA, embB,* and *embC*, as well as mutations in codon 306 of the *embB* gene (embB306) that are present in around 50% of all ethambutol-resistant clinical isolates. The minimum inhibitory concentration (MIC) of ethambutol was increased by 8- to 16-fold for each mutation. Due to the association described above, *embB306* mutations is suggested as a marker for ethambutol resistance in diagnostic tests[14].

5. Potential Strategies to Improve the Current Pharmacological Management of Tuberculosis

Drug-resistant tuberculosis remains a major problem of the global tuberculosis pandemic, thus more effective, safer, and shorter treatment regimens are required to combat tuberculosis. To manage and improve the current pharmacological management of drug-resistant tuberculosis treatment failure, the approved regimen of pretomanid tablets that was used in combination with linezolid and bedaquiline by the U.S. Food and Drug Administration (FDA) on 14 August 2019 was suggested for the treatment of drug-resistant tuberculosis[39].

Pretomanid is a nitroimidazooxazine and its mechanism of action that act against non-replicating and replicating *M. tuberculosis* is via the release of nitric oxide release and the inhibition of mycolic acid biosynthesis, respectively[40]. Besides, the *in vitro* activity of

pretomanid was found to be against both drug-susceptible and drug-resistant strains of *M. tuberculosis*[40].

Linezolid is an oxazolidinone antibiotic that was used for the treatment of MDR-TB and XDR-TB. It was suggested that the second-line regimen for every patient should include linezolid unless it was contraindicated. Linezolid can bind to the 70S initiation complex of the ribosome to disrupt the protein synthesis of *M. tuberculosis*. However, discontinuation and adverse effects of linezolid are commonly observed during the tuberculosis treatment[41]. One of the most frequently observed side effects of linezolid is peripheral neuropathy, and its risk factors include dose and duration of linezolid treatment, nutritional status, concurrent medication usage, coexisting conditions, and possible genetic factors[40].

Bedaquiline is a recently developed antibiotic that was used to treat tuberculosis infections that developed resistance to multiple drugs. It is a diarylquinoline drug that inhibits the specific adenosine triphosphate (ATP) synthase subunit of *M. tuberculosis*, causing a decrease in their intracellular ATP levels. Bedaquiline has less affinity of 20,000 times for human ATP synthase. In addition, upon interferon-gamma (IFN-γ) activation, bedaquiline has a crucial role in the host response to coordinate the granuloma formation, kill the bacillus, and present the antigens of the mycobacteria to the T lymphocytes[42].

The bedaquiline–pretomanid–linezolid is a fully oral regimen that was assigned for a treatment duration of 26 weeks. Based on a randomized trial that was conducted (ZeNix ClinicalTrials.gov number NCT03086486), participants with XDR-TB were recruited and received 200 mg of pretomanid tablets daily for 26 weeks and 200 mg of bedaquiline tablets daily for 8 weeks, followed by 100 mg daily for the next 18 weeks. Additionally, the participants also received 1200 mg of linezolid daily for up to 26 weeks, however, the dosage was reduced in a stepwise manner from 1200 mg to 600 mg, followed by 300 mg and 0 mg, depending on the response of participants to the adverse effects of linezolid. Intriguingly, the results showed that 84 to 93% of the participants across four treatment groups had a desirable outcome, with fewer dose modifications of linezolid and lesser adverse events were reported. The bedaquiline–pretomanid–linezolid regimen was also reported to achieve 90% therapeutic efficacy against tuberculosis with highly drug-resistant cases[40]. Thus, this regimen could be a recommendation for the treatment of drug-resistant tuberculosis.

Furthermore, new innovations of drug delivery can be utilised for efficient anti-tuberculosis drugs. For example, nanoparticle drug delivery can be an attractive method to administer drugs. Encapsulation and conjugation of TB antibiotics to polymeric nanoparticles enable enhanced effectiveness of the drugs as well as reduced toxicity effects by improving the release of drugs[43]. Other forms of nanoparticles include silver nanoparticles[44] and lipid nanoparticles[45].

Lastly, patient adherence to the treatment regime is probably the most crucial aspect of reducing incidences of TB drug resistance. A study in Ethiopia reported up to 21.3% of

non-adherence among patients[46]. Among the factors for patient non-compliance include lack of social support, perceived and experienced stigma, financial constraints, lack of education, pill burden especially among HIV patients, and persistence of symptoms even after starting treatment[47]. It is important that patients understand the importance of adhering to the treatment regime, hence healthcare providers and government bodies can work together to provide an educational and support programs designed to target this issue.

The following image illustrates the summary of antibiotics used to treat TB and its limitations as well as the potential drugs to treat MDR-TB and XDR-TB effectively.

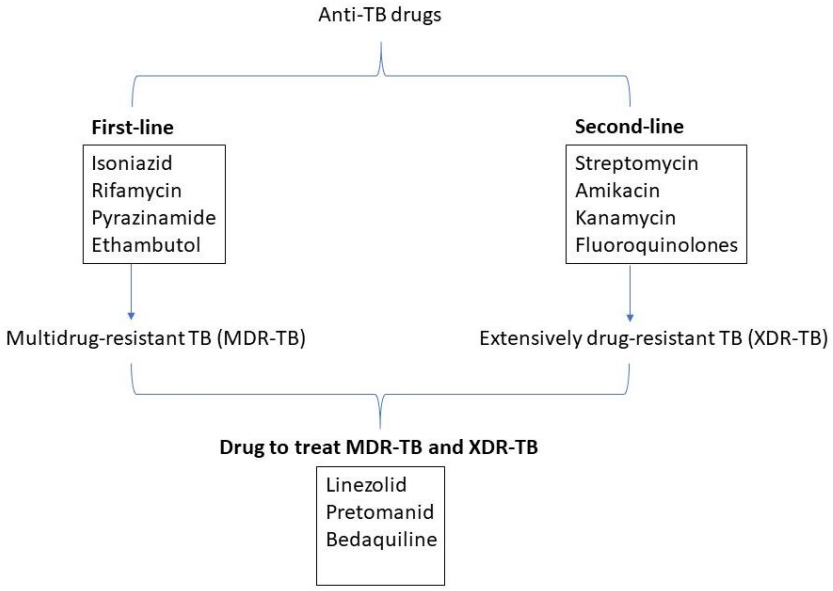

Figure 1. Summary of the types of antibiotics used to treat TB. This figure illustrates the types of antibiotics used to treat TB and its limitations of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) as well as the potential drugs to combat MDR-TB and XDR-TB effectively.

6. Conclusion

TB is a serious illness and an airborne disease that affects millions of people annually. With the increase of drug-resistant TB, the number of people get affected and mortality rates are alarmingly increased. Conventional TB drugs are less effective due to the occurrence of resistance caused by improper or incomplete administration of drugs. If the problem persists, TB patients have fewer options, particularly those with XDR-TB. However, the new treatment regime using bedaquiline, pretomanid, and linezolid was introduced as a means to manage drug-resistant TB patients. Based on clinical trial results, the treatment regime improves the outcome of TB patients. Despite that, side effects are still an issue encountered, particularly exerted by linezolid.

Hence, treatment of TB, especially drug-resistant TB should be approached with the utmost care to prevent more incidences of drug resistance in *M. tuberculosis*. Educational

programs and support systems can be set up by government bodies to improve patient understanding and awareness of the importance of proper and complete treatment regime. Furthermore, newer treatment strategies such as enhanced drug delivery using nanoparticles can be a great option to improve anti-TB treatment outcomes.

Author Contribution: Y.S.W. designed the flow of the review, planned the manuscript, and supervised the entire work. B.X.J and A.S. collected the data and wrote the manuscript. All the co-authors reviewed and revised the final draft. All authors agreed to be accountable for all aspects of work to ensure integrity and accuracy. All authors have read and agreed to the published version of the manuscript.

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