Drug Saf (2015) 38:253–269
DOI 10.1007/s40264-015-0267-y

REVIEW ARTICLE

Safety and Tolerability Profile of Second-Line Anti-Tuberculosis Medications

Geetha Ramachandran · Soumya Swaminathan

Published online: 13 February 2015

Abstract Tuberculosis (TB) remains a major public health problem, representing the second leading cause of death from infectious diseases globally, despite being nearly 100 % curable. Multidrug-resistant (MDR)-TB, a form of TB resistant to isoniazid and rifampicin (rifampin), two of the key first-line TB drugs, is becoming increasingly common. MDR-TB is treated with a combination of drugs that are less effective but more toxic than isoniazid and rifampicin. These drugs include fluoroquinolones, aminoglycosides, ethionamide, cycloserine, aminosalicyclic acid, linezolid and clofazimine among others. Minor adverse effects are quite common and they can be easily managed with symptomatic treatment. However, some adverse effects can be life-threatening, e.g. nephrotoxicity due to aminoglycosides, cardiotoxicity due to fluoroquinolones, gastrointestinal toxicity due to ethionamide or para-aminosalicylic acid, central nervous system toxicity due to cycloserine, etc. Baseline evaluation may help to identify patients who are at increased risk for adverse effects. Regular clinical and laboratory evaluation during treatment is very important to prevent adverse effects from becoming serious. Timely and intensive monitoring for, and management of adverse effects caused by, second-line drugs are essential components of drug-resistant TB control programmes; poor management of adverse effects increases the risk of non-adherence or irregular adherence to treatment, and may result in death or permanent morbidity. Treating physicians should have a thorough knowledge of the adverse effects associated with the use of second-line anti-TB drugs, and routinely monitor the occurrence of adverse drug reactions. In this review, we have compiled safety and tolerability information regarding second-line anti-TB drugs in both adults and children.

Key Points

Most of the second-line tuberculosis (TB) drugs cause adverse effects.

Minor adverse effects are common, and most are manageable with symptomatic treatment.

Timely and intensive monitoring for, and management of, adverse effects caused by second-line drugs are essential components of drug-resistant TB control programmes, because poor management of adverse effects increases the risk of non-adherence or irregular adherence to treatment, and may result in death or permanent morbidity.

1 Introduction

Tuberculosis (TB) remains a major global health problem. It causes ill health among millions of people each year and ranks as the second leading cause of death from an infectious disease worldwide, after HIV. Multidrug-resistant (MDR)-TB is a form of the disease resistant to isoniazid and rifampicin (rifampin), two of the most important first-line TB drugs. In 2012, the WHO estimates that 450,000 people globally developed MDR-TB, and 170,000 people died of MDR-TB [1].

G. Ramachandran · S. Swaminathan (✉)
National Institute for Research in Tuberculosis (Indian Council of Medical Research), Mayor VR Ramanathan Road, Chetpet, Chennai 600 031, India
e-mail: doctorsoumya@yahoo.com; soumyas@nirt.res.in

2 Treatment of Tuberculosis (TB)

The chronic nature of mycobacterial infections generally necessitates prolonged therapy over several months. An ideal agent should have minimal toxicity with maximal efficacy. Regimens containing multiple drugs are necessary to prevent the development of drug-resistant strains, since spontaneous mutations in the bacteria occur at varying frequencies for different drugs [2]. A list of drugs used in the treatment of TB is given in Table 1. *Mycobacterium tuberculosis* grows slowly; hence, patient compliance, drug toxicity, drug tolerance and the development of bacterial resistance present special therapeutic problems.

The long-term goal of TB chemotherapy research now is to develop short, safe and effective regimens, which can be effective in both patients with drug-resistant and drug-sensitive TB [3]. Currently, treatment of drug-sensitive TB lasts for a minimum of 6 months, while MDR-TB is treated for 20–24 months and extensively drug-resistant TB even longer (24–30 months) [4].

Table 1 Groups of drugs used to treat tuberculosis [61]

Group name	Drugs
Oral agents	Isoniazid
	Rifampicin (rifampin)
	Ethambutol
	Pyrazinamide
	Rifabutin
	Rifapentine
Injectables	Kanamycin
	Amikacin
	Capreomycin
	Streptomycin
Fluoroquinolones	Moxifloxacin
	Levofloxacin
	Ofloxacin
Oral bacteriostatic agents	Ethionamide
	Prothionamide
	Cycloserine
	Terizidone
	Para-aminosalicylic acid
Others with unclear efficacy	Clofazimine
	Linezolid
	Amoxicillin–clavulanic acid
	Thiacetazone
	Meropenem–clavulanic acid
	Imipenem/cilastin
	High-dose isoniazid
	Clarithromycin

3 Methods Used for Data Collection

A structured review of the literature was performed to evaluate the drugs in this review. The PubMed database was searched using the keywords TB, MDR-TB, second-line anti-TB drugs, safety, tolerability, adults and children. Children refer to the age group 0–18 years. However, findings may not be generalisable to neonates and young infants in all cases, since developmental changes can affect drug pharmacokinetics. Reference lists of identified articles were also reviewed for additional relevant reports. Abstracts from meetings and review articles were also included.

Two searches were performed for each drug reviewed. The first was a more general search on the drug. The second search was more focussed on the safety and tolerability of each drug in adult and paediatric populations. The search period was from August 2014 to January 2015.

4 Fluoroquinolones: Ofloxacin, Levofloxacin and Moxifloxacin

Ofloxacin, levofloxacin and moxifloxacin are fluorinated quinolones, a synthetic class of antibacterials. Ofloxacin is generally considered to be a second-generation fluoroquinolone, levofloxacin a second- or third-generation fluoroquinolone and moxifloxacin a fourth-generation fluoroquinolone. Fluoroquinolones target the enzymes, DNA gyrase and topoisomerase IV [5, 6]. Levofloxacin is the I-isomer and more active component of the racemate ofloxacin [7], and has approximately twice the activity of ofloxacin against most bacterial pathogens [8–10]. Moxifloxacin has an additional methoxy group, which increases its affinity towards DNA gyrase and topoisomerase IV [6]. Further, moxifloxacin has a different metabolic pathway, which may influence the occurrence of adverse effects [11]. The US FDA approved ofloxacin, levofloxacin and moxifloxacin in 1990, 1997 and 1999, respectively.

4.1 Safety Data

Generally, fluoroquinolones are well-tolerated when given for a short duration in adults [5]. There are limited data in children, especially when used for a long duration. However, the toxicity profile of fluoroquinolones in children and adults are similar [12].

4.1.1 Gastrointestinal Adverse Effects

Gastrointestinal events, such as nausea, anorexia, diarrhoea, vomiting and abdominal pain, are the most common

adverse effects of the fluoroquinolones. These gastrointestinal effects have been reported in 3–17 % of adults in clinical trials, but are mild, rarely requiring discontinuation of the drug [5]. Treatment with fluoroquinolones was found to be associated with *Clostridium difficile*-associated diarrhoea [5, 13, 14]. In a systematic review and meta-analysis of children with MDR-TB, ofloxacin was potentially implicated as a cause of nausea in some patients [15].

4.1.2 CNS Adverse Effects

CNS adverse effects have been described to occur in 0.9–11 % of adults treated with fluoroquinolones [5, 16]. The CNS manifestations of fluoroquinolone toxicity vary from less serious effects such as insomnia, dizziness, headaches, confusion, somnolence and muscle jerks to more serious effects such as delirium, psychosis and seizures. Most of these could be related to inhibition of GABA or activation of NMDA receptors [17] by fluoroquinolones [16, 18, 19]. Sleep disturbance has been reported in about 4.7 % of patients receiving fluoroquinolones [20]. Seizures have been reported to occur with ofloxacin [20] and levofloxacin [21, 22], which could be related to drug interactions with NSAIDs, antidepressants, theophylline and metoclopramide. CNS manifestations are quite common in those with seizure disorders, electrolyte abnormalities, the elderly and those with renal failure, but, overall, occur in less than 1 % of patients [17, 19–22].

Two cases of seizures associated with nalidixic acid overdose in children have been reported [23, 24], but reports of seizures attributed to ofloxacin, levofloxacin or moxifloxacin in children are lacking. Sleep disorders, nightmares and insomnia related to ofloxacin have been described in children [25]. A systematic review describing adverse effects in 182 children with MDR-TB did not report any CNS effects attributed to fluoroquinolones [15]. A report from a cohort of children receiving an ofloxacin-containing MDR-TB preventive treatment regimen observed nine and four of 193 experiencing Grade 1 or 2 mood/sleep disturbances, respectively [26]. In general, mild sleep disturbances and nightmares are quite common in children receiving ofloxacin, but are usually mild, more frequent at start of treatment and resolve spontaneously without discontinuing treatment.

4.1.3 Prolongation of the QT Interval

The fluoroquinolones are known to cause prolongation of the QT interval in a dose-dependant manner by inhibition of potassium channels, especially the delayed rectifier potassium current I_{KR}, coded by the hERG (human ether-à-go-go) gene [18, 27]. QT interval prolongation predisposes to Torsades de pointes, which could be fatal. Although this effect could vary between agents, prolongation is minimal for most drugs, averaging 3–6 ms. Further, the clinical significance of such small degrees of QT prolongation remains questionable [27, 28]. Electrophysiology studies evaluating the inhibition of I_{KR} HERG channels by fluoroquinolones have shown the rank order of inhibition to be sparfloxacin > grepafloxacin > moxifloxacin [concentration that produces 50 % inhibition (IC_{50}) 129 μmol/L] > gatifloxicin > levofloxacin (IC_{50} 915 μmol/L) > ciprofloxacin > ofloxacin (IC_{50} 1,420 μmol/L) [29].

Clinical studies have shown the effect of levofloxacin on the QT interval to be minimal, even at doses of 1,000 and 1,500 mg [30–32]. It was observed that after doses of 500, 1,000 and 1,500 mg of levofloxacin, corrected QT intervals (QTc) were unchanged from baseline [32]. In the USA from 1996 to 2001, the FDA database showed 37 individual cases of Torsades de pointes associated with the use of fluoroquinolones [33]. Studies linking fluoroquinolone use with cardiac arrhythmias have been consistent with these findings [34].

Although the absolute effect of fluoroquinolones on the QT interval appears to be minimal, this is likely to assume clinical significance in the presence of certain risk factors for Torsades de pointes [35], such as female sex, familial long QT syndromes, other heart diseases, renal and liver dysfunction, electrolyte abnormalities and interactions with multiple drugs that prolong the QT interval [27]. In the report from the FDA database, 19 of the 37 patients with reported fluoroquinolone-associated Torsades de pointes were taking other drugs known to prolong the QT interval, and some additional patients had other predisposing conditions such as hypokalaemia [33]. An additional consideration for patients on MDR-TB treatment is the frequent drug-induced hypothyroidism related to para-aminosalicylic acid (PAS) or ethionamide. Hypothyroidism and subclinical hypothyroidism are associated with prolongation of the QT interval [36, 37], and treatment with L-thyroxine has been shown to normalise the QT interval [38, 39]. An additional important consideration in malaria endemic areas is the QT-prolonging effects of many existing antimalarials [40]. The use of most of these antimalarials in combination with fluoroquinolones is currently contraindicated; however, more data on the potential clinical significance are required [40].

No reports are available on the effect of fluoroquinolones on the QT interval or fluoroquinolone-associated arrhythmia in children. However, understanding this potentially significant adverse effect is important, especially in children with known risk factors for a prolonged QT interval. Based on existing knowledge, concerns about QT prolongation should not limit the use of fluoroquinolones in children.

4.1.4 Arthropathy

Concern about arthropathy has been a major factor limiting use of fluoroquinolones in children. Fluoroquinolone-induced damage to the cartilage of weight-bearing joints has been observed in certain animal models, with several mechanisms proposed for this damage, including magnesium chelation by the fluoroquinolones [41]. In fact, juvenile dogs were found to be the most sensitive, with beagle puppies treated with nalidixic acid developing arthropathy at half the dose recommended for children [41]. Reviews of fluoroquinolone safety in children have consistently concluded that there could be an association between fluoroquinolones and reversible arthralgia in children; however, evidence is lacking for severe or irreversible athropathy [6, 12, 42–47]. A review of 31 published reports of 7,045 children treated with short courses of nalidixic acid, norfloxacin, pefloxacin, ciprofloxacin and ofloxacin did not find any report of arthropathy beyond the severity of that of the underlying disease process [41]. In a prospective non-blinded long-term follow-up study in 2,345 children treated with short courses of levofloxacin, a statistically significant increase in musculoskeletal disorders, primarily subjective arthralgia, was observed in 2.1–3.4 % of children treated with levofloxacin [48]. Prospective clinical experience of levofloxacin safety and tolerability in children for treatment lasting more than 14 days is lacking [49]. Yee et al. [41] did not observe an increased risk of tendon or joint complaints in about 6,000 children treated with ciprofloxacin, ofloxacin or levofloxacin compared with azithromycin-treated children [50]. Joint imaging after fluoroquinolone use did not show any long-term abnormalities in children.

A systematic review on adverse effects in 182 children with MDR-TB reported a single case of temporary Achilles tendinitis, potentially associated with levofloxacin use [15]. In recently presented data on children receiving ofloxacin 15–20 mg/kg for 6 months for MDR-TB preventive treatment, five of 189 reported Grade 1, one of 189 reported Grade 2, and none reported Grade 3 or 4 joint/muscle/bone pain [26]. A 2011 review of fluoroquinolones use and safety in children commissioned by the WHO and endorsed by the WHO Essential Medicine Committee concluded that existing information was sufficient to support their appropriate use in infants and children, and recommended their wide availability for use in children with a clear clinical indication in combination with close monitoring [51]. A prospective 5-year follow-up safety study in children by Bradley and others observed that the risk of cartilage injury with levofloxacin was low [52].

Fluoroquinolone-associated arthropathy has also been described in adults receiving ofloxacin [53, 54] and moxifloxacin [55] for treatment of TB.

4.1.5 Other Rare Adverse Effects

Other adverse effects, including Stevens-Johnson syndrome and toxic epidermal necrolysis [18] and dysglycaemia [18, 56], have been described but are uncommon with levofloxacin and ofloxacin. The fluoroquinolones are generally considered to be well-tolerated in the context of liver disease. Ofloxacin has been shown to be safe for use in patients with chronic liver disease [57, 58], and moxifloxacin and levofloxacin been shown to be safe for use in those with anti-TB drug-induced hepatitis [59, 60].

5 Injectable Agents

The aminoglycosides amikacin and kanamycin and the cyclic polypeptide capreomycin are WHO Group II drugs [61], and are discussed together in view of their having a similar mechanism of action, pharmacology, routes of administration, and profile of adverse effects. They are often referred to as second-line injectable (SLI) drugs in the context of treatment for drug-resistant TB. Aminoglycosides exert their action by tightly binding to the 16S ribosomal RNA (rRNA) in the 30S ribosomal subunit, leading to a conformational change in the rRNA subunit, preventing mRNA translation and translocation, and inhibiting protein synthesis [62, 63].

Kanamycin is a product of the *Streptomyces* species of soil bacteria [61]. Amikacin is a semi-synthetic derivative of kanamycin [64]. Capreomycin is isolated from *Streptomyces capreolus*, and is chemically similar to viomycin [65–67]. The US FDA approved capreomycin, kanamycin and amikacin in 1971, 1973 and 1981, respectively.

5.1 Safety Data

The most common adverse effects of aminoglycosides and cyclic polypeptides are nephrotoxicity, ototoxicity, vestibular toxicity and electrolyte abnormalities [68]. While streptomycin is usually used in first-line treatment for a period of 8–12 weeks, kanamycin, amikacin and capreomycin are used for treatment of drug-resistant TB for up to 6–12 months [69].

5.1.1 Nephrotoxicity and Electrolyte Abnormalities

Aminoglycoside-induced nephrotoxicity is reversible, and is associated with uptake of aminoglycosides by renal tubular cells after glomerular filtration, leading to intracellular accumulation and subsequent tubular necrosis, resulting in oliguric renal failure [68]. The uptake into tubular cells is a saturable process, suggesting that higher, less frequent dosing might attenuate nephrotoxicity [70].

This has been confirmed by studies of extended-interval dosing of aminoglycosides in adults [71]. In two adult cohort studies treated for MDR-TB, 24 of 244 patients (9.8 %) [72] and ten of 107 patients (9.3 %) [73] had nephrotoxicity during treatment.

Aminoglycosides can cause hypokalaemia, hypomagnesaemia and hypocalcaemia by inducing renal wasting of these electrolytes, and by induction of secondary hypoaldosteronism leading to urinary loss of magnesium and potassium [68]. Electrolyte abnormalities have been associated with high cumulative doses of aminoglycosides [74, 75]. The risk is reported to be higher with capreomycin, occurring in 4–15 % of patients on capreomycin for a long duration [74, 76, 77]. In a cohort of 115 adults with MDR-TB, 34.8 % had an electrolyte abnormality during treatment, with 31.3 % having hypokalaemia, 15.7 % hypomagnesaemia and 12.2 % both [74]. Hypokalaemia was noted in 33.2 % of an adult MDR-TB cohort in Russia, resulting in discontinuation of capreomycin in 7.4 % of patients [72]. In a cohort of extensively drug-resistant (XDR)-TB patients in South Africa, six of 67 patients died due to presumed capreomycin-associated adverse effects such as rapidly progressive renal failure ($n = 5$) and hypokalaemia ($n = 1$) [78]. Nephrotoxicity has generally not been a common problem among children with MDR-TB, with a systematic review reporting only one of 182 children to have an asymptomatic elevation in creatinine [15].

5.1.2 *Ototoxicity*

The mechanism of aminoglycoside-induced ototoxicity has been studied well, yet some questions remain unanswered. Aminoglycosides enter cochlear hair cells early after infusion through a membrane channel which acts as a one-way valve, and, since they are not metabolised, remain in hair cells for long periods of time [79]. Aminoglycosides cause disruption of hair cell mitochondrial integrity and leakage of pro-apoptotic factors into the cytoplasm resulting in cell death by producing reactive oxygen species generated by the creation of aminoglycoside complexes with iron, and also by interactions with the 12 s subunit of mitochondrial rRNA [79]. This damage begins at high frequencies, above the range of normal speech, and progresses to lower frequencies over time, explaining why patients do not report subjective hearing difficulty at an early stage [79]. To date, six genetic mutations in the mitochondrial gene encoding 12s rRNA have been identified that confer increased risk of ototoxicity [79–82].

Little information is available on the factors that could help to identify individuals at higher risk for ototoxicity. A study conducted in adult patients with cystic fibrosis treated with aminoglycosides showed hearing loss in seven of 38 (18 %); this was associated with trough drug concentrations above 10 μg/mL for amikacin or above 2 μg/mL for gentamicin/tobramycin [83]. In another study of hearing loss in three combined trials of aminoglycosides, trough concentrations and older age were associated with ototoxicity in univariate analysis, but only age remained associated in multivariate analysis [84]. Although animal data suggest that extended-interval dosing of aminoglycosides could lower their ototoxicity [85–87], data in humans have not shown such a benefit [71, 88]. A study that compared a 15 mg/kg daily dose of streptomycin, kanamycin or amikacin (5 days a week) with a three times weekly dose of 25 mg/kg did not observe any difference in the risk of hearing loss between the two groups [88]. Older age, total dose and the related duration of treatment were associated with ototoxicity. The risk of hearing loss increased 6.9-fold for every 10-fold increase in total dose received.

Limited data are available on the toxicity of prolonged courses of SLI agents given to patients with drug-resistant TB. Though most of the studies reported less than 10 % of patients having hearing loss, there was a wide range, with rates as high as 50 % reported [89]. In a cohort of 153 South African MDR-TB patients treated with SLIs, 57 % developed high-frequency hearing loss, with HIV-infected individuals having a higher risk of 70 % [90]. Despite the known association of hearing loss with mitochondrial mutations, none of the patients had mutations in the mitochondrial gene. In view of the low population frequency of these mutations, it is unlikely that they are implicated in the majority of patients having ototoxicity [80, 90].

A retrospective analysis of a cohort of children treated for MDR-TB observed that 24 % had documented hearing loss, stressing the frequency and importance of this adverse effect [91]. In two other studies, two of 38 (6.7 %) and one of ten (10 %) children were reported to have hearing loss [15, 92, 93]. Though less frequent than in adults, hearing loss in children during crucial periods of language development could have a profound impact on speech and overall development. Hence, strategies that maintain the efficacy of MDR-TB treatment regimens but limit ototoxicity are required.

6 Ethionamide and Prothionamide

2-Ethyl thioisonicotinamide or ethionamide was synthesised in 1956 by Grumbach et al. This compound was later reported to have anti-mycobacterial activity [94]. Prothionamide is the propyl analogue of ethionamide [95]. Both ethionamide and prothionamide are structurally similar to isoniazid [96]. They are prodrugs that are activated by the flavin monoxygenase enzyme EthA, encoded by the *ethA* gene [96]. The activated forms of ethionamide and prothionamide form adducts with nicotinamide adenine

dinucleotide (NAD) which are tight binding inhibitors of the InhA enzyme in *M. tuberculosis*, also the target of isoniazid, and inhibit mycolic acid synthesis [96, 97]. Ethionamide and prothionamide can be interchanged. In addition to their use in the treatment of TB, they are also used in the treatment of leprosy [96]. The US FDA approved ethionamide in 1965.

6.1 Safety Data

6.1.1 Gastrointestinal Adverse Effects

Gastrointestinal intolerance is a well-known adverse effect of both ethionamide and prothionamide. In an early evaluation of retreatment regimens using ethionamide at a 750–1,000 mg dose divided three to four times daily, it was observed that the majority of patients reported some degree of gastrointestinal intolerance which usually improved or resolved within 2–3 weeks without any dose adjustment [98]. In 26 % of the patients, gastrointestinal intolerance was sufficiently serious to switch to the suppository form of ethionamide [98]. The gastrointestinal intolerance had immediate and delayed components, consisting of anorexia, metallic taste, nausea, vomiting, upper abdominal discomfort and diarrhoea [98]. Gastrointestinal intolerance is also known to be a common adverse effect of ethionamide in children, but has not been reported very often. In the first few weeks of treatment, splitting the once-daily dose into two or three divided doses a day has been recommended to improve tolerability in children [99].

It has been suggested that prothionamide may be better tolerated than ethionamide [100]. In a study in adults treated with ethionamide 375 mg twice daily, 24 of 48 (50 %) reported gastrointestinal symptoms, with nine of 48 (19 %) being severe, compared with 17 of 53 (32 %) with any and three of 53 (6 %) with severe gastrointestinal symptoms in those taking prothionamide 375 mg twice daily [101]. A similar trend in improved gastrointestinal tolerability was seen in a trial comparing ethionamide- with prothionamide-containing regimens, with gastrointestinal intolerance reported in 56 of 167 (33.5 %) and 41 of 160 (25.6 %) of patients, respectively, on ethionamide and prothionamide [102].

6.1.2 Hypothyroidism

Hypothyroidism is a known reversible adverse effect of prolonged therapy with ethionamide and prothionamide [103–105]. Ethionamide, which is structurally similar to methimazole, is thought to inhibit organification of iodine and possibly blocks uptake of iodine [103, 106]. In a cohort of 186 adults with MDR-TB, the majority of whom were treated with both ethionamide or prothionamide and PAS, 129 (69 %) had hypothyroidism defined as a thyroid-stimulating hormone (TSH) level >10 mIU/L [107]. Hypothyroidism was reported in 73 of 213 (34.2%) in a retrospective cohort from Botswana, five of seven (71.4 %) in a cohort from the UK, and 11 of 52 (21 %) in an Indian cohort who also reported death from myxoedema coma in one patient [108–110].

In a cohort of ethionamide-treated children with MDR-TB, 79 of 137 (58 %) had abnormal thyroid function, with at least 41 % likely due to ethionamide treatment [106].

An increased risk of hypothyroidism was found to be associated with ethionamide/prothionamide and PAS co-treatment [106] and with HIV in a paediatric cohort [106] but not in an adult cohort [107].

6.1.3 Other Rare Adverse Effects

Hepatitis [111], pellagra-like rash [112], CNS effects [113, 114], gynecomastia [115, 116] and hypoglycaemia [117] have rarely been associated with ethionamide or prothionamide [118].

7 Cycloserine and Terizidone

D-Cycloserine is a cyclic analogue of the amino acid D-alanine, and was discovered in the 1950s [119]. The US FDA approved cycloserine in 1964. The antimycobacterial activity of cycloserine is related to its inhibition of two enzymes required for the synthesis of peptidoglycan, an important component of the bacterial cell wall [120–122]. Terizidone is a Schiff base of two molecules of D-cycloserine combined with terephthalic di-aldehyde [123].

7.1 Safety Data

Cycloserine is known to cause CNS adverse effects, which are reported to occur in about 20–30 % of patients [19]. The neurological manifestations vary widely, and include dizziness, excitation, headache, slurred speech, tremor, insomnia, lethargy, anxiety and an inability to concentrate. Other more serious effects include severe depression, suicidal ideation, psychosis, seizures and encephalopathy [19, 124, 125]. The nervous system adverse effects are dose related and associated with increased serum concentrations [124]. It was demonstrated that maintaining serum concentrations between 20 and 40 μg/mL produced a favourable clinical response, with only four of 60 patients experiencing neuropsychiatric effects [126], all of whom had cycloserine concentrations above 40 μg/mL [126]. However, toxicity could occur even at low serum concentrations [124]. Neurotoxicity is usually reversible and responds to decreasing the dose or discontinuing the drug.

Cycloserine is a pyridoxine antagonist and increases the renal excretion of pyridoxine, thereby resulting in neuropathy. It is therefore advisable to prescribe cycloserine in combination with pyridoxine [127]. It has been suggested that the neurotoxic effects of cycloserine can be reduced when co-administered with pyridoxine, though this has not been proved [19]. In a cohort of 75 adult MDR-TB patients in Lima, Peru, 52.2 and 8.7 % had depression and anxiety, respectively, at baseline, with 13.3, 12.0 and 12.0 % experiencing incident depression, anxiety and psychosis, respectively, during treatment that included cycloserine in 74 of the 75 patients [128]. Cycloserine was continued in all but one of the patients by effectively managing the adverse effects, including psychiatric pharmacotherapy [128]. The frequency of psychiatric disorders is lower during treatment with terizidone than with cycloserine [123]. Cycloserine has also been associated with other more rare adverse effects, including encephalopathy [128] and dermatological reactions, including Stevens-Johnson syndrome in an HIV-infected person [129, 130]. There are several reports indicating that terizidone has fewer adverse effects than cycloserine (1 vs. 11 %) [123, 131, 132].

Safety data for cycloserine or terizidone are lacking in children. No toxic effect was observed in either of the paediatric case series of cycloserine treatment [132–135]. In a systematic review, six of 182 children treated for MDR-TB had adverse effects related to cycloserine use such as depression, anxiety, hallucinations, transitory psychosis and blurred vision [15].

8 Para-Aminosalicylic Acid

PAS was one of the first drugs developed for the treatment of TB in humans in 1944 [136]. The US FDA approved PAS in 1950. Despite being one of the oldest drugs, the mechanism of action of PAS against *M. tuberculosis* remains unclear. The inhibition of folate synthesis and iron utilisation have both been hypothesised [137–140]. Though falling out of favour due to its poor tolerability and the availability of potent anti-TB drugs, there has been a resurgence in the interest in PAS in view of the global increase in drug-resistant TB.

8.1 Safety Data

8.1.1 Gastrointestinal Intolerance

Gastrointestinal intolerance such as vomiting, diarrhoea, anorexia and abdominal discomfort have been reported as some of the common adverse effects associated with the use of PAS [141, 142]. Enteric-coated granules of PAS were found to lower this effect [141, 143]. A few drops of opiate or a teaspoon of magnesium oxide given just before PAS administration were also noted to reduce the gastrointestinal adverse effects [141]. In a large cohort of 244 adults treated for MDR-TB, 88.9 % of whom were treated with PAS, PAS was permanently discontinued in nine patients due to nausea and vomiting [72].

8.1.2 Hypothyroidism

Hypothyroidism is a known adverse effect of PAS that was observed shortly after its introduction into clinical use [144–146], including a case of symptomatic hypothyroidism in an 8-year-old child [147]. Goiter has been reported in 20 of 83 patients (23 %) treated with PAS 20 g daily, with the earliest onset 5 months after starting treatment [148]. Goiter was found to resolve after administration of thyroid extract or discontinuation of PAS [148]. Hypothyroidism due to PAS is believed to be due to blocking of organification of iodide in the thyroid gland [148–150]. A combination of PAS and ethionamide was likely to increase the risk of hypothyroidism [107]. A retrospective study of adults with MDR-TB observed that 129 of 186 (69 %) patients had hypothyroidism (TSH >10 mIU/L) during treatment; of these, 179 of 186 patients were receiving both PAS and ethionamide/prothionamide [107]. In an evaluation of ethionamide-associated hypothyroidism in a cohort of South African children with MDR-TB, those on a regimen containing both PAS and ethionamide were more than twice as likely to develop hypothyroidism compared with those on ethionamide alone [106]. An increased risk of hypothyroidism has also been reported in another cohort of children with MDR-TB treated with PAS [151].

8.1.3 Hypersensitivity Reactions

Matsaniotis et al. [152] reported that a hypersensitivity reaction occurred in about 2–3 % of adults within 2–6 weeks of starting PAS. The symptoms vary widely, and mostly include fever and rash, which is normally maculopapular but may take many other forms such as exfoliative dermatitis [152]. PAS-associated hypersensitivity reactions have been described in children also, and have a similar frequency to that in adults [152, 153].

8.1.4 Other Rare Adverse Effects

PAS has been reported to mildly prolong the prothrombin time, which is reversible with administration of vitamin K, but may not be clinically relevant in otherwise healthy individuals [153]. PAS-induced hepatotoxicity has also been reported [154].

9 Linezolid

Linezolid belongs to the oxazolidinone class of antibacterials [155]. The oxazolidinones bind to the 50s ribosomal subunit, and inhibit formation of the initiation complex, thereby preventing translation and protein synthesis [155–157]. The US FDA approved linezolid in 2000.

9.1 Safety Data

In general, linezolid is well-tolerated in short courses; however, several adverse effects are dose and time dependent [158, 159]. For example, a 300 mg dose caused fewer adverse effects than a 600 mg dose [160]. Adverse effects are reported to a lesser extent in linezolid-treated children than adults [161, 162]. Inhibition of mitochondrial protein synthesis is likely to be the main reason of many of the adverse effects of linezolid [158].

9.1.1 Gastrointestinal Toxicity

The most common adverse effect of linezolid is gastrointestinal intolerance, but is rarely serious enough to require a change or discontinuation of the drug [159]. In a review of clinical trials in children where linezolid was used for a short duration, diarrhoea, vomiting and loose stools (1.2–3.5 %) were the most common drug-related adverse effects [163].

9.1.2 Haematological Toxicity

Dose- and time-dependent myelosuppression were observed in pre-clinical evaluations of linezolid (600 vs. 300 mg) in animals [159]. A review of adult clinical trial data of linezolid administered for less than 28 days did not show any difference in haematological toxicity between the linezolid and comparator groups, though there was a trend towards increased mild anaemia and thrombocytopenia in the linezolid group for those treated for more than 2 weeks [159, 163]. Although the exact mechanism of thrombocytopenia due to linezolid is not known, an immune-mediated phenomenon is likely to be responsible for this adverse effect [158]. Prolonged treatment of MDR-TB with linezolid caused anaemia in 38.1 % and thrombocytopaenia in 11.8 % [164]. Further, higher drug doses were significantly associated with these adverse effects in a small clinical trial in XDR-TB [165].

Paediatric data from clinical trials using linezolid in short courses were similar to that in adults, with a trend towards mild reversible thrombocytopaenia in children treated for >14 days [166].

9.1.3 Neurotoxicity

Peripheral neuropathy due to linezolid has been well-described among patients on prolonged durations of linezolid, but not in clinical trials [159, 167]. It usually presents as paraesthesia and numbness in distal extremities in a "stocking and glove" distribution, with lower extremities affected more commonly than upper [154], and is generally not reversible after cessation of linezolid [159, 167] and does not respond to vitamin B_6 [168]. Linezolid is also associated with toxic optic neuropathy, with painless, bilateral central vision loss, often of sudden onset, and gradual loss of colour vision and visual acuity [159]. In a systematic review of linezolid-treated adults with MDR-TB, 47.1 % reported peripheral neuropathy and 13.2 % optic neuritis [164].

A review identified eight cases of neuropathy in children—five with peripheral neuropathy alone, one with optic neuropathy, and two with both peripheral and optic neuropathy [169]. Seven of these children were on prolonged courses ranging from 4 weeks to 7 months at the time of onset.

A higher dose of linezolid (600 mg daily) (74.5 %) was reported to be associated with statistically increased risk of adverse effects, such as anaemia (60 vs. 2.5 %), leukopenia (17.1 vs. 2.0 %) and gastrointestinal symptoms (29.4 vs. 8.0 %), compared with a lower dose (46.7 %) [164]. In a clinical trial using linezolid in XDR-TB patients, it was observed that the group that those who received linezolid 600 mg were 2.7 times more likely to experience an adverse event than those who received 300 mg [160].

9.1.4 Other Rare Adverse Effects

Hyperlactatemia and lactic acidosis have been reported to be associated with linezolid, with discontinuation of the drug reversing the effect [159]. Yogev et al. [169] described metabolic acidosis in two of 79 (2.5 %) children treated with linezolid in a randomised trial. Three additional cases were described in children with liver disease and other co-morbidities [170], and more recently a case was described in a child receiving long-term linezolid for drug-resistant-TB [171]. Pancreatitis due to linezolid has also been reported rarely [172].

10 Clofazimine

Clofazimine is a member of the riminophenazine class of compounds and was observed to have in vitro activity against *M. tuberculosis* in the 1950s [173, 174]. The US FDA approved clofazimine in 1986. Later studies showed activity against *M. leprae* also. Thus, clofazimine remains

an important component of anti-leprosy treatment regimens [173, 175]. Clofazimine has also been used in the treatment of *M. avium* complex infections. With the increase in drug-resistant TB, there has been a renewed interest in clofazimine in TB treatment.

Multiple possible mechanisms of action for clofazimine have been postulated, including generation of intracellular hydrogen peroxide, binding to guanine bases in DNA, stimulation of phospholipase A_2 activity leading to intracellular accumulation of lysophospholipids [173], generation of reactive oxygen species [176, 177], and interference with electron transport [174], though to date this remains unclear.

10.1 Safety Data

10.1.1 Gastrointestinal Adverse Effects

Gastrointestinal intolerance is one of the commonly reported adverse effects related to clofazimine use, with abdominal pain, nausea, vomiting and diarrhoea reported in 40–50 % of patients [174]. In an adult cohort treated with clofazimine for leprosy, severe abdominal symptoms were reported in nine of 84 patients [178]. Crystalline deposits of clofazimine have been found in organs where it concentrates, including organs of the gastrointestinal system, but severe abdominal complications related to this are rare [174]. It has been suggested that severe abdominal pain would be an indication to discontinue clofazimine [179].

Gastrointestinal adverse effects in children have been reported to a lesser extent. Discontinuation of clofazimine in a child after an episode of severe haematemesis has been reported [180]. Severe enteropathy has also been reported in a child [181].

10.1.2 Dermatological Adverse Effects

Dermatologic adverse effects are common and quite striking. About 75–100 % of patients develop a reddish-black or orange skin discoloration within a few weeks of starting treatment [173, 174]. Discoloration of the eyes as well as the urine, faeces, sputum and sweat are known to occur [174]. However, the skin colour changes are reversible over time, with traces of the drug found in the skin 1–2 years after its discontinuation [182]. This colour change is not serious but can be very distressing to patients. Ichthyosis has been reported in 8–28 % of patients, and other rashes or skin dryness are reported in another 1–5 % of patients [174]. It has been reported that most patients accepted the skin colour change but felt stigmatised due to ichthyosis [178]. It was reported that co-administration of isoniazid appeared to reduce adverse effects, including skin colour change [178].

11 Management of Adverse Effects

Directly observed treatment (DOT) providers, nurses in hospital and clinicians must monitor and record all adverse effects routinely and laboratory screening tests must be performed on a routine basis. The initial evaluation will help to establish a baseline and identify patients at increased risk of adverse effects. Laboratory screening is invaluable for detecting certain adverse effects that are more occult, and before serious harm is caused. Close monitoring of patients is necessary to ensure that the adverse effects of the drugs are recognised quickly and appropriate action is taken. The commonly encountered adverse drug effects include rashes, toxic epidermal necrolysis, gastrointestinal symptoms (nausea, vomiting, diarrhoea), psychiatric symptoms (psychosis, depression, anxiety), jaundice, ototoxicity, peripheral neuropathy, nephrotoxicity, symptoms of electrolyte wasting (muscle cramping, palpitations) and convulsions [183]. If the adverse effect is mild and not serious, the drug(s) can be continued, with the help of ancillary drugs. Since most of the adverse effects of second-line drugs are dose dependent, reducing the dosage of the offending drug or terminating it is another option for management [183]. Most recommendations are the same in adults and children. Symptomatic drugs used in the management of adverse effects are given in Table 2.

The following recommendations should be followed when adverse effects arise:

1. Gastrointestinal symptoms (nausea and vomiting) are more likely to be due to ethionamide or PAS. Patients who complain of nausea or vomiting can be advised to take the drugs embedded in a banana [183]. This could help reduce the bad taste/odour associated with the drug to some extent (e.g. the metallic taste of ethionamide). Symptomatic drugs can be given. If vomiting persists, the drugs can be withheld and further tests should be performed to rule out other causes of vomiting such as hepatitis.
2. Giddiness could be due to aminoglycosides, ethionamide or fluoroquinolones. Whenever a patient complains of giddiness, drowsiness or poor concentration, the patient is advised on the next course of action. If severe, the dose of the offending drug may be adjusted or terminated, if required.
3. Renal toxicity is most likely due to aminoglycosides. Prior to starting treatment the renal function of all patients must be evaluated. During treatment, if any patient presents with symptoms and/or signs of renal impairment, such as oliguria, anuria, puffiness of face or pedal oedema, all drugs should be withheld, renal function tests should be performed and the patient

Table 2 Common adverse effects, the likely responsible agents and the suggested management strategies [183]

Adverse effects	Suspected agent(s)	Suggested management strategies	Comments
Gastrointestinal adverse effects			
Nausea and vomiting	Ethionamide PAS Moxifloxacin Linezolid Clofazimine	Patients who complain of nausea or vomiting can be advised to take the drugs embedded in banana Initiate anti-emetic therapy If vomiting persists, drugs must be administered 1 h after 1 tablet of domperidone and/or a course of proton pump inhibitor or histamine H_2 receptor inhibitor (omeprazole, famotidine, ranitidine) can be initiated Other antacids are not to be given since they interfere with absorption of fluoroquinolones Reduce the dose of suspected agent If problem persists, discontinue suspected agent; rarely necessary	Almost all patients experience nausea and vomiting during the early weeks of therapy due to the bulk of drugs; the symptoms usually subside over the treatment course Electrolytes should be monitored and repleted if vomiting is severe Reversible upon discontinuation of suspected agent Rarely, severe abdominal distress and acute abdomen have been reported with the use of clofazimine. In such cases, clofazimine should be suspended
Gastritis	Ethionamide PAS Levofloxacin Moxifloxacin Linezolid Clofazimine	Treat with H_2 antagonists, proton pump inhibitors; no other antacids to be used Stop suspected agent(s) for short periods of time (e.g. 1–7 days) Patients can be advised to take the drugs embedded in banana Reduce the dose of suspected agent If problem persists, discontinue suspected agent	Dosing of any medications should be carefully timed so as to not interfere with the absorption of anti-TB drugs (take 2 h before or 3 h after anti-TB medications) Reversible upon discontinuation of suspected agent(s)
Hepatitis	Ethionamide PAS Linezolid Clofazimine	Stop all therapy pending resolution of hepatitis Eliminate other potential causes of hepatitis Consider suspending most likely agent permanently. Reintroduce remaining drugs, one at a time with the most hepatotoxic agents first, while monitoring liver function	History of previous hepatitis should be carefully analysed to determine most likely causative agent(s); these should be avoided in future regimens Hepatotoxicity is generally reversible upon discontinuation of suspected agent
Cutaneous and hypersensitivity reactions			
Hypersensitivity	PAS Linezolid Clofazimine	Withhold all drugs and treat symptomatically with antihistamines/corticosteroids till the reaction subsides Identify offending drug in severe forms If problem persists, discontinue suspected agent	Hypersensitivity reactions could range from mild itching/rashes to rare forms like toxic epidermal necrolysis or exfoliative dermatitis necessitating termination of the offending drug
Cutaneous	Linezolid Clofazimine	Treat symptomatically with antihistamines till the reaction subsides Patient should be counselled on the skin discoloration with long-term use of clofazamine	Cutaneous reaction could range from rashes, pruritis, alopecia to bullous skin eruptions rarely
Psychiatric adverse effects			
Psychosis, suicidal tendencies, anxiety	Cycloserine	Counselling is necessary In severe cases, drug dose can be reduced or drug discontinued	Monitoring plasma cycloserine concentrations might be useful to adjust drug doses

Table 2 continued

Adverse effects	Suspected agent(s)	Suggested management strategies	Comments
Neurological adverse effects			
Peripheral neuropathy	Linezolid	Increase pyridoxine to maximum daily dose (200 mg/day) Initiate therapy with tricyclic antidepressants such as amitriptyline. NSAIDs or acetaminophen may help alleviate symptoms Reduce the drug dose If problem persists, discontinue the drug	Patients with co-morbid disease (e.g. diabetes, HIV, alcohol dependence) may be more likely to develop peripheral neuropathy, but these conditions are not contraindications to the use of the drug Neuropathy may be irreversible; however, some patients may experience improvement when the drug is suspended
Convulsions	Moxifloxacin Linezolid Cycloserine	Suspend suspected agent pending resolution of convulsions Initiate anticonvulsant therapy (e.g. phenytoin, valproic acid) Increase pyridoxine to maximum daily dose (200 mg/day) Restart suspected agent or reinitiate suspected agent at lower dose, if essential to the regimen If problem persists, discontinue suspected agent	Anticonvulsant is generally continued until treatment is completed or drug discontinued History of previous seizure. disorder is not a contraindication to the use of agents listed here if a patient's seizures are well-controlled and/or the patient is receiving anticonvulsant therapy Patients with history of previous seizures may be at increased risk for development of convulsions during therapy
Hearing loss	Aminoglycosides	Document hearing loss and compare with baseline audiometry if available Increase frequency and/or lower dose of suspected agent (consider administration 3 times per week) If problem persists, discontinue suspected agent	Patients with previous exposure to aminoglycosides may have baseline hearing loss In such patients, audiometry may be helpful at the start of therapy Hearing loss is generally not reversible The risk of further hearing loss must be weighed against the risks of stopping the injectable in the treatment regimen
Ocular	Linezolid	Consult an ophthalmologist	Periodic ocular monitoring for ocular toxicity such as optic neuropathy is necessary
Musculoskeletal adverse effects			
Arthralgia	Levofloxacin Moxifloxacin	Initiate therapy with NSAIDs	Symptoms of arthralgia generally diminish over time, even without intervention Caution should be taken with non-steroidal agents to avoid exacerbating gastritis
Musculoskeletal	Levofloxacin Moxifloxacin Clofazimine	Consult an orthopaedician	Rarely, tendon rupture occurs with levo/moxifloxacin; can cause bone pain
Haematological adverse effects			
Haematalogic	Linezolid Capreomycin PAS	Monitor for anaemia, bleeding tendency and cell counts	Patients may present with thrombocytopenia, reduced haemoglobin, pancytopenia or leukopenia Elevation of prothrombin time can occur
Renal adverse effects			
Renal toxicity	Aminoglycosides Linezolid	Discontinue suspected agent Consider dosing 2–3 times a week if drug is essential to the regimen and patient can tolerate (close monitoring of serum creatinine) Adjust drug doses according to creatinine clearance	History of diabetes or renal disease is not a contraindication to the use of the agents listed here, although patients with these co-morbidities may be at increased risk for developing renal failure Renal impairment may be permanent

Table 2 continued

Adverse effects	Suspected agent(s)	Suggested management strategies	Comments
Metabolic and electrolyte disturbances			
Metabolic and electrolyte	Aminoglycosides	Periodic monitoring of serum electrolytes and blood sugar is necessary	Reduction in magnesium, potassium and calcium with aminoglycosides can occur
	Linezolid		Hyperlactacaemia, reduction in potassium, increase in creatine phosphokinase and alkaline phosphatase with linezolid can occur
	Clofazimine		Increase in fasting glucose and reduction in serum potassium can occur
	Moxifloxacin		Dysglycaemia with moxifloxacin can occur
Endocrine adverse effects			
Thyroid dysfunction	Ethionamide Sodium PAS	Supplement with thyroxine	Monitor clinically and undertake estimations of thyroid hormones regularly to adjust thyroxine dose
Cardiovascular adverse effects			
QT prolongation	Moxifloxacin	Monitor for QT prolongation with moxifloxacin	These are rarely seen, but regular monitoring is necessary
thromboembolism	Clofazimine	Monitor platelet count, bleeding tendencies Consult a cardiologist, if necessary	

PAS para-aminosalicylic acid, *TB* tuberculosis

referred to a nephrologist. Re-introduction of drugs can be done in consultation with the nephrologist, and frequent monitoring of renal parameters is important.

4. Arthralgia could be due to fluoroquinolones. Patients who complain of arthralgia can be prescribed paracetamol (acetaminophen) 500 mg three times a day or aspirin 300 mg three times a day. If there is no improvement after 1 week, an NSAID can be prescribed (e.g. ibuprofen or diclofenac sodium), and uric acid checked if indicated. If the problem persists, drug dosages should be reduced or withheld temporarily.
5. Cutaneous reactions such as pruritis or rash can occur with any of the drugs used, and are commonly managed with antihistamines. For severe reactions that do not respond to antihistamines, an attempt must be made to identify the offending drug by challenging with individual drugs. The dose of the offending drug may be reduced or the drug terminated if required. For several hypersensitivity reactions the offending drug may need to be stopped. If there is a generalised erythematous rash, especially if it is associated with fever and/or mucous membrane involvement, all drugs should be withheld immediately. When the rashes subside, the medications can be restarted one by one, at intervals of 2–3 days.
6. Hepatitis could be due to the combined effect of potentially hepatotoxic drugs such as PAS and ethionamide. If a patient presents with symptoms/signs of hepatitis (anorexia, nausea, vomiting, abdominal discomfort and/or dark-coloured urine), he/she must be examined for clinical jaundice, and blood must be checked for liver function tests. If the results are abnormal, the drugs must be withheld. Such patients must be reviewed at weekly intervals and liver function tests repeated when jaundice subsides clinically. The drugs can be re-introduced after the liver function returns to normal.
7. Neurological symptoms:

   (i) Peripheral neuropathy can be caused by either cycloserine or ethionamide. This can be prevented by prescribing daily pyridoxine 100 mg. If peripheral neuropathy develops, an additional 100 mg of pyridoxine can be given. If there is no improvement or symptoms worsen, amitriptyline 25 mg can be added, and if there is no improvement, the patient should be referred to a neurologist.

   (ii) Seizures can be due to either fluoroquinolone and/or cycloserine. If a patient develops seizures, these drugs must be withheld and the opinion of a neurologist sought. Anticonvulsants can be prescribed in consultation with the neurologist.

(iii) Psychiatric disturbances are most likely due to cycloserine, but can also be due to fluroquinolone and/or ethionamide. Minor problems can be solved by counselling. In the case of suicidal tendencies and other serious problems, the drugs must be withheld and further management of the patient must be done in consultation with the psychiatrist.

8. Vestibulo-auditory disturbances are most likely due to aminoglycosides. Patients may present with tinnitus, unsteady gait or loss of hearing. Aminoglycoside must be withheld and the patient referred for a specialist opinion.
9. Hypothyroidism can be due to PAS and/or ethionamide. A combination of these drugs may increase the possibility of hypothyroidism. Patients may present with slowing of activities, puffiness of face and/or thyroid swelling. Patients need to be evaluated for hypothyroidism and, if present, may be treated with thyroxine. The thyroxine dosage should be adjusted based on clinical status and laboratory results.

12 Discussion and Conclusions

A major challenge faced by patients treated with second-line drugs is the toxic nature of these drugs due to the long duration of treatment [184]. This is exacerbated in settings with high co-infection and co-morbidity. Adherence to treatment is also a critical factor in the management of MDR-TB, and adverse events associated with second-line drugs could have a severe impact on adherence [185]. Patients must be provided with a detailed explanation of the potential adverse effects of second-line drugs, and advised, if and when they occur, to notify the treating physician. Proper management of adverse effects begins with pre-treatment patient education. Psychosocial support is an important component of the management of adverse effects. Clinicians have to be watchful for the occurrence of adverse effects and appropriate action should be taken immediately. A thorough knowledge of the safety, tolerability and management of the adverse effects of second-line drugs used in the treatment of TB is very important.

Funding and Conflicts of interest No sources of funding were used to prepare this review. Geetha Ramachandran and Soumya Swaminathan have no conflicts of interest that are directly relevant to the content of this review.

References

1. World Health Organisation. Global tuberculosis report, 2010. Geneva: WHO; 2010.
2. Crofton J. Global challenge of TB. Lancet. 1994;344(8922):609.
3. Crofton J, Chaulet P, Maher D. Guidelines for the management of drug-resistant tuberculosis. WHO/TB/96.210 (Rev 1). Geneva: WHO; 1997.
4. Fox W, Mitchison DA. Short course chemotherapy for pulmonary tuberculosis. Am Rev Respir Dis. 1975;111:845–8.
5. Hooper DC, Strahilevitz J. Quinolones. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 7th ed. Philadelphia: Churchill Livingstone; 2010. p. 487–510.
6. Leibovitz E. The use of fluoroquinolones in children. Curr Opin Pediatr. 2006;18(1):64–70.
7. Hayakawa I, Atarashi S, Yokohama S, Imamura M, Sakano K, Furukawa M. Synthesis and antibacterial activities of optically active ofloxacin. Antimicrob Agents Chemother. 1986;29(1):163–4.
8. Fu KP, Lafredo SC, Foleno B, Isaacson DM, Barrett JF, Tobia AJ, et al. In vitro and in vivo antibacterial activities of levofloxacin (l-ofloxacin), an optically active ofloxacin. Antimicrob Agents Chemother. 1992;36(4):860–6.
9. Neu HC, Chin NX. In vitro activity of S-Ofloxacin. Antimicrob Agents Chemother. 1989;33(7):1105–7.
10. Une T, Fujimoto T, Sato K, Osada Y. In vitro activity of DR-3355, an optically active ofloxacin. Antimicrob Agents Chemother. 1988;32(9):1336–40.
11. Moxifloxacin. Tuberculosis (Edinb). 2008;88 (2):127–131.
12. Hampel B, Hullmann R, Schmidt H. Ciprofloxacin in pediatrics: worldwide clinical experience based on compassionate use–safety report. Pediatr Infect Dis J. 1997;16(1):127–9 (discussion 60–2).
13. Yew WW, Chau CH, Wen KH. Pseudomembranous colitis in a patient treated with ofloxacin for tuberculosis. Tuber Lung Dis. 1996;77(5):484.
14. Pépin J, Saheb N, Coulombe M-A, Alary M-E, Corriveau M-P, Authier S, et al. Emergence of fluoroquinolones as the predominant risk factor for *Clostridium difficile*–associated diarrhea: a cohort study during an epidemic in Quebec. Clin Infect Dis. 2005;41(9):1254–60.
15. Ettehad D, Schaaf HS, Seddon JA, Cooke GS, Ford N. Treatment outcomes for children with multidrug-resistant tuberculosis: a systematic review and meta-analysis. Lancet Infect Dis. 2012;12(6):449–56.
16. Tome AM, Filipe A. Quinolones: review of psychiatric and neurological adverse reactions. Drug Saf. 2011;34(6):465–88.
17. Kushner JM, Peckman HJ, Snyder CR. Seizures associated with fluoroquinolones. Ann Pharmacother. 2001;35(10):1194–8.
18. Liu HH. Safety profile of the fluoroquinolones: focus on levofloxacin. Drug Saf. 2010;33(5):353–69.
19. Kass JS, Shandera WX. Nervous system effects of antituberculosis therapy. CNS Drugs. 2010;24(8):655–67.
20. Walton GD, Hon JK, Mulpur TG. Ofloxacin-induced seizure. Ann Pharmacother. 1997;31(12):1475–7.
21. Christie MJ, Wong K, Ting RH, Tam PY, Sikaneta TG. Generalized seizure and toxic epidermal necrolysis following levofloxacin exposure. Ann Pharmacother. 2005;39(5):953–5.
22. Bellon A, Perez-Garcia G, Coverdale JH, Chacko RC. Seizures associated with levofloxacin: case presentation and literature review. Eur J Clin Pharmacol. 2009;65(10):959–62.
23. Jo M, Tachi N, Shinoda M. Convulsions from excessive dosage of nalidixic acid: a case report. Brain Dev. 1979;1(4):327–9.

24. Islam MA, Sreedharan T. Convulsions, hyperglycemia, and glycosuria from overdose of nalidixic acid. JAMA. 1965;21 (192):1100–1.
25. Upton C. Sleep disturbance in children treated with ofloxacin. BMJ. 1994;309(6966):1411.
26. Seddon J, Hesseling A, Finlayson L, Schaaf HS. Toxicity and tolerability of multidrug-resistant tuberculosis preventive treatment in children [abstract no. PC-646-17]. In: 43rd World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease (The Union): Kuala Lumpur; 2012.
27. Falagas ME, Rafailidis PI, Rosmarakis ES. Arrhythmias associated with fluoroquinolone therapy. Int J Antimicrob Agents. 2007;29(4):374–9.
28. Makaryus AN, Byrns K, Makaryus MN, Natarajan U, Singer C, Goldner B. Effect of ciprofloxacin and levofloxacin on the QT interval: is this a significant "clinical" event? South Med J. 2006;99(1):52–6.
29. Kang J, Wang L, Chen X-L, Triggle DJ, Rampe D. Interactions of a series of fluoroquinolone antibacterial drugs with the human cardiac K+ channel HERG. Mol Pharmacol. 2001;59(1):122–6.
30. Tsikouris JP, Peeters MJ, Cox CD, Meyerrose GE, Seifert CF. Effects of three fluoroquinolones on QT analysis after standard treatment courses. Ann Noninvasive Electrocardiol. 2006;11(1): 52–6.
31. Noel GJ, Natarajan J, Chien S, Hunt TL, Goodman DB, Abels R. Effects of three fluoroquinolones on QT interval in healthy adults after single doses. Clin Pharmacol Ther. 2003;73(4): 292–303.
32. Noel GJ, Goodman DB, Chien S, Solanki B, Padmanabhan M, Natarajan J. Measuring the effects of supratherapeutic doses of levofloxacin on healthy volunteers using four methods of QT correction and periodic and continuous ECG recordings. J Clin Pharmacol. 2004;44(5):464–73.
33. Frothingham R. Rates of Torsades de pointes associated with ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, and moxifloxacin. Pharmacotherapy. 2001;21(12):1468–72.
34. Lapi F, Wilchesky M, Kezouh A, Benisty JI, Ernst P, Suissa S. Fluoroquinolones and the risk of serious arrhythmia: a population-based study. Clin Infect Dis. 2012;55(11):1457–65.
35. Demolis J-L, Kubitza D, Tenneze L, Funck-Brentano C. Effect of a single oral dose of moxifloxacin (400 and 800 mg) on ventricular repolarization in healthy subjects. Clin Pharmacol Ther. 2000;68(6):658–66.
36. Osborn LA, Skipper B, Arellano I, MacKerrow SD, Crawford MH. Results of resting and ambulatory electrocardiograms in patients with hypothyroidism and after return to euthyroid status. Heart Dis. 1999;1(1):8–11.
37. Bakiner O, Ertorer ME, Haydardedeoglu FE, Bozkirli E, Tutuncu NB, Demirag NG. Subclinical hypothyroidism is characterized by increased QT interval dispersion among women. Med Princ Pract. 2008;17(5):390–4.
38. Unal O, Erturk E, Ozkan H, Kiyici S, Guclu M, Ersoy C, et al. Effect of levothyroxine treatment on QT dispersion in patients with subclinical hypothyroidism. Endocr Pract. 2007;13(7): 711–5.
39. Kweon KH, Park BH, Cho CG. The effects of L-thyroxine treatment on QT dispersion in primary hypothyroidism. J Korean Med Sci. 2007;22(1):114–6.
40. Murphy ME, Singh KP, Laurenzi M, Brown M, Gillespie SH. Managing malaria in tuberculosis patients on fluoroquinolone-containing regimens: assessing the risk of QT prolongation. Int J Tuberc Lung Dis. 2012;16(2):144–9 (i–iii).
41. Burkhardt JE, Walterspiel JN, Schaad UB. Quinolone-induced arthropathy in animals versus children. Clin Infect Dis. 1997;25 (5):1196–204.
42. Grady R. Safety profile of quinolone antibiotics in the pediatric population. Pediatr Infect Dis J. 2003;22(12):1128–32.
43. Schaad UB. Fluoroquinolone antibiotics in infants and children. Infect Dis Clin N Am. 2005;19(3):617–28.
44. Schaad UB. Use of quinolones in pediatrics. Eur J Clin Microbiol Infect Dis. 1991;10(4):355–60.
45. Jafri HS, McCracken GH Jr. Fluoroquinolones in paediatrics. Drugs. 1999;58(Suppl 2):43–8.
46. Alghasham AA, Nahata MC. Clinical use of fluoroquinolones in children. Ann Pharmacother. 2000;34(3):347–59 (quiz 413–4).
47. Adefurin A, Sammons H, Jacqz-Aigrain E, Choonara I. Ciprofloxacin safety in paediatrics: a systematic review. Arch Dis Child. 2011;96(9):874–80.
48. Noel GJ, Bradley JS, Kauffman RE, Duffy CM, Gerbino PG, Arguedas A, et al. Comparative safety profile of levofloxacin in 2,523 children with a focus on four specific musculoskeletal disorders. Pediatr Infect Dis J. 2007;26(10):879–91.
49. Li F, Nandy P, Chien S, Noel GJ, Tornoe CW. Pharmacometrics-based dose selection of levofloxacin as a treatment for postexposure inhalational anthrax in children. Antimicrob Agents Chemother. 2010;54(1):375–9.
50. Yee CL, Duffy C, Gerbino PG, Stryker S, Noel GJ. Tendon or joint disorders in children after treatment with fluoroquinolones or azithromycin. Pediatr Infect Dis J. 2002;21(6):525–9.
51. Goldman JA, Kearns GL. Fluoroquinolone use in paediatrics: focus on safety and place in therapy. 18th Expert Committee on the Selection and Use of Essential Medicines. World Health Organization; 2011. http://www.who.int/selection_medicines/committees/expert/18/applications/fluoroquinolone_review.pdf. Accessed 18 Sept 2012.
52. Bradley JS, Kauffman RE, Balis DA, Duffy CM, Gerbino PG, Maldonado SD, Noel GJ. Assessment of musculo-skeletal toxicity five years after therapy with levofloxacin. Paediatr. 2014;134(1):e146–53.
53. Tumbanatham A, Vinodkumar S. Ofloxacin induced arthropathy in patients with multi-drug resistance tuberculosis. J Assoc Physicians India. 2000;48(6):647–8.
54. Arora VK, Tumbanatham A. Severe arthropathy with ofloxacin in two cases of MDR tuberculosis. Int J Tuberc Lung Dis. 1998;2(11):941–3.
55. Wong HY, Chau CH, Yew WW. Moxifloxacin-induced arthropathy. Int J Tuberc Lung Dis. 2007;11(1):117.
56. Friedrich LV, Dougherty R. Fatal hypoglycemia associated with levofloxacin. Pharmacotherapy. 2004;24(12):1807–12.
57. Saigal S, Agarwal SR, Nandeesh HP, Sarin SK. Safety of an ofloxacin-based antitubercular regimen for the treatment of tuberculosis in patients with underlying chronic liver disease: a preliminary report. J Gastroenterol Hepatol. 2001;16(9): 1028–32.
58. Yew WW, Lee J, Wong PC, Kwan SY. Tolerance of ofloxacin in the treatment of pulmonary tuberculosis in presence of hepatic dysfunction. Int J Clin Pharmacol Res. 1992;12(4):173–8.
59. Ho CC, Chen YC, Hu FC, Yu CJ, Yang PC, Luh KT. Safety of fluoroquinolone use in patients with hepatotoxicity induced by anti-tuberculosis regimens. Clin Infect Dis. 2009;48(11): 1526–33.
60. Roberts CH, Smith C, Breen R, Gadhok R, Murphy M, Aryee A, et al. Hepatotoxicity in the treatment of tuberculosis using moxifloxacin-containing regimens. Int J Tuberc Lung Dis. 2011;15(9):1275–6.
61. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis: emergency update 2008. 2008. http://whqlibdoc.who.int/publications/2008/9789241547581_eng.pdf.
62. Gilbert DN, Leggett JE. Aminoglycosides. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas, and Bennett's

principles and practice of infectious diseases. 7th ed. Philadelphia: Churchill Livingstone; 2010. p. 359–84.
63. Amikacin. Tuberculosis. 2008;88(2):87–8.
64. Kawaguchi H. Discovery, chemistry, and activity of amikacin. J Infect Dis. 1976;134:S242–8.
65. Capreomycin. Tuberculosis (Edinb). 2008;88(2):89–91.
66. Evaluation of a new antituberculous agent. Capreomycin sulfate (capastat sulfate). JAMA. 1973;223(2):179–80.
67. Bycroft BW, Cameron D, Croft LR, Hassanali-Walji A, Johnson AW, Webb T. Total structure of capreomycin IB, a tuberculostatic peptide antibiotic. Nature. 1971;231(5301):301–2.
68. Dauby N, Payen MC. Amikacin-induced hypomagnesaemic tetany complicating multidrug-resistant tuberculosis treatment. Int J Tuberc Lung Dis. 2010;14(5):657–8.
69. Lemos AC, Matos ED. Multidrug–resistant tuberculosis. Braz J Infect Dis. 2013;17(2):239–46.
70. Mingeot-Leclercq MP, Tulkens PM. Aminoglycosides: nephrotoxicity. Antimicrob Agents Chemother. 1999;43(5):1003–12.
71. Rybak MJ, Abate BJ, Kang SL, Ruffing MJ, Lerner SA, Drusano GL. Prospective evaluation of the effect of an aminoglycoside dosing regimen on rates of observed nephrotoxicity and ototoxicity. Antimicrob Agents Chemother. 1999;43(7):1549–55.
72. Shin SS, Pasechnikov AD, Gelmanova IY, Peremitin GG, Strelis AK, Mishustin S, et al. Adverse reactions among patients being treated for MDR-TB in Tomsk, Russia. Int J Tuberc Lung Dis. 2007;11(12):1314–20.
73. de Jager P, van Altena R. Hearing loss and nephrotoxicity in long-term aminoglycoside treatment in patients with tuberculosis. Int J Tuberc Lung Dis. 2002;6(7):622–7.
74. Shin S, Furin J, Alcantara F, Hyson A, Joseph K, Sanchez E, et al. Hypokalemia among patients receiving treatment for multidrug-resistant tuberculosis. Chest. 2004;125(3):974–80.
75. Keating MJ, Sethi MR, Bodey GP, Samaan NA. Hypocalcemia with hypoparathyroidism and renal tubular dysfunction associated with aminoglycoside therapy. Cancer. 1977;39(4):1410–4.
76. Holmes AM, Hesling CM, Wilson TM. Capreomycin-induced serum electrolyte abnormalities. Thorax. 1970;25(5):608–11.
77. Hesling CM. Treatment with capreomycin, with special reference to toxic effects. Tubercle. 1969;50(Suppl):39–41.
78. Dheda K, Shean K, Zumla A, Badri M, Streicher EM, Page-Shipp L, et al. Early treatment outcomes and HIV status of patients with extensively drug-resistant tuberculosis in South Africa: a retrospective cohort study. Lancet. 2010;375(9728):1798–807.
79. Huth ME, Ricci AJ, Cheng AG. Mechanisms of aminoglycoside ototoxicity and targets of hair cell protection. Int J Otolaryng. 2011;2011:1–19.
80. Bardien S, Human H, Harris T, Hefke G, Veikondis R, Schaaf HS, et al. A rapid method for detection of five known mutations associated with aminoglycoside-induced deafness. BMC Med Genet. 2009;10:2.
81. Human H, Hagen CM, de Jong G, Harris T, Lombard D, Christiansen M, et al. Investigation of mitochondrial sequence variants associated with aminoglycoside-induced ototoxicity in South African TB patients on aminoglycosides. Biochem Biophys Res Commun. 2010;393(4):751–6.
82. Xing G, Chen Z, Cao X. Mitochondrial rRNA and tRNA and hearing function. Cell Res. 2007;17(3):227–39.
83. O'Donnell EP, Scarsi KK, Scheetz MH, Postelnick MJ, Cullina J, Jain M. Risk factors for aminoglycoside ototoxicity in adult cystic fibrosis patients. Int J Antimicrob Agents. 2010;36(1):94–5.
84. Gatell JM, Ferran F, Araujo V, Bonet M, Soriano E, Traserra J, et al. Univariate and multivariate analyses of risk factors predisposing to auditory toxicity in patients receiving aminoglycosides. Antimicrob Agents Chemother. 1987;31(9):1383–7.
85. Tran Ba Huy P, Deffrennes D. Aminoglycoside ototoxicity: influence of dosage regimen on drug uptake and correlation between membrane binding and some clinical features. Acta Otolaryngol. 1988;105(5–6):511–5.
86. Pettorossi VE, Ferraresi A, Errico P, Draicchio F, Dionisotti S. The impact of different dosing regimens of the aminoglycosides netilmicin and amikacin on vestibulotoxicity in the guinea pig. Eur Arch Otorhinolaryngol. 1990;247(5):277–82.
87. Takumida M, Nishida I, Nikaido M, Hirakawa K, Harada Y, Bagger-Sjoback D. Effect of dosing schedule on aminoglycoside ototoxicity: comparative cochlear ototoxicity of amikacin and isepamicin. J Otorhinolaryngol Relat Spec. 1990;52(6):341–9.
88. Peloquin CA, Berning SE, Nitta AT, Simone PM, Goble M, Huitt GA, et al. Aminoglycoside toxicity: daily versus thrice-weekly dosing for treatment of mycobacterial diseases. Clin Infect Dis. 2004;38(11):1538–44.
89. Seddon JA, Godfrey-Faussett P, Jacobs K, Ebrahim A, Hesseling AC, Schaaf HS. Hearing loss in patients on treatment for drug-resistant tuberculosis. Eur Respir J. 2012;40(5):1277–86.
90. Harris T, Bardien S, Schaaf HS, Petersen L, De Jong G, Fagan JJ. Aminoglycoside-induced hearing loss in HIV-positive and HIV-negative multidrug-resistant tuberculosis patients. S Afr Med J. 2012;102(6):363–6.
91. Seddon JA, Thee S, Jacobs K, Ebrahim A, Hesseling AC, Schaaf HS. Hearing loss in children treated for multidrug-resistant tuberculosis. J Infect. 2013;66(4):320–9.
92. Drobac PC, Mukherjee JS, Joseph JK, Mitnick C, Furin JJ, del Castillo H, et al. Community-based therapy for children with multidrug-resistant tuberculosis. Pediatrics. 2006;117(6):2022–9.
93. Fairlie L, Beylis NC, Reubenson G, Moore DP, Madhi SA. High prevalence of childhood multi-drug resistant tuberculosis in Johannesburg, South Africa: a cross sectional study. BMC Infect Dis. 2011;11:28.
94. Rist N, Grumbach F, Libermann D. Experiments on the antituberculous activity of alpha-ethylthioisonicotinamide. Am Rev Tuberc. 1959;79(1):1–5.
95. Ethionamide. Tuberculosis. 2008;88(2):106–8.
96. Wang F, Langley R, Gulten G, Dover LG, Besra GS, Jacobs WR Jr, et al. Mechanism of thioamide drug action against tuberculosis and leprosy. J Exp Med. 2007;204(1):73–8.
97. Banerjee A, Dubnau E, Quemard A, Balasubramanian V, Um KS, Wilson T, et al. inhA, a gene encoding a target for isoniazid and ethionamide in *Mycobacterium tuberculosis*. Science. 1994;263(5144):227–30.
98. Kass I. Chemotherapy regimens used in retreatment of pulmonary tuberculosis. Observations on the efficacy of combinations of kanamycin, ethionamide and either cycloserine or pyrazinamide. Tubercle. 1965;46:151–65.
99. Seddon JA, Furin JJ, Gale M, Del Castillo Barrientos H, Hurtado RM, Amanullah F, et al. Caring for children with drug-resistant tuberculosis: practice-based recommendations. Am J Respir Crit Care Med. 2012;186(10):953–64.
100. Lee HW, Kim DW, Park JH, Kim SD, Lim MS, Phapale PB, et al. Pharmacokinetics of prothionamide in patients with multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2009;13(9):1161–6.
101. A comparison of the toxicity of prothionamide and ethionamide: a report from the research committee of the British Tuberculosis Association. Tubercle. 1968;49(2):125–35.
102. Comparison of the clinical usefulness of ethionamide and prothionamide in initial treatment of tuberculosis: tenth series of controlled trials. Tubercle. 1968;49(3):281–90.
103. Drucker D, Eggo MC, Salit IE, Burrow GN. Ethionamide-induced goitrous hypothyroidism. Ann Intern Med. 1984;100(6):837–9.

104. Soumakis SA, Berg D, Harris HW. Hypothyroidism in a patient receiving treatment for multidrug-resistant tuberculosis. Clin Infect Dis. 1998;27(4):910–1.
105. McDonnell ME, Braverman LE, Bernardo J. Hypothyroidism due to ethionamide. N Engl J Med. 2005;352(26):2757–9.
106. Thee S, Zollner EW, Willemse M, Hesseling AC, Magdorf K, Schaaf HS. Abnormal thyroid function tests in children on ethionamide treatment. Int J Tuberc Lung Dis. 2011;15(9): 1191–3 (i).
107. Satti H, Mafukidze A, Jooste PL, McLaughlin MM, Farmer PE, Seung KJ. High rate of hypothyroidism among patients treated for multidrug-resistant tuberculosis in Lesotho. Int J Tuberc Lung Dis. 2012;16(4):468–72.
108. Gupta J, Breen RAM, Milburn HJ. Drug-induced hypothyroidism in patients receiving treatment for multidrug-resistant tuberculosis in the UK [correspondence]. Int J Tuberc Lung Dis. 2012;16(9):1278.
109. Modongo C, Zetola NM. Prevalence of hypothyroidism among MDR-TB patients in Botswana [correspondence]. Int J Tuberc Lung Dis. 2012;16(11):1561–2.
110. Dutta BS, Hassan G, Waseem Q, Saheer S, Singh A. Ethionamide-induced hypothyroidism. Int J Tuberc Lung Dis. 2012;16(1):141.
111. Hollinrake K. Acute hepatic necrosis associated with ethionamide. Br J Dis Chest. 1968;62(3):151–4.
112. Swash M, Roberts AH, Murnaghan DJ. Reversible pellagra-like encephalopathy with ethionamide and cycloserine. Tubercle. 1972;53(2):132–6.
113. Narang RK. Acute psychotic reaction probably caused by ethionamide. Tubercle. 1972;53(2):137–8.
114. Lansdown FS, Beran M, Litwak T. Psychotoxic reaction during ethionamide therapy. Am Rev Respir Dis. 1967;95(6):1053–5.
115. Sharma PK, Bansal R. Gynecomastia caused by ethionamide. Indian J Pharmacol. 2012;44(5):654–5.
116. Dixit R, George J, Sharma AK, Chhabra N, Jangir SK, Mishra V. Ethionamide-induced gynecomastia. J Pharmacol Pharmacother. 2012;3(2):196–9.
117. Ticholov K, Dobrev P. Severe hypoglycemic manifestations in tuberculous diabetes treated with ethionamide. Tuberkulosearzt. 1963;17:439–46.
118. Prothionamide. Tuberculosis. 2008;88(2):139–40.
119. Cycloserine. Tuberculosis (Edinb). 2008;88(2):100–1.
120. Chen JM, Uplekar S, Gordon SV, Cole ST. A point mutation in cycA partially contributes to the D-cycloserine resistance trait of Mycobacterium bovis BCG vaccine strains. PLoS One. 2012;7(8):e43467.
121. Bruning JB, Murillo AC, Chacon O, Barletta RG, Sacchettini JC. Structure of the Mycobacterium tuberculosis D-alanine: D-alanine ligase, a target of the antituberculosis drug D-cycloserine. Antimicrob Agents Chemother. 2011;55(1):291–301.
122. Halouska S, Chacon O, Fenton RJ, Zinniel DK, Barletta RG, Powers R. Use of NMR metabolomics to analyze the targets of D-cycloserine in mycobacteria: role of D-alanine racemase. J Proteome Res. 2007;6(12):4608–14.
123. Zitkova L, Tousek J. Pharmacokinetics of cycloserine and terizidone. A comparative study. Chemotherapy. 1974;20(1): 18–28.
124. Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis. Drugs. 2002;62(15):2169–83.
125. Kwon HM, Kim HK, Cho J, Hong YH, Nam H. Cycloserine-induced encephalopathy: evidence on brain MRI. Eur J Neurol. 2008;15(7):e60–1.
126. Holmes CX, Martin GE, Fetterhoff KI. The role of the cycloserine (seromycin) blood level in the treatment of pulmonary tuberculosis and the prevention and control of cycloserine (seromycin) toxicity. Dis Chest. 1959;36:591–3.
127. Donald PR. Cerebrospinal fluid concentrations of antituberculosis agents in adults and children. Tuberculosis (Edinb). 2010;90(5):279–92.
128. Vega P, Sweetland A, Acha J, Castillo H, Guerra D, Smith Fawzi MC, et al. Psychiatric issues in the management of patients with multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2004;8(6):749–59.
129. Shim JH, Kim TY, Kim HO, Kim CW. Cycloserine-induced lichenoid drug eruption. Dermatology. 1995;191(2):142–4.
130. Akula SK, Aruna AS, Johnson JE, Anderson DS. Cycloserine-induced Stevens-Johnson syndrome in an AIDS patient with multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 1997;1(2):187–90.
131. Vora A. Terizidone. J Assoc Physicians India. 2010;58:267–8.
132. Weyer K. Annexure 2: DOTS-Plus for multidrug resistant tuberculosis patients in South Africa. Systematic evaluation of a standardised treatment regimen applied under tuberculosis control programme conditions. 2004. http://www.kznhealth.gov.za/chrp/National/TB?SA TB guidelines 2004.pdf. Accessed 12 Aug 2014.
133. Steiner M. Newer and second-line drugs in the treatment of drug-resistant tuberculosis in children. Med Clin N Am. 1967;51(5):1153–67.
134. Battaglia B, Kaufman I, Lyons HA, Marsh W. Toxicity of cycloserine combined with isoniazid in the treatment of tuberculosis in children. Am Rev Respir Dis. 1961;83:751–2.
135. Schloss J, Ismail Z. Cycloserine and isoniazid in childhood tuberculous infections. Antibiotic Med Clin Ther. 1960;7:244–8.
136. Lehmann J. Para-aminosalicylic acid in the treatment of tuberculosis. Lancet. 1946;1(6384):15.
137. Para-aminosalicylic acid. Tuberculosis. 2008;88(2):137–8.
138. Ratledge C. Iron, mycobacteria and tuberculosis. Tuberculosis (Edinb). 2004;84(1–2):110–30.
139. Durham NN, Hubbard JS. Mechanism of competitive inhibition of *p*-aminobenzoic acid oxidation by *p*-aminosalicylic acid. J Bacteriol. 1960;80:225–31.
140. Durham NN, Hubbard JS. Antagonism of the oxidative dissimilation of *p*-aminobenzoic acid by *p*-aminosalicylic acid. Nature. 1959;184(Suppl 18):1398.
141. Lehmann J. The treatment of tuberculosis in Sweden with para-aminosalicylic acid; a review. Dis Chest. 1949;16(6):684–703.
142. Woolley PB. The use of antrenyl in gastro-intestinal irritation due to PAS compounds. Br J Tuberc Dis Chest. 1957;51(4): 382–4.
143. Peloquin CA, Berning SE, Huitt GA, Childs JM, Singleton MD, James GT. Once-daily and twice-daily dosing of *p*-aminosalicylic acid granules. Am J Respir Crit Care Med. 1999;159(3): 932–4.
144. Hamilton RR. Effect of PAS on the thyroid gland. Br Med J. 1953;1(4800):29–30.
145. Balint JA, Fraser R, Hanno MG. Radio-iodine measurements of thyroid function during and after P.A.S. treatment of tuberculosis. Br Med J. 1954;1(4873):1234–7.
146. Davies HT, Galbraith H-JB. Goitre and hypothyroidism developing during treatment with PAS. BMJ. 1953;1(4822):1261.
147. Komrower GM. Case of Myxoedema developing during *p*-aminosalicylic acid therapy. BMJ. 1951;2(4741):1193–4.
148. Macgregor AG, Somner AR. The anti-thyroid action of para-aminosalicylic acid. Lancet. 1954;267(6845):931–6.
149. Macgregor AG, Somner AR. Iodide in goitre due to P.A.S. BMJ. 1954;1(4877):1494.
150. Edwards DA, Rowlands EN, Trotter WR. The mechanism of the goitrogenic action of *p*-aminosalicylic acid. Lancet. 1954;267 (6847):1051–2.
151. Satti H, McLaughlin MM, Omotayo DB, Keshavjee S, Becerra MC, Mukherjee JS, et al. Outcomes of comprehensive care for

children empirically treated for multidrug-resistant tuberculosis in a setting of high HIV prevalence. PLoS One. 2012;7(5):e3 7114.
152. Matsaniotis N, Jacobs J, Smith MH. Hypersensitivity reactions associated with sodium para-aminosalicylate therapy; four case reports and review of the literature. Pediatrics. 1958;21(5): 781–92.
153. Lynch MJ. Effect of para-amino-salicylic acid on prothrombin time. J Clin Pathol. 1950;3(2):114–7.
154. Ge QP, Wang QF, Duan HF, Wang J, Chu NH. Clinical analysis of prothionamide and para amino salicylic acid induced hepatotoxicity. Zhonghua Jie He He Hu Xi Za Zhi. 2013;36(10): 737–40.
155. Diekema DJ, Jones RN. Oxazolidinone antibiotics. Lancet. 2001;358(9297):1975–82.
156. Shinabarger DL, Marotti KR, Murray RW, Lin AH, Melchior EP, Swaney SM, et al. Mechanism of action of oxazolidinones: effects of linezolid and eperezolid on translation reactions. Antimicrob Agents Chemother. 1997;41(10):2132–6.
157. Lin AH, Murray RW, Vidmar TJ, Marotti KR. The oxazolidinone eperezolid binds to the 50S ribosomal subunit and competes with binding of chloramphenicol and lincomycin. Antimicrob Agents Chemother. 1997;41(10):2127–31.
158. De Vriese AS, Coster RV, Smet J, Seneca S, Lovering A, Van Haute LL, et al. Linezolid-induced inhibition of mitochondrial protein synthesis. Clin Infect Dis. 2006;42(8):1111–7.
159. Vinh DC, Rubinstein E. Linezolid: a review of safety and tolerability. J Infect. 2009;59(Suppl 1):S59–74.
160. Garazzino S, Tovo PA. Clinical experience with linezolid in infants and children. J Antimicrob Chemother. 2011;66(Suppl 4):iv23–41.
161. Chiappini E, Conti C, Galli L, de Martino M. Clinical efficacy and tolerability of linezolid in pediatric patients: a systematic review. Clin Ther. 2010;32(1):66–88.
162. Saiman L, Goldfarb J, Kaplan SA, Wible K, Edge-Padbury B, Naberhuis-Stehouwer S, et al. Safety and tolerability of linezolid in children. Pediatr Infect Dis J. 2003;22(9 Suppl):S193–200.
163. Gerson SL, Kaplan SL, Bruss JB, Le V, Arellano FM, Hafkin B, et al. Hematologic effects of linezolid: summary of clinical experience. Antimicrob Agents Chemother. 2002;46(8):2723–6.
164. Lee M, Lee J, Carroll MW, Choi H, Min S, Song T, et al. Linezolid for treatment of chronic extensively drug-resistant tuberculosis. N Engl J Med. 2012;367(16):1508–18.
165. Meissner HC, Townsend T, Wenman W, Kaplan SL, Morfin MR, Edge-Padbury B, et al. Hematologic effects of linezolid in young children. Pediatr Infect Dis J. 2003;22(9 Suppl):S186–92.
166. Bressler AM, Zimmer SM, Gilmore JL, Somani J. Peripheral neuropathy associated with prolonged use of linezolid. Lancet Infect Dis. 2004;4(8):528–31.
167. Spellberg B, Yoo T, Bayer AS. Reversal of linezolid-associated cytopenias, but not peripheral neuropathy, by administration of vitamin B6. J Antimicrob Chemother. 2004;54(4):832–5.
168. Nambiar S, Rellosa N, Wassel RT, Borders-Hemphill V, Bradley JS. Linezolid-associated peripheral and optic neuropathy in children. Pediatrics. 2011;127(6):e1528–32.
169. Yogev R, Patterson LE, Kaplan SL, Adler S, Morfin MR, Martin A, et al. Linezolid for the treatment of complicated skin and skin structure infections in children. Pediatr Infect Dis J. 2003;22(9 Suppl):S172–7.
170. Su E, Crowley K, Carcillo JA, Michaels MG. Linezolid and lactic acidosis: a role for lactate monitoring with long-term linezolid use in children. Pediatr Infect Dis J. 2011;30(9):804–6.
171. Rose PC, Hallbauer UM, Seddon JA, Hesseling AC, Schaaf HS. Linezolid-containing regimens for the treatment of drug-resistant tuberculosis in South African children. Int J Tuberc Lung Dis. 2012;16(12):1588–93.
172. French G. Safety and tolerability of linezolid. J Antimicrob Chemother. 2003;51(Suppl 2):ii 45–53.
173. Reddy VM, O'Sullivan JF, Gangadharam PR. Antimycobacterial activities of riminophenazines. J Antimicrob Chemother. 1999;43(5):615–23.
174. Clofazimine. Tuberculosis. 2008;88(2):96–9.
175. World Health Organization. Chemotherapy of leprosy. Geneva: WHO; 1994. http://www.who.int/lep/resources/Chemotherapy.pdf. Accessed 10 Jan 2013.
176. Yano T, Kassovska-Bratinova S, Teh JS, Winkler J, Sullivan K, Isaacs A, et al. Reduction of clofazimine by mycobacterial type 2 NADH:quinone oxidoreductase: a pathway for the generation of bactericidal levels of reactive oxygen species. J Biol Chem. 2011;286(12):10276–87.
177. Grant SS, Kaufmann BB, Chand NS, Haseley N, Hung DT. Eradication of bacterial persisters with antibiotic-generated hydroxyl radicals. Proc Natl Acad Sci. 2012;109(30):12147–52.
178. Ramu G, Iyer GG. Side effects of clofazimine therapy. Lepr India. 1976;48(4 Suppl):722–31.
179. Hameed A, Beach FX, Kennedy RH, Barry RE. A case of clofazimine enteropathy. Int J Clin Pract. 1998;52(6):439–40.
180. Singh H, Nel B, Dey V, Tiwari P, Dulhani N. Adverse effects of multi-drug therapy in leprosy, a two years' experience (2006–2008) in tertiary health care centre in the tribal region of Chhattisgarh State (Bastar, Jagdalpur). Lepr Rev. 2011;82(1): 17–24.
181. Parizhskaya M, Youssef NN, Di Lorenzo C, Goyal RK. Clofazimine enteropathy in a pediatric bone marrow transplant recipient. J Pediatr. 2001;138(4):574–6.
182. Balakrishnan S, Desikan KV, Ramu G. Quantitative estimation of clofazimine in tissue. Lepr India. 1976;48(4 Suppl):732–8.
183. Revised National Tuberculosis Control Programme. DOTS-Plus guidelines, January 2010. http://www.tbcindia.nic.in. Accessed 12 Dec 2014.
184. Orenstein EW, Basu S, Shah NS, Andrews JR, Friedland GH, et al. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. Lancet Infect Dis. 2009;9:153–61.
185. Suarez PG, Floyd K, Portocarrero J, et al. Feasibility and cost-effectiveness of a standardized second line drugs treatment for chronic tuberculosis patients: national cohort study in Peru. Lancet. 2002;359:1980–9.