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Adverse effects induced by second-line antituberculosis drugs: an update based on last WHO treatment recommendations for drug-resistant tuberculosis

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Abstract

English:

Introduction: *Tuberculosis (TB), a common condition worldwide, is still among the main infectious diseases with high mortality rates, both in adults and infants. Drug-resistant tuberculosis (DR-TB) drugs, revised by the World Health Organization (WHO) in 2018, are a prolonged and complex therapy associated with many adverse drug effects (ADEs).*
Aim: *To systematically review the ADEs of second-line anti-TB drugs reported in multicentric studies published after the latest WHO guidelines, compared with those from clinical trials published before 2018.*
Material and methods: *A PubMed search, using keywords (TB OR DR-TB) AND (adverse effects) AND "second-line anti-TB drugs", resulted in 56 studies. Only two studies, published after the last update of WHO guidelines in 2018, reported ADEs.*
Results: *A total of 223 participants were included in the two selected studies. The use of multidrug regimens has been associated with an increased incidence of ADEs: 42 ADEs were recorded in 30 patients (26.3%) in the first study, while all patients had at least one ADE that occurred or worsened during treatment; and 19 (17%) had severe ADEs in the second study. However, both studies had a good favourable outcome rate (90% and 79.8%, respectively). Gastrointestinal disturbances, hepatotoxicity, headache and dizziness are the most common ADEs induced by a majority of second-line DR-TB treatments. A special attention should be given in the case of association of drugs determining QT interval (QT) prolongation on electrocardiogram, or psychiatric disorders.*
Conclusions: *Proper strategies about ADE management have to be planned for timely detection of the possible ADEs that can be induced by second-line anti-TB therapy.*

Keywords

DR-TB • second-line drugs • adverse drug effects

Reacțiile adverse induse de medicamentele antituberculoase de linia a doua: un update bazat pe ultimele recomandări ale OMS privind tratamentul tuberculozei drog rezistente

Rezumat

Romanian:

Introducere: *Tuberculoza (TB), o afecțiune comună la nivel mondial, se numără în continuare printre principalele boli infecțioase cu rată ridicată a mortalității, atât la adulți, cât și la copii. Medicația împotriva TB drog-rezistente (TB-DR), revizuită de Organizația Mondială a Sănătății (OMS) în 2018, constituie o terapie prelungită și complexă, asociată cu numeroase efecte adverse (EA).*

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Scop: *Revizuirea sistematică a EA ale medicației anti-TB de linia a doua, raportate în studii multicentrice publicate după ultima revizie a ghidurilor OMS, comparativ cu raportările din studiile clinice publicate înainte de 2018.*
Material și metode: *Prin cercetarea în PubMed, utilizând cuvintele-cheie (TB OR DR-TB) AND (adverse effects) AND "second-line anti-TB drugs", s-au obținut 56 de studii. Doar două studii, publicate după ultima revizie a ghidurilor OMS din 2018, au raportat EA.*
Rezultate: *Un total de 223 participanți au fost incluși în cele două studii selectate. Prescrierea regimurilor multidrog a fost asociată cu o incidență crescută a EA: 42 de EA au fost înregistrate la 30 de pacienți (26.3%) în primul studiu, în timp ce în al doilea studiu toți pacienții au avut cel puțin un EA care a avut loc sau s-a agravat în timpul tratamentului, iar 19 (17%) au avut EA severe. Cu toate acestea, ambele studii au avut o rată bună a rezultatelor favorabile (90%, respectiv 79.8%). Tulburările gastro-intestinale și hepatotoxicitatea, cefaleea și amețelile sunt cele mai frecvente EA induse de majoritatea medicamentelor terapiei TB-DR. O atenție deosebită trebuie acordată asocierii de medicamente care determină prelungirea QT sau tulburări psihiatrice.*
Concluzii: *Trebuie planificate strategii adecvate privind gestionarea EA pentru a detecta la timp posibilele EA care pot fi induse de terapia anti-TB de linia a doua.*

Cuvinte-cheie
TB-DR • medicamente de linia a doua • efecte adverse la medicamente

Introduction

Tuberculosis (TB) is a contagious infectious disease with chronic evolution and is widespread throughout the world's population; and it presents an important degree of fatality in terms of incorrectly treated or untreated cases (1). Since the time of Robert Koch's immensely significant discovery of *Mycobacterium tuberculosis* (*Mtb*), the global TB epidemic has been uncontrollable (2).

According to the World Health Organization (WHO), TB is one of the main causes of death worldwide (1,3). Approximately 10 million new cases have been reported worldwide, with an incidence of approximately 130 new cases for every 100,000 inhabitants. An estimated 1.4 million deaths have also been reported, even though TB is a curable disease (1). The WHO Global TB Report 2021 shows declines in the TB incidence (the number of new people developing TB each year) as a result of the Coronavirus disease 2019 (COVID-19) pandemic (1). In the context of COVID-19 disruption of TB services (4,5), it is anticipated that the number of drug-resistant tuberculosis (DR-TB) cases will increase in 2021 and 2022 and will affect treatment outcomes further (1,5).

Anti-TB treatment must meet two main objectives, given the fact that TB is an important public health issue: First of all, the treatment of TB is aimed at curing the disease; decreasing the risk of relapses; preventing death, complications and the appearance of drug resistance; and, at the same time, preserving the work capacity together with the social and economic position (6–8); the second objective is to protect the community to which the patient belongs by interrupting the transmission of the infection, thus helping to improve the level of the TB endemic (1,6).

Chemotherapy of *Mtb* infections is classified into first-line drugs used to treat pulmonary TB infections that are not drug-resistant [isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E)] and second-line drugs used to treat multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) (9). In 2018, the WHO recommendation of MDR-TB treatment classified the antituberculosis drugs into three groups: group A consisting of fluoroquinolone [levofloxacin (Lfx)/moxifloxacin (Mfx)], bedaquiline (Bdq) and linezolid (Lzd); group B consisting of clofazimine and cycloserine (Cs)/terizidone (Tzd); and group C consisting of E, delamanid (Dlm), Z, imipenem–cilastatin (Imp-Cln)/meropenem (Mpm), amikacin (Am), streptomycin (Sm), ethionamide (Eto)/prothionamide (Pto) and para-aminosalicylic acid (PAS) (Figure 1) (10,11).

Adverse drug effect (ADEs) incidences during anti-TB treatment are increasing due to the necessity of utilization of multidrug regimens. Anti-TB drugs may produce adverse effects that range in their severity from unimportant to life-threatening (12). A severe side effect of a second-line anti-TB drug might lead to the discontinuation of that drug and complications resulting in increased morbidity and mortality (12). At the same time, the use of alternative agents may result in greater problems of toxicity and compliance. Therefore, the risk of treatment failure and relapses is higher (12). The treatment of MDR-TB and rifampicin-resistant tuberculosis (RR-TB) requires long-term therapy with a combination of multiple second-line drugs, which are less effective, more costly and more toxic than first-line drugs (13).

Therefore, this study was designed to systematically review the ADEs of second-line anti-TB drugs reported in multicentric studies published after the introduction of the latest WHO

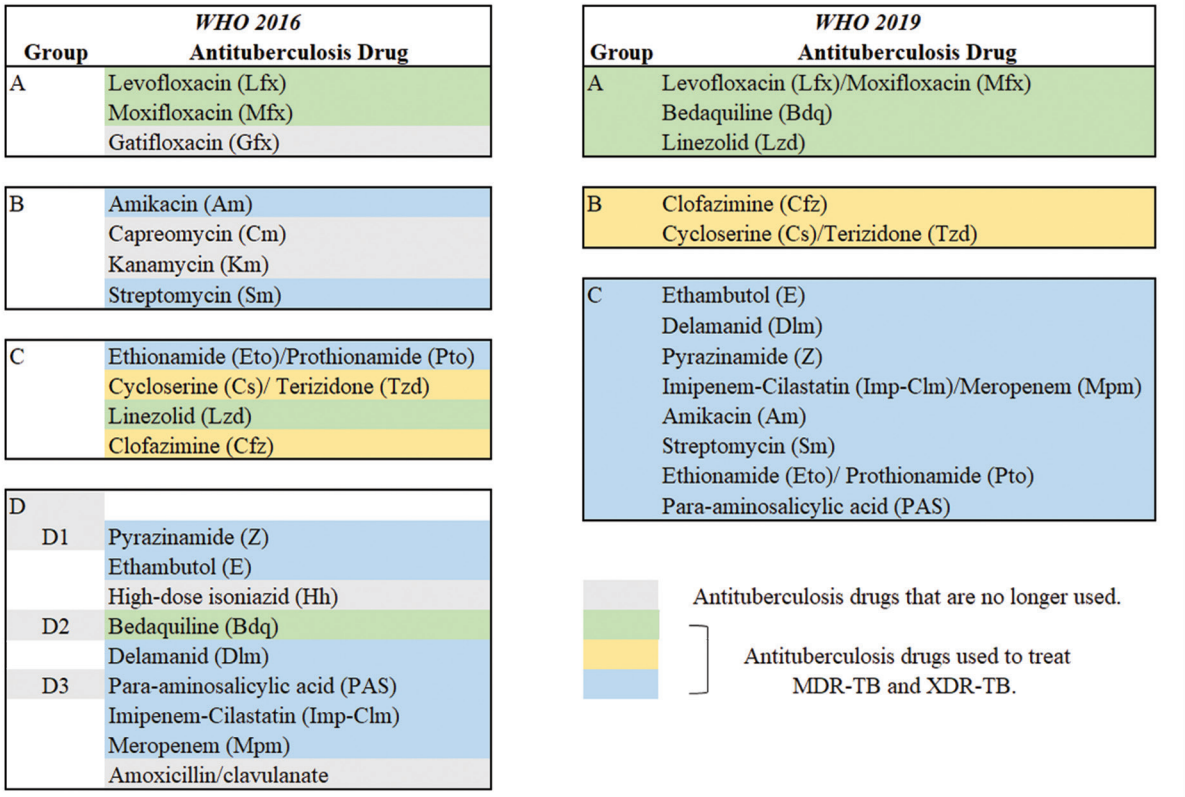


Figure 1. Differences in the two classifications of anti-TB drugs (for MDR-TB and XDR-TB treatment): WHO 2016 and WHO 2019 (10,11,24,29); grey – anti-TB drugs that are no longer part of group A, B or C; green, yellow and blue – anti-TB drugs that are used to treat DR-TB and are included in group A, B or C. DR-TB, drug-resistant tuberculosis; TB, tuberculosis; MDR-TB, multidrug-resistant tuberculosis; PAS, para-aminosalicylic acid; WHO, World Health Organization; XDR-TB, extensively drug-resistant tuberculosis.

guidelines, compared with those from clinical studies published before the latest updates from 2018.

Material and methods

We searched for articles in PubMed with the use of the following keyword combinations to meet the aim of this study: ("tuberculosis" OR "drug-resistant tuberculosis") AND ("adverse effect" OR "side effect" OR "adverse drug reactions") AND ("levofloxacin" OR "moxifloxacin" OR "bedaquiline" OR "linezolid" OR "clofazimine" OR "cycloserine" OR "terizidone" OR "ethambutol" OR "delamanid" OR "pyrazinamide" OR "imipenem-cilastatin" OR "meropenem" OR "amikacin" OR "streptomycin" OR "ethionamide" OR "prothionamide" OR "para-aminosalicylic acid"). We included clinical trials and randomised controlled trials written in English and published from 2018 to January 2022. A flow diagram of article selection is illustrated in Figure 2. Only original research studies with quantitative methods were selected. Articles on unrelated topics were excluded. Inclusion criteria are the following: patients with XDR-TB or MDR-TB, those aged ≥18 years and those negative for human immunodeficiency virus (HIV). Exclusion criteria are the following: patients aged <18 years, those positive for HIV antibody, those with acquired immune deficiency syndrome (AIDS) and those under other autoimmune chronic disease treatment. Three researchers extracted the data independently, and a common agreement was subsequently reached on all the analysed studies. ADEs reported in the clinical studies published after 2018 were compared to those from the reviews and clinical studies published before 2018.

Results and discussions

Electronic research of the medical literature from PubMed database resulted in a total of 56 references, from which 49 records were removed after reading the abstract. After reading

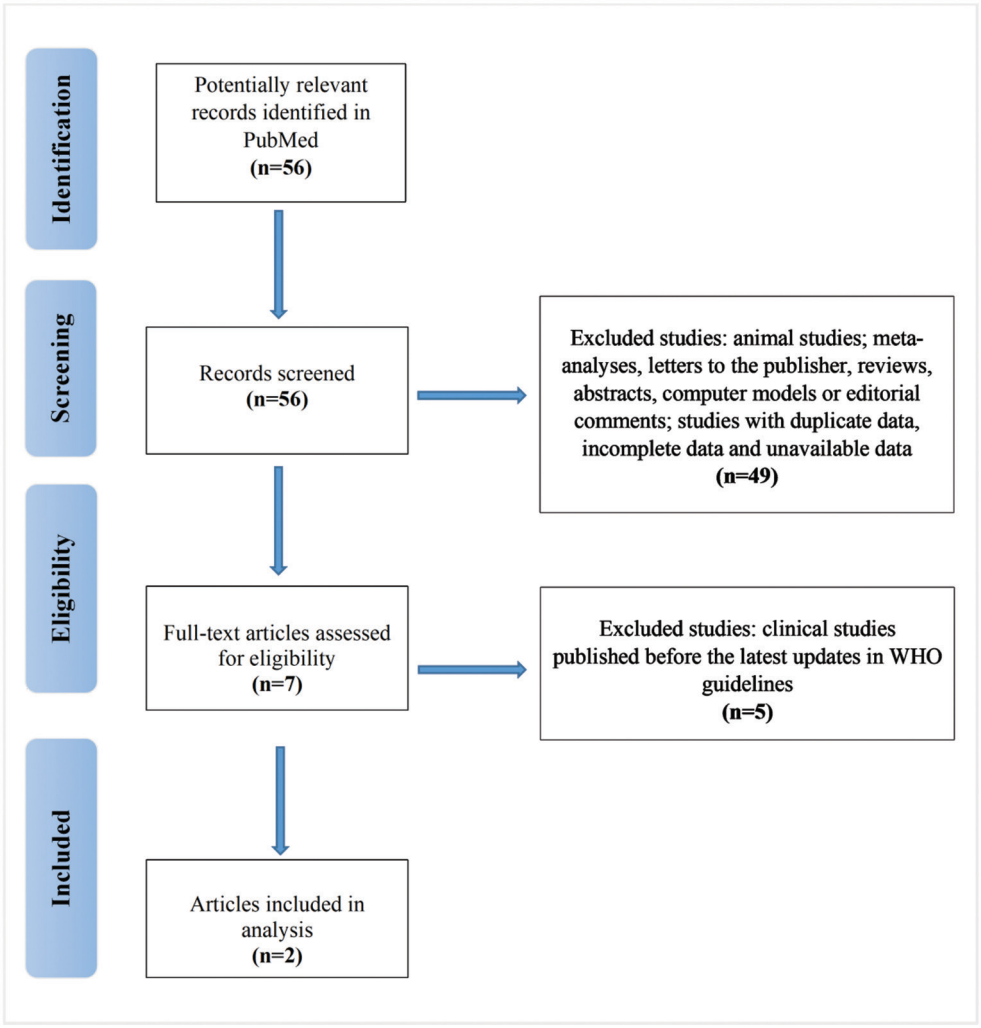


Figure 2. Graphical PRISMA flow diagram showing the process of selecting studies. WHO, World Health Organization.

the full text of the remaining seven articles, we identified two eligible studies for inclusion in this review (Figure 2).

The two studies included a total of 223 participants from two study sites: South Africa and China (Table 1). The largest study, performed by Sun et al. (14), had 114 participants with MDR-TB treated with second-line anti-TB drugs and an overall favourable treatment rate of 79.8% (91 of 114 patients), especially as high as 91.7% (33 of 36 patients) in newly treated patients, and this study employed the combination of Am, fluoroquinolones, Cs, Pto, pasiniazine and Z, which was given for 18 months. In 2020, Conradie et al. (15) published the results of a regimen of three oral drugs, namely, Bdq, pretomanid and Lzd, given for 26 weeks in patients with XDR-TB. In this study, 109 patients were enrolled, and at the end of treatment, 98 patients (90%) had a favourable outcome, which suggested that the combination of Bdq, pretomanid and Lzd leads to a favourable outcome among a high percentage of patients with fluoroquinolone resistance.

The study conducted in China by Sun et al. (14), in 2021, showed that the incidence of ADEs was low, especially in newly treated patients (6/36, 16.67%), and the majority of ADEs (n = 40, 40/42) were mild to moderate. The investigators recorded mild hearing loss, mild renal dysfunction and mild dizziness (linked to Am use); elevated alanine aminotransferase (ALT) to twice the upper limit of the normal range (at Z and P to use); gout (Z involved); gastrointestinal reaction (at Pto and Mfx administration); and allergic rash (to Mfx). Hearing loss, renal dysfunction, elevated ALT and allergic rash were four ADEs that required permanent discontinuation of the suspected drug (Am or Mfx) and were reported in two patients.

Table 1. Study analysis of clinical trials reporting ADEs in DR-TB patients published after 2018.

Reference	Conradie et al. (2020) (15)	Sun et al. (2021) (14)
Study design	Open-label, single-group study	Open-label, prospective cohort study
Setting	South Africa	China
Target population	MDR-TB and XDR-TB patients	MDR-TB patients
Period	April 2015–November 2017	January 2017–June 2018
Duration of treatment	26–39 weeks (if they were culture-positive at week 16)	6 months (six drugs), followed by 12 months (five drugs, without amikacin)
No. participants	*n* =109	*n* = 114
Age (years)	Median age = 35 (17–60)	Mean ± standard deviation: – Newly treated = 32.1 ± 12.4 – Retreated = 35.5 ± 11.5
Gender	Male: *n* = 57 (52%) Female: *n* = 52 (48%)	Male: *n* = 72 (63%) Female: *n* = 42 (37%)
Summary of result	Favourable outcome: *n* = 98 (90%) Unfavourable outcome: *n* = 11 (10%)	Favourable outcome: *n* = 91 (79.8%) Unfavourable outcome: *n* = 23 (20.2%)
Anti-TB drug	Linezolid (Lzd) Bedaquiline (Bdq) Pretomanid	Amikacin (Am) Fluoroquinolones Cycloserine (Cs) Protionamide (Pto) Pasiniazine Pyrazinamide (Z)
ADEs	Lzd: peripheral neuropathy, myelosuppression, elevated ALT and AST, and QT prolongation	Am: mild hearing loss, mild renal dysfunction and mild dizziness Z – ALT elevated to twice the upper limit of the normal range and gout Pto: ALT elevated twice the upper limit of the normal and gastrointestinal reaction Mfx: allergic rash and gastrointestinal reaction
Management	Dose reductions or interruptions in treatment with linezolid None had the regimen permanently discontinued	– Dose reductions or interruptions – Change in treatment regimen – ADEs improved after symptomatic treatment – Permanent discontinuation for hearing loss, renal dysfunction, elevated and allergic rash

ADEs, adverse drug effects; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Bdq, bedaquiline; DR-TB, drug-resistant tuberculosis; Lzd, linezolid; MDR-TB, multidrug-resistant tuberculosis; TB, tuberculosis; XDR-TB, extensively drug-resistant tuberculosis.

In the study by Conradie et al. (15), peripheral neuropathy, even though mild and manageable, was reported in 88 patients (81%); therefore, toxic effects associated with high doses of Lzd are a real concern. Myelosuppression was the second most common ADE and occurred in 52 patients (48%). Although common, it was manageable, often leading to dose reductions or interruptions in treatment with Lzd. Other ADEs were elevated transaminase levels in 17 patients, and these higher levels, which were thrice the upper limit of the normal range of ALT and of aspartate aminotransferase (AST), were found, respectively, in 12 and 11 patients. All eight patients who had the regimen interrupted for hepatic adverse events resumed and completed the full 26 weeks of treatment. QT prolongation was another ADE, and the maximum mean increase in the corrected QT Fridericia (QTcF) interval was 10 ms in week 16 of treatment.

The results demonstrated in the study of Sun et al. (14) indicate that the regimen used in that study has a high efficacy and safety against ADEs in specific MDR-TB patients. Although patients taking the regimen used in the study of Conradie et al. (15) should be monitored carefully, these toxic effects were manageable.

ADEs reported in clinical studies before 2018 and in reviews

Fluoroquinolones

Levofloxacin (Lfx) and moxifloxacin (Mfx), the only fluoroquinolones used as anti-TB drugs according to the latest WHO guidelines (11,16), determine a frequency of ADEs of 4.5% and 3.2%, respectively, as pooled absolute risk of adverse effects (13). Pooling consists of adding the number of events observed in a given treatment group across the trials and dividing the results by the total number of patients included in this group (17). In a study by Palma-Alvarez et al. (18) in 2020, quinolones are commonly described as being well tolerated, and the adverse event rate is 9.2 per 10,000 prescriptions (18,19).

Adverse effects

Dyspepsia, nausea, vomiting, diarrhoea, aerophagy, anorexia, abdominal discomfort and other reactions of the gastrointestinal tract are among the most frequently registered ADEs during therapy with fluoroquinolones (20). *Clostridioides difficile*-associated diarrhoea is an important

risk during therapy (20–22). Insomnia, anxiety, restlessness, nervousness, tremors, euphoria and nightmares are not uncommon, while seizures and psychiatric events are rare. Neuropsychiatric reactions (convulsions and hallucinations) are concerns for the elderly patients and in those using theophylline or nonsteroidal anti-inflammatory drugs (20). The common manifestations of arthropathy and cartilage erosion were joint pain, stiffness and swelling of weight-bearing joints, particularly knees (23), and QT prolongation (24). More recent concerns regarding musculoskeletal adverse effects of fluoroquinolones involve the possibility of tendinitis and tendon rupture (more often Achilles tendon) (23). These manifestations are often associated with rheumatoid arthritis, kidney failure and haemodialysis (22). Hypoglycaemia and hyperglycaemia have been observed to occur in patients with diabetes mellitus who use oral hypoglycaemic agents or insulin in conjunction with fluoroquinolone therapy (22,25). The haematological ADE is severe thrombocytopenia (25,26).

Diarylquinoline

Bedaquiline (Bdq), formally named TMC 207, now in group A MDR-TB treatment of the last guideline (11,16), has a frequency of ADEs of 3.1% as pooled risk of adverse events according to Lan et al. (13).

Adverse effects

Significantly, QTcF prolongation leads to interruption in the treatment administration. Other common ADEs are gastrointestinal symptoms (nausea and vomiting), followed by hepatotoxicity, central nervous system toxicity and musculoskeletal symptoms (myalgia, arthralgia and tendinitis). In a surveillance study by Borisov et al. (27) on ADEs in DR-TB treatment, it was seen that only 2.4% (16/678) of the patients had a significant QTcF prolongation of 500 ms with Bdq; however, the drug needed to be withdrawn in only two patients. Bdq needed to be stopped in 6.7% (3/45) of the patients in a study by Guglielmetti et al. (28), due to significant QTcF prolongation. Severe adverse events were reported in 2.8% of the patients (13,29).

Oxazolidinone

Linezolid (Lzd), group A according to the last guidelines (11,16), has a frequency of ADEs of 16.8% as pooled risk of ADEs (13).

Adverse effects

Haematological abnormalities, noticed after at least 14 d of treatment, manifested as reversible anaemia (38%) (26,30), thrombocytopenia (12%) (26,30) and leukopenia (26). The most severe abnormality is myelosuppression and pancytopenia, both time- and dose-dependent (26). Other ADEs are peripheral neuropathy, optic neuritis (13%), visual manifestations (24) and other gastrointestinal disturbances (30,31).

Hydrophobic riminophenazine

Clofazimine (Cfz) has a 3.8% pooled risk of ADEs (13). In a systematic review by Gopal et al. (32), the analysis of the observational studies up to 2013 revealed a percentage of ADEs attributable to Cfz in eight cohort studies, of which 11.4% resulted in discontinuation of the drug in <1% of the patients (31).

Adverse effects

Orange to brownish skin pigmentation, the most frequent ADE, occurs within a few weeks with concomitant reversible long-lasting discolouration of fluids and secretions (33). QTcF prolongation is the most severe ADE and needs temporary discontinuation of the drug administration (6,13,34). Different types of anaemia are associated with Cfz administration (26).

Cycloserine

Cycloserine (Cs), part of group B according to the WHO 2019 guidelines (11,16), has an 8% pooled absolute risk of ADEs (13).

Adverse effects

The most common neurological manifestations are headaches and peripheral neuropathy, while the rare ones include convulsion and epilepsy (31,35). The most common psychiatric manifestations are depression and behavioural disturbance and rarely paranoid reactions (risk of suicide). Stevens–Johnson syndrome, haematological manifestations (megaloblastic and sideroblastic anaemia) and skin rash are rare ADEs that can occur in treatment with Cs (22,26,36).

Ethylenediamine

Ethambutol (E) belongs to group C of MDR-TB treatment (11,16) and has a 4.2% pooled absolute risk of ADE (13).

Adverse effects

Visual impairment and optic neuritis, followed by joint pain and rash, are considered the most common ADEs (31). Haematological ADEs anaemia, agranulocytosis, thrombocytopenia and neutropenia are rare ADEs (26).

Nitro-dihydro-imidazo-oxazole

Delamanid (Dlm) is part of group C of MDR-TB drugs in accordance with the WHO guidelines (11,16).

Adverse effects

QT prolongation is the most severe ADE and requires frequent monitoring of electrocardiogram (31). Gastrointestinal

symptoms (nausea, vomiting and dizziness) (13,31) are the most common ADE.

Pyrazine analogue of nicotinamide

Pyrazinamide (Z), a group C drug (11,16), has a pooled incidence of ADEs of 9.8% among MDR-TB patients in a meta-analysis by Lan et al. (13).

Adverse effects

Gastrointestinal symptoms and hepatotoxicity are common ADEs, followed by arrhythmia and rash (31), arthralgia and dermatological disorders (24). Thrombocytopenia and sideroblastic anaemia are very rare ADEs (26).

Carbapenems

Imipenem (Imp) and meropenem (Mpm) are group C drugs (11,16) and have a pooled incidence of ADEs of 7.7% among MDR-TB patients (13).

Adverse effects

Gastrointestinal symptoms and rash are frequent ADEs (31). More severe, but rare, events include increased liver transaminases, increased levels of creatinine and haematologic effects, including thrombocytosis, neutropenia and haemolytic anaemia (19,26).

Aminoglycosides

Amikacin (Am) and streptomycin (Sm) are group C drugs (11,16) and have a pooled incidence of ADEs of 13.8% and 5.4%, respectively, among MDR-TB patients (13). Kanamycin and capreomycin have been removed from WHO groupings of drugs due to poor treatment-related outcomes (11,16,31).

Adverse effects

Ototoxicity is the most severe ADE caused by aminoglycosides (37). Ototoxicity risk increases with age, duration of treatment and accumulated dose. The risk is also higher in patients who are under treatment with diuretics, in dehydrated patients and in patients with a history of hearing loss (37,38). Neurotoxicity is a benign adverse effect that manifests as perioral paraesthesia immediately after administration (37,38). The nephrotoxicity of aminoglycosides is caused by the accumulation of the drugs in the renal tubules (39,40). Elderly patients, those under long-term treatment and those with a history of kidney disease have a higher occurrence of renal toxicity (30,41). The most significant manifestations of nephrotoxicity include decreased creatinine clearance, electrolyte imbalance (24) and increased serum levels of urea and creatinine, proteinuria and oliguria (37,40,41). Aminoglycosides can cause respiratory failure due to rapid intravenous injection of the drug in patients who are under treatment with anaesthetics or neuromuscular blocking agents (37). Urticaria, drug rash with eosinophilia and systemic symptoms (DRESS) syndrome and anaphylactic reactions represent rare and severe allergic manifestations (26,37,38).

Thioamides

Ethionamide (Eto) and prothionamide (Pto) are part of group C drugs (11,16) and have a summedup pooled incidence of ADEs of 10.9% among MDR-TB patients (13).

Adverse effects

The most common ADEs associated with these drugs are intense gastrointestinal effects (anorexia, nausea, vomiting, metallic taste in the mouth and gastric irritation) (37,42), hepatotoxicity (31) and a variety of neurological symptoms (peripheral neuritis, peripheral neuropathy, optic neuritis, diplopia, irritability, anxiety, depression, hallucinations, convulsions and psychosis) (22,37,43). Postural hypotension, drowsiness, asthenia, convulsions, allergic skin rashes, purpura, hypothyroidism, gynaecomastia (24), impotence, menorrhagia and alopecia can occur in patients treated with Eto (42–44). The neurological effects can be minimised by administering pyridoxine (43). Vision changes such as blurred, decreased or double vision and colour blindness are rare side effects of Eto (42). Agranulocytosis and leukopenia are very rare haematological manifestations (26).

Amino derivative of salicylic acid

PAS belongs to group C of MDR-TB drugs (11,16) and has a 17.9% pooled absolute risk of ADEs (13).

Adverse effects

The most common ADEs in patients treated with PAS are hypothyroidism (when administered concomitantly with Eto); gastrointestinal manifestations such as diarrhoea, nausea, vomiting and anorexia; hepatitis; and malabsorption syndrome (45). Eosinophilic pneumonia, encephalopathy and optic neuritis are adverse effects that need to be carefully monitored (22,45). Also, during therapy with PAS, haematological changes (haemolytic anaemia, agranulocytosis, leukopenia, thrombocytopenia and methemoglobinemia) and allergic reactions (pruritus and fever) can occur (26,45,46).

Other considerations

Exploration of initiatives for MDR-TB treatment started decades ago but increased in size and scope only in the past few years (47). The WHO 2018 guidelines for DR-TB (10) proposed a three-drug combination treatment plan comprising Mfx, Lzd and Bdq, which represented the arrival of the era of totally oral treatment (47). In 2020, the WHO consolidated guidelines on TB (Module 4) revised current policy recommendations on the treatment strategy for DR-

TB (11). The 2020 recommendations have witnessed two important trends in the MDR-TB treatment: to shorten the duration of MDR-TB treatment and to research the strengths of effective novel and repurposed oral agents (15,47).
Based on comparing the studies brought out before 2018 with those published after the new updates in the WHO guidelines, we ascertain that there were fewer ADEs reported in the latter, and the majority of them were mild to moderate, and thus manageable, which seems to be in favour of the use of the new associations.

Conclusions

Both studies included in the analysis were conducted before the latest WHO guidelines and published after 2018. Both eligible studies contain one active substance (pretomanid and pasiniazine) that is not found in the new MDR-TB treatment groups A, B and C, according to the new WHO recommendations. Studies published after 2018 reveal a lower number of ADEs for the active substances found in the new WHO guidelines than studies published before 2018. However, new studies are needed to be carried out on cohorts of patients under MDR-TB therapy according to the new guidelines in order to monitor and improve the management of ADEs.
Gastrointestinal disturbances, hepatotoxicity, headache and dizziness are the most common ADEs induced by a majority of second-line DR-TB drugs. Special attention should be paid in the case of association of drugs determining QT prolongation (fluoroquinolones, Bdq, Cfz and Dlm) or psychiatric disorders (fluoroquinolones and Cs). Some ADEs are specific for some drugs, such as ototoxicity induced by aminoglycosides, gynaecomastia induced by Eto or skin discoloration induced by Cfz. Common neurological ADEs are peripheral neuropathy (Lzd, Cs and Eto) and optic neuritis (Lzd, E, Eto and PAS), while convulsions and hallucinations are special concerns for elderly patients. Haematological manifestations were described for the majority of MDR-TB drugs but not yet reported for Dlm. Other common ADEs are arthralgia (fluoroquinolones, Bdq and Z), electrolyte imbalance (aminoglycosides), hypothyroidism (Eto and PAS) and dermatological disorders (Cfz and Z).
The knowledge of ADEs induced by anti-TB drugs is important because there is a need to continue to closely observe and monitor all TB cases and to detect in time the possible ADEs that can be induced by second-line anti-TB therapy. In the context of the global pandemic with the severe acute respiratory syndrome Coronavirus 2 (SARS CoV-2) infection, there is a false decrease in the global incidence of TB, which, in subsequent years, can lead to an increase in the number of cases with extended TB (multiple lesions and fibrothorax) as well as in the number of cases of MDR-TB and XDR-TB.

Conflict of interest statement

None of the authors have any conflicts of interest or financial interest to disclose.

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