complications of antituberculous medications (Kim *et al.*, 2013b). Risk may increase in patients co-infected with HIV (Lehloenya *et al.*, 2012). Isoniazid and ethionamide that have close structural similarities would be expected to cross-induce these syndromes. However, a recent study has shown that the risk of cross-reactivity is lower than expected and in some situations guidance can be sought from results of cutaneous patch testing (Arai, 2015; Lehloenya *et al.*, 2015). Hypoglycemia (Ticholov and Dobrev, 1963), hypothyroidism (McDonnell *et al.*, 2005; Moulding and Fraser, 1970), gynecomastia (Dixit *et al.*, 2012; Sharma and Bansal, 2012), impotence, alopecia (Sister, 1964), acne, and other skin rashes (Holdiness, 1985) have also been attributed to ethionamide. Patients taking ethionamide, PAS, or both have a significant risk of developing hypothyroidism during treatment, and baseline and monthly TSH assessments are recommended (Andries *et al.*, 2013; Thee *et al.*, 2011b). The management of patients with diabetes mellitus may become more difficult in those receiving ethionamide (Hussey, 1974; DailyMed, 2015). There has been a case report of pellagra (dermatitis, diarrhea, and dementia) caused by a deficiency of niacin or its precursor tryptophan in a 13-year-old girl taking ethionamide. Her illness responded to niacin (Gupta and Shah, 2015). Pellagroid dermatitis due to ethionamide has also been reported (Garg and Khopkar, 2011).

7. CLINICAL USES OF THE DRUG

7a. Tuberculosis

The thioamides are regarded as the most active of the so-called group 4 second-line agents for drug resistant tuberculosis and are included in most MDR-TB regimens worldwide (Caminero *et al.*, 2010). Ethionamide should only be used in conjunction with two to four other drugs to which susceptibility is likely on clinical grounds or has been demonstrated. Before the availability of rifampicin, ethionamide was a standard component of retreatment regimens for disease due to isoniazid- and streptomycin-resistant strains (Crofton, 1969; Somner and Brace, 1962). Ethionamide is regarded by some as an effective bactericidal agent (Crofton, 1969), although others classify ethionamide as bacteriostatic (Lakshmi *et al.*, 2011). In 2011, WHO updated its guidance on the management of MDR-TB. Current recommendations (necessarily based mainly on experience and opinion) for patients with MDR-TB are regimens that include at least pyrazinamide, a fluoroquinolone, a parenteral agent (kanamycin, amikacin or capreomycin), ethionamide (or prothionamide), and either cycloserine or PAS. The intensive phase which includes a second-line injectable agent should be at least 8 months, and total duration of treatment 20 months and at least 18 months following culture conversion (Falzon *et al.*, 2011).

There is increasing interest in shorter total durations of treatment for MDR-TB, often with higher doses of some oral drugs and the addition of clofazamine. In a series of overlapping cohort studies performed in Bangladesh 1997–2007, the total duration of successful treatment was reduced to 9 months, and some important observations were made about the value of prothionamide. HIV infection was rare in the 427 patients available for analysis; all had MDR-TB and none had a past history of treatment with second-line drugs for tuberculosis > 1 month. Approximately 19% of isolates from these patients had primary resistance to prothionamide, but drug sensitivity testing was not performed for all patients, particularly early in the study period. When available, these results were used to steer some decisions in the intensive phase. Regimen changes associated with improved results were reduced duration of the thioamide, replacing the thioamide with clofazimine during the continuation phase, and using a fourth-generation fluoroquinolone. The worst performing regimen was ofloxacin-based with prothionamide throughout without the addition of isoniazid (but including a second-line injectable). The best performing regimen was high doses of gatifloxacin, clofazimine, ethambutol, and pyrazinamide throughout, supplemented by kanamycin, prothionamide, and medium to high doses of isoniazid during an intensive phase until sputum conversion or for at least 4 months. Weight-based prothionamide was given daily at the following doses: 250 mg weight < 33 kg; 500 mg 33–55 kg; 750 mg > 55 kg. At least two patients who failed treatment had isolates that were initially resistant to ethionamide or prothionamide, indicating the continuing importance of the thioamide class. The evolution of this final regimen was based on replacing prothionamide with clofazamine after the intensive phase because of improved tolerability. A 12-month version of this regimen has also been successful in 65 patients with MDR-TB in Niger 2008–2010 in which 89% of patients were cured (1.7% were HIV-positive) (Piubello *et al.*, 2014).

Patients with HIV and tuberculous meningitis have a high mortality rate. Ethionamide given together with levofloxacin, pyrazinamide, and a double dose of rifampicin and isoniazid for an intensive initial period with a median of 7 days has been associated with improved survival in a small study performed in Egypt. The drugs were selected because of their propensity enter the brain and CSF (Alvarez-Uria *et al.*, 2013).

In Cape Town, South Africa, from January 2003 to April 2009 a variation from the WHO-recommended treatment protocol in 123 children with tuberculous meningitis has been associated with improved outcomes. Initial treatment is with isoniazid (20 mg/kg, maximum 400 mg daily), rifampin (20 mg/kg, maximum 600 mg daily), pyrazinamide (40 mg/kg, maximum 2 g daily), and ethionamide (20 mg/kg, maximum 1 g daily) for 6 months with HIV-infected children treated for 9 months. Isoniazid monoresistance did not affect outcome but multidrug resistance did (Seddon *et al.*, 2012).

An individual patient data meta-analysis of 9153 patients with MDR-TB from 23 countries and all WHO regions was published in 2012 (Ahuja *et al.*, 2012). The use of later-generation quinolones, ofloxacin, and ethionamide-prothionamide