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Early View

Research letter

Cycloserine did not increase depression incidence or severity at standard dosing for MDR-TB

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Cycloserine did not increase depression incidence or severity at standard dosing for MDR-TB

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Summary: In a longitudinal cohort of MDR-TB patients receiving individualized, DST-based treatment, neither the inclusion of cycloserine in a multidrug regimen nor the dose used (up to 750mg daily) significantly increased incidence of depression during treatment.

Dear Editor:

In 2018 cycloserine was elevated to WHO group B status for multidrug-resistant tuberculosis (MDR-TB), and is recommended in longer MDR-TB treatment regimens [1]. Inclusion of cycloserine is associated with improved MDR-TB treatment success and reduced mortality, but is limited by treatment-associated depression, psychosis, and neuropathy, forcing 9% of patients to stop therapy [1-3]. Cycloserine also demonstrates wide inter-individual pharmacokinetic variation, with significant food and drug interactions, leaving nearly half of patients with inappropriate drug levels [4, 5]. Optimal dosing is unknown [6], but modeling studies suggest doses from 250mg-750mg twice-daily, with 500mg twice-daily for paucibacillary disease and 750mg twice-daily for cavitary pulmonary disease [7]. Clinicians must therefore balance the known benefits of cycloserine with the dearth of susceptibility and drug monitoring capacity and the spectre of treatment-limiting side effects. To evaluate the impact of cycloserine prescription and dose on incident depression during MDR-TB treatment, we analyzed longitudinal cohort data from India.

Outpatients aged 15 years and older seeking MDR-TB care at a private hospital in Mumbai, India were recruited for a prospective observational cohort study approved by the institutional review boards of the PD Hinduja National Hospital and Medical Research Centre and Johns Hopkins University School of Medicine [8]. After informed consent (guardian consent for 15-18-year-olds), participants' medical records were abstracted for demographic characteristics, treatment history, laboratory and imaging studies, and treatment-associated side-effects. Due to additional drug resistance, most participants were ineligible for short-course regimens and received individualized, susceptibility-guided multidrug therapy for 24 months. This study predates guidelines prioritizing all-oral regimens, so injectable MDR-TB drugs were often included. Regimen was determined by resistance profile, not study participation or comorbidity. Cycloserine was initially prescribed at 250mg daily, then increased as tolerated to 250mg twice-daily or 250mg daily plus 500mg nightly [1]. For simplicity, doses are presented as total mg/day (0mg, 250mg, 500mg, or 750mg/day). Participants were followed for 1 year after treatment completion. Each visit, participants reported employment status, tobacco and alcohol use, social support [9], neuropathy, hallucinations, and depression symptoms using the Patient Health Questionnaire-9 (PHQ-9) [10].

Data were analyzed per-participant and per-visit. PHQ-9 scores were modelled as an ordinal variable with scores indicating mild or no depression (<10), moderate depression (10-13), and moderately severe or severe depression (≥14). Alcohol use by AUDIT score [11], and body mass index (BMI, kg/m^2) were calculated each visit. Underweight was defined as BMI<18.5kg/m^2. Differences in participant characteristics by depression status was assessed by χ^2 test, with $p<0.05$ considered significant. Depression incident rate ratios (IRRs) were calculated for each covariate. Mixed effects models with random intercepts, random slopes, and unstructured correlation assessed univariable odds ratios (OR) for depression at each visit by covariate including cycloserine prescription, dose, weight-adjusted dose (mg/kg-day), and treatment duration (months). Significant features from univariable models were included in a multivariable model.

From October 2017–March 2021, 140 participants completed 881 PHQ-9 questionnaires over 200.4 person-years of treatment. Of these, 122 participants (87%) received cycloserine. Participants had a median age of 27 years (interquartile range: 21-35), and 91 (65%) were female. Most had culture positive (90%) pulmonary (89%) tuberculosis, 12% had diabetes, and 3% were HIV-coinfected. Smoking was uncommon (4%), and no participants reported hazardous drinking (AUDIT≥8). Tobacco use was more frequent among those with depression (15% vs. 2% for PHQ-9≥14 and <10, respectively, p=0.047). Though not significant, those with higher PHQ-9 scores more frequently stopped working due to MDR-TB (55% vs. 26%, p=0.051), and underweight was more common among those with depression (median BMI 17.7kg/m^2 vs. 21.1 kg/m^2 for PHQ-9≥14 and <10, respectively, p=0.509). No other clinical features differed significantly by depression status or cycloserine prescription.

Overall, 40 participants (28%) reported prevalent depression (PHQ-9≥10) at enrollment. Of those without prevalent depression, 38% reported incident depression during treatment; an incidence of 102.6/1,000 person-years. Incidence increased with AUDIT score (IRR:2.98, 95% confidence interval (CI):1.86–4.77), but not with cycloserine prescription (IRR:1.11, 95% CI:0.46–2.68), duration of cycloserine use (monthly IRR:0.83, 95% CI:0.34–2.02), higher cycloserine dose (IRR:0.98, 95% CI:0.34–2.79 and IRR:2.03, 95% CI:0.48–8.66 for 500mg and 750mg total/day, respectively), or higher doses in mg/kg-day (IRR:1.03, 95% CI:0.93–1.15). In addition, 78 participants (55.7%) reported treatment-associated peripheral neuropathy. Of note, 3 participants taking cycloserine 250g twice-daily reported hallucinations (all ≥9 months into cycloserine), as

did 3 participants never prescribed cycloserine and 4 participants previously taking cycloserine (all ≥2 months after discontinuation).

Moderately severe and severe depression declined for all participants during tuberculosis treatment, impacting 7.9% of participants at enrolment, 3.1% after 2 months, and no participants at treatment completion (Figure). PHQ-9 scores declined after 6-months, when injectable drugs–if prescribed–were discontinued. Though not significant, PHQ-9 scores were higher throughout treatment among participants not prescribed cycloserine than those prescribed cycloserine (Figure 1A). Importantly, PHQ-9 scores were not higher among those prescribed higher cycloserine doses (Figure 1B).

Unadjusted odds of depression were significantly associated with pulmonary disease, underweight, alcohol use, social support, injectable MDR-TB drugs (OR:2.71, 95% CI:1.66–4.42), and shorter cycloserine treatment (monthly OR:0.91, 95% CI:0.86–0.95). Peripheral neuropathy was associated with a non-significant increase in depression (OR:1.78, 95% CI:0.98–3.23). Importantly, current cycloserine treatment and dose were not associated with increased odds of depression. Adjusted odds of depression were associated with weight and social support, but not with current cycloserine use (aOR:0.85, 95% CI:0.48–1.51), while longer cycloserine treatment reduced odds of depression (monthly aOR:0.95, 95% CI:0.90–1.00).

This longitudinal cohort study had several important findings. While depression was common, odds of moderate, moderately severe, and severe depression were not significantly increased by prescription of cycloserine, cycloserine dose, weight-adjusted dose, or dosing frequency. Underweight, social support, alcohol use, and prescription of injectable tuberculosis drugs were associated with depression, and rates of depression were similar to those reported elsewhere for MDR-TB [12-13]. Not surprisingly, neuropathy and unemployment increased depression. PHQ-9 scores declined over time independent of cycloserine prescription. This may reflect the stress of diagnosis and treatment initiation, with improvement as symptoms resolve, treatment is simplified, and injections cease. Importantly, these findings shift blame from cycloserine as the cause of depression in MDR-TB treatment and creates an opportunity for cycloserine dose-intensification.

This observational, single-site study had several limitations. Findings from this young, female-predominant cohort may not be generalizable to older patients, those with comorbidities such as HIV, diabetes complicated by neuropathy, or meningitis with functional impairment, or to

populations with higher rates of tobacco and alcohol use, as reported elsewhere in India [14]. Similarly, changing MDR-TB treatment guidelines may impact the durability of these results as guidelines prioritize shorter, all-oral regimens to avoid injections.

While cycloserine is recommended, data on optimized dosing are lacking, and wide inter-individual pharmacokinetic variability makes cycloserine exposure unpredictable [1-6]. Cycloserine clearance and trough concentrations are associated with clinical neuropathy, but the individual dose has not been consistently associated with the neuropsychiatric side effects studied in this cohort [15]. Until dose-specific outcomes data are available, higher cycloserine doses suggested by modeling studies should be considered [7]. Our data suggest that the challenges of MDR-TB diagnosis and treatment initiation were larger drivers of depression than cycloserine use alone. While clinicians should remain vigilant to the impact of depression on MDR-TB treatment, total doses up to and potentially above 750mg are likely to be reasonably tolerated.

Figure 1. Serial Measurement of Patient Health Questionnaire-9 (PHQ-9) Depression Scores over the Course of Treatment for Multidrug Resistant Tuberculosis

Patient health questionnaire-9 (PHQ-9) scores reported over time during the course of treatment for multidrug resistant tuberculosis. Figure 1a (left) indicates histograms and smoothed regression curves of participants' PHQ-9 scores among those taking cycloserine during the visit (blue) and those not taking cycloserine (red). The right panel indicates smoothed regression curves (lines) and 95% confidence interval ranges (shading) for participants' PHQ-9 scores, stratified by their daily total dose of cycloserine in milligrams per day at each visit. There were no significant differences in PHQ-9 scores by either prescription of cycloserine or cycloserine dose, though participants that did not take cycloserine tended to have higher PHQ-9 scores throughout the course of treatment.

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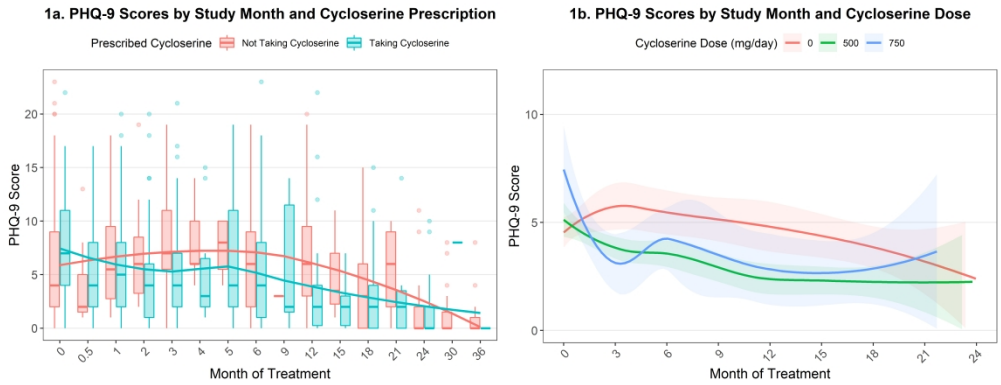

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