Cycloserine did not increase depression incidence or severity at standard dosing for multidrug-resistant tuberculosis

To the Editor:

In 2018 cycloserine was elevated to World Health Organization (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 interindividual 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 modelling studies suggest doses from 250 mg to 750 mg twice daily, with 500 mg twice daily for paucibacillary disease and 750 mg twice daily for cavitary pulmonary disease [7]. Therefore, clinicians must 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 analysed longitudinal cohort data from India.

Outpatients aged ⩾15 years 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 P.D. Hinduja National Hospital and Medical Research Centre (Mumbai, India) and Johns Hopkins University School of Medicine (Baltimore, MD, USA) [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 individualised, susceptibility-guided multidrug therapy for 24 months. This study pre-dates guidelines prioritising 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 250 mg daily, then increased as tolerated to 250 mg twice daily or 250 mg daily plus 500 mg nightly [1]. For simplicity, doses are presented as total mg per day (0 mg, 250 mg, 500 mg or 750 mg per day). Participants were followed for 1 year after treatment completion. At 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 analysed 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 Alcohol Use Disorders Identification Test (AUDIT) score [11] and body mass index (BMI) were calculated at each visit. Underweight was defined as BMI <18.5 kg·m^{-2}. Differences in participant characteristics by depression status was assessed by Chi-squared 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 for depression at each visit by covariate including cycloserine prescription, dose, weight-adjusted dose (mg·kg^{-1} per day) and treatment duration (months). Significant features from univariable models were included in a multivariable model.

Shareable abstract (@ERSpublications)

In a longitudinal cohort of MDR-TB patients receiving individualised, DST-based treatment, neither the inclusion of cycloserine in a multidrug regimen nor the dose used (up to 750 mg daily) significantly increased incidence of depression during treatment https://bit.ly/3GtQmOH

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

Overall, 40 (28%) participants reported prevalent depression (PHQ-9 $\geqslant 10$) at enrolment. Of those without prevalent depression, 38% reported incident depression during treatment; an incidence of 102.6 per 1000 person-years. Incidence increased with AUDIT score (IRR 2.98, 95% 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 500 mg and 750 mg per day, respectively), or higher doses in mg·kg^{-1} per day (IRR 1.03, 95% CI 0.93–1.15). In addition, 78 (55.7%) participants reported treatment-associated peripheral neuropathy. Of note, three participants taking cycloserine 250 g twice daily reported hallucinations (all $\geqslant 9$ months into cycloserine), as did three participants never prescribed cycloserine and four participants previously taking cycloserine (all $\geqslant 2$ 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 1). 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 nonsignificant 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 (a) odds of depression
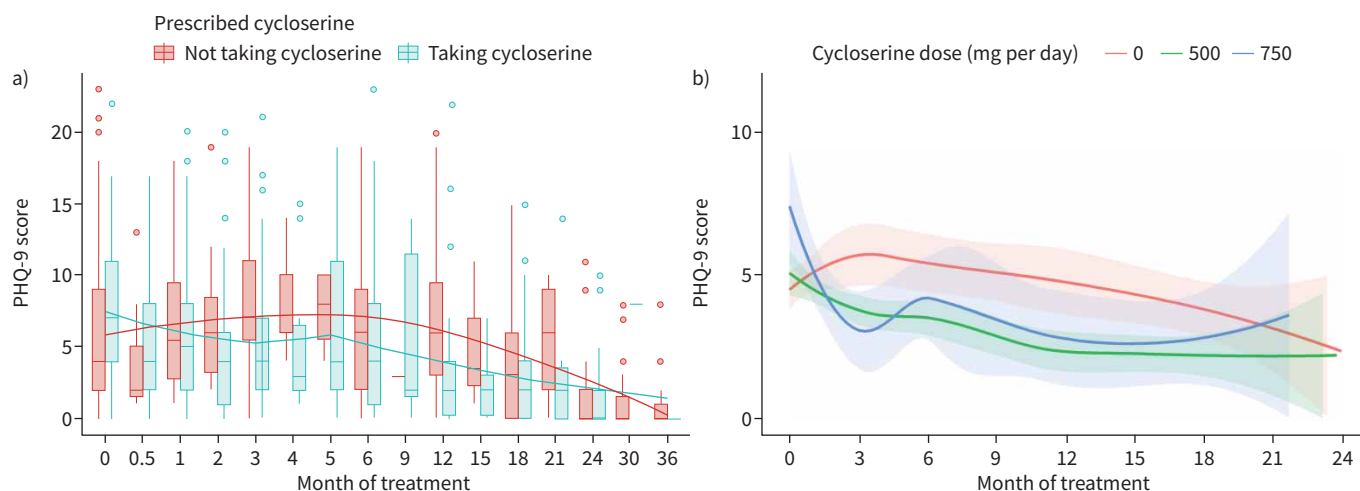

FIGURE 1 Serial measurement of Patient Health Questionnaire (PHQ)-9 depression scores over the course of treatment for multidrug-resistant tuberculosis. a) Histograms and smoothed regression curves of participants' PHQ-9 scores among those taking cycloserine during the visit and those not taking cycloserine. b) Smoothed regression curves (lines) and 95% confidence interval ranges (shading) for participants' PHQ-9 scores, stratified by their daily total dose of cycloserine (mg per day) at each visit. There were no significant differences in PHQ-9 scores by either prescription of cycloserine or cycloserine dose, although participants who did not take cycloserine tended to have higher PHQ-9 scores throughout the course of treatment.

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 generalisable 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 prioritise shorter, all-oral regimens to avoid injections.

While cycloserine is recommended, data on optimised dosing are lacking, and wide interindividual 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 modelling 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 750 mg are likely to be reasonably tolerated.

Jeffrey A. Tornheim ©[1], **Zarir F. Udwadia**[2], **Prerna R. Arora**[3], **Ishita Gajjar**[3], **Nikhil Gupte**[1,4], **Samridhi Sharma**[3], **Megha Karane**[3], **Namrata Sawant**[3], **Nisha Kharat**[3], **Alexander J. Blum**[5], **Shri Vijay Bala Yogendra Shivakumar**[4], **Jai B. Mullerpattan**[2], **Lancelot M. Pinto** ©[2], **Tester F. Ashavaid**[3], **Amita Gupta**[1,6] and **Camilla Rodrigues**[7]

[1]Center for Clinical Global Health Education, Division of Infectious Diseases, Dept of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA. [2]Dept of Respiratory Medicine, P.D. Hinduja National Hospital and MRC, Mumbai, India. [3]Dept of Lab Medicine, P.D. Hinduja National Hospital and MRC, Mumbai, India. [4]Johns Hopkins University – India office (CCGHE), Pune, India. [5]Johns Hopkins University School of Medicine, Baltimore, MD, USA. [6]Dept of International Health, Johns Hopkins Bloomberg School of Public Heath, Baltimore, MD, USA. [7]Dept of Microbiology, P.D. Hinduja National Hospital and MRC, Mumbai, India.

Corresponding author: Zarir F. Udwadia (zfu@hindujahospital.com)

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