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Mental health interventions for rifampicin-resistant tuberculosis patients with alcohol use disorders, Zhytomyr, Ukraine

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Abstract

Introduction: Despite concerted efforts, Ukraine is challenged by increasing rates of multidrug and rifampicin-resistant tuberculosis (MDR/RR-TB) comorbid with alcohol use disorder (AUD). This study describes a cohort of RR-TB patients with high alcohol consumption treated in MSF Zhytomyr Project, Ukraine.

Methodology: We used programmatic data for 73 RR-TB patients screened with the AUD Identification Test March-July 2019 and followed-up for culture conversion/TB treatment outcome till 31 January 2020. We described socio-demographic, behavioral, and clinical characteristics, the level of depressive symptoms, and TB treatment outcomes in three groups: 1) patients with AUD who received mental health interventions (MHI); 2) patients with AUD who did not receive MHI; 3) patients with no AUD. We also found three potential contributors to declining to receive MHI.

Results: Main characteristics of the study groups did not differ substantially. Those receiving MHI (mean: nine sessions) were rated for alcohol consumption as 'hazardous '(41%), 'harmful '(43%) and 'dependence '(36%) and had higher depression scores versus the second (p=0.009) and third (p=0.095) groups at baseline. Depressive symptoms declined at 9-month follow-up for all patients. Culture conversion was seen at 77%, 73%, and 83% for each group respectively. We also found three reasons for declining from MHI.

Conclusions: We detected little differences across the groups. However, our study cohort demonstrated substantially higher adherence rates, culture conversion and reduction of depressive symptoms than reported globally. We recommend further research on the effectiveness of MHI in changing the drinking habits, quality of life and/or TB treatment outcomes of patients with AUD.

Key words: Tuberculosis; alcohol use disorder; mental health intervention; SORT IT.

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Introduction

Tuberculosis (TB) control is complicated by a high-rate of Alcohol Use Disorders (AUD), which is a risk factor associated with develop multidrug-resistant (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) [1]. Systematic reviews with meta-analyses conducted in 2018 and 2019 showed that MDR/XDR-TB patients who had AUD were at higher risk of unsuccessful treatment outcomes (risk ratio 1.45; 95% confidence interval 1.21-1.74) [2]. AUD is associated with an increased risk of concomitant physical and mental health disorders, including gastrointestinal disorders, liver disease, neurological and cardiovascular diseases, as well as depression and/or anxiety [3,4]. MDR/XDR-TB patients having these comorbidities, in addition to psychosocial and economic challenges, are subject to decreased adherence to treatment, followed by high rates of treatment failure and loss to follow up [5-8].

Ukraine is among those countries with a high burden of MDR/RR-TB as defined by World Health Organization (WHO) (2016–2020) and among five countries that reported the largest numbers of XDR-TB cases in 2019 [9]. This status is reflected in high rates of disease TB incidence (29/100,000) and death (9.4/100,000) [9]. The problem of TB control and

management in Ukraine has been exacerbated by high levels of alcohol consumption: 13.8 liters of pure alcohol per capita (>15 years old) [10]. Ukraine ranks second in the world in the number of years lost due to disability or premature death attributable to alcohol consumption (Disability-Adjusted Life Year – DALY) and in the number of years Ukrainians live with AUD (Years Lost due to Disabilities – YLD). The country is in ninth place in the world for mortality from alcohol consumption [11]. At the same time, the level of specialized assistance and access to AUD treatment in Ukraine remains at a low level [12]. International practice shows that brief behavioral interventions addressing AUD combined with pharmacotherapy (Table 1) can be effective in reducing alcohol use in dangerous and harmful drinkers and may improve patients' adherence to TB treatment and therefore result in more favorable TB treatment outcomes [13 - 15].

Zhytomyr region of Ukraine is an area of high RR-TB prevalence (21% among all cases of TB) and related problems of AUD (47% among RR-TB cohort of 2019) [16,17]. Médecins Sans Frontières (MSF), in partnership with the Public Health Center and Zhytomyr Regional Authority, implemented a pilot project to strengthen RR-TB care and treatment supplemented with a comprehensive psychosocial support package for all RR-TB patients. In addition to the medications, the package of psychosocial service includes: psychoeducational sessions for patients and their families about TB, comorbidities and stigma, individual and group sessions, social support in referrals to other local organization, help with administrative issues, provision of food and solid fuel in winter time, etc. At the time of the project's opening, there were no systemic actions aimed at countering harmful alcohol use in the system providing TB care. Therefore, MSF addressed the need for specialized services for patients with AUD by developing a support package, based on a biopsychosocial model of AUD [18]. The psychological part included motivational interviewing (MI) and cognitive behavioral therapy (CBT) used in treating AUD [19,20]. Biological interventions implied the use of pharmacotherapy. The social part of the assistance consisted in the involvement of families, communities, and organizations providing assistance to those who suffer from AUD [21].

This study aimed to describe the clinical and socio-demographic characteristics, depression scores, and TB treatment outcomes of patients in the Zhytomyr Project Ukraine, from March 2019 to July 2019. Further, it describes patients with AUD who accepted and refused

Table 1. Sociodemographic, behavioral, and clinical characteristics of RR-TB patients with AUD in Zhytomyr project, Ukraine, March 2019 – July 2019.

Characteristics		MHI offered patients				Non-AUD	
		Received N = 22		Not received N = 11		N = 40	
		N	(%)	N	(%)	N	(%)
Age, *mean (SD)*		*41.6*	*(10.1)*	*46.1*	*(10.1)*	*42.6*	*(12.7)*
Gender male		17	(77)	10	(91)	27	(68)
Residency urban		10	(46)	4	(36)	20	(50)
Employed	yes	1	(5)	3	(27)	8	(20)
	no	12	(55)	6	(55)	16	(40)
	other (retired, students, etc.)	9	(41)	2	(18)	16	(40)
Tobacco users		17	(77)	8	(73)	22	(55)
HIV-positive		5	(23)	0	(0)	10	(25)
Hepatitis C	yes	5	(23)	0	(0)	29	(73)
	no	16	(73)	9	(82)	6	(15)
	not recorded	1	(4)	2	(18)	5	(12)
Diabetes	yes	0	(0)	1	(9)	4	(10)
	no	19	(86)	8	(73)	29	(73)
	not recorded	3	(14)	2	(18)	7	(17)
RR-TB treatment in months, *mean (SD)*		*7.4*	*(1.2)*	*7.7*	*(1.0)*	*7.6*	*(1.1)*
TB category	new	9	(41)	5	(46)	25	(63)
	re-treated	13	(59)	6	(55)	15	(37)
Sputum smear	negative	1	(5)	1	(9)	4	(10)
	positive	21	(95)	10	(91)	36	(90)
AUDIT score	minimal		N/A			40	(100)
	hazardous use	9	(41)	8	(73)		
	harmful use	5	(23)	2	(18)	N/A	
	dependence	8	(36)	1	(9)		

AUD: alcohol use disorder; AUDIT: alcohol use disorder identification test; HIV: human immunodeficiency virus; MHI: mental health intervention; SD: standard deviation.

mental health interventions with an exploration of the reasons why individuals declined mental health interventions.

Methodology

Study Design

This is a descriptive study nested as part of the operational research entitled: "Treatment of Rifampin-Resistant Tuberculosis with an All-Oral Regimen Containing New Drugs in Zhytomyr, Ukraine: An Uncontrolled, Longitudinal Quasi-Experimental Study", approved by both the MSF Ethics Review Board (ERB) and the Medical Ethics Committee of the Yanovsky National Institute of Phthisiology and Pulmonology of the National Academy of Medical Sciences of Ukraine" (Yanovsky TB Institute).

Setting

Ukraine is one of the former Soviet Union republics located in the eastern part of Europe with a population of 42.3 million. The capital of Ukraine is Kyiv with close to three million people. The annual average income is 1,700 USD, and it is recognized as a low-income country. It is currently in a conflict with Russia over occupation of Crimea and eastern Ukraine. Zhytomyr Region is located in the north of Ukraine and includes an estimated 1.2 million people [16,22].

TB Control in Ukraine

The TB control program in Ukraine is managed by the Public Health Center of the Ministry of Health of Ukraine and follows the WHO strategy of TB care. Currently, there are 89 inpatient and 530 outpatient units in Ukraine, as well as 56 TB convalescent centers. Zhytomyr region has one inpatient unit with 300 hospital beds, 25 outpatient units, and two TB convalescent centers. Uniquely in the Zhytomyr region MSF implemented a short course regimen with all oral drugs for RR-TB treatment using new and repurposed drugs for 9-12 months combined with adherence support. This was approved by the national ERBs of Yanovsky TB Institute and MSF. TB drugs were provided to patients free of charge along with all other diagnostic tests and comorbidity treatments [16].

The Zhytomyr Project

In March 2019, an operational research study using an all-oral short duration regimen has been launched in partnership with the Ministry of Health, Yanovsky TB Institute and TB Dispensary. That study examines the effectiveness, safety, and acceptability of all-oral short duration regimen for RR-TB using either 9-12 months of Bedaquiline-Levofloxacin-Linezolid-Clofazimine-Cycloserine or Bedaquiline-Linezolid-Clofazimine-Delamanid-Cycloserine depending on resistance to fluoroquinolones. The treatment was divided into 2 stages: inpatient and outpatient, depending on where the patient was receiving treatment. All RR-TB patients, regardless of previous history of TB treatment, were invited to participate and asked to give a written consent. RR-TB patients who did not consent or who had prolonged QTcF at baseline or hypersensitivity to any of the drugs in the regimen were excluded. The project intended to enroll 255 patients to achieve statistical significance and ran for 48 months.

For new TB cases in Zhytomyr, the proportion of people who had AUD in 2017 and 2018 was 19.5% and 28.1%, respectively [16]. According to the data collected by MSF, the proportion of patients suffering from RR-TB with concomitant AUD was 51% (including patients on individual treatment regimens) [17].

Study Participants

This study included all RR-TB patients who consented to participate in the above mentioned operational research and were screened using the AUDIT from March 2019 to July 2019. They were followed up until 31 January 2020, the cut-off date set for the analysis of this study.

Study Procedure

In the Zhytomyr Project, the initial assessment was conducted over four consecutive sessions (one per day for four days). After the TB diagnosis was confirmed, all patients were screened for AUD, using the AUDIT and were confirmed by the conducted standardized interviews. For the presence of depressive symptoms, the Patient Health Questionnaire (PHQ-9) was used [23,24]. Data collection was carried out by the project's patient support team that included nurses, social workers, and psychologists. Interpretation of the screening tests was conducted by the psychiatrist.

Patients identified with AUD were offered inclusion into a specialized program adapted from the United States Department of Veterans Affairs Guidelines for the Management of Substance Abuse [25].

All patients with an AUDIT score ≥ 8 were offered MHI. This included psychosocial support, as well as additional targeted psychological interventions: brief interviews, cognitive-behavioral therapy techniques, and the use of pharmacotherapy (naltrexone, disulfiram, acamprosate) according to the algorithm shown in

Figure 1 [26,27]. Those having AUD scores between 8-15 points were offered motivational consultation to keep their alcohol consumption within the safe weekly amount (four standard doses for men and three for women per week in the absence of contraindications for use or the risk of interaction with other drugs). Patients having AUD scores between 15-19 on the AUDIT were offered a consultation with a psychologist with the possibility of a recommendation for a psychiatric consultation. Patients having scores >19 were offered a consultation with the psychiatrist. If the patients declined the interventions, this was recorded in the additional psychological data-forms (psy-database) in a paper.

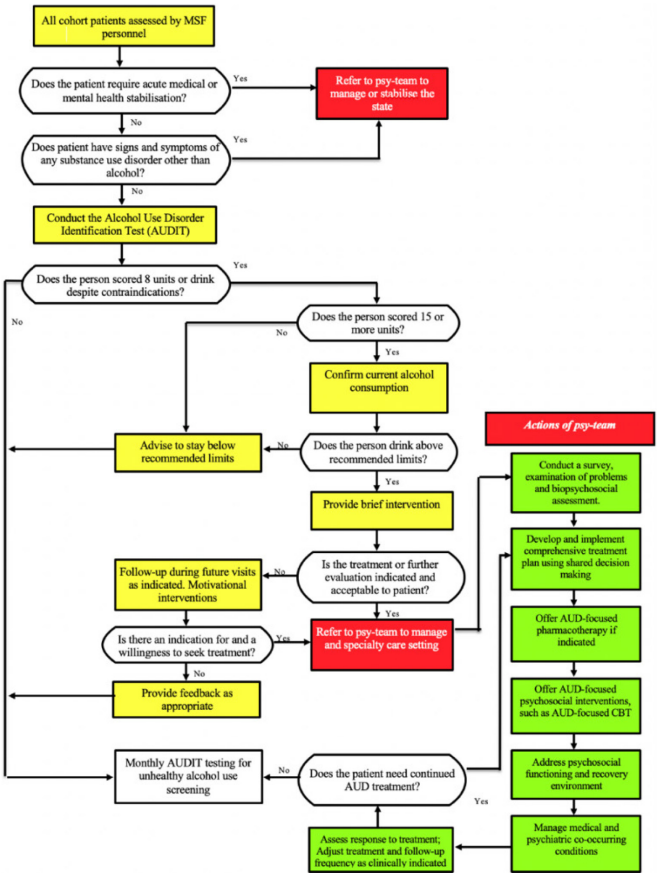
Study instruments

The AUDIT is a WHO screening tool for AUD. It consists of 10 items constructed across three domains: consumption, dependence, and problems. The AUDIT has a maximum score of 40 with the following categories: 1 to 7 – low-risk drinking; 8 to 13 for women and 8-15 for men – hazardous drinking; 13 to 19 for women and 15-19 for men – harmful drinking; and 20 or more, possible alcohol dependence (Table 1). It is one of the most accurate alcohol screening tests available, rated at 92% sensitivity in detecting hazardous or harmful drinking [23].

We began to use the AUDIT-C as a screening tool to measure the changes in alcohol consumption during treatment, but at the beginning, information was collected irregularly, and correct data collection was started too late, so we could not include this data in our study.

The PHQ-9 is a well validated tool to screen for depressive symptoms [24]. It consists of nine questions with four options for each and scores of 0-3 for each option. A higher score corresponds to a higher level of depressive symptoms. The values were added up and recorded in the patient's medical record with subsequent transfer to electronic databases.

Figure 1. Algorithm of assessment and assistance for tuberculosis patients with alcohol use disorders.



Variables

The variables used in this study were categorical and continuous and included: 1) *sociodemographic characteristics*: age, gender, place of residence (urban/rural), employment; 2) *behavioral characteristics*: smoking; 3) *clinical characteristics:* comorbidities (human immunodeficiency virus [HIV], hepatitis C, diabetes), TB treatment duration, new/retreated, sputum smear (+/-); 4) *psychosocial characteristics*: level of alcohol consumption (AUDIT score), depressive symptoms (PHQ-9 score); and 5) *TB treatment outcome characteristics:* adherence rate, duration of treatment interruptions, and treatment success/nonsuccess.

Analysis and statistics

We conducted a secondary data analysis. Information was retrieved from four project databases and merged into one Excel document (Microsoft Inc., USA). The cleaned data were analyzed using R, version 3.5.2. software [28]. Data were analyzed descriptively using Chi square to compare proportions and T-test to compare means. All statistics 'results were reported within 95% confidence intervals considering the significance level at $p \leq 0.05$.

Based on the AUDIT score, patients were assigned to the four alcohol consumption categories mentioned above. To analyze the data, we divided the respondents into three groups based on the status of mental health interventions received: 'MHI received', 'MHI non-received', and 'non-AUD". We described these three groups of TB patients separately, as well as in total for the sociodemographic, behavioral and clinical

characteristics. We compared the level of patients ' depressive symptoms using the PHQ-9 score at baseline and at three, six and nine months of follow-up, and evaluated the TB treatment adherence and treatment success rates. For those patients who completed TB treatment by 31 January 2020, final TB treatment outcomes were reported. The TB treatment adherence rate was calculated as a ratio of TB drugs daily dose taken (DDT) by the patient to the daily dose prescribed (DDP) by the physician. The duration of TB treatment interruptions due to drinking were categorized as lasted 'short '(≤ 7 days), 'medium '(8-31 days), and 'long '(32-61 days). In addition, we questioned participants directly and then presented the reasons why patients in 'MHI non-received' group declined the MHIs.

Ethics issues

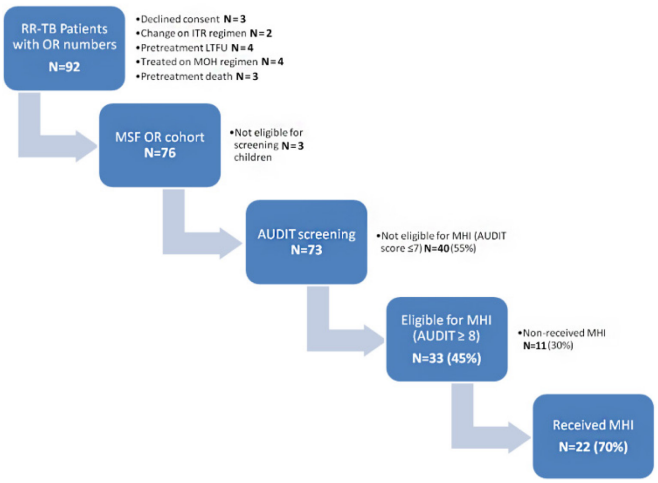
This protocol was approved by the Medical Ethics Committee of Yanovsky TB Institute and by the MSF ERB, Geneva, Switzerland.

Results

Sociodemographic, behavioral, and clinical characteristics

A total of 73 eligible RR-TB patients were obtained from 92 RR-TB patients initially identified from the Zhytomyr Project as shown in Figure 2. Of these 73 screened by the AUDIT, 33 (45%) screened positive and were offered the MHI. Sociodemographic characteristics of the sample are shown in Table 2. The majority of study participants were males with a mean age of 43. About half of patients were residing in urban areas, were unemployed, and had been previously treated for TB. The overwhelming majority were both smokers, and sputum smear-positive at the start of treatment. Sociodemographic, behavioral, and clinical characteristics of TB patients in the MHI intervention groups and group with no AUD were not significantly different.

Figure 2. Cascade of tuberculosis patients in the study cohort.



AUDIT: Alcohol Use Disorder Identification Test; ITR: individualized treatment regimen; LTFU: lost to follow-up; MHI: mental health intervention; MOH: ministry of health; MSF: Médecins Sans Frontières; OR: operational research; RR-TB: rifampicin-resistant tuberculosis.

Table 2. Treatment adherence and treatment outcomes among RR-TB patients with AUD in Zhytomyr project, Ukraine, March 2019 – January 2020.

RR-TB treatment		MHI offered patients						Non-AUD N = 40	
		Received N = 22		Not received N = 11		Total N = 33			
		N	(%)	N	(%)	N	(%)	N	(%)
Adherence rate, *mean (SD)* (DD taken/DD prescribed)		*98.5*	*(1.9)*	*97.9*	*(2.67)*	*98.3*	*(2.2)*	*93.0*	*(11.9)*
RR-TB treatment interruptions	None	7	(32)	4	(36)	11	(33)	16	(40)
	Short (≤7 days)	7	(32)	1	(9)	8	(24)	9	(23)
	Moderate (8-31 days)	4	(18)	2	(18)	6	(18)	6	(15)
	Long (32-61 days)	1	(4)	1	(9)	2	(6)	2	(5)
	Not recorded	3	(14)	3	(27)	6	(18)	7	(17)
Interim Outcome	Culture Conversion	17	(77)	8	(73)	25	(76)	33	(83)
Success	Total	2	(9)	2	(18)	4	(12)	9	(23)
	Treatment completed	2	(9)	2	(18)	4	(12)	9	(23)
	Cured*	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Nonsuccess	Total	2	(9)	3	(27)	5	(15)	4	(10)
	Treatment failed	1	(5)	0	(0)	1	(3)	0	(0)
	Died	1	(5)	3	(27)	4	(12)	3	(8)
	Lost to follow-up	0	(0)	0	(0)	0	(0)	1	(2)
In progress		3	(14)	0	(0)	3	(9)	3	(8)

AUD: alcohol use disorder; DD: daily dose; MHI: mental health intervention; RR-TB: rifampicin-resistant tuberculosis; SD: standard deviation; *At the time of analyses no patient has been declared cured.

TB treatment adherence and outcomes

Adherence to TB treatment regimens was defined as the ratio of the number of drug doses taken (DDT) to the number of drug dose prescribed (DDP). Treatment monitoring modes were presented by direct observation treatment (DOT), video observation treatment (VOT) and self-administered treatment (SAT). No additional monitoring devices were used. For the registration of the drugs taken, a special table was kept by the employees of MOH. Interruptions in treatment occurred due to refusal of treatment and on the recommendation of clinicians due to side effects of drugs.

Patients in all three groups were highly adherent to TB treatment, showing the mean DDT/DDP rate of 98.5% for the MHI group, 97.9% for non-receivers and 93.0% for non-AUD group (Table 2).

Culture conversion by January 2020 was 77% for the MHI group, 73% for non-receivers, and 83% for non-AUD. By the time of this analysis, six patients were still on the TB treatment with no outcome results (Table 2).

Depressive symptoms

Figure 3 shows the changes in mean depression score (PHQ-9) over time. The MHI group had a significantly higher depression score at the outset. The scores decreased at different rates over nine months, but the non-received group dropped the most with 50% mean difference, then the group with no AUD with 40% and the MHI-received group, the least at 11%.

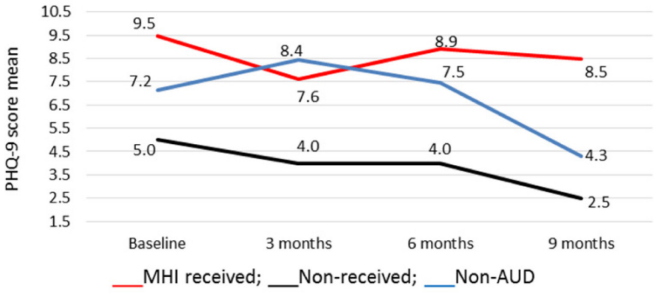
AUD and reasons for MHI refusal

Patients offered MHI had AUDIT scores associated with hazardous use (52%), harmful use (21%) and alcohol dependence (27%). Of the 33 MHI-offered patients, 22 (67%) consented and participated in interventional sessions, receiving on average 9±7.5 sessions (range: 1-32). Eleven (33%) patients declined (non-receivers) the intervention due to three main reasons: 1) denied having problems with alcohol consumption 7/11 (64%); 2) mistrusted specialists (psychologists, psychiatrists) 3/11 (27%); and 3) were not confident on effectiveness of help 1/11 (9%). Among these 11 patients who did not receive MHI, eight patients practiced alcohol hazardous use, two – harmful use, and one had alcohol dependence.

Discussion

The health of our target population was significantly compromised not only by RR-TB and high alcohol consumption, but also by other comorbidities, including HIV, hepatitis C, and diabetes all extremely high rates (76%) of tobacco use.

Figure 3. The trend of depressive symptoms changed from baseline to three, six and nine-month follow-ups for those who received MHI, not received MHI and group without AUD among patients with rifampicin-resistant tuberculosis in Zhytomyr project, Ukraine, March 2019 – January 2020.



AUD: alcohol use disorder; MHI: mental health intervention; PHQ-9: Patient Health Questionnaire.

We found a high level of AUD (45%) compared to the prevalence of this disorder in Ukraine (11.5% for males, 6% for both sexes), as well as compared with the level recorded by the Ministry of Health among patients with TB (28%) [10].

We also noted a large (33%) number of patients who declined the package of help which was offered to change alcohol use. The reasons for refusal to apply for AUD-related MHI fell into three categories. Some patients denied that they had a drinking problem, which often indicates that the patient is not ready for a change in alcohol use behavior. Unwillingness to change may be due to low levels of motivation, which in turn may be due to low self-esteem, lack of alternative coping strategies to deal with distress, strong cravings, or the destructive effect of alcohol on the prefrontal cortex [29,30]. The second recorded reason was mistrust of specialists (psychologists, psychiatrists), possibly related to stigmatization, which is quite common in post-Soviet countries. The third reason cited by one patient was a belief that nothing would help him, likely related to low self-esteem and failed attempts to quit drinking in the past. Some studies have shown a relationship between self-esteem, effectiveness and helplessness in AUD and depression [31].

This study found that the adherence to RR-TB regimens was exceptionally high in all groups and that, overall, the frequency of treatment interruptions and their duration were lower than in similar studies conducted elsewhere [32]. Because we did not see a

significant difference in adherence to treatment between groups, it may be assumed that this is a consequence of improved treatment regimens (short regimens, no injections, short intensive phase, safety drugs, psychosocial support, including MHI, etc.).

This study showed good interim outcomes (culture conversion) from 77 to 83% in all groups and although at the time of writing the study we could not talk about the final results of treatment; culture conversion was a good predictor of the success of TB therapy [33]. It is assumed that this is a consequence of the introduction of more effective medications. Based on other studies, a 1.5-2-fold worsening of treatment outcomes was expected in the group of patients with AUD based on other studies, we did not note this in our study [34,35]. Failing to detect the differences in our results is likely explained by the small sample size and its lack of representativeness.

The initial average level of depressive symptoms, as noted in the PHQ-9 score, in all groups was 7.6 points, and the number of patients who noted depressive symptoms of moderate severity and higher was 23 (32%), which is significantly higher than the average in the population (4.6%) and in Ukraine (6.3%) [36]. Note that this included both patients who did not consume alcoholic beverages in risky quantities and patients who suffered from AUD. We know that withdrawal symptoms can cause depressive symptoms. Therefore, those with a large number of depressive symptoms may be experiencing withdrawal [37]. According to international data, people with high alcohol consumption are more vulnerable to mental disorders, and depressive disorders may be a primary cause in relation to alcohol use [38,39]. It can be assumed that the presence of AUD may be comorbid with depression and be a manifestation of self-medication [40].

It was important for us to assess the trend of changes in depressive symptoms, because a reduction in adherence to treatment is especially characteristic of patients with depression, due to the fact that the motivational sphere changes in humans [41,42]. This study showed a decrease in depressive symptoms in all three study groups with a significant decrease by the nineth month of treatment. This could be due to many factors: psychological and psychopharmacological support, a general improvement in the quality of life, a decrease in the amount of alcohol consumed, and the effect of Linezolid, as a mild monoamine oxidase inhibitor, or others as described in the literature [43]. It is not possible to differentiate and identify the cause-and-effect relationship to determine which would require additional research in this direction.

Study strengths

Due to the research infrastructure put in place for the larger study, the resources available for these interventions were exceptional for this context. Patients received individual treatment care, and follow-up was recorded carefully.

Study limitations

The use of all-oral short duration regimen was implemented in one region only and does not represent the situation at the country level. A limited sample resulted in the inability to make meaningful comparisons among groups. The study relied on patients 'subjective assessment of their alcohol status and may not represent an objective level of consumption. Moreover, the reasons cited as to why non-receivers did not agree to receive MHI were not collected deliberately as part of a qualitative research. It was rather in the venue of a health worker-patient consultation, aiming at what strategies the program could implement to improve patients 'acceptance of the intervention. We were also unable to explore the family/social status of study participants to better understand their backgrounds, as these factors significantly affect health among TB patients [44]. Clearly, though, this study suggests a more detailed analysis with larger samples sizes may lead to a better understanding of the potential improvements in TB treatment outcomes from a concurrent care program for those with AUD as well as TB.

Conclusions

We detected little differences across the three groups. However, our study cohort demonstrated substantially higher adherence rates, culture conversion and reduction of depressive symptoms than reported globally. We recommend further research on the effectiveness of MHI in changing the drinking habits, quality of life and/or TB treatment outcomes of patients with AUD.

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Authors 'contributions

VP: Conception of the study; designing the protocol; data collection, analysis and interpretation; writing first draft of the paper; critically reviewing the paper and giving approval for the final version to be published. NT, AR: designing the protocol; data analysis and interpretation; writing first draft of the paper; critically reviewing the paper and giving approval for the final version to be published. MD, LC, CY, KM, PI, DD, OS, MP, NL: designing the protocol; data collection; critically reviewing the paper and giving approval for the final version to be published.

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