Nonadherence to Antituberculosis Medications: The Impact of Stigma and Depressive Symptoms

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Abstract. Medication nonadherence is common among tuberculosis (TB) patients in China and is of great concern. Herein, we determined the incidence of nonadherence in TB patients in central China and the impact of stigma and depressive symptoms on adherence; these issues are relatively unexplored. A cross-sectional survey was performed, and 1,342 TB patients were recruited from TB dispensaries in three counties in Hubei province using a multistage sampling method. The patients completed structured questionnaires that addressed medication adherence, TB-related stigma, and depressive symptoms. The independent effects of stigma and depressive symptoms on adherence were determined via multinomial logistic regression analysis. The mean medication adherence score was 6.03 ± 1.99 . The percentage of TB patients with high, medium, and low medication adherence was 32.12%, 34.58%, and 33.31%, respectively. The impact of stigma and depressive symptoms on medication adherence was significant. TB patients with medium (odds ratios [OR]: 1.54, 95% confidence interval [CI]: 1.08–2.21) or high (OR: 5.32, 95% CI: 3.34–8.46) stigma or patients with mild (OR: 1.92, 95% CI: 1.34–2.75) or severe (OR: 3.67, 95% CI: 2.04–6.61) depressive symptoms showed a higher likelihood of having low adherence than those with low stigma or without depressive symptoms. TB-related stigma and depressive symptoms were common among TB patients in China, as was nonadherence, and independently associated with their adherence behavior. Social and psychological interventions that combat stigmatization and depression in TB patients should be adopted and optimized to improve medication adherence.

INTRODUCTION

Tuberculosis (TB) is a major public health problem throughout the world, and nonadherence to anti-TB treatments impedes global TB control. According to the World Health Organization, China had the third largest TB burden in 2015, accounting for 9% of all TB cases.¹ In China, more than 40% of TB patients do not comply adequately with anti-TB treatments.^{2,3} This high level of nonadherence is of great concern, given the serious consequences of treatment failure and the transmissibility and drug resistance of the disease. Interventions that improve medication adherence in TB patients are, therefore, urgently needed.

Determining the complex reasons for nonadherence and identifying those that are modifiable are critical to explore effective interventions. Many studies have identified the socio-demographic and clinical characteristics and support systems associated with medication adherence in TB patients.^{4–6} In fact, patients' mental health may also affect their medication adherence. For example, research has shown that depression is associated with poor adherence in patients with chronic illness (e.g., hypertension and diabetes),⁷ potentially leading to worse medical outcomes. In addition, some studies have explored the association between social stigma and adherence in patients with infectious diseases. For instance, social stigma has been shown to impede adherence in patients with infectious diseases.⁸ Whether social stigma and depression also affect adherence in TB patients remain to be established.

TB is an infectious disease that severely and negatively impacts the mental health of the patient. Previous studies have illustrated that depressive symptoms were common among TB patients.^{9,10} In addition, TB has been and still is

often considered a “dirty disease,” and social stigma is a common problem met by TB patients.^{11,12} Herein, we test the hypothesis that TB-related stigma and depressive symptoms affect medication adherence in TB patients in central China. The incidence of nonadherence in this population was also determined.

METHODS

Ethics statement. The study protocol and questionnaire were reviewed and approved by the ethics committee of Huazhong University of Science and Technology, Wuhan, China. Informed consent was obtained from all study participants.

Participants and sampling. A cross-sectional survey was conducted between October 1, 2013 and March 31, 2014 in Hubei province in central China. Because of the gap in the level of economic development across counties in Hubei province, government funds invested in healthcare system varied in the county-level, which result in an unbalanced healthcare system. To ensure that the participants were recruited from counties with different levels of economic development, study populations were identified by using a multistage sampling method. First, counties across Hubei province were divided into three categories (upper, middle, and lower) according to their economic development status (i.e., the gross domestic product of each county in 2012), and a county was randomly selected from each category. Second, TB patients who visited TB dispensaries at the study sites in the selected counties were recruited. The participants of this study met the following three criteria: 1) diagnosis of TB according to national TB program guidelines, 2) without psychosis, and 3) willingness to participate in the study. During the study period, 1,430 individuals were enrolled and completed a structured self-administered anonymous questionnaire. Because of large amounts of missing data, 88 individuals were excluded, resulting in a sample size of 1,342 TB patients.

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Measurements. Data were collected by trained medical personnel by using a standard structured anonymous questionnaire. The questionnaire was developed by reviewing the literature and was pretested in a pilot study with 25 TB patients to ensure that the questions were clear and understandable to all participants. The questionnaire had four sections: medication adherence, TB-related stigma, depressive symptoms, and confounding factors potentially associated with medication adherence. These factors included sociodemographic characteristics (sex, age, education, marital status, race, and religious beliefs), history of prior anti-TB treatment, knowledge about TB, family function, and doctor–patient communication.

Medication adherence was measured by using the 8-item Morisky Medication Adherence Scale (MMAS-8), which was developed by Morisky et al. in 2008.¹³ Each item on the MMAS-8 measures a specific medication-taking behavior. Responses are yes/no for each item, with a dichotomous response and a five-point Likert response for the last item. The total MMAS-8 score ranges from 0 to 8, with higher scores indicating higher adherence. Scores of 8, 6 to less than 8, and less than 6 were classified as high, medium, and low adherence, respectively. The MMAS-8 has been widely used in China, with good reliability and validity.¹⁴ In our previous study, it had high internal consistency (Cronbach's $\alpha = 0.79$).¹⁵

The presence and severity of depressive symptoms were assessed by using the Center for Epidemiologic Studies Depression (CES-D) scale, which consists of 20 items and measures depressive symptoms across four domains: depressed affect, positive affect, somatic complaints/activity inhibition, and interpersonal difficulties. A cut-off point of 15 was set, and patients with scores of 16 and above were considered as having probable depression. A score of 16–25 and scores above 26 represented mild to moderate depression and severe depression, respectively. The CES-D has been used extensively in China and is very reliable (Cronbach's $\alpha = 0.86$).

Stigma was measured by using the TB-related Stigma Scale, which was developed by our colleagues and has shown excellent validity and good internal consistency (Cronbach's $\alpha = 0.88$).¹⁶ The scale consists of nine items, and each item is scored on a four-point Likert scale, ranging from “strongly disagree” to “strongly agree” coded with values from 0 to 3. The stigma index ranges from 0 to 27, with higher scores indicating a higher level of TB-related stigma.

Knowledge about TB was measured via six questions; scores range from 0 to 8, with a higher score indicating greater knowledge. Family function was measured by using the family Adaptability, Partnership, Growth, Affection, and Resolve index developed by Smilkstein in 1978.¹⁷ The index assesses the degree to which respondents are satisfied with the social support received from their family members. It has been widely used in China, with good reliability and validity¹⁸ and had a high internal consistency in our previous study (Cronbach's $\alpha = 0.86$).¹⁵

Doctor–patient communication was measured via a four-item scale: 1) satisfaction with the doctor's attitude when providing service, 2) extent to which the doctor explained the illness, 3) extent to which the doctor explained the medication doses and schedules, and 4) extent to which the doctor explained the adverse reactions to anti-TB agents. Patients were asked to rate their level of satisfaction from 1 to 3. The total score ranged from 4 to 12, with higher scores reflecting

TABLE 1
Participants' characteristics (N = 1,342)

Variables	n	%
Age (years)	47.72 ± 17.06	
Males	905	67.44%
Education		
Primary or less	574	42.77%
Secondary	540	40.24%
High school or higher (above)	228	16.99%
Marital status		
Married	1,030	78.69%
Single	224	17.11%
Separated/Divorced/Widowed	55	4.20%
Race		
Han	945	71.00%
Ethnic minorities	386	29.00%
Having religious beliefs	144	11.11%
Having prior anti-TB treatment	168	12.52%
Knowledge about TB	4.86 ± 2.02	
Family APGAR index	7.57 ± 2.39	
Doctor–patient communication	11.33 ± 1.25	
Stigma	9.33 ± 4.25	
Depressive symptom	15.85 ± 8.19	

APGAR = adaptability, partnership, growth, affection, and resolve; TB = tuberculosis.

better doctor–patient communication. The doctor–patient communication scale had a high internal consistency in our study (Cronbach's $\alpha = 0.79$).

Statistical analysis. Statistical procedures were performed by using Statistical Analysis System 9.4 software for Windows (SAS Institute Inc., Cary, NC). Descriptive analyses of the baseline characteristics of the patients were first performed. The patients were then divided into three groups for all remaining analyses based on their MMAS-8 scores. One-way analysis of variance and the Tukey's Studentized range test were conducted to compare stigma and depressive symptoms scores between the high, medium, and low adherence groups. As the final step, the independent effects of stigma and depressive symptoms on adherence (medium or low, with high adherence as the reference category) were estimated via multinomial logistic regression analysis. All comparisons were two-tailed. The significance threshold was set at $P = 0.05$.

RESULTS

Table 1 presents the baseline characteristics of the TB patients in our study. Patient age ranged from 15 to 88 years (mean: 47.72 ± 17.06 years). The mean MMAS-8 score was 6.03 ± 1.99. The proportion of patients with high, medium, and low medication adherence was 32.12%, 34.58%, and 33.31%, respectively. Analysis of variance indicated that there are differences in stigma and depressive symptoms among TB patients with different medication adherence (Table 2). Patients in the low adherence group experienced

TABLE 2
Stigma and depressive symptoms among tuberculosis patients' with different medication adherence

Variables	Medication adherence			P
	Low (N = 447)	Medium (N = 464)	High (N = 431)	
Stigma	11.07 ± 3.80 ^a	8.65 ± 4.25 ^b	8.26 ± 4.16 ^b	< 0.0001
Depressive symptom	19.87 ± 8.02 ^a	14.60 ± 7.44 ^b	13.03 ± 7.51 ^c	< 0.0001

Different uppercase letters demonstrate significant difference by the Tukey's Studentized range test ($P < 0.05$).

TABLE 3
Multinomial logistic regression† of factors associated with medication adherence in tuberculosis (TB) patients

Variable	Medication adherence		
	High	Medium	Low
Stigma‡ (ref: stigma ≤ 9)			
Medium (stigma: 10–12)	1.00	0.82 (0.59–1.13)	1.54 (1.08–2.21)*
High (stigma ≥ 13)	1.00	1.34 (0.84–2.13)	5.32 (3.34–8.46)***
Depressive symptoms (ref: depressive symptoms ≤ 15)			
Mild (depressive symptoms: 16–25)	1.00	1.26 (0.91–1.74)	1.92 (1.34–2.75)**
Severe (depressive symptoms ≥ 26)	1.00	1.00 (0.53–1.90)	3.67 (2.04–6.61)***

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.0001$.

† Adjusting for age, sex, educational level, marital status, race, religion beliefs, and prior anti-TB treatment.

‡ Median value and P75 were used as cut off point.

significantly more stigma than patients in the other two groups, which experienced similar amounts of stigma (Tukey's Studentized test) (Table 2). Patients with low adherence were significantly more depressed than patients with medium adherence, and patients with medium adherence were significantly more depressed than patients with high adherence.

Multinomial logistic regression analysis indicated that TB patients with high stigma scores were more likely to have low rather than high adherence (odds ratio [OR]: 5.32; 95% confidence interval [CI]: 3.34–8.46) compared with those with stigma scores less than 10. Patients with severe (OR: 3.67; 95% CI: 2.04–6.61) or mild (OR: 1.92; 95% CI: 1.34–2.75) depressive symptoms were more likely to have low rather than high adherence compared with those without depressive symptoms (Table 3).

DISCUSSION

In this study, the proportion of TB patients with poor medication adherence in Hubei province was 33.31%, and the mean MMAS-8 score was 6.03 ± 1.99 . These values are similar to those in other studies of Chinese populations. In four counties in Hunan province, the mean MMAS-8 score was 6.6 ± 1.4 , and 28.1% of TB patients had poor medication adherence.¹⁹ In six counties in Shandong Province, the mean MMAS-8 score was 6.25 ± 1.89 , and 29.7% of TB patients had poor medication adherence.²⁰

Meulemans et al.²¹ found that stigmatization negatively affected medication adherence in TB patients. In agreement, the adjusted ORs in our study indicate that stigma is an independent risk factor for nonadherence. TB patients with high stigma scores were 5.32 times more likely to have low adherence versus those with low stigma scores. Many studies have addressed the mechanism whereby stigma affects medication adherence.^{22,23} Some suggest that stigmatization lowers the self-esteem, self-efficacy, and self-confidence of patients, which in turn lowers their adherence to treatment regimens. Our observations are consistent with this premise. Alternatively, stigmatized TB patients may avoid taking their medications or collecting them from dispensaries to hide their condition from their acquaintances. Although our study did not determine how social stigma affects medical adherence in TB patients, it is clear that reducing its occurrence would improve adherence.

Studies of medication adherence in a variety of contexts (e.g., hypertension, acquired immunodeficiency syndrome, and renal transplantation) identified depression as a risk factor for nonadherence.^{7,24,25} This was confirmed in the present study. Mild and severe depressive symptoms both had detrimental effects on medication adherence. In fact, half of the TB patients in our study experienced depressive symptoms, 34.80% with

mild depressive symptoms and 13.19% with severe depressive symptoms. This high prevalence suggests that psychological interventions would improve adherence to anti-TB medications. Psychological counseling of patients and psychological intervention training of medical practitioners should be mandatory at all TB dispensaries.

The results of this study should be interpreted in light of its potential limitations. Because the MMAS-8 is an indirect adherence measurement, it may be less reliable than direct measures owing to imperfect patient recall, underreported instances of nonadherence, and memory bias issues.²⁶ However, the MMAS-8 is widely used to measure medication adherence, and its reliability and validity in TB patients in China has been established.¹⁵

The impact of stigma and depressive symptoms on medication behavior has been studied in patients with chronic or infectious diseases, but rarely in patients with TB. To our knowledge, we are the first to report on this issue in TB patients in China. Our results provide a valid rationale for improving social and psychological intervention strategies for TB control in China.

In conclusion, medication nonadherence was common among TB patients in China, and the impact of stigma and depressive symptoms on nonadherence was significant. Social and psychological interventions that combat stigmatization and depressive symptoms in TB patients should be adopted and optimized to improve medication adherence.

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