

Original Research Article

Effect of psychiatric co-morbidity on adherence to anti tubercular treatment: a cross sectional study from North India

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ABSTRACT

Background: Study explores relationship between depressive disorder and adherence to DOTS (Directly Observed Therapy Short Course) and whether treatment of depressive disorder according to severity of depressive disorder should be an option to improve adherence to DOTS.

Methods: Study included 182 newly diagnosed adult cases of tuberculosis who were on anti-tuberculosis therapy (ATT) as per program guidelines and were in third month under DOTS category I and category II therapy. Patients were screened for depressive and anxiety disorder using PHQ-9 and GAD-7. Modified ACTG baseline questionnaire was used to collect data about adherence and reasons for partial adherence.

Results: Overall prevalence of depressive disorder amongst participants was found to be 37.9% and that of partial adherence (missed two or more than two doses) was 12.1%. Partial adherence was mostly seen in the first month, followed by third and second month of DOTS. Twenty-two percent patients with depressive disorder were partially adherent to ATT. Odds ratio suggests higher risk being partially adherent to ATT were greater in the participants who had depressive disorder.

Conclusions: This study highlights the benefit of screening patients while diagnosing tuberculosis patients for depressive disorder, to improve disease outcome and reduce likelihood of MDR-TB.

Keywords: Adherence, Anxiety, Depressive Disorder, Depression, Prevalence, Tuberculosis

INTRODUCTION

Tuberculosis (TB) remained a sporadic disease for centuries. However, with the development of civilization reports of TB became numerous. Today, TB is concentrated in low- and middle-income countries. Of the nine million people who developed TB in 2013, 56% were from the South East Asia and Western Pacific regions.¹ Five countries of BRICS (Brazil, Russian Federation, India, China and South Africa) account for 45% of all incident cases of TB and 40% of all TB related mortality.² India has the highest burden of tuberculosis in

the world, accounting for approximately 21% of the global incidence.³

Pulmonary tuberculosis spreads by interpersonal contact through aerosolization of droplet nuclei which contain viable bacteria.⁴ Each case of TB, if untreated, can infect on an average 10-15 people every year. Therefore, TB control programs emphasize early case detection and treatment. Directly observed treatment short course (DOTS) has been implemented to improve adherence to tuberculosis treatment. Treatment adherence is influenced by socio-economic, socio-cultural, perceived health benefits, stigma and subjective experience with the

illness.⁵ The RNTCP DOTS delivery guidelines on alternate days was promoting relapse and generated drug resistant strains in TB patient, therefore the RNTCP moved to daily dose regimen a few years back. In our study we consider patient as non-adherent if they miss two or more doses and are at higher risk of treatment failure/relapse and may develop drug resistant TB. The idea was to understand how change in drug delivery on a continuous basis along with focus on psychological stress effects the patients on DOTS, even if the patient is missing a single dose from the weekly regimen. We understand the definition for non-adherence is different than what was considered by RNTCP, but the idea is to bring a change in treatment delivery and prevent treatment relapses and failures in the future. The study was ahead of its time and provides supporting evidence to the current drug delivery methods used by RNTCP presently. Anxiety, depression and psychological stress may also play a role in the adherence behaviour.⁶ Several authors have described how psychosocial factors may complicate adherence to drug regimens, and emphasized the importance of attention to mental illnesses to ensure positive treatment outcomes.⁷⁻⁹ We investigated the prevalence of anxiety and depressive disorders in persons having tuberculosis and their association with adherence to tuberculosis treatment in Chandigarh, North India.

METHODS

City of Chandigarh, North India has a population of 10,54,686 and a sex ratio of 818 females per thousand males. The population of the city is covered by 3 tuberculosis units (TU) and 17 Designated Microscopy Centers (DMC) under the RNTCP. Newly diagnosed adult cases of tuberculosis who had been classified for treatment under Category I & II, had completed the first two months of the intensive phase of DOTS and were currently in the third month of DOTS were included in the study. Category I patients are newly diagnosed sputum smear positive or new sputum smear negative pulmonary cases, extra-pulmonary cases and others who did not have any previous history of anti-tuberculosis treatment and category II patients are previously treated smear-positive relapse, smear-positive failure, smear-positive treatment after default. All TB patients under 15 years of age, those in the intensive phase of treatment, patients with diabetes and HIV, patients who had stopped taking DOTS for more than two months, those who had already completed the third month and those who did not give consent were excluded from the study.

Various studies have reported prevalence of depression in newly diagnosed TB patients to vary from 50-82%.¹⁰⁻¹⁴ The prevalence of depression for this study was assumed to be 50%. Vijay S et al in 2010 found that about 78% of TB patients who were adherent to DOTS as per program guidelines had actually missed some of the doses.¹⁵ Assuming that 40% of the patients who are depressed and 20% of people who are not depressed miss doses of

DOTS, a sample size of 182 was estimated to give results with power of 80% and 95% confidence.

During 2012, 2,800 cases of TB were treated under category I and 555 cases under category II in Chandigarh. An average of 234 newly diagnosed TB patients were initiated on DOTS category I and 46 patients on DOTS category II every month. A take all approach was used to take into consideration those who do not give consent for the interview or were defaulters. Out of 217 patients found eligible for the study, 182 gave written consent. Seven had died before completion of 2 months of intensive phase, 14 were out of station and could not be contacted, 5 were transferred out, 2 had defaulted on treatment, medication for 2 was discontinued by physician due to side effects, 4 refused to participate and one did not understand the local language as was from different state.

A semi structured questionnaire based on modified Kuppaswamy scale was used to record the socio demographic details, the AIDS Control Trial Group (ACTG) questionnaire was used to explore factors and reasons for partial adherence, screening for depression was done with Patient Health Questionnaire-9 (PHQ-9) and screening for anxiety was done by using Generalized Anxiety Disorder Assessment-7 (GAD-7).¹⁶⁻¹⁹ Cut of score off 5 or more was taken as presence of anxiety disorder. Data for missed doses of DOTS was recorded from the RNTCP registers with the DOTS centers. The ACTG questionnaire was modified to suit the local patterns of substance abuse, the treatment plan for DOTS in India. Questions on how the patient thought the infection was contracted and questions related to methadone treatment were dropped.

All interviews were conducted by the investigator at the respective centers where the patients were registered for receiving DOTS. Interview of each participant took about 20 minutes. Patients who were diagnosed for depressive disorder and anxiety were referred to Department of Psychiatry, PGIMER, Chandigarh for appropriate management.

Adherence to treatment record was gleaned from the DOTS registers maintained at the centers. Patients were classified as partially adherent if they had missed two or more than two doses during the duration of their treatment.

Data management was done using Epi Info version 7. Frequencies, percentages, arithmetic mean and standard deviation, chi square test and logistic regression were carried out to analyse data. Data is available with the authors upon request.

RESULTS

Out of the 182 study participants, 101 were males (55.5%) and 81 were females (44.5%). The mean age of

study participants was 32.2 years (SD 14.3; range 15-73 years). Forty two (23.1%) of them were regular salary/wage employee, 42 (23.1%) were unpaid family workers, 31(17.03%) were unemployed, 20(10.9%) were nonagricultural laborers, 11 (6.04%) were rentier/pensioners and remaining 8 (4.4%) were self-employed and 28 (15.4%) had other occupations. Table 1 shows the distribution of study population according to age group, religion, gender, marital status and socioeconomic status.

The overall prevalence of depressive disorder amongst study participants was 37.9% (95% CI 30.8% - 45.4%). According to PHQ 9, the mean score of depressive disorder was 5.6 (SD 4.2) and median score was 4.00 (Range 0-27). Thirty one (17.0%) were diagnosed as mild depressive disorder, twenty four (13.2%) as moderate and fourteen (7.7%) were diagnosed as severe depressive disorder.

Table 1: Socio-demographic characteristics of study participants (n=182).

Variables	N	%
Age group (years)		
15-35	127	69.8
36-55	37	20.3
56-75	18	9.9
Religion		
Hindu	154	84.6
Sikh	12	6.6
Muslim	14	7.7
Christian	1	0.5
Buddhist	1	0.5
Gender		
Male	101	55.5
Female	81	44.5
Marital status		
Currently married	102	56.0
Single	72	39.6
Divorced/ separated	2	1.1
Widowed	6	3.3
Socioeconomic status of family		
Upper	34	18.7
Middle	34	18.7
Lower	114	62.6

Prevalence of anxiety disorder amongst the participants was 12.6% (95% CI 8.2-18.4). None of the socio-demographic variables was significant associated with depressive disorder or anxiety (Table 2).

Twenty participants had both anxiety and depressive disorder, 49 were diagnosed with depressive disorder and did not have anxiety disorder. Whereas 110 participants were neither depressive disorder nor anxiety disorder, and only 3 participants had anxiety disorder that were not diagnosed with depressive disorder.

Table 2: Association of socio- demographic characteristics with depressive and anxiety disorder among TB patients.

Variable(n)	N	Depressive disorder N (%)	Anxiety disorder N (%)
Age Group (years)			
15-35	127	46 (36.2)	18 (14.2)
36-55	37	16 (43.2)	3 (8.1)
56-75	18	7 (38.9)	2 (1.1)
Religion			
Hindu	153	56 (36.6)	20 (13.1)
Non-hindu*	29	13 (44.8)	3 (10.3)
Gender			
Female	81	33 (40.7)	11 (11.9)
Male	101	36 (35.6)	12 (13.6)
Marital status			
Married	102	38 (37.2)	15 (14.7)
Single	80	31 (38.7)	8 (10.0)
Socioeconomic Status			
Upper	34	12 (35.3)	2 (5.9)
Middle	34	15 (44.1)	5 (14.7)
Lower	114	42 (36.8)	16 (14.0)
Employment status of the patient			
Employed***	73	22 (30.1)	9 (12.3)
Unemployed****	81	36 (44.4)	12 (14.8)
Student	28	11 (39.3)	2 (7.1)

*Non-Hindu category comprise of Sikh, Muslim, Christian, Buddhist and Jain religions.

** Includes divorced, separated and widowed. *** Includes self-employed.

****Includes retired population

The side effects perceived by the study participants (n=111, 61%) were nausea and vomiting (25.2%), weakness (11.7%), anxiety (8.1%), giddiness (8.1%), flushing of skin (7.2%), loss of appetite (5.4%), rashes (5.4%), acidity (4.5%), breathlessness (3.6%), fever (3.6%), itching (3.6%), headache (2.7%), dizziness (1.8%), pain in the stomach (1.8%), tingling sensation in the extremities (1.8%), confusion (0.9%), hemoptysis (0.9%), difficulty in hearing (0.9%), irritability (0.9%), pain in the extremities (0.9%) and swelling of feet (0.9%). If the participant was experiencing side effects to ATT, the odds of having depressive disorder were significantly higher as compared to the ones who did not experience any side effects to the treatment (OR 2.8; 95% CI 1.4-5.4).

The only treatment factor found to be significantly associated with depressive disorder and anxiety was experiencing side effects due to anti-tuberculosis therapy (Table 3).

Majority (57%) of the participants had not missed a single dose, 31% had missed a single dose and 12.1% had missed two or more doses of ATT. However, all of them were classified as adherent as per revised national

tuberculosis control program definitions. Partial adherence was found to be 12.1% (n=22) with most doses missed in the first month and third month followed by second month. Most doses were missed on Mondays. Major reason for partial adherence was sudden declaration of holiday where dose could not be given in

advance (n=45), dose vomited out immediately (n=25), participant being away from home (n=5). Other factors included falling sick (n=5), forgetting to take medicine (n=3), delay in shifting treatment box for patients who had moved from one place to other (n=2) having side effects or being depressed or overwhelmed.

Table 3: Association of treatment factors with depression and anxiety.

Variable (n)	N	Depressed participants	P value	Anxious participants	P value
Treatment					
Category I	152	53 (34.7)	0.06	20 (13.2)	0.7
Category II	30	16 (53.3)		3 (10.0)	
Disease classification					
Pulmonary	117	44 (37.6)	0.9	15 (12.8)	0.9
Extra-pulmonary	65	24 (38.5)		8 (12.3)	
Side effects of anti-tubercular therapy					
Yes	111	52 (46.8)	<0.01	19 (17.1)	0.02
No	71	17 (23.9)		4 (5.6)	

Table 4: Logistic regression results for being partially adherent as the outcome variable.

Variables	Odds ratio (95% CI)	Z statistic	P value
Depressive disorder	2.0 (0.8-5.2)	1.5	0.1
Side effects to ATT	6.5 (1.4 -29.2)	2.4	<0.01

None of the socio-demographic variables was found to be significantly associated with partial adherence. Of the treatment related factors, only having experienced treatment side effects was significantly associated with being partially adherent ($\alpha^2 = 9.42$, $p < 0.01$). Being depressed was significantly associated with being partially adherent (OR=2.7; 95% CI =1.1-6.7; $\alpha^2 = 4.8$; $p = < 0.03$). Having anxiety did not show a significant association with partial adherence.

Logistic regression was carried out using being depressed and having treatment side effects as independent variables and being partially adherent as dependent variable. Only having treatment side effects was significantly associated with partial adherence and missing DOTS doses (Table 4).

DISCUSSION

Non adherence to therapy is thought to be the principle obstacle in eliminating tuberculosis.²⁰ Studies indicate that patients non adherent to treatment contribute to prolonged infectiousness, drug resistance, relapse of tuberculosis and death.^{21,22} Literature indicates psychiatric co-morbidity as a factor leading to missing doses.²³ We examined the relationship between being depressed and anxious and missing doses of ATT.

We find that prevalence of depressive disorders and anxiety in adult patients of tuberculosis was 37.9% (95% CI 30.8%-45.4%) and 12.6% (95% CI 8.2-18.4) respectively. There was significant association of being

depressed or anxious with having side effects due to ATT.

About 12% of persons on ATT missed two or more doses, though they fulfilled the criteria for being adherent to treatment according to RNTCP treatment guidelines. There was statistically higher likelihood of missing doses if the patient experienced side effects or was depressed. On logistic regression it was found that only having side effects was associated with missing doses of DOTS. Being depressed did not have any significant association with missing doses.

Prevalence of depression in our study was lower than the prevalence observed in a study from Bangalore in 1985 but higher than the prevalence found in a similar study in Nigeria in 2009.^{24,25} Both these studies used the PHQ- 9 scale as we did. Depressive disorder was observed to be higher in category II patients than in category I patients. This may be due to longer duration of therapy and possibly due to greater perceived gravity of illness and also discomfort due to side effects. None of the socio-demographic factors was found to be associated with depressive disorders unlike in other studies where depressive disorder was found to be more in the elderly, females, labor class, widows, illiterates and persons with low per capita income.

Studies have observed that though missing doses before stopping treatment by those who default is common, people who successfully completed their treatments also missed a few doses. In one recent study (2011) it was

found that nearly 72% of persons on treatment had missed a few doses by the end of third month with the maximum interruptions being between 2nd and 3rd month of treatment.²⁶ Another study (2010) found that nearly 78% of the treatment adherent persons had missed a few doses during treatment.²⁷ Similarly Vijay s et al (2003) found that 52% of persons who successfully completed their treatment had missed one or more doses.²⁸ In our study, 43% of the persons had missed at least one dose by the time of interview and 12.1% had missed two or more doses. The lower levels of missed doses may be due to stricter monitoring of the DOTS program and close follow up and contact with patients as is being now followed. Similar to other studies, doses were missed most often on Mondays.

Program side factor (sudden declaration of holiday) was the most common reason for missing doses followed by patient factors like vomiting, patients being away from home, having competing priorities and simply forgetting to take the dose. The side effects make it difficult to take medicine and make the patient miserable. Having a duty roster of community health workers for replacement in case of sudden declaration of holidays may solve the problem of non-availability of medicines due to such events. Availability of supplementary doses in case the patient vomits may also reduce the missed doses.

Having treatment side effects was significantly associated with being depressed and anxious. Being depressed and having treatment side effects were significantly associated with being partially adherent on bivariate analysis. However, on multivariate analysis, it was found that only having treatment side effects was significantly associated with missing doses of ATT. Since depression can also be a side effect of anti-tubercular treatment, the temporal association of which came first can only be established in a cohort study.

CONCLUSION

To conclude, this study shows that even patients who are considered 'adherent' as per program guidelines also miss a few doses of therapy. We found that psychiatric comorbidity does not significantly affect adherence to anti tubercular treatment. However, other common factors which can affect adherence can be addressed by having a roster of health workers to cover for any sudden holidays. Also, intensive counseling, monitoring and management of side effects like vomiting and provision of supplementary doses to replace vomited doses may also reduce prevalence of missed doses.

This study uses PHQ 9 and GAD 7 as screening tools for depression and anxiety respectively. Both these tools have been translated to local languages and validated in Indian settings. Hence they provide reliable figures for the prevalence of depression and anxiety. Also the validity and reliability of the ACTG questionnaire (adapted) to monitor adherence is well established.

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