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Adverse drug reactions to first-line anti-tuberculosis drugs in a chest hospital, Ibadan

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ABSTRACT

Background: Patients treated for TB frequently experience adverse drug reactions caused by multiple medications taken for long duration. These reactions have the potential of causing poor adherence, treatment failure, relapse or emergence of drug resistance. Preventing or minimizing such reactions can improve patient's adherence and treatment success rate.

Objectives: This study assessed the incidence and risk factors for adverse drug reactions (ADRs) to first line anti-TB drugs among patients treated for drug susceptible TB at Government Chest Hospital, Jericho Ibadan.

Methods: This was a cross sectional retrospective study. Data from medical records of patients treated between January and December 2018 was retrieved and analyzed with SPSS statistical package. This study was approved by the Research Ethics Review Committee of Oyo State Ministry of Health.

Results: Case files of 252 patients were included in the study. Overall incidence of ADRs was 49.6%. Majority of the patients had only one type (32.5%) of ADRs and the most common was arthralgia (28.2%,). Risk factors for ADRs among patients include age, female gender and comorbidities.

Conclusion: About half of the patients experienced ADRs during TB treatment and major risk factors identified were age, female gender and presence of comorbidities.

Key words: Adverse drug reactions, Incidence, Risk factors, Tuberculosis, Nigeria

Effets Indésirables Des Médicaments Antituberculeux De Première Intention Dans Un Hôpital Thoracique D'ibadan

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RÉSUMÉ

Contexte : Les patients traités contre la tuberculose présentent fréquemment des réactions indésirables dues à la prise de plusieurs médicaments pendant une longue période. Ces réactions peuvent entraîner une mauvaise observation du traitement, un échec thérapeutique, une rechute ou l'émergence d'une résistance aux médicaments. La prévention ou la minimisation de ces réactions peut améliorer l'observation par les patients et le taux de réussite du traitement.

Objectifs : Cette étude a évalué l'incidence et les facteurs de risque des effets indésirables des médicaments antituberculeux de première intention chez les patients traités pour une tuberculose sensible aux médicaments l'hôpital thoracique gouvernemental de Jericho à Ibadan (Government Chest Hospital).

Méthodes : Il s'agit d'une étude rétrospective transversale. Les données issues des dossiers médicaux des patients traités entre janvier et décembre 2018 ont été recueillies et analysées avec le progiciel statistique SPSS. Cette étude a été approuvée par le comité d'examen éthique de la recherche du ministère de la Santé de l'État **d'Oyo.**

Résultats : Les dossiers médicaux de 252 patients ont été inclus dans l'étude. L'incidence globale des EIM était de 49,6 %. La majorité des patients n'ont présenté qu'un seul type d'effets indésirables (32,5 %) et le plus fréquent était l'arthralgie (28,2 %). Les facteurs de risque d'EIM chez les patients sont l'âge, le sexe féminin et les comorbidités.

Conclusions : Près de la moitié des patients ont présenté des effets indésirables au cours du traitement de la tuberculose et les principaux facteurs de risque identifiés sont l'âge, le sexe féminin et la présence de comorbidités.

Mots clés : Effets indésirables des médicaments, Incidence, Facteurs de risque, Tuberculose, Nigéria

INTRODUCTION

Tuberculosis (TB) is a major public health problem worldwide, being one of the top 10 causes of death and the second leading infectious cause of death after HIV/AIDS.[1] Nigeria ranked sixth among the eight countries that bear the highest burden of TB disease in 2018.[1] This communicable infectious bacterial disease caused by Mycobacterium tuberculosis and transmitted through the respiratory route among humans is preventable, treatable and curable.[2] Treatment of drug susceptible TB is achieved with the use of four first-line antimicrobial drugs, given in two phases for a period of 6-8 months under direct supervision and support strategy known as DOTS.[3] The first-line drugs - Isoniazid, Rifampicin, Pyrazinamide and Ethambutol are very effective but sometimes cause different kinds of adverse reactions.[4]

Patients experience adverse drug reactions (ADRs) as a result of use of multiple medications taken over a long duration.[5-7] Occurrence of ADR during treatment has a huge impact on treatment effectiveness, treatment outcome and TB epidemic control.[8-9] This is because adverse drug reactions are known to contribute to non-adherence, interruption and non-completion of treatment which can lead to treatment failure, as well as relapse or emergence of drug resistance.[8,10] Most common ADRs to first-line anti-TB drugs include fever, rash, jaundice, hepatotoxicity, neurological disorders, skin reactions, gastrointestinal disorders and arthralgias.[7,9]

Overall incidence of ADRs to first-line TB medications ranges from 5.5% to 57.8%.[12-15] Incidence of 53% was reported by Gholami *et al.* in 2006, 12.6% by Xia *et al.* in 2010, 41.5% by Damasceno *et al.* in 2013, 39% by Przybylski *et al*. in 2014 and 22.1% by Zhang *et al*. in 2016.[4,12-15] Further analysis of incidence of individual ADRs by Przybylski *et al*. showed that hepatotoxicity had the highest incidence at 25.8% followed by hematological problems (19.0%), gastrointestinal disturbance (14.0%), psychiatric disorders (11.7%) neurological disorders (8.7%), arthralgia (5.9%), ototoxicity (5.8%) and dermatological effects (4.0%).[4]

Risk of developing adverse reactions depends on the patient's characteristics and also on concomitant medication during therapy.[16] Advance age, female gender, HIV infection, alcohol use, smoking and comorbidities have been identified as common factors that predispose patients to risk of ADRs during TB treatment.[6,8,17] Identifying risk factors for adverse reactions among TB patients prior to treatment and taking steps to prevent or minimize such reactions will not only improve patients adherence but also improve treatment success rate and ultimately, TB control program.

This study was carried out to determine the incidence of adverse drug reactions to first-line anti-TB chemotherapeutic drugs and assess the risk factors for ADRs among patients who received treatment between January and December 2018 at Government Chest Hospital, Jericho, Ibadan.

METHODS

Study design

This was a 12-month retrospective cross-sectional study of all case files of drug susceptible TB patients treated with first line anti-TB drug regimen at the study center.

Study setting

Government Chest Hospital, Jericho, Ibadan is a 39 bed capacity specialist hospital where Drug Susceptible TB, Multi-Drug Resistant TB (MDR-TB) and Extensively Drug Resistant TB (XDR-TB) are treated. The facility is a TB treatment specialist hospital that receives referrals from all States in the country.

Study population and sampling

Case files of patients treated for drug susceptible tuberculosis with first line anti-TB drugs as outpatients were used. Medical information of patients was retrieved from the case files from January to December 2018. All case files with documented cases of adult patients (15 years and above) who received either first treatment or re-treatment were purposively selected and included in the study while those who did not meet above criteria were excluded.

Data collection Instrument

Data extraction tool was developed and validated by the researcher and used to extract specific information regarding adverse drug reactions experienced by patients from selected treatment folders. Information regarding socio-demographic variables, types of adverse drug reactions and risk factors for ADRs among selected patients were extracted.

Ethical consideration

This study was reviewed and approved by the Research Ethics Review Committee of Oyo State Ministry of Health with approval number AD13/479/2011[A].

Data analysis

Extracted data was analyzed using SPSS version 22.0. Descriptive statistics were used to summarize the results. Chi square test was used to determine association between ADRs and different population parameters. Statistical significance was set at $p< 0.05$.

RESULTS

A total of two hundred and fifty-two (N=252) eligible case files of patients were retrieved for data collection and used for the study.

Socio-demographic characteristics of patients

The age group with the highest number of patients was 25-34 years (n=66, 26.2%) while the lowest number of patients were aged 65 years and above (n=20, 7.9%). Majority of the study population were male (n=161, 63.9) and more than two-thirds were self-employed (n=174, 69%). Except for a small fraction (n=4, 1.6%), all patients were new patients who received TB treatment for the first time. Table 1 summarizes the results.

Incidence of adverse drug reactions

From the records, the incidence of adverse drug reactions (ADRs) among patients treated with first-line anti-TB drugs for drug susceptible TB at the study facility is as shown in Figure 1. Almost half of the patients experienced ADRs, giving an incidence of 49.6%.

Figure 2 further describes the incidence by number of types of ADRs documented in patients' case files. Majority (32.5%) had only one type of ADR, less than a quarter (14.3%) had two types while only a small fraction of 2.8% had three types of ADRs.

Description of the various types of ADRs with respect to affected organs among patients whose case files were reviewed is shown in Figure 3. Majority of the ADRs experienced by patients was arthralgia (28.2%), followed by neurological disorder (17.9%) and gastrointestinal problems (9.5%).

Association between incidence of ADR and socio-demographic details

Significant association was observed between incidence of ADRs and age (p=0.0001), gender (p=0.0001), occupation (p=0.008) and comorbidity with hypertension (p=0.023). See Table 2.

Risk factors for adverse drug reactions

The most common risk factor identified is age of 35 years and above (n=159, 63.1%), followed by female gender (n=91, 36.1%), as shown on Table 3.

Table 1: Socio-demographic characteristics of patients

	Frequency (N= 252)	Percentage (100%)
Age group		
15 – 24 years	32	12.7
25 – 34 years	66	26.2
35 – 44 years	62	24.6
45 – 54 years	51	20.2
55 – 64 years	21	8.3
=65 years	20	7.9
Gender:		
Male	161	63.9
Female	91	36.1
Occupation:		
Student	21	8.3
Civil servant	36	14.3
Unemployed	21	8.3
Self-employed	174	69.0
Treatment type:		
New treatment	248	98.4
Retreatment	4	1.6
	252	**100.0**

Average age = 40.3±14.0 years

Table 2: Association between incidence of ADR and Socio-demographic details

	Incidence of ADR			
	Had ADR (N = 125) N (%)	Without ADR (N = 127) N (%)	Total N (%)	χ^2, p-value
Age:				
15 – 24 years	17 (13.6)	15 (11.8)	32 (12.7)	24.598; **<0.0001**
25 – 34 years	22 (17.6)	44 (34.6)	66 (26.2)	
35 – 44 years	42 (33.6)	20 (15.7)	62 (24.6)	
45 – 54 years	23 (18.4)	28 (22.0)	51 (20.2)	
55 – 64 years	6 (4.8)	15 (11.8)	21 (8.3)	
>65 years	15 (12.0)	5 (3.9)	20 (7.9)	
Gender:				
Male	64 (51.2)	97 (76.4)	161 (63.9)	17.310; **<0.0001**
Female	61 (48.8)	30 (23.6)	91 (36.1)	
Occupation:				
Student	3 (2.4)	18 (14.2)	21 (8.3)	11.873; **0.008**
Civil servant	18 (14.4)	18 (14.2)	36 (14.3)	
Unemployed	10 (8.0)	11 (8.7)	21 (8.3)	
Self-employed	94 (75.2)	80 (63.0)	174 (69.0)	
Treatment:				
New treatment	124 (99.2)	124 (97.6)	248 (98.4)	0.984; 0.317
Retreatment	1 (0.8)	3 (2.4)	4 (1.6)	
Comorbidities*:				
Diabetes	0 (0.0)	2 (1.6)	2 (0.8)	1.984; 0.159
Hypertension	5 (4.0)	0 (0.0)	5 (2.0)	5.183; **0.023**

*Multiple responses allowed

Table 3: Risk factors for ADRs to first-line anti-TB drugs among patients

	Frequency (n= 252)	Percentage (100%)
Advance age (≥35)	159	63.1
Gender risk (Female):	91	36.1
Smoking	0	0.0
Alcohol	0	0.0
HIV positive	0	0.0
Anaemia	2	0.8
Co-morbidities:		
Diabetes	2	0.8
Hypertension	5	2.0
None	246	97.6
	252	**100.0**

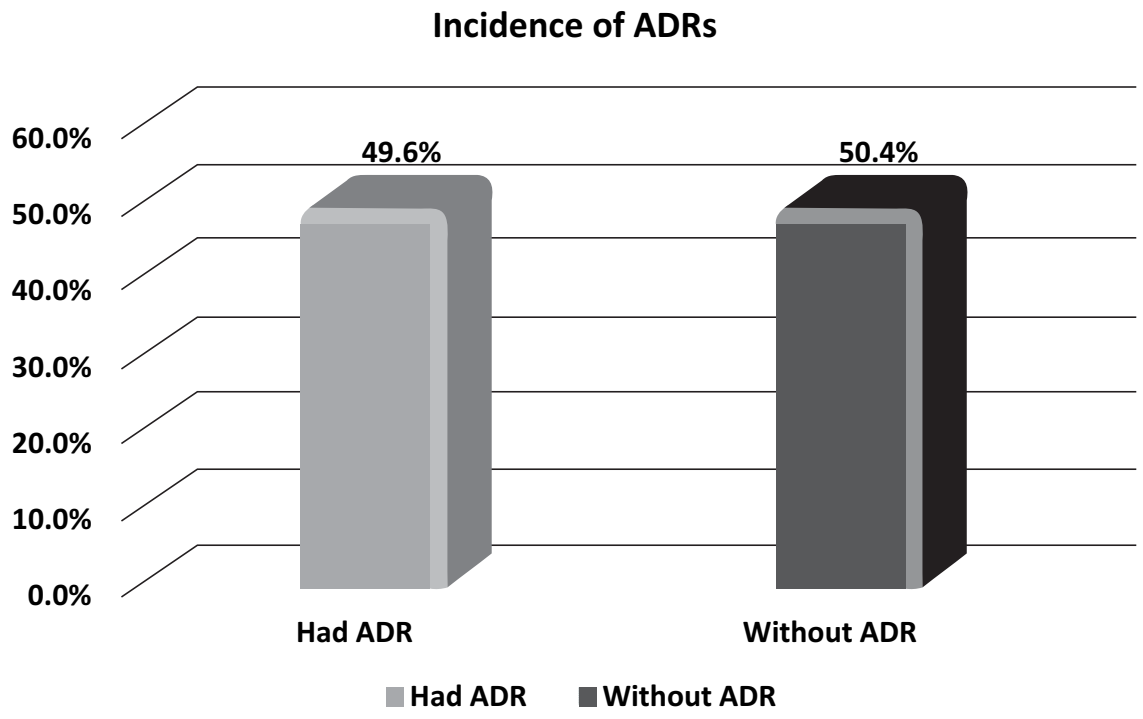

Figure 1: Incidence of ADRs among patients treated for drug susceptible TB with first line TB drugs at the study center

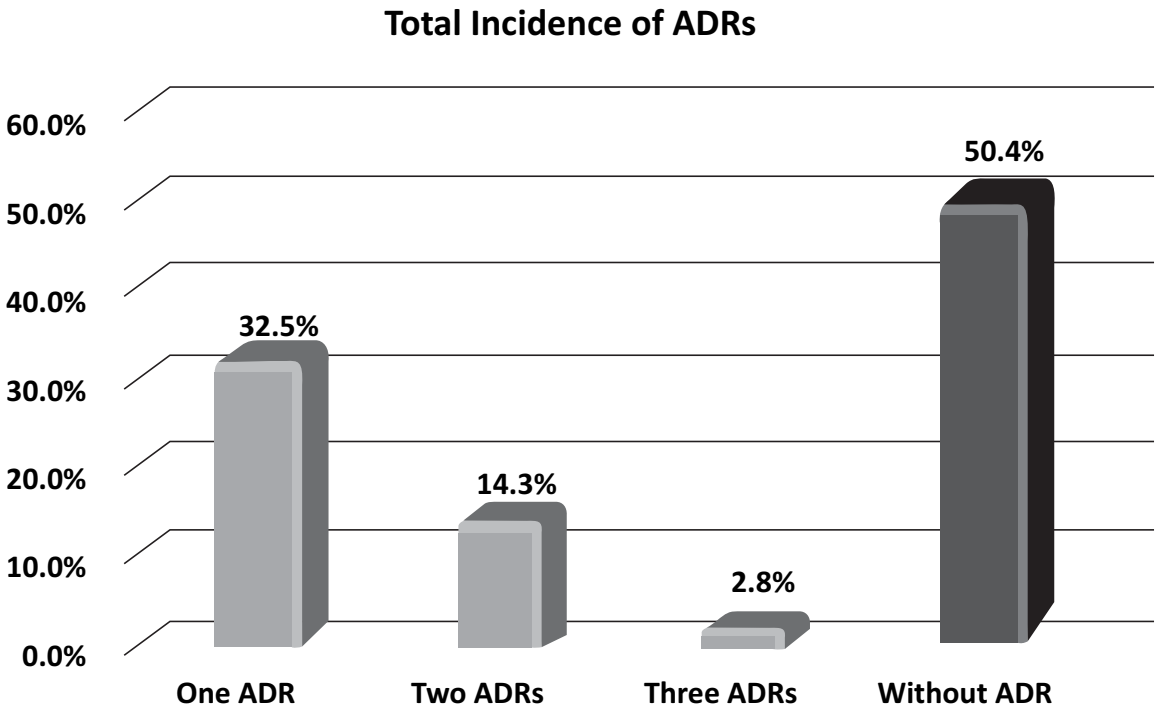

Figure 2: Total incidence of ADRs among patients

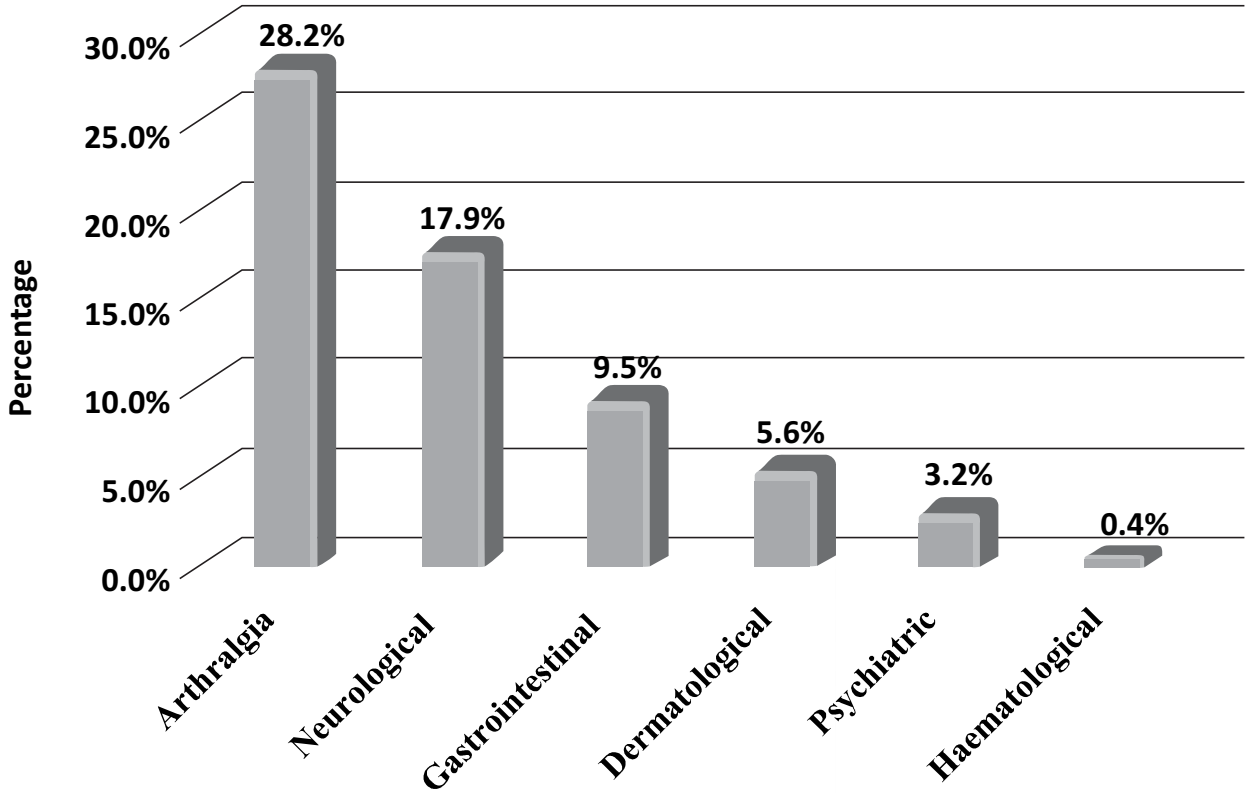

Figure 3: Types of ADRs by organ affected with first line drugs during TB treatment

DISCUSSION

This study showed that almost half of the patients experienced ADRs during TB treatment, giving an overall incidence of 49.6%. Compared to other studies, the incidence in this study is relatively high. The incidence reported by Xia *et al*. was 12.6% while Zhang *et al*. reported 22.1% among Chinese patients.[4,15] An incidence rate of 39% has also been reported in a study conducted in Poland.[14] The incidence of ADRs in this study is however comparable with the study of Damasceno *et al*.[13] A higher incidence (53%) than the one in this study was reported by Gholami *et al*.[12]

In Nigeria, varying incidence rates have been reported. A study conducted by Dosumu reported 13% and 14% incidences at 6 and 8 months of treatment respectively, while Micheal *et al*. reported 44.4% and 74.2% in a two-arm study of TB patients with and without HIV respectively.[16,17] The incidence in this study is thus comparable to the latter study. The variability reported from different studies may be due to differences in study design, sample size, patients' genetic makeup, morbidities and comorbidities, difficulties in ADR diagnosis and other factors specific to study location. [4,12-15]

The result of this study showed that most patients experienced only one type of ADR (32.5%), followed by two (14.3%) and three (2.0%) types of ADRs during treatment. This is similar to the report of Damasceno *et al*. where 39 patients were reported to develop only one ADR while 34 patients developed two or more ADRs during treatment.[13]

Hepatotoxicity, neurological disorders, skin reactions, gastrointestinal disorders and arthralgias have been reported by Horsburgh *et al*. to be relatively common adverse drug reactions of anti-TB medications.[7] Analysis of the different types of ADRs documented in patients' case files showed that the highest reported ADR was arthralgia with an incidence of 28.2%, followed by neurological disorders (17.9%) and gastrointestinal problems (9.5%). Less than 10% of the patients experienced dermatological, hematological and psychiatric adverse reactions altogether. This result differs from that of Przybylski *et al*. where gastrointestinal disorder was 14%, hematological problem - 19.0%, psychiatric disorders - 11.7%, neurological disorders - 8.7%, arthralgia - 5.9% and dermatological effects - 4.0%.[14]

Several studies have shown that hepatotoxicity is the most common ADR of anti-TB drugs,[18-20] however, in this study, no incidence of hepatotoxicity was recorded. This may be due to the fact that baseline investigations were not conducted before patients were started on anti-TB drugs at the study center and active monitoring of patients for development of ADRs was not a frequent practice.

Assessment of association between incidence of ADRs and socio-demographic characteristics revealed significant association between patients' age and incidence of ADR (χ^2 = 24.598; p = 0.0001). Similar observation has been reported in previous studies.[15,22] Furthermore, there was significant association between TB patients' gender and incidence of ADR (χ^2 = 11.873; p = 0.0001). Contrary to reports of Farazi *et al*.[6] and Tweed *et al*.,[21] the incidence of ADR was slightly higher in this study among male patients (51.2%) than among female patients (48.8%). This is however in line with reports of Xiang *et al*. and Zhang *et al*. where the incidence of ADRs was claimed to be higher among males.[15,20]

The results also showed that not less than 75% of the TB patients who were self-employed had highest incidence of ADR. Chi-square test indicated that there was significant association between patients' occupation and incidence of ADR (χ^2 = 11.873; p = 0.008). Though few patients had comorbidity in this study, significant association between patients' comorbidity status of hypertension and incidence of ADR was also observed (χ^2 = 5.183; p = 0.023). This finding agrees with that of a previous study where comorbidity was reported to influence incidence of ADRs among patients.[23]

The result of this study supports and confirms the reports of Farazi *et al*. and Tweed *et al*.[6,21] They reported that advance age, female gender, HIV infection and co-morbidities were risk factors for ADRs among patients treated for TB. In our findings, the case files showed that 63.1% of the patients who experienced ADRs were 35 years and older and 36.1% of them were of the female gender. Only a few of these patients, 0.8% and 2.0% had diabetes and hypertension as comorbidities. It is also to be noted that only limited demographic and medical history information were obtained and documented in patients' case files at the studied facility and this may account for the few numbers of patients who had comorbidities.

CONCLUSION

This study showed that the incidence of ADRs at the study center is relatively higher than those reported in most

studies, but still within the range reported across the world. The risk factors for ADRs in this study were similar to those found in literature, but the findings were limited due to insufficient demographic and medical history information available in patients' medical records.

These findings call for baseline investigations and active monitoring of patients before and during TB treatment for adverse drug reactions in order to improve adherence and optimize patient treatment outcome.

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