Psychiatric issues in the management of patients with multidrug-resistant tuberculosis

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SUMMARY

INTRODUCTION: Psychiatric issues present a challenge in the treatment of patients with multidrug-resistant tuberculosis (MDR-TB). Both baseline psychiatric disorders and development of psychiatric complications related to anti-tuberculosis drugs and psychosocial factors require aggressive management.

SETTING: A community-based non-governmental health organization in Lima, Peru.

OBJECTIVE: To review the literature for psychiatric complications associated with anti-tuberculosis medications, to describe the incidence and prevalence of depression, anxiety and psychosis among individuals receiving MDR-TB therapy, and to detail the management approach used in this cohort.

METHODS: A retrospective case series was performed among the first 75 patients to receive individualized MDR-TB therapy in Lima, Peru, between 1996 and 1999.

RESULTS: Baseline depression and baseline anxiety were observed in respectively 52.2% and 8.7% of this cohort. Most individuals with baseline depression experienced improvement of depressive symptoms during the course of TB therapy. The incidence of depression, anxiety and psychosis during MDR-TB treatment was 13.3%, 12.0% and 12.0%, respectively. While the majority of individuals with depression, anxiety and psychosis required psychiatric pharmacotherapy, cycloserine was successfully continued in all but one case.

CONCLUSION: Psychiatric comorbidities are not a contraindication to MDR-TB therapy. Management of psychiatric complications is possible without compromising anti-tuberculosis treatment.

KEY WORDS: multidrug-resistant tuberculosis; psychosis; depression; anxiety; cycloserine; Peru; review

MORE THAN 50 YEARS after the advent of effective therapy, tuberculosis (TB) remains one of the leading causes of adult deaths in the world, disproportionately affecting people in poor countries. Individuals at highest risk for exposure and illness are thus precisely those with the least means to overcome the disease. Furthermore, drug-resistant strains are contributing increasingly to a global public health disaster. In a survey performed in 2000, multidrug-resistant TB (MDR-TB) was identified in each of the 72 countries surveyed. Current estimates indicate that 273 000 new MDR-TB cases occur each year. Although recently removed from the list of high-burden countries, Peru continues to have one of the highest rates in the Americas, with 15% of reported cases, despite representing only 3% of the population.

By definition, MDR-TB refers to strains of Mycobacterium tuberculosis that are resistant to at least isoniazid (INH) and rifampicin, the two most powerful anti-tuberculosis agents. Second-line anti-tuberculosis drugs, including cycloserine (CS), the fluoroquinolones, ethionamide/prothionamide (ETH), kanamycin/amikacin, capreomycin and para-aminosalicylic acid, are generally weaker and more toxic than first-line agents. For this reason, prolonged therapy (18–24 months) and frequent adverse reactions are significant challenges to successful treatment of MDR-TB patients, particularly in resource-poor settings. Management of these side effects is complicated by the fact that discontinuation of the drug or treatment interruption may compromise treatment efficacy, especially in cases of high-grade drug resistance. Rather than suspending the suspected agent, which may be one of few therapeutic resources available to treat the infection, medical providers are required to develop strategies to aggressively manage the symptoms through secondary medications and other biosocial interventions.

While adverse effects associated with MDR-TB...
treatment may be managed effectively, certain side effects require special attention. In particular, psychiatric complications, such as anxiety, depression, and psychosis, can greatly impact patient quality of life, as well as physicians’ attitudes toward MDR-TB therapy. Successful control of psychiatric symptoms is therefore crucial not only for favorable patient outcome, but also for patients’ overall well-being and physicians’ comfort with managing MDR-TB therapy. The most commonly reported management strategy to control psychiatric symptoms is to remove the offending agent. However, a few published reports describe management strategies that avoid the discontinuation of the drug, for example lowering the dose or simultaneously administering antidepressant or antipsychotic therapy. The use of B6 supplementation to prevent neurotoxicity associated with ETH, INH and CS has also been advocated. Similar protective effects may be observed with psychiatric symptoms induced by these medications.

Psychiatric complications have been associated with anti-tuberculosis therapy since the 1950s. Although significant psychiatric symptomatology has been most commonly associated with CS and INH, other drugs implicated at the case report level include ETH, ethambutol (EMB) and the fluoroquinolones. Severe psychiatric manifestations—including hallucinations, anxiety, depression, euphoria, behavioral disorders, and suicidal ideation and/or attempts—have been reported to occur in 9.7–50% of individuals receiving CS. CS-associated neurotoxicity is likely due to diminished central nervous system (CNS) production of γ-aminobutyric acid (GABA) caused by inhibition of glutamic decarboxylase and facilitated by effective penetration of the blood-brain barrier. In the majority of these cases, the drug was discontinued, with rapid recovery of mental status and no recurring symptoms. Psychiatric symptoms appear most likely to present within the first 3 months of treatment. Increased risk of CNS toxicity may be associated with supratherapeutic levels of CS, concomitant use of ETH, INH or fluoroquinolones, and ethanol ingestion.

Less commonly, INH has been associated with neuropsychiatric side effects, including depression, irritability, obsessive-compulsive neurosis, and attempted suicide. In the Boston Collaborative Drug Surveillance Program performed in 1974, more than 35% of adverse effects associated with INH were psychiatric in nature, with an incidence of 1.9%. Similarly, in Peru, severe psychiatric syndromes associated with INH occurred in approximately 1.0% of tuberculosis cases between 1991 and 1999. Pallone, Goldman and Fuller performed a review of the literature on INH-induced psychosis in 1993. They found that the most common psychiatric symptoms associated with INH were delusions, generally presenting after approximately 4 weeks of taking the drug, and among patients of an average age of 35 years (range 17–53). They summarize risk factors as receiving a dose above 5 mg/kg; age 50 years or older; co-morbid disease including diabetes mellitus, hepatic insufficiency, alcoholism, and hyperthyroidism; and past psychiatric history. Several mechanisms have been proposed to account for INH-associated toxicity. INH may act as a monoamine oxidase (MAO) inhibitor; alternatively, psychiatric effects may be caused by INH-induced pyridoxine deficiency, with subsequently diminished production of norepinephrine, serotonin, dopamine, and GABA. Further review has uncovered several more case reports detailing psychotoxic reactions to INH with similar observations.

Several case reports associate the use of ETH with occurrence of depression, anxiety, psychosis, and suicide. The mechanism for INH and ETH neurotoxicity is likely the same. EMB may also be associated with mania, confusion, and psychosis, although the mechanism for this effect is unknown. Finally, the fluoroquinolones have been implicated in rare occurrences of psychosis, depression, delirium, and nightmares. A large-scale retrospective study by Hollweg et al. reported psychiatric disturbance in 0.7% of 4189 individuals treated with either ofloxacin or ciprofloxacin. In this study, while elderly individuals were more likely to experience delirium or paranoia, younger individuals had greater rates of depressive and manic syndromes. Underlying hepatic or renal dysfunction, concomitant antibiotics or immunosuppressants, and baseline psychiatric disorders or psychosocial stressors, were identified as risk factors for quinolone-associated psychiatric disturbance.

In addition to drug toxicity, psychosocial factors contribute to psychiatric complications during MDR-TB therapy, and consequently patients’ adherence to these regimens. Two early reports on sanatorium care discuss several emotional aspects associated with TB, including depression, anxiety, and suicidal ideation. Considering that these reports pre-date the development of effective antibiotics for the treatment of TB, it is apparent that psychiatric complications occur even in the absence of drug therapy. Some of the psychosocial issues that are often prominent concerns of individuals with MDR-TB include: social stigma and discrimination; fear and guilt associated with infectious risk; the socio-economic and psychological burdens of living with a chronic, life-threatening illness; increased dependence on others; multiple treatment failures and being told in health centers that no further therapy was available; losing family members to the disease; and comorbid poverty. The impact of social stigma has been examined with regard to other infectious diseases, such as the human immunodeficiency virus and the acquired immune-deficiency syndrome (HIV/AIDS), the impact of which include...
depression, low self esteem, and shame. Fear of infection is one of the factors contributing to social stigma, which may produce social isolation, diminished marriage prospects, limited social support, and result therefore in the denial of diagnosis and consequent rejection of treatment. Despite the fact that TB infection is not necessarily associated with specific ‘risk behaviors’, TB patients are still generally held responsible for their illness and blamed for not taking better care of themselves. Further, poverty alone has been demonstrated to have a clear association with increased risk for mental illness. Several authors have described how these psychosocial factors complicate adherence to drug regimens, and emphasize the importance of attention to mental health needs to ensure positive treatment outcomes. Adherence is especially important in the case of MDR-TB, as this is often a patient’s last treatment option; failure to complete this treatment leads to a high rate of fatality, in addition to ongoing transmission of highly drug-resistant strains.

Despite such challenges, a community-based initiative in Lima, Peru, has demonstrated successful outcomes in treating MDR-TB patients, in part through comprehensive management of psychiatric side effects and psychosocial factors. One of the fundamental components of this program has been the aggressive management of adverse reactions using protocols and community-based outreach to minimize the need for treatment interruption or discontinuation of anti-tuberculosis drugs. Here, we describe the incidence, characteristics, and management of psychosis, depression, and anxiety occurring among patients receiving individualized treatment for MDR-TB in Lima, Peru.

METHODS

Study population
All patients had documented MDR-TB and were enrolled in treatment between 1 August 1996 and 31 January 1999 through collaborative effort between two non-governmental organizations (Partners In Health and Socios En Salud—Sucursals Perú) and the Peruvian Ministry of Health’s National Tuberculosis Program (NTP). The catchment area included three districts of Northern Lima (Carabayllo, Comas and Independencia), a shanty town hosting roughly 762,000 people in 1997 with high rates of poverty, violence, unemployment, and mental illness. In addition, through active case finding, this area was identified as a ‘hot spot’ for the disease in Peru, with estimated TB rates higher than the national incidence.

Treatment protocol
All patients were referred by the NTP for suspicion of MDR-TB based on history of treatment failure or household contact with a known MDR-TB patient. Comorbidities, including psychiatric conditions, were not a contraindication to treatment. Written informed consent was obtained from all patients and one family member prior to initiating therapy. Multidrug resistance was confirmed by conventional or BACTEC methods performed by the Massachusetts State Laboratory Institute on sputum specimens. Individualized therapy was based on each patient’s resistance pattern. Of note, individuals with resistance to INH only at low concentrations received high-dose INH (900 mg twice a week) as part of their regimens. Pyridoxine (150–300 mg/day) was administered with MDR-TB regimens. All patients participated in an unstructured clinical interview with a psychiatrist to screen for baseline psychiatric disorders prior to initiation of individualized therapy. Patients received treatment under the auspices of the Peruvian NTP: community-based directly observed therapy delivered in health centers and in patients’ houses by community health workers. All treatment was provided to patients free of charge.

Patients were evaluated at least once a month by an NTP physician trained in the management of MDR-TB. These evaluations included screening for psychosis, depression, and anxiety. Patients were additionally assessed for any side effects identified by health care workers. Patients with psychiatric symptoms were referred to a psychiatrist at the physician’s discretion. The psychiatrist used clinical criteria based on DSM-IV to diagnose psychiatric syndromes. In general, symptoms were managed according to protocols that were developed by the physicians trained at Socios En Salud in the management of MDR-TB (see Appendices 1 and 2). Anti-depressants, anxiolytics, anti-psychotics, and psychotherapy were prescribed by both primary MDR-TB physicians and psychiatrists, and provided free of charge.

Study design and data collection
A case series with a retrospective chart review was conducted among all patients who had initiated individualized treatment between 1 August 1996 and 31 January 1999. All patients had completed treatment at the time of chart review. The follow-up period for all patients who were still alive was at least 18 months after completion of treatment. All charts were reviewed by a physician trained in the management of MDR-TB, then all cases with suspected new onset of psychiatric disorders were further reviewed by the treating psychiatrist. The case definition of psychosis was based on DSM-IV criteria by a physician. Categorization of depression was based on DSM-IV criteria by a psychiatrist, and included the following diagnoses: major depressive disorder, dysthymia, adjustment disorder with depressed mood, and substance-induced mood disorder with depressive features. The diagnosis of anxiety was also based on DSM-IV criteria for generalized anxiety disorder or substance-
induced anxiety disorder by a psychiatrist. Other variables extracted from the chart review for all patients included age, sex, drugs in the individualized regimen, number of previous treatment regimens, treatment outcome, baseline psychiatric illness using DSM-IV criteria according to a psychiatrist, history of alcohol or drug abuse, hypothyroidism (before or during treatment), HIV, diabetes mellitus, and malnutrition. The charts of all cases of psychiatric disorders were reviewed in more detail with respect to timing and duration of presentation of symptoms, clinical management, and treatment outcome.

Statistical analysis
The following risk factors were analyzed for association with incidence of depression, psychosis or anxiety: sex; age; baseline depression; education level; unemployment; marital status; presence of dependent children; presence of TB household contacts; presence of household contacts who died of TB; hypothyroidism; presence of comorbidities (i.e., diabetes, HIV, malnutrition, history of alcoholism or drug abuse); history of institutionalization (i.e., incarceration or extended hospitalization) or homelessness; receipt of medications associated in the literature with psychiatric side effects (i.e., CS, INH, EMB, ETH, fluoroquinolones); and CS dose. Multivariable analysis for occurrence of each side effect was also performed using a multiple regression model including all variables associated with a \( P \)-value of 0.05 or an odds ratio (OR) >2.0 on univariate analysis.

All data were entered in Microsoft Excel 97 (Microsoft Corporation, Seattle, WA, USA); all statistical analysis was performed using SAS, version 8.2 (SAS Institute, Cary, NC, USA). Reported \( P \) values were based on two-sided Fishers exact tests, or for continuous variables, \( t \)-tests or, if non-parametric, the Wilcoxon test. For binary variables, ORs with 95% confidence intervals (95%CIs) were also calculated.

RESULTS
Baseline characteristics, incidence of psychiatric complications, and treatment outcomes
Between August 1996 and January 1999, 75 patients initiated treatment. Charts were available and reviewed for all cases. The baseline prevalence, as well as incidence during treatment of psychosis, depression and anxiety, are summarized in Table 1. Of note, roughly half of the cohort had a baseline diagnosis of depression, including three individuals who also had a co-existing anxiety disorder. None had baseline psychosis. During the course of MDR-TB therapy, 10 (13.3%) patients developed depression, nine (12.0%) developed anxiety disorders, and nine (12%) experienced psychosis. While psychosis tended to occur earlier in MDR-TB treatment (mean 3.6 months, range 1–8), the onset of depression and anxiety was more variable. For both depression and anxiety, the mean time of presentation was 7.3 months, with a range of 1–17 and 2–16 months, respectively.

Table 2 summarizes the demographic and clinical characteristics of this cohort and has been described in more detail elsewhere. MDR-TB regimens included CS in all but one case, with a median daily dose of 1000 mg. Twenty-five patients (33.3%) received high doses of INH, 52 (69.3%) ETH, 11 (14.7%) EMB, and 72 (96.9%) received a fluoroquinolone. While the occurrence of psychiatric complications during MDR-TB therapy was not significantly associated with adverse treatment outcome, there was a trend toward increased risk of default among individuals who developed psychosis (OR = 6.0, 95%CI 0.9–42.3).

Risk factors and management of psychiatric complications
Psychosis
Among the nine patients (12%) who developed psychosis during treatment, younger age (average 24.1 vs. 29.7 years among those with and those without psychosis, \( P = 0.008 \)) was identified as a risk factor. Furthermore, none of the individuals who developed psychosis were married vs. 36.4% among those who did not develop psychosis (\( P = 0.05 \)). In a multivariable analysis, including female sex, age, baseline depression, unmarried status, number of dependent children, and presence of an MDR-TB household contact, no variable was found to be significantly associated with psychosis. In three (33.3%) cases CS was suspended temporarily, in two (22.2%) the CS dose was decreased, and in one (11.1%) the drug was suspended then resumed at a lower dose (Table 3). It was never necessary to discontinue CS indefinitely. No changes in other TB drugs were required. Only one (11.1%) patient was hospitalized due to psychosis, while the rest were managed through close monitoring by community health promoters, nurses, and doctors in the patients’ homes. All but one individual received antipsychotic drug therapy. Psychotic episodes recurred in two (22.2%) individuals, but were effectively

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### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Prevalence prior to MDR-TB therapy (n = 69)</th>
<th>Persistent symptoms among those with baseline diagnosis (n = 69)</th>
<th>Incidence during MDR-TB therapy (n = 75)</th>
<th>Prevalence during MDR-TB therapy (n = 69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychosis</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>9 (12.0)</td>
<td>9 (12.0)</td>
</tr>
<tr>
<td>Depression</td>
<td>36 (52.2)</td>
<td>12/36 (33.3)</td>
<td>10 (13.3)</td>
<td>22 (29.3)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>6 (8.7)</td>
<td>3/6 (50.0)</td>
<td>9 (12.0)</td>
<td>12 (16.0)</td>
</tr>
</tbody>
</table>

MDR-TB = multidrug-resistant tuberculosis (defined as resistance to at least isoniazid and rifampicin).
Table 2  Baseline characteristics among 75 patients receiving individualized MDR-TB therapy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>26.8</td>
<td>(11.8–65.1)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>37 (49.3)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>38 (50.7)</td>
<td></td>
</tr>
<tr>
<td>Education level (n = 53)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed elementary school or less</td>
<td>7 (13.2)</td>
<td></td>
</tr>
<tr>
<td>Some high school or more</td>
<td>46 (86.8)</td>
<td></td>
</tr>
<tr>
<td>Household size (n = 70)</td>
<td>7 (2–20)</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/living with partner</td>
<td>24 (34)</td>
<td></td>
</tr>
<tr>
<td>Unmarried (single, divorced, widowed, separated)</td>
<td>47 (66)</td>
<td></td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not working</td>
<td>12 (16.0)</td>
<td></td>
</tr>
<tr>
<td>Student</td>
<td>19 (25.3)</td>
<td></td>
</tr>
<tr>
<td>Homemaker</td>
<td>14 (18.7)</td>
<td></td>
</tr>
<tr>
<td>Worker, aside from professional</td>
<td>30 (40.0)</td>
<td></td>
</tr>
<tr>
<td>Professional</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Number of dependent children</td>
<td>0 (0–7)</td>
<td></td>
</tr>
<tr>
<td>TB and MDR-TB household contacts</td>
<td>58 (77.3)</td>
<td></td>
</tr>
<tr>
<td>Household contacts who died of TB</td>
<td>28 (37.3)</td>
<td></td>
</tr>
<tr>
<td>Number of previous treatment regimens</td>
<td>3.0 (0–8)</td>
<td></td>
</tr>
<tr>
<td>Number of drugs to which patient is resistant</td>
<td>6.0 (2–12)</td>
<td></td>
</tr>
<tr>
<td>Comorbidity*</td>
<td>23 (30.7)</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism before or during ITR</td>
<td>11 (14.7)</td>
<td></td>
</tr>
<tr>
<td>Prior institutionalization or homelessness</td>
<td>9 (12.0)</td>
<td></td>
</tr>
<tr>
<td>Maximum cycloserine dose (mg)</td>
<td>1000 (750–1000)</td>
<td></td>
</tr>
<tr>
<td>Cycloserine</td>
<td>74 (98.7)</td>
<td></td>
</tr>
<tr>
<td>Isoniazid (high dose)</td>
<td>25 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Ethionamide</td>
<td>52 (69.3)</td>
<td></td>
</tr>
<tr>
<td>Ethambutol</td>
<td>12 (16.0)</td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>72 (96.0)</td>
<td></td>
</tr>
</tbody>
</table>

* Chronic disease included diabetes mellitus (1), HIV (1), malnutrition (15), and history of alcoholism or drug use (7).

MDR-TB = multidrug-resistant tuberculosis; TB = tuberculosis; ITR = individualized treatment regimen; HIV = human immunodeficiency virus.

managed in both cases. While patients receiving anti-psychotic medications at the conclusion of therapy generally continued their use for an additional 30–45 days, in only one (11.1%) case was it necessary for the patient to continue taking anti-psychotic medications beyond this window. Psychosis resolved in eight (88.9%) of the cases, with a median duration of psychotic symptoms of 4 weeks (range 0.71–28). Two (22.2%) patients who experienced psychosis abandoned treatment, one (11.1%) of whom was psychotic at the time of default. Of note, three (33.3%) of these cases occurred among sisters in one family.

Table 3  Characteristics and management of psychiatric symptoms (n = 75)

<table>
<thead>
<tr>
<th>Management</th>
<th>New psychosis (n = 9)</th>
<th>New depression (n = 10)</th>
<th>New anxiety (n = 9)</th>
<th>Baseline depression with persistent symptomatology (n = 12)</th>
<th>Baseline anxiety with persistent symptomatology (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced dose of cycloserine</td>
<td>3 (33.3)</td>
<td>1 (10.0)</td>
<td>4 (44.4)</td>
<td>10 (8.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Temporary suspension of cycloserine</td>
<td>4 (44.4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Terminated dose of cycloserine</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Required psychiatric medications</td>
<td>9 (88.9)</td>
<td>8 (80)</td>
<td>8 (88.9)</td>
<td>6 (50)</td>
<td>3 (100)</td>
</tr>
<tr>
<td>Persistent psychiatric symptoms throughout MDR-TB treatment requiring psychiatric medications</td>
<td>3 (33.3)</td>
<td>1 (10.0)</td>
<td>3 (33.3)</td>
<td>2 (16.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Required hospitalization due to psychiatric symptoms</td>
<td>1 (11.1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

MDR-TB = multidrug-resistant tuberculosis.
Depression
Among the 36 (52.2%) patients with baseline depression, two thirds (66.7%) did not require psychiatric attention or medications for depressive symptoms during therapy due to mild symptomatology or remission. Ten (13.3%) patients without baseline symptomatology experienced a new onset of depression during TB therapy; no significantly associated risk factor was identified on univariate analysis. In a multivariable analysis including number of dependent children, hypothyroidism, and presence of a TB household contact, no variable was identified to be significantly associated with depression. The dose of CS was lowered in one (10.0%) new case for the duration of treatment; no other modification of TB therapy was made for other patients presenting with depression during treatment. Anti-depressant medications were indicated in 80% of the new cases, although symptoms were generally effectively managed and they were not needed throughout treatment. Finally, no patients in this cohort were hospitalized for depression.

Anxiety
Of the six (8.7%) patients with baseline anxiety, half (50.0%) had persistent symptoms requiring psychiatric intervention, and one (16.7%) experienced a manic episode. Furthermore, nine (12%) patients had a new onset of anxiety during treatment. Risk factors significantly associated with onset of anxiety during MDR-TB treatment were having more dependent children ($P = 0.007$) and a higher average dose of CS (972 mg vs. 884 mg among those with and those without anxiety, $P = 0.04$). Eight of nine patients (88.9%) were receiving CS at the maximum dose of 1000 mg. The multivariable analysis included the following factors: age, married status, number of dependent children, CS dose, TB household contact, and lack of chronic disease. Among these variables, only higher dose of CS ($P = 0.01$) and greater number of dependents ($P = 0.002$) were significantly associated with occurrence of anxiety. In four (44.4%) cases, the dose of CS was lowered for the duration of treatment; no other changes in anti-tuberculosis therapy were made. While anxiolytic medications were necessary in eight (88.9%) of the nine cases, only three (33.3%) required medications for the duration of treatment. There were no hospitalizations due to anxiety.

DISCUSSION
The baseline prevalence of depression observed in our cohort was greater than the prevalence in the general population of Lima, Peru (52.2% vs. 6.7%).1 On the other hand, baseline rates of anxiety and psychosis were comparable to those of the general population of Lima.1 High rates of depression and anxiety among tuberculosis patients have been reported elsewhere,78 and are likely related to social stigma, inad-
small sample size limits the analysis of risk factors and effect of psychiatric complications on treatment outcome. A larger cohort will likely be necessary to identify risk factors associated with development of depression and psychosis. Moreover, given the retrospective nature of this study, the incidence of psychiatric complications could be underestimated because of lack of reporting or appropriate diagnosis.

CONCLUSIONS

Baseline prevalence of depression, anxiety, and psychosis in our cohort was 52.5%, 8.7% and 0%, respectively. Nonetheless, the presence of a baseline psychiatric disorder was not a contraindication to MDR-TB therapy nor to the use of CS. Furthermore, individuals with initial depression and/or anxiety often experienced an improvement in their symptoms during the course of MDR-TB treatment. Depression, anxiety and psychosis each occurred in approximately 12–13% of our cohort during treatment. Aggressive use of psychiatric medications (in particular for psychosis), in addition to psychosocial support, has permitted successful resolution of symptoms, usually without the need for hospitalization. Compared with other MDR-TB cohorts, our cohort experienced higher or comparable rates of psychiatric complications, and yet discontinuation of medications, in particular CS, occurred less frequently.12,80–82 Thus, psychiatric disorders among patients with MDR-TB can be successfully managed without endangering effective MDR-TB therapy.

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References

APPENDICES

EVALUATION

Does the patient see or hear things that others do not perceive? Unintelligible thoughts or speech? Bizarre behavior?

Yes

Suicidal or homicidal ideation?

Yes

Rule out other causes of psychosis, including depression, illicit drugs, other medications such as antidepressants, benzodiazepines, narcotics, seizure, alcohol withdrawal, etc.

TREATMENT

• Hold clozapine
  • Administer risperidone 0.5-2.0 mg po bid (usual effective dose 2-6 mg/day) or consider starting haloperidol, 1-5 mg PO, IV, or IM, repeat every hour or as needed (IV may be less effective)
  • Evaluate psychosocial stressors

IF NO IMPROVEMENT

• Continue to hold clozapine until psychosis has resolved.
  • Consider benzodiazepines if concomitant anxiety (use benzodiazepines with caution if tenuous respiratory status and at risk of retaining CO2). Also, paradoxical effect of increased psychosis may be observed with benzodiazepine use, especially in elderly
  • Consider psychiatric consult

ONCE PSYCHOSIS RESOLVED

• Consider reintroduction of clozapine at low dose, increasing dose as tolerated.
  • Antipsychotic therapy can often be discontinued after several weeks without recurrence

IF RECURRENCE

• Continue antipsychotic until completion of DOTS-Plus treatment
  • Use antipsychotic drug with fewer extrapyramidal side effects (e.g., risperidone, 0.5–3 mg PO)
  • Coadminister biperidene 2 mg PO TID or benztropine mesylate 1-2 mg PO QID

Appendix 1 Management of psychosis in individualized MDR-TB therapy (adapted from reference 69). PO = per os; IV = intravenous; IM = intramuscular; TID = thrice daily; QD = four times daily; BID = twice daily.
**INTRODUCTION** : Les problèmes psychiatriques représentent un défi lors du traitement des patients atteints de tuberculose à germes multirésistants (TB-MR). Une prise en charge vigoureuse s’impose à la fois pour les maladies psychiatriques préexistantes et pour le développement de complications psychiatriques liées aux médicaments antituberculeux et aux facteurs psycho-sociaux.

**CONTEXTE** : Une organisation de santé non-gouvernementale basée sur la collectivité à Lima, Pérou.

**OBJECTIF** : Revue de la littérature concernant les complications psychiatriques associées aux médicaments antituberculeux, description de l’incidence et de la prévalence de la dépression de l’anxiété et de la psychose parmi les individus atteints de TB-MR et détails de l’approche de prise en charge utilisée dans cette cohorte.

**MÉTHODES** : Une série rétrospective de cas a été formée par les 75 premiers patients qui ont bénéficié d’un traitement individualisé pour TB-MR à Lima, Pérou, entre 1996 et 1999.

**RESULTATS** : On a observé une dépression et une anxiété initiales chez respectivement 52,2% et 8,7% des patients de cette cohorte. La plupart des individus ayant eu une dépression initiale ont ressenti une amélioration des symptômes de dépression au cours du traitement de la tuberculose. L’incidence de la dépression, de l’anxiété et de la psychose au cours du traitement de la TB-MR a été respectivement de 13,3%, de 12,0% et de 12,0%. Alors que la majorité des individus atteints de dépression, d’anxiété et de psychose ont nécessité une pharmacothérapie psychiatrique, on a pu poursuivre avec succès l’administration de cyclosérine dans tous les cas sauf un.

**CONCLUSION** : Les comorbidités psychiatriques ne représentent pas une contre-indication au traitement de la TB-MR. La prise en charge des complications psychiatriques est possible sans compromettre le traitement antituberculeux.
RESUMEN

MARCO DE REFERENCIA: Las complicaciones psiquiátricas presentan un desafío en el tratamiento de pacientes con la tuberculosis multidrogo-resistente (TB-MDR). Trastornos psiquiátricos de inicio y también la presentación de nuevas complicaciones psiquiátricas relacionadas con las drogas anti-tuberculosas y factores psicosociales requieren un manejo agresivo.

LUGAR: Una organización no-gubernamental basada en la comunidad en Lima, Perú.

OBJETIVO: Revisar la literatura para complicaciones psiquiátricas asociadas con los medicamentos antituberculosos, describir la incidencia y prevalencia de la depresión, ansiedad y psicosis entre los individuos recibiendo terapia TB-MDR, y resumir con detalle los protocolos de manejo usados con este cohorte.

MÉTODOS: Una serie retrospectiva de casos fue realizada entre los primeros 75 pacientes que recibían terapia TB-MDR individualizado en Lima, Perú, de 1996 a 1999.

RESULTADOS: Depresión y ansiedad de inicio fueron observadas en 52,2% y 8,7%, respectivamente, de este cohorte. La mayoría de individuos con depresión de inicio experimentaron una mejora de síntomas depresivos durante el curso de su terapia antituberculosa. La incidencia de depresión, ansiedad y psicosis durante el tratamiento TB-MDR fue de 13,3%, 12,0%, y 12,0%, respectivamente. Aunque en la mayoría de individuos con depresión, ansiedad y psicosis requerían psicofármacos, se logró continuar el uso de cicloserina en todos menos un caso.

CONCLUSIÓN: Comorbididades psiquiátricas no son contraindicación para terapia TB-MDR. Manejo de complicaciones psiquiátricas es posible sin comprometer tratamiento anti-tuberculoso.