

**CASE REPORT****Psychosis During Multidrug Resistant Tuberculosis Treatment:  
A Case Report**

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**Abstract**

The use of second line antituberculous agents in the treatment of multidrug resistant tuberculosis has frequently be associated with the emergence of psychiatric side effects such as delirium, psychosis and depression. Even though the side effects usually resolved once the agent is withdrawn or antipsychotic treatment is started, the symptoms might still persist in some people making the management of tuberculosis itself difficult. In this case report, we demonstrated a case of a young lady who developed psychiatric side effects on the different antituberculous agents used and the challenge of managing her psychotic symptoms and medical illness.

**Keywords:** Delirium, Tuberculosis, Antituberculous Drug, Psychosis

**Introduction**

In Malaysia, although once has been eradicated, tuberculosis re-emerged with more resistant pathogen leading to complexity of treatment [1]. Tuberculosis is caused by Mycobacterium tuberculosis which is spread by the infected person through airborne droplets and primarily affect the lung (pulmonary tuberculosis) but other organs can be affected as well such as spine and brain (extrapulmonary tuberculosis) [2].

Antituberculous drug is the mainstay of treatment of tuberculosis; namely Isoniazid, Rifampicin, Ethambutol and Pyrazinamide as first line drugs [1]. Tuberculosis which is resistant to the treatment of Isoniazid and

Rifampicin is considered as multidrug resistant tuberculosis [2]. Poor compliance to antituberculous drug, inadequate treatment regime and comorbid medical illness have been identified as factors attributed to this condition which warrant the use of more extensive second line antituberculous treatment eg Cycloserine, Ethionamide and Moxifloxacin [2].

It has long been recognised that some patients on antituberculous drugs developed psychiatric manifestation secondary to the agents used. Confusion, insomnia, irritability, agitation, depression and psychosis has been associated with different types of antituberculous agent such as Isoniazid, Cycloserine and Fluroquinolone group [3]. This case presented is of interest

as it demonstrated the psychiatric side effects of different types of antituberculous drugs used, not merely a single agent as often discussed in other case reports.

### Case Report

We illustrate a case of Miss SAR, 22 year old lady who was admitted to the Respiratory Ward for management of multidrug resistant tuberculosis with history of being treated for two months but then defaulted treatment for 3 months. In the ward, she was given the regime of Isonazide, Ethionamide, Rifampicin, Pyrazinamide, Moxifloxacin, Cycloserine and Kanamycin.

Nine days after that, she was noted to have labile mood, irritability and aggressive behaviour. She would suddenly cried during conversation with her family members, scolding the doctors and staff nurses without reasons and shouting erratically. Referral to psychiatry team was made and Cycloserine was discontinued. Before the psychiatric team come to review the patient, the family requested for discharge against doctor advice as they believed that the symptoms were related to evil spirit and the want to seek traditional treatment. Antituberculosis drugs were continued at home.

Patient was readmitted again 10 days after that, as family members had difficulties managing her psychosis and aggressive behaviour at home. CT brain did not show any abnormal brain pathology. Lumbar puncture was also done which revealed normal result after that. She was seen by the psychiatric team and treated as delirium secondary to query TB encephalitis initially with differential diagnosis of Cycloserine induced psychosis, thus T Haloperidol 1.5mg twice daily was prescribed. She became well in 2 days. After a week, the

dose of Haloperidol was reduced to 1.5mg at night. At this point, antituberculosis drugs regime remained the same

Five days after dose reduction of Haloperidol, psychotic symptom re-emerged. As her mental state worsen despite dose increment of psychotropics, she began to exhibit some manic symptoms as well in which she had elated mood, laughing inappropriately, became overfamiliar with the staff and visitors of other patients and easily irritable with frequent profanities towards the others. She took off her clothes in the presence of male and making kissing gestures. The antipsychotic was then switched to Olanzapine. As for the antituberculosis treatment, Ethionamide was added to the regime. At maximum dose of 20 mg of Olanzapine after 2 weeks of initiation, patient became calm for the first time. The dose of Ethionamide was then increased. Within a week, her mental state deteriorated. Augmentation with sodium valproate was done. Concurrently, Ethionamide, Isoniazid and Rifampicin was stopped and para-aminosalicylic acid (PAS) was added. Patient became well again after four days of initiation of sodium valproate. Sodium valproate was ceased after a week but recommenced once more as the manic symptoms recurred. It is important to note that during all this while, her sputum AFB was still positive.

Her symptoms did not improved despite being on T Sodium Valproate 400mg twice daily and T Olanzapine 20mg at night. Electroconvulsive therapy (ECT) was considered but we were not able to proceed as patient was still smear positive and can't be transferred over to Psychiatry Ward. After 52 days of antituberculosis treatment, despite sputum AFB remained positive, PAS was stopped due to patient refusal. Psychotropic medications were continued.

3 days after stopping antituberculosis drugs, patient became well again with no mood or psychotic symptoms. After a week of being well, PAS was reintroduced and within 5 days, manic symptoms recurred, leading to its discontinuation. Family requested for discharge against medical advice after being in ward for almost 3 months as patient had tried running away from the hospital several times. At this point, she was not on any antituberculosis medication.

Upon review in clinic after 3 weeks, patient returned to her usual self. Family admitted that the psychiatric medications were only given to patient for about 3 days after discharge, then withheld until the time of review as the patient became well. She was readmitted again after 2 weeks to rechallenge the antituberculosis treatment. The antituberculosis medication was reintroduced one by one and each agent was given adequate time for observation for any side effects before introduction of the other; starting with IM Kanamycin, followed by Pyrazinamide, Bedaquiline, Linezolid, Pyridoxine and lastly Ethambutol in the duration of 6 weeks. There was no recurrence of mood or psychotic symptoms. Patient seroconverted after 2 weeks of Ethambutol reinitiation.

## Discussion

The emergence of psychiatric symptoms in patients treated on antituberculosis agents pose a challenge in the treatment of multidrug resistance tuberculosis. The use of multiple agents with similar side effects profile worsen the condition.

About 32.8% on patient on antituberculosis treatment developed psychiatric symptomatology [4]. Psychosis is one of the common side effects observed in patient on antituberculosis treatment. 5-12% of patients

with multidrug resistance tuberculosis developed psychosis during the course of treatment [5, 6]. Higher risk is observed in patient on multiple antituberculosis therapy [7]. Psychosis can occur as early as month after initiation of therapy and lasted for a month [6]. In most cases, to manage the psychosis, antipsychotic is introduced. In term of managing the psychotic symptoms occur as side effect of antituberculosis drugs, several strategies can be employed. Cessation of the drug can be done (if it won't give much effect to the whole treatment regime) for 1 to 4 weeks till the psychotic symptoms is controlled with antipsychotic drugs. In other instances, lowering the dose of offending drugs can be carried out as well [6].

In the case of Miss SAR, we can appreciate that even after the cessation of the suspected agent, the psychotic symptoms ceased but only to recur with the introduction of new agent. As the psychotic symptoms worsened, higher doses of antipsychotics and augmentation with mood stabiliser were used. This raised a question whether there is an underlying functional psychotic disorder which has been precipitated by the use of antituberculosis agent. The possibility was suggested as withdrawing antipsychotic when patient is symptom free in the absence of the antituberculosis agent led to recurrence of psychosis but was later rebuked as there was time when patient start to re-experienced psychotic symptoms after the introduction of antituberculosis drugs, despite having the antipsychotics on board.

The mechanism of development of psychosis in the first generation antituberculosis agent like isoniazid is still not well understood though it has been associated with the action of GABA antagonism [8]. As for the second generation antituberculosis drugs, several

research has been done on Cycloserine due to its marked effect on producing psychosis. Studies have found that as Cycloserine is a partial NMDA receptor antagonist [8]; its action on GABA and glutamate neurotransmitters can produce schizophrenia-like psychosis [9].

Starting with the use of cycloserine which reported 20-33% of psychiatric side effects [10], other antituberculosis agents that were used thereafter produced psychotic symptoms including para-aminosalicylic acid (PAS). PAS has not been reported to have any association with psychosis. Can the brain vulnerability be altered after the repeated exposure to multiple antituberculosis? Surprisingly, after a period of antituberculosis holiday, psychotic symptoms did not return with the slow reintroduction of the same multiple antituberculosis agents. More case discussion and research might give better insight into this enigma.

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