CASE SERIES

Isoniazid-Associated Psychosis: A Case Series from a Tertiary Care Hospital

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Abstract

Isoniazid (INH) is a cornerstone first-line antitubercular drug widely used in the treatment of tuberculosis. Although generally well tolerated, INH can rarely cause neuropsychiatric adverse effects, including acute psychosis, which may pose diagnostic and therapeutic challenges.

We report four cases of pulmonary tuberculosis in which patients developed acute-onset psychotic symptoms following the initiation of therapeutic doses of INH. The onset of symptoms occurred without prior psychiatric history and was temporally related to INH administration. The proposed mechanisms include INH-induced inhibition of monoamine oxidase and pyridoxine (vitamin B6) deficiency, both of which can alter neurotransmitter metabolism. All patients showed clinical improvement following withdrawal or dose modification of INH, administration of low-dose atypical antipsychotics, and pyridoxine supplementation. Causality and severity of adverse drug reactions were assessed using the World Health Organization–Uppsala Monitoring Centre (WHO-UMC) scale, the Karch-Lasagna algorithm, and the Modified Hartwig-Siegel severity scale. All cases were reported to the Adverse Drug Reaction Monitoring Centre under the Pharmacovigilance Programme of India (PvPI). INH-induced psychosis, though rare, is a clinically significant adverse drug reaction that requires early recognition and prompt management. Awareness of this potential complication, routine patient counselling, and vigilant pharmacovigilance are essential to ensure patient safety and optimize tuberculosis treatment outcomes.

Keywords: *Antipsychotic agents, isoniazid, psychosis, adverse drug reaction, brief psychiatric rating scale.*

INTRODUCTION

Isoniazid (isonicotinic acid hydrazide), commonly referred to as INH, remains a cornerstone in the first-line pharmacological management of tuberculosis (TB) [1]. Despite its longstanding use over several decades, INH remains one of the most efficacious and disease-specific agents available for TB treatment. Nevertheless, INH is known to be associated with a broad spectrum of adverse drug reactions (ADRs), particularly those involving the central and peripheral nervous systems. Reported neuropsychiatric manifestations include insomnia, headache, muscle fasciculations, optic neuropathy, peripheral neuropathy, psychotic symptoms, and increased psychomotor activity [2]. In some instances, psychiatric ADRs may present as hallucinations, delusional thinking, behavioural disturbances, disorganized cognition, and episodes of euphoria [3]. This paper presents four clinical cases suggestive of INH-induced psychosis, aiming to highlight this potentially serious but underrecognized complication. In this case series, none of the patients had a history of psychiatric illness before the start of ATT. In Case 1, alcohol withdrawal was initially included in the differential diagnosis. However, the patient denied recent or heavy alcohol consumption, had no prior history of withdrawal, and showed no evidence of autonomic hyperactivity, such as tremors, diaphoresis, tachycardia, hypertension, or agitation. The patient did not meet CIWA-Ar (Clinical Institute Withdrawal Assessment for Alcohol–Revised) criteria. Based on these findings, alcohol withdrawal was excluded, and the symptoms were attributed to INH. These cases were reported between December 2024 and April 2025.

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CASE PRESENTATION

Table 1 describes the clinical presentation and other clinical parameters for four cases.

DISCUSSION

In 1957, Jackson raised to light the first evidence of isoniazid causing psychosis [4]. Numerous case reports have since been published demonstrating the link between isoniazid therapy and psychosis [5]. The patients in this case series were diagnosed with primary pulmonary tuberculosis. They were initially placed on a rigorous two-month regimen that included the standard four first-line medications: pyrazinamide, ethambutol, rifampicin, and INH. One of the earliest rating scales, the BPRS, is used by physicians to assess a variety of psychological disorders, ranging from psychosis, anxiety, and depression. Higher scores indicate more severe psychopathology; the total scores range from 24 to 168. The BPRS scale has three severity levels: mild (total score 31-40), moderate (total score 41-52), and severe (total score>52) [6].

The severity and causality of adverse drug reactions (ADRs) were evaluated using three established tools: the Modified Hartwig and Siegel scale [7], the Karch

Table 1: Case series of 4 cases of isoniazid-induced psychosis.

Variable	Case 1	Case 2	Case 3	Case 4
Age and sex	38 years/male	33 years/female	56 years/female	27 years/female
Type of TB	Pulmonary tuberculosis	Pulmonary tuberculosis	Pulmonary tuberculosis	Pulmonary tuberculosis
Onset of psychosis diagnosis since isoniazid initiation	6 weeks	4 weeks	5 weeks	10 weeks
Psychiatric symptoms	Singing Bollywood songs loudly, aggressive, abusive behaviour, wandering, sudden weeping and laughing spells, poor oral intake, and disturbed sleep for 7 days.	Decreased social interaction; unprovoked anger outbursts, occasional episodes of smiling with muttering to himself, poor self-care, and decreased sleep. For 20 days.	incoherent speech, echolalia, paranoid delusions of familial conspiracy to seize property, auditory hallucinations, intermittent insomnia, and a one-month preference for darkness.	Disinhibited behaviour, aimless wandering, poor self-care, and decreased sleep and appetite for 8 days.
Comorbidities/ previous medical history	Chronic alcoholic and smoker	Undernutrition, Anaemia	Anaemia, diabetes	Undernutrition
BPRS Score* (severity)	58 (severe)	47 (moderate)	44 (moderate)	47 (moderate)
MMSE Score* (cognitive impairment)	16 (Moderate)	12 (Moderate)	14 (Moderate)	11 (Moderate)
Dechallenge was done	Yes	Yes	Yes	Yes
Treatment				
Antipsychotics	Olanzapine	Risperidone	Aripiprazole	Olanzapine
Response	Psychiatric features showed a good response	Behaviour improved	Behaviour improved	Behaviour improved
Psychotic symptoms emerging following the rechallenge of isoniazid	Rechallenge not done, modified ATT therapy was given	Rechallenge not done, modified ATT therapy was given	Rechallenge not done, modified ATT therapy was given	Rechallenge not done, modified ATT therapy was given

***BPRS:** Brief Psychiatric Rating Scale, **MMSE:** Mini-Mental State Examination.*

and Lasagna scale [8], and the WHO-UMC criteria [9] (**Table 2**). These ADRs were documented and submitted to the Adverse Drug Reaction Monitoring Centre under the Pharmacovigilance Programme of India (PvPI). The clinical features and symptom resolution observed in our case series closely resembled those of a 21-year-old female patient with no prior psychiatric history, who developed acute paranoid delusions, restlessness, and sleep disturbances within four days of starting isoniazid (INH) during the intensive phase of anti-tuberculosis therapy (ATT). Her symptoms resolved entirely within three weeks following antipsychotic intervention [10]. Two primary theories have been proposed to explain how isoniazid may trigger psychosis: (A) a reduction in pyridoxine (vitamin B6) levels, and (B) the inhibition of monoamine oxidase, which subsequently impacts neurotransmitters such as serotonin and catecholamines [11].

Table 2: Evaluation of causality and severity grading of reported adverse drug reactions associated with isoniazid-induced psychosis cases.

Case No.	WHO-UMC Scale	Karch and Lasagna Scale	Modified Hartwig and Siegel scale
Case 1	Probable	Moderate	Moderate (Level 3)
Case 2	Probable	Moderate	Moderate (Level 3)
Case 3	Probable	Moderate	Moderate (Level 3)
Case 4	Probable	Moderate	Moderate (Level 3)

In the present case series, discontinuing INH and initiating an antipsychotic drug resulted in complete remission. This emphasises the need to promptly treat

the psychiatric ADR as the outcome of the latter varies greatly from complete resolution of symptoms to suicide in a few cases [12]. Psychiatric ADR is one of the reasons responsible for non-compliance to medication, which increases disease burden as well as mortality rates. The caregivers must also be counseled appropriately in cases of neuropsychiatric ADR, paying special emphasis on adherence to medications prescribed thereafter and the possible outcomes.

CLINICAL IMPLICATIONS

The findings of this study support the hypothesis that psychosis associated with isoniazid (INH) may share a pathophysiological mechanism, characterized by elevated dopamine levels and reduced serotonin and GABA concentrations, with certain patients diagnosed with schizophrenia who exhibit significant responsiveness to low doses of atypical antipsychotic medications. Furthermore, supplementation with pyridoxine may enhance the therapeutic efficacy of atypical antipsychotics in preventing psychosis through the augmentation of GABAergic inhibition of dopamine.

CONCLUSION

Patients receiving isoniazid for TB infection should be closely monitored for psychotic and other neuropsychiatric symptoms, particularly during the first two months of treatment. Additional studies are needed to clarify the role of underlying risk factors, including genetic susceptibility and isoniazid pharmacokinetics, and to determine the effectiveness and appropriate dosing of pyridoxine in the management of isoniazid-associated psychosis.

CONSENT FOR PUBLICATION

Written informed consent was taken from the patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORS' CONTRIBUTION

VSD - Drafting the article, data collection, draft manuscript preparation

RRSD - Analysis and interpretation of results

GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work the author(s) limitedly used ChatGPT (GPT-4, OpenAI) to get language suggestions and do minor proofreading in some parts of the manuscript. After using this tool/ service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.

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