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Psychotropic Drugs and Liver Disorders: A Case Report

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Abstract | **Case Report**

Introduction: The World Health Organization (WHO) defines an adverse drug reaction (ADR) as "a noxious and unwanted reaction occurring at doses normally used in humans for the prophylaxis, diagnosis, or treatment of disease or the modification of a physiological function, or resulting from misuse of the drug or product." This definition implies that there is a certain degree of causal relationship (attributability) between the drug intake and the occurrence of the effect. Since all medications can cause adverse drug reactions, a risk-benefit analysis is essential whenever a medication is prescribed. Our work will focus on drug-induced liver injury (DILI), particularly psychotropic drugs. ***Objectives:*** We report the case of a young woman who developed liver enzyme disturbances while taking psychotropic medications. We discuss the importance of early diagnosis, risk-benefit assessment, and therapeutic window. The patient's overall hospital care will also be discussed. Our work will also address the literature on drug-related hepatotoxicity, particularly psychotropic drugs, and the appropriate course of action when assessing the benefit-risk ratio of their prescription. ***Conclusion:*** Drug-induced hepatotoxicity is a common problem in all medical disciplines. It is a diagnosis of exclusion, and the course following discontinuation of the offending medication helps clarify the imputability, thus raising the question of the risk-benefit ratio of treatment, particularly with regard to psychotropic medications. An effective, multidisciplinary assessment will allow for better management of these patient.

Keywords: Drug-induced, hepatotoxicity, imputability, psychotropic medications, undesirable effects.

INTRODUCTION

The World Health Organization (WHO) defines an adverse drug reaction (ADR) as "a harmful and unintended response to a medicinal product occurring at doses normally used in humans for the prophylaxis, diagnosis, or treatment of disease, or for the modification of physiological function, or resulting from misuse of the drug or product." This also includes reactions resulting from misuse, abuse, drug dependence, withdrawal syndrome, medication errors, drug inefficacy, defective or poor-quality products [1].

This definition implies a certain degree of causal relationship (accountability) between drug intake and the onset of the effect. In the absence of a causal link or if one is not investigated, the event is classified as an adverse event. Genetic polymorphisms affecting drug-metabolizing enzymes or drug targets can explain interindividual variations in pharmacokinetics or pharmacodynamics that may lead to these adverse effects.

Based on their mechanisms, ADRs are classified into 7 categories (A to G), with three main groups:

- **A (Augmented):** directly related to pharmacological properties of the drug
- **B (Bizarre):** unrelated to pharmacological action
- **C (Chronic):** associated with prolonged use

An ADR may be:

- **Severe:** causing death, life-threatening conditions, hospitalization (or prolonged stay), disability, significant impairment, congenital anomalies
- **Serious:** requiring drug discontinuation and additional care
- **Moderate or Mild:** not life-threatening

Most ADRs are dose-dependent; others are allergic or idiosyncratic. Symptoms can appear after the first dose or only with chronic use.

As all drugs can potentially cause ADRs, a benefit-risk analysis is crucial when prescribing. The

National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance Project (NEISS–CADES) estimated that there were 6 emergency visits per 1,000 persons annually in 2017–2019 due to medication-related issues. Roughly 39% led to hospitalization. Previous U.S. data showed that 3–7% of hospitalizations were due to ADRs [2].

To prevent ADRs, knowledge of drugs and their possible effects is essential, along with proper treatment choice, dose adjustment (based on age, liver/kidney function, interactions), early detection, gradual discontinuation when necessary, and thorough patient monitoring. Healthcare professionals are obligated to report any ADRs to pharmacovigilance systems for documentation and causality assessment.

Focus on Drug-Induced Liver Injury (DILI)

First described in the 1960s, DILI encompasses a range of liver pathologies following exposure to potentially hepatotoxic chemical compounds. DILI symptoms vary from asymptomatic liver enzyme elevation to severe hepatic damage. These are typically idiosyncratic, i.e., unpredictable and not dose-, route-, or duration-dependent.

DILI is responsible for 11–13% of acute liver failures, which may require liver transplantation. Frequently implicated drugs include:

- Antibiotics (e.g., amoxicillin/clavulanic acid)
- Antituberculars (especially isoniazid)
- NSAIDs
- Herbal compounds

There has been a significant rise in cases involving cardiovascular agents (9.8%), central nervous system drugs (9.1%), antineoplastic agents (5.5%), and analgesics (3.7%) over the past decade [3].

DILI is the most common cause of acute liver failure in the Western world. Apart from paracetamol overdose, most DILIs are idiosyncratic and immune-mediated, often linked to genetic susceptibility (e.g., HLA variants). With no specific diagnostic tests or biomarkers, DILI diagnosis relies on clinical suspicion after excluding other liver diseases.

Antibiotics are the most frequently associated class with idiosyncratic DILI. However, recent studies highlight the growing role of herbal and dietary supplements. Upon DILI onset, the offending drug must be stopped—especially with elevated transaminases (AST/ALT ≥5× upper normal limit) and/or jaundice (4). Given the poor prognosis without liver transplantation, early consideration of transplant is crucial.

DILI types include:

- Hepatocellular
- Cholestatic
- Mixed

They can also be categorized by immune involvement:

- Immune-mediated (allergic)
- Non-immune-mediated (non-allergic)

Psychotropics and Hepatotoxicity

Though often suspected in clinical practice, common psychotropics have a relatively low hepatotoxic potential. They are not consistently listed among high-risk agents. However, a pharmacovigilance case-control study identified several psychotropics with probable or highly probable DILI risk:

- **Antiepileptics** (e.g., valproic acid)
- **Antipsychotics** (clozapine, olanzapine, risperidone, amisulpride)
- **Antidepressants** (escitalopram, citalopram, mirtazapine)

In psychiatric practice, elevated liver enzymes may be incidentally discovered or investigated due to clinical signs. Since drug-induced liver injury is the fourth leading cause of hepatic disorders in the West, these findings frequently raise questions about continuing or discontinuing suspect medications—especially when data on hepatotoxicity is scarce, as with most psychotropics.

DILI is a diagnosis of exclusion. Improvement after discontinuing the suspected drug supports causality. However, interrupting psychotropic treatment may risk relapse or deterioration. Thus, psychiatrists play a key role not just in modifying pharmacotherapy but also in managing overall care.

Objectives:

We report the case of a young woman who presented with elevated liver enzymes while under psychotropic treatment. We discuss the importance of early diagnosis, assessment of the risk-benefit ratio, the concept of a therapeutic window, and the overall inpatient management of the patient. This case also provides an opportunity to review the existing literature on drug-induced hepatotoxicity—particularly related to psychotropics—and to outline the recommended approach for evaluating the benefit-risk balance in their prescription.

Case Report

We present the case of a 31-year-old unmarried woman, unemployed, from a middle socioeconomic background, with a one-year history of psychiatric follow-up for a manic episode in 2023 and substance use disorder involving tobacco and cannabis. She had no medical or surgical history and no family history of note.

She was brought to the emergency department by her family for the management of psychomotor agitation, grandiose delusions, and insomnia. The

clinical interview revealed delusional, manic, and hallucinatory syndromes, along with impaired judgment and lack of insight. A diagnosis of schizoaffective disorder was made.

She was started on 20 mg/day of olanzapine and 400 mg/day of the mood stabilizer Tegretol (carbamazepine). A few days after initiating treatment, she developed generalized redness and pruritus, prompting discontinuation of carbamazepine and a change in her regimen. She was switched to olanzapine 10 mg/day and quetiapine 150 mg/day, due to suspected carbamazepine allergy.

During her hospital stay, risperidone (6 mg/day) and chlorpromazine (Largactil 100 mg/day) were added to her antipsychotic regimen. After six weeks of hospitalization, her psychomotor state began to stabilize. However, she developed abdominal pain, nausea, vomiting, eyelid edema, and fever, without conjunctival jaundice. Liver function tests showed AST levels twice the upper limit of normal and gamma-glutamyl transpeptidase (GGT) 15 times the normal level, while alkaline phosphatase (ALP) and total bilirubin remained within normal limits.

An outpatient consultation with gastroenterology was arranged, and an extended workup failed to identify the cause of the liver enzyme disturbance. Drug-induced liver injury (DILI) was considered as a potential cause. The patient was switched to diazepam 20 mg/day, and a therapeutic drug holiday was implemented, resulting in a favorable outcome four weeks after drug cessation. Liver function tests returned to normal, raising suspicion about a psychotropic-induced hepatotoxicity.

In the case of Ms. W.C., several psychotropic medications were discontinued to assess causality. Chlorpromazine was stopped first, with no improvement after three days. Risperidone was tapered to 3 mg/day and subsequently discontinued. A few weeks after tapering off risperidone, GGT levels significantly decreased—dropping to twice the normal value within four weeks and eventually returning to normal.

Ms. W.C. was discharged six weeks later on solian (amisulpride) 300 mg/day, trileptal (oxcarbazepine) 600 mg/day, and disulfiram (Esperal) 100 mg/day. Psychiatric outpatient follow-up was initiated post-discharge. The adverse drug reactions were reported to the psychopharmacology department.

DISCUSSION

The management of severe psychiatric disorders requires an appropriate treatment regimen, the continuation of which largely depends on its tolerability. The prescription of antipsychotics is guided by a careful evaluation of the benefit-risk ratio of the selected molecule, always aiming for the lowest effective dose.

Most psychotropic drugs carry a variable risk of iatrogenic effects, which are not always easy to identify. Medication prescription, in general, is a medical act guided by clinical reasoning aimed at achieving therapeutic efficacy while minimizing the risk of adverse drug reactions (ADRs).

When selecting an antipsychotic, hepatic tolerance should often be considered due to the notable incidence of pre-existing liver disorders in psychotic patients (including risk factors such as alcoholism, addictive behavior, and polypharmacy involving potentially hepatotoxic substances) and the hepatotoxicity induced by these medications.

The incidence of drug-induced liver injury (DILI) is estimated to be 14 to 19 cases per 100,000 individuals. While the most common presentation is asymptomatic elevation of liver enzymes, DILI remains the leading cause of acute liver failure in most Western countries (accounting for over 50% of cases). Liver injury may occur at both therapeutic and overdose levels and may be the result of either direct intrinsic toxicity or idiosyncratic (unpredictable) reactions.

Symptoms of drug-induced hepatitis are nonspecific, making diagnosis challenging and the causal relationship between the medication and the liver injury often hard to establish. A reliable chronological link between drug exposure and the onset of liver injury is therefore critical. The latency period typically ranges from 1 to 5 days for intrinsic toxicity and from 5 to 90 days for idiosyncratic toxicity—although earlier onset may occur if there has been prior exposure. The pattern of liver enzyme elevation may be hepatocellular, cholestatic, or mixed; however, specific patterns cannot be reliably linked to particular drugs.

Atypical antipsychotics (amisulpride, clozapine, olanzapine, risperidone) are generally well tolerated hepatically. The incidence of hepatic disorders varies by compound but remains infrequent or rare overall. However, some published case reports exist, with difficult-to-establish causality due to highly variable onset (ranging from one day to several months) and frequent polypharmacy. Cases involving clozapine, olanzapine, and risperidone have been most frequently reported. Hepatic disorders are typically reversible upon discontinuation, although they may occasionally be accompanied by neurological, metabolic, or systemic disturbances. Given the potentially irreversible consequences, reintroducing the offending antipsychotic is contraindicated.

In some patients, limited hepatic disturbances (e.g., isolated enzyme elevations) may resolve without discontinuing the antipsychotic. Risk factors may

include high dosage or overdose, age (elderly or pediatric populations), obesity, and co-administration with other hepatotoxic agents or addictive substances. Multicenter studies would be beneficial to compare drugs by frequency of hepatic injury and long-term tolerability, as well as to identify risk factors.

Unfortunately, the mechanisms of hepatotoxicity are not fully understood for all implicated molecules. However, experimental studies have identified several pathways with specific drugs (e.g., paracetamol, valproic acid, halothane, nucleoside analogues). These include the formation of reactive metabolites through cytochrome P450, oxidative stress, lipid peroxidation, and mitochondrial membrane dysfunction leading to necrosis or apoptosis. Mitochondrial dysfunction may also result in steatosis or steatohepatitis. Other mechanisms involve disrupted lipid metabolism or bile acid secretion. Hepatocytes are not the only cells implicated; Kupffer cells and hepatic stellate cells may also play roles, particularly in chronic cases. Genetic, physiological, metabolic, and nutritional factors further modulate risk.

Although rare, hepatic reactions to atypical antipsychotics are documented, including in our case. The temporal link between drug introduction and symptom onset, rapid clinical and biological resolution after discontinuation, and the absence of other organic causes suggest a probable causal relationship. Medication causality was therefore confirmed.

Given the nonspecific presentation, diagnosis involves reviewing all ingested medications regardless of class. A detailed medical history is essential, focusing on timing and dosing. This is followed by an etiologic work-up to identify possible drug-induced hypersensitivity reactions. The Roussel Uclaf Causality Assessment Method (RUCAM) is a helpful tool in estimating the likelihood of drug-induced liver injury.

Management involves early discontinuation of the offending agent to halt hepatic damage and allow for spontaneous recovery in most cases. Although rechallenge may confirm causality, it is generally avoided in clinical practice due to ethical concerns.

In our patient, early hepatic symptoms, rapid worsening of liver function tests (LFTs) within 20 days, initial elevation of GGT and ALP followed by progressive normalization after a drug-free period, and fluctuation of LFTs aligned with medication changes—support risperidone as the likely culprit.

Risk factors described in the literature include female gender, advanced age, pre-existing liver disease, obesity, alcohol dependence, and polypharmacy. Ms. W.C. was female with no prior liver issues or alcohol use.

She was treated with a therapeutic window and diazepam 20 mg/day, which was well tolerated and led to improvement in hepatic and psychiatric symptoms. A new psychotropic regimen with lower hepatic risk (Solian 300 mg/day, Trileptal 600 mg/day, and Esperal 100 mg/day) was introduced with regular monitoring, and it was well tolerated.

According to the literature, antipsychotics can cause liver enzyme elevations—usually benign (up to three times the upper limit of normal) and not requiring treatment discontinuation. Among second-generation antipsychotics, clozapine and risperidone are most often implicated, with 30–50% of patients showing asymptomatic liver enzyme elevations. Olanzapine causes transient elevations in 9% of cases. Quetiapine is rarely associated with hepatotoxicity.

In a published case-control study, the risk of hepatotoxicity was 34.6% for clozapine and 18.6% for olanzapine. First-generation antipsychotic haloperidol is associated with a two-fold liver enzyme increase in 17% and three-fold in 2.4% of patients. Chlorpromazine has also been implicated—1–2% of patients may develop jaundice within five weeks of starting treatment. Mild and transient LFT elevations are common but usually resolve despite ongoing therapy.

Among mood stabilizers, carbamazepine is a known hepatotoxin. Valproic acid can cause mitochondrial toxicity with enzyme elevations and steatosis.

Finally, in patients with schizophrenia, schizoaffective disorder, or bipolar disorder, antipsychotics contribute to metabolic syndrome and associated liver complications.

Discontinuing a psychotropic is a necessary but delicate decision, given the risk of psychiatric decompensation, depending on the underlying condition and tapering speed. Abrupt cessation increases the risk of relapse. Psychotherapeutic support and close monitoring are crucial during this vulnerable period.

CONCLUSION

Drug-induced hepatotoxicity is a common issue across all medical fields. It remains a diagnosis of exclusion, with confirmation generally based on clinical improvement after withdrawal of the suspected drug. The decision to discontinue a medication raises the question of benefit-risk balance—especially for psychotropics, where literature remains limited. Suspending treatment risks psychiatric relapse and may hinder therapeutic outcomes. Therefore, enhanced non-drug therapies and psychiatric monitoring are critical. Effective, multidisciplinary evaluation will ensure optimal care for these patients.

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