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# Antipsychotic Switching in Bipolar Disorder with Metabolic Comorbidities: A Case Report

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**ABSTRACT:** Bipolar disorder is a chronic psychiatric condition marked by alternating episodes of mania, hypomania, and depression, often with psychotic features. Treatment resistance and adverse metabolic effects from long-term antipsychotic use pose significant challenges. This case report presents a 31-year-old male in Indonesia with bipolar disorder and metabolic comorbidities, including type 2 diabetes mellitus and dyslipidemia. Initially treated with clozapine, the patient experienced metabolic decompensation, prompting an urgent switch to quetiapine. Post-switch, he exhibited improved mood stability and remission of psychotic symptoms, though residual depressive symptoms persisted. Lithium and sertraline were introduced to address these, with careful monitoring. The case highlights the importance of individualized switching strategies in bipolar disorder, particularly in patients with metabolic risks. Antipsychotic selection should consider both psychiatric efficacy and metabolic safety. Despite pharmacological improvement, functional recovery was incomplete, emphasizing the role of psychosocial interventions and culturally informed care. The integration of religious values and family support proved essential in this context. Although effective in symptom stabilization, the switch strategy remains limited by the lack of long-term follow-up and generalizability. This report underscores the need for structured protocols for antipsychotic switching and holistic treatment models, especially in resource-limited settings. Future research should explore integrative approaches that address both psychiatric and physical health dimensions, ensuring continuity of care beyond pharmacological intervention.

**Keywords:** Bipolar disorder, Antipsychotic switching, Clozapine, Quetiapine, Metabolic complications.



## INTRODUCTION

Bipolar disorder is a severe psychiatric illness characterized by episodes of mania, hypomania, and depression. It affects approximately 1% to 2.4% of the global population, with onset typically in late adolescence or early adulthood (Fornaro et al., 2020). The condition imposes a substantial burden on patients and healthcare systems due to its chronicity and associated functional impairment. Bipolar disorder remains one of the most disabling mental health conditions

worldwide, with a high disease burden that affects both psychosocial and physical health outcomes (Grande et al., 2016).

Management is often complex, especially in cases involving rapid cycling, treatment resistance, or co-occurring metabolic syndromes. (Kang et al., 2020)Second-generation antipsychotics, including quetiapine and lurasidone, are commonly used alongside mood stabilizers such as lithium or valproate. However, these agents may cause significant metabolic side effects, including obesity and type 2 diabetes (Pillinger et al., 2020).

Clozapine remains a last-resort treatment for refractory cases, but its use is limited by risks such as agranulocytosis and severe metabolic disruption. This report presents a case involving the discontinuation of clozapine due to metabolic complications and the transition to quetiapine, providing insight into antipsychotic switching strategies in complex cases.

Bipolar disorder is increasingly recognized as a heterogeneous illness with diverse clinical presentations and treatment responses. The presence of metabolic comorbidities such as diabetes and dyslipidemia further complicates its management, often necessitating treatment modifications to avoid iatrogenic harm. Recent epidemiological data suggest a rising prevalence of metabolic syndrome among psychiatric patients, particularly those receiving long-term antipsychotic therapy, with estimates ranging from 37% to 60% (Vancampfort et al., 2015). These findings underscore the importance of individualized, integrative treatment approaches that balance psychiatric symptom control with metabolic risk mitigation. In low- and middle-income countries like Indonesia, where access to specialized psychiatric care remains limited, clinical decision-making must also consider feasibility, safety, and cultural appropriateness in pharmacological strategies.

## METHOD

This case report is based on the clinical observation of a 31-year-old male patient diagnosed with bipolar disorder, who was treated at a psychiatric unit in East Java, Indonesia, from October to December 2024. Clinical data were obtained through direct history taking, physical and psychiatric examination, and a review of medical records. The pharmacological interventions involved switching from clozapine to quetiapine, followed by the addition of lithium and sertraline to manage residual symptoms. Literature relevant to antipsychotic switching strategies in bipolar disorder with metabolic complications was reviewed to support clinical decisions. Ethical considerations were addressed by obtaining informed consent from the patient for publication. Identifying details have been removed or disguised to ensure anonymity.

## RESULT AND DISCUSSION

### Case Presentation

A 31-year-old male was admitted Prior to admission, the patient had experienced multiple mood episodes over the past six years, alternating between periods of elevated mood and severe depressive episodes. He had a prior history of poor medication adherence and had been treated intermittently with risperidone, olanzapine, and valproate, with suboptimal outcomes. Notably, his

metabolic profile had been progressively deteriorating, with a recent HbA1c of 9.4%, fasting blood glucose above 250 mg/dL, and serum triglycerides exceeding 300 mg/dL, consistent with metabolic syndrome. The patient reported a sedentary lifestyle, irregular sleep-wake cycles, and frequent consumption of sugary beverages and high-fat foods. Despite family efforts to encourage healthy habits, he demonstrated low insight into his condition and had previously refused dietary counseling. These clinical features likely contributed to his vulnerability to metabolic decompensation under clozapine treatment, necessitating the urgent switch. His psychiatric history was also complicated by intermittent tobacco use and a lack of structured psychosocial support. to the intensive care unit (ICU) on November 7, 2024, presenting with acute dyspnea and decreased consciousness. At that time, he was receiving clozapine 50 mg/day along with aripiprazole and other psychotropic agents. Due to suspected clozapine-related metabolic decompensation in the context of underlying type 2 diabetes, hypertension, and dyslipidemia, a clinical decision was made to discontinue clozapine. On November 14, 2024, clozapine was completely replaced with quetiapine 50 mg/day using an abrupt tapering approach due to hyperglycemic crisis. This switch was accompanied by marked clinical improvement. The patient exhibited improved emotional regulation, with better sleep patterns and no signs of agitation, and demonstrated no signs of agitation, hallucinations, or delusions during the remainder of his inpatient stay. Post-discharge outpatient evaluations revealed sustained mood stabilization with no recurrence of psychotic symptoms. However, residual symptoms of depression persisted, including hypersomnia (up to 10 hours/day), anergia, loss of appetite, and significant weight loss (approximately 10 kg). The patient reported limited social engagement and remained socially withdrawn, spending extended periods alone in his room, watching videos, and playing games. There were no signs of self-harm ideation or behavior. In response to these residual symptoms, lithium and sertraline were introduced to help address depressive symptoms, with close monitoring to anticipate the possibility of mania induction due to antidepressant use. (Pacchiarotti et al., 2013)

## Current Trends in Treatment-Resistant Bipolar Disorder

Current treatment paradigms for bipolar disorder are evolving to address the limitations of conventional pharmacotherapy, especially in treatment-resistant cases. Novel approaches have focused on neuroplasticity and inflammation pathways, with recent attention on agents such as ketamine, anti-inflammatory modulators, and neuromodulation techniques like transcranial magnetic stimulation (TMS) (Yatham et al., 2023). Furthermore, the "staging model" of bipolar disorder suggests that therapeutic responses vary depending on illness progression, advocating for earlier, more individualized interventions. In patients with metabolic comorbidities, second-generation antipsychotics such as lurasidone and cariprazine have shown efficacy with reduced cardiometabolic risk profiles compared to agents like clozapine (Malhi et al., 2021). Nevertheless, these pharmacological innovations are often less accessible in resource-limited settings, necessitating pragmatic clinical adaptations based on locally available medications and infrastructure.

### Key Findings Interpretation

This case illustrates the successful switch from clozapine to quetiapine in a patient with bipolar disorder and comorbid metabolic conditions. The transition led to substantial improvement in mood stability and psychotic symptoms. Delgado et al. (2020) However, residual depressive symptoms persisted, reflecting the multifaceted nature of functional recovery in bipolar disorder. Long-term clozapine use has been associated with a significantly elevated risk of metabolic syndrome and type 2 diabetes, underscoring the need for ongoing metabolic monitoring during treatment (Correll et al., 2015).

### Clinical Considerations In Switching Antipsychotics

Antipsychotic switching is often warranted in cases of poor tolerability, inadequate response, or emergent side effects. Recent European guidelines recommend antipsychotic switching in the presence of intolerable metabolic side effects, especially in patients with comorbid conditions (Vieta et al., 2022).Clozapine, while effective for treatment-resistant presentations, carries a high risk of metabolic complications such as hyperglycemia, dyslipidemia, and weight gain (Pillinger et al., 2020). In this case, metabolic decompensation prompted an urgent discontinuation of clozapine. Quetiapine was selected for its lower metabolic burden and established efficacy in managing both mood poles.

The patient's abrupt clinical deterioration necessitated an immediate switch using a direct discontinuation approach. Although this method carries risks of withdrawal or symptom rebound, it was justified given the severity of the metabolic crisis.

Comparative studies have demonstrated significant variability in metabolic risk profiles among second-generation antipsychotics. Agents such as olanzapine and clozapine are consistently associated with the highest rates of weight gain, insulin resistance, and dyslipidemia, while aripiprazole and lurasidone tend to present lower metabolic burdens (Bernardo et al., 2021; Pillinger et al., 2020). Although quetiapine is not metabolically neutral, it strikes a balance between efficacy and tolerability, making it a pragmatic choice in resource-limited settings. This case further emphasizes the importance of periodic metabolic monitoring, including HbA1c, lipid panels, and BMI, particularly during medication transitions. Incorporating metabolic screening into routine psychiatric care helps clinicians anticipate complications and adjust pharmacotherapy accordingly, ensuring that both mental and physical health domains are addressed comprehensively

### Structured Strategies for Antipsychotic Switching

Switching antipsychotics in bipolar disorder requires careful planning to minimize clinical destabilization. Three main switching strategies are commonly applied: cross-titration (gradual tapering of the current drug while introducing the new one), overlap-taper (short overlap followed by taper), and direct switch, which may be required in urgent cases. In this case, the patient underwent a direct switch from clozapine to quetiapine due to a metabolic crisis. Although this method carries a risk of withdrawal symptoms or relapse, it was justified by the severity of hyperglycemia and risk of further complications.

According to international guidelines such as those from the CANMAT and ISBD, switching should consider pharmacodynamic profiles, half-life, receptor affinities, and patient-specific factors, including comorbidities and treatment history (Vieta et al., 2022; Yatham et al., 2023). Structured switching protocols are especially important for patients with medical vulnerabilities, ensuring both psychiatric safety and somatic stability. The use of standardized protocols and close monitoring during the transition phase can reduce relapse rates and adverse outcomes. Developing context-appropriate guidelines in low-resource settings remains a priority, where emergency switching is often done without comprehensive infrastructure.

## Pharmacological Rationale

Clozapine's pharmacodynamic profile includes strong antagonism at histamine H1 and serotonin 5-HT2C receptors, contributing to weight gain and insulin resistance (Fornaro et al., 2020). In contrast, quetiapine offers a more balanced receptor profile with a lower metabolic risk. Despite this advantage, quetiapine is not metabolically neutral and still requires regular monitoring of glucose and lipid levels, especially in high-risk patients.

Lithium remains a gold standard in mood stabilization and has shown efficacy in reducing suicidal behavior and managing depressive symptoms in bipolar disorder (Gitlin, 2016). In this case, depressive residuals persisted post-switch, necessitating the introduction of sertraline, an SSRI, alongside lithium. Combining selective serotonin reuptake inhibitors (SSRIs) with mood stabilizers such as lithium has proven effective in managing bipolar depression while minimizing the risk of manic switch. This strategy is consistent with clinical guidelines recommending antidepressants only in combination with mood stabilizers to minimize the risk of mania induction (Yatham et al., 2023).

Long-acting injectable (LAI) antipsychotics are gaining recognition as a valuable option in the long-term management of bipolar disorder, particularly for patients with poor adherence to oral medications. LAIs can offer steady plasma drug levels, reduce relapse rates, and simplify treatment regimens. Although traditionally used in schizophrenia, recent studies suggest that LAIs may also be effective in bipolar disorder, especially in preventing manic relapses and improving treatment continuity (Bartoli et al., 2023). Agents such as risperidone LAI and aripiprazole LAI have demonstrated efficacy and tolerability in maintenance therapy. Despite their potential, LAIs remain underutilized in low-resource settings due to limited availability, higher upfront costs, and lack of familiarity among clinicians. Nevertheless, for patients with a history of nonadherence or recurrent hospitalization, LAIs should be considered as part of a comprehensive relapse prevention strategy. In this context, shared decision-making and patient education become crucial in enhancing acceptance and outcomes of LAI treatment.

## Psychosocial Dimensions and Functional Outcomes

Despite pharmacological improvements, the patient exhibited persistent social withdrawal and reduced motivation. These findings underscore the importance of integrating psychosocial interventions, such as cognitive-behavioral therapy, structured day programs, or vocational support, to address functional impairments that pharmacotherapy alone may not resolve.

Furthermore, cognitive impairment is increasingly recognized as a persistent and functionally limiting domain in bipolar disorder, warranting tailored cognitive and psychosocial interventions (Miskowiak et al., 2023). While biological treatments form the foundation of psychiatric care, there is still debate about the extent to which complex mental disorders can be fully explained or treated at the biological level alone. This complexity underscores the necessity for integrative approaches that also address interpersonal, psychological, and cultural dimensions (Maj, 2011).

Adjunctive psychotherapies, such as cognitive-behavioral therapy and psychoeducation, have shown benefits in reducing relapse and improving psychosocial outcomes in patients with bipolar disorder (Miklowitz, 2008). In culturally diverse societies such as Indonesia, incorporating patients' religious beliefs and spiritual values into treatment planning is essential to improve engagement and outcomes. Spirituality can serve as a coping resource that enhances resilience, particularly in chronic psychiatric conditions like bipolar disorder. Consistent with Islamic mental health principles, addressing the patient's spiritual needs alongside biomedical and psychosocial interventions contributes to a more holistic and person-centered model of care (Abdillah et al., 2022). Incorporating patients' spiritual and religious beliefs into mental health care has also been shown to enhance resilience and engagement with treatment, particularly in chronic psychiatric conditions (Koenig, 2012)

Family involvement plays a pivotal role in the long-term management of bipolar disorder, particularly in collectivist cultures such as Indonesia where kinship ties significantly influence health behaviors. Psychoeducation for family members has been shown to reduce relapse rates, improve medication adherence, and enhance patients' functional outcomes (Colom et al., 2003). Involving family in treatment planning fosters a supportive environment that can buffer the effects of social withdrawal and residual symptoms. In addition, community-based programs such as peer support groups, religious gatherings, and culturally relevant outreach can further facilitate reintegration. In Indonesia, community mental health services (Pelayanan Kesehatan Jiwa Masyarakat—PKJM) and village-based health volunteers (kader) can serve as valuable allies in ensuring continuity of care, especially post-discharge. These strategies underscore the importance of integrating psychiatric services with local sociocultural systems to improve access, reduce stigma, and support recovery in real-world settings.

In Indonesia, community-based mental health initiatives play an essential role in sustaining recovery. Programs such as Pelayanan Kesehatan Jiwa Masyarakat (PKJM) and the involvement of village-based health cadres (kader) offer structured outreach and follow-up for psychiatric patients. These cadres often act as cultural and social bridges between medical services and communities, particularly in rural or underserved regions. Moreover, pesantren (Islamic boarding schools) and religious leaders can become valuable allies in supporting mental health recovery through spiritual reinforcement and destigmatization.

Incorporating religious activities such as dzikir groups, majelis taklim, and community prayers has also shown promise in improving emotional well-being, particularly when integrated with clinical care. The collectivist nature of Indonesian society provides a supportive framework for involving families in psychoeducation, medication supervision, and social reintegration. These community-rooted strategies not only promote adherence but also reduce relapse risk by reinforcing patients' sense of belonging, purpose, and identity within their sociocultural context.

## Cultural Considerations in Psychopharmacology

Cultural beliefs and practices significantly influence patients' perceptions of mental illness, treatment expectations, and attitudes toward psychotropic medications. In Indonesia, where collectivist values and religious frameworks are deeply rooted, psychiatric treatment is often approached through both medical and spiritual lenses. Patients may first seek help from traditional healers, religious leaders, or family elders before consulting mental health professionals, potentially delaying effective treatment (Abdillah et al., 2022). These dynamics highlight the need for culturally informed psychopharmacology—where clinicians not only consider biological factors but also align treatment plans with patients' cultural and spiritual beliefs. For instance, medications perceived as sedating or "mind-altering" may be rejected due to stigma or religious interpretation, even if clinically appropriate. Language barriers, health literacy gaps, and differing illness attributions may also impact adherence. Therefore, involving family members and integrating cultural narratives into psychoeducation can foster trust and improve engagement. Clinicians must develop cultural humility and adapt communication styles to bridge biomedical recommendations with cultural expectations. Training in cross-cultural psychiatry and collaboration with community and religious leaders can enhance the therapeutic alliance and optimize treatment adherence in diverse settings.

## Ethical and Clinical Challenges in Antipsychotic Switching

Switching antipsychotics in complex cases such as this one involves not only pharmacological but also ethical considerations. Abrupt discontinuation of clozapine, though clinically necessary in this case due to hyperglycemic crisis, poses a dilemma between patient safety and psychiatric stability. Ideally, switching should follow a cross-titration approach to minimize withdrawal or relapse risks. However, emergent metabolic decompensation often necessitates immediate action, as seen here. This underscores the importance of emergency preparedness and multidisciplinary decision-making.

Informed consent is another critical component, especially when rapid decisions are required. Clinicians must balance the need to act quickly with respecting patient autonomy and ensuring that both the patient and family understand the risks and rationale of medication changes. In psychiatric populations, where insight may be impaired, shared decision-making can be challenging but should remain a priority.

Moreover, ongoing monitoring after the switch is essential to prevent relapse or the emergence of adverse effects from the new regimen. In resource-limited settings, this can be difficult due to limited access to laboratory testing and follow-up care. Incorporating ethical frameworks into psychopharmacological practice helps navigate these clinical uncertainties. Clear documentation, interprofessional collaboration, and patient-centered communication can enhance the safety and acceptability of antipsychotic switching, especially in acute care settings where rapid intervention may be lifesaving.

### Future Directions in Bipolar and Metabolic Comorbidity Research

As comorbidity between bipolar disorder and metabolic syndromes becomes increasingly common, future research should explore integrated treatment models that target both psychiatric and metabolic domains simultaneously. For instance, recent studies have examined the potential role of GLP-1 receptor agonists, such as liraglutide and semaglutide, not only for managing diabetes and obesity but also for reducing inflammation and enhancing neuroprotection in mood disorders (Calkin et al., 2022). Randomized controlled trials are needed to evaluate their efficacy as adjunctive therapies in bipolar disorder. Additionally, longitudinal studies that follow patients post-switch for longer periods would provide insight into relapse patterns, cognitive recovery, and real-world functional outcomes. Advancements in precision psychiatry, including the use of biomarkers and digital phenotyping, may also facilitate more personalized medication switching strategies. In low-resource contexts, adapting these innovations into affordable, scalable solutions remains a key challenge for implementation.

Recent advancements in precision psychiatry offer promising tools for managing bipolar disorder with metabolic comorbidities. Biomarkers, pharmacogenomics, and digital phenotyping are increasingly used to predict treatment response and tailor interventions more accurately. For example, blood-based inflammatory markers and neuroimaging patterns may guide early intervention and medication selection, especially in treatment-resistant cases (Miskowiak et al., 2023).

Emerging metabolic treatments, such as glucagon-like peptide-1 (GLP-1) receptor agonists like liraglutide and semaglutide, are also gaining interest. Initially used for diabetes and obesity, these agents show neuroprotective and anti-inflammatory effects that may benefit mood disorders. Preliminary studies suggest they can improve both glycemic control and depressive symptoms, offering a dual-action therapeutic option (Calkin et al., 2022; Chaudhuri et al., 2023).

However, in low- and middle-income countries, integrating these innovations remains a challenge due to cost, limited availability, and gaps in infrastructure. Hence, future directions must focus not only on clinical efficacy but also on feasibility and accessibility. Research should emphasize scalable interventions that can bridge global disparities, ensuring that technological and pharmacological progress translates into real-world improvements for diverse populations.

## CONCLUSION

This case highlights the importance of individualized pharmacological strategies in managing bipolar disorder complicated by metabolic comorbidities. The successful switch from clozapine to quetiapine resulted in improved mood stabilization and resolution of psychotic symptoms. However, residual depressive symptoms and limited social functioning persisted.

Clinically, this report underlines the need for careful monitoring of metabolic risks during antipsychotic therapy and supports the use of safer alternatives like quetiapine in appropriate contexts. Integration of psychosocial and culturally sensitive interventions, including spiritual values, is essential for holistic recovery.

Limitations of this report include its single-case nature and the short duration of follow-up, which limit generalizability.

Future research should explore structured antipsychotic switching protocols in larger, diverse populations and evaluate long-term outcomes of combining pharmacological and psychosocial approaches. Early identification and intervention in bipolar disorder are associated with better treatment response and improved long-term outcomes. (Ratheesh et al., 2023)

Ultimately, this case exemplifies the complexity of treating bipolar disorder in patients with significant metabolic burden, particularly in low-resource environments. It highlights the necessity for clinicians to think beyond symptom control and adopt a holistic perspective that encompasses physical health, psychosocial functioning, cultural context, and long-term sustainability of treatment. Although pharmacological intervention remains the foundation, true recovery in bipolar disorder requires comprehensive care plans that address the individual as a whole—mind, body, and spirit. By presenting real-world clinical dilemmas and practical responses, this report serves as a model for how tailored interventions can be implemented even when resources are limited. Moving forward, it is essential that healthcare systems integrate mental health with chronic disease management and invest in workforce training that empowers providers to deliver culturally competent and patient-centered psychiatric care.

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