# RESEARCH ARTICLE

# BLOOD MONITORING OF MOOD STABILIZERS AND ANTIPSYCHOTICS IN BIPOLAR DISORDER

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## ARTICLE INFO

## ABSTRACT

***Background:*** Bipolar disorder (BD) is a lifelong episodic mental disorder that causes powerful mood swings. It is manageable through a variety of pharmacological interventions of mood stabilizers and antipsychotics, of which encompass several different adverse drug effects (ADEs) and have narrow therapeutic windows. Therefore, it is crucial to conduct routine blood monitoring based on standard international recommendations such as that of the National Institute of Clinical Excellence (NICE). ***Objectives and Rationale:*** To conduct an Audit that looks at long-term adherence of blood monitoring of mood Stabilizers and antipsychotics to NICE guidelines in the behavioural medicine department, Sultan Qaboos University Hospital (SQUH)to provide recommendations. Methods: Patients of all ages who were diagnosed with BD on antipsychotics and mood stabilizers were admitted to the Department of Behavioral Medicine for a period of 1 year were included. The data was collected retrospectively and compared to the NICE guidelines for blood monitoring. ***Results:*** A total of 249 BD patients met the inclusion criteria in the study. 219 of them were prescribed with Antipsychotics. Lipid, prolactin and glucose were measured only 9.1 %( 9), 29.7 %( 65) and 18.6 %( 40) respectively. 144 of thepatients were prescribed with Sodium Valproate. Complete Blood Count and Liver Function were measured only 31.7 % (97) and 32.6(45) respectively. 41 patients were prescribed with Lithium; urea, thyroid and plasma drug levels were measured 61.5 %( 24), 51.2 %( 21) and 57.5 %( 23) respectively. Finally, 12 patients were prescribed with Carbamazepine. Urea, CBC and Plasma drug levels were only measured 8.3 %( 1), 25 %( 3) and 8.3 %( 1) respectively. ***Conclusion:*** Blood monitoring of Mood Stabilizers and Antipsychotics in BD patients at SQUH falls below standards when compared to NICE guidelines. The findings could be due to several organizational and patient factors. Measures need to be taken and further audits need to be conducted to improve adherence to monitoring recommendations.

# INTRODUCTION

Bipolar Disorder (BD), also known as Manic-depressive illness, is a life-long mental disorder that causes strong and powerful mood swings. Those mood swings vary between energetic moods, extreme happiness, elation "emotional highs" and sad, hopelessness, loss of any interest, irritability, and depression "emotional lows". BD mood swings affect the ability of the patient to think, judge and behave appropriately and clearly. Therefore, prompt treatment is mandatory. These episodes can occur a few or many times during a year and most people will behave emotionally between episodes (Mayo clinic, 2020). According to The Global Burden of Diseases, Injuries, and Risk Factors Study 2017, the bipolar disorder affects about 45 million people globally, which makes it a huge burden causing many suicides and problems worldwide. (James et al., 2018) (Girardi et al., 2016). The BD can be managed and treated with pharmacological treatment plan of mood stabilizers, anti-psychotics (NIMH, 2020) and psychotherapy.

The pharmacological anti-psychotics include older or also known as typical anti-psychotics (such as; Chlorpromazine, Fluphenazine, Haloperidol, Perphenazine, Thioridazine, and Trifluoperazine). As well as, newer or also known as atypical antipsychotics (such as Aripiprazole, Asenapine, Clozapine, Olanzapine, Quetiapine, Risperidone and Ziprasidone) (AHRQ, 2013) (Girardi et al., 2016). Anti-psychotics work by predominantly acting on the D2-like subfamily of receptors and blocking them (Seeman and Kapur, 2000). Mood stabilizers include lithium, sodium valproate, carbamazepine, and lamotrigine. Lithium is considered as the golden standard for the treatment of bipolar disorders, even with the decline of its use in the past few years, it is still viewed as the go-to drug for bipolar disorder patients and is very effective in reducing suicide and symptoms in these patients (Girardi et al., 2016). Despite the well-known efficacy and success of those medications, they are long-term medications and are known to have many adverse drug effects (ADEs). Atypical anti-psychotics can cause obesity and weight gain, leading to metabolic syndrome. This is caused by either the 5-hydroxytryptamine2 antagonism of the feeding centre in the hypothalamus or by its deficiency.

However, the exact cause is not yet known and due to those adverse effects, it is important to look at the tolerability of the antipsychotics (Joshi et al., 2019). However, typical antipsychotics can cause extrapyramidal side effects (e.g., dystonia, akathisia, parkinsonian features, and tardive dyskinesia). As for lithium, the adverse drug effects are nausea, lethargy, fatigue, tremors, and an increase in the appetite and in the white blood cell count of the patient,as well as, causing polydipsia and polyuria. Also, a risk factor that increases those adverse drug effects for the lithium mood stabilizer is its narrow therapeutic window, which could be very detrimental when it causes lithium toxicity (Joshi et al., 2019). Other mood stabilizers, can cause nausea, vomiting and teratogenic side effects making them less likely to be used in childbearing women. Therefore, due to those significant drug adverse effects for antipsychotics and mood stabilizers, it is important to conduct regular blood monitoring. Blood safety monitoring is an essential component in the therapy of BD patients. The recommendations for monitoring are given by several health organizations such as the International Society for Bipolar Disorders (ISBD) and National Institute for Clinical Excellence (NICE) (Ng et al., 2013). According to an audit conducted in 2016 in Sultan Qaboos University Hospital (SQUH) in Oman, it was found that the quality of blood monitoring, particularly of that of lithium wasshort. Only 30% were found to have acceptable lithium testing, 9% had adequate serum urea and creatinine monitoring and 11% had adequate thyroid function tests (Al-senawi, 2016). Additionally, there are no audits in Oman on other mood stabilizers and antipsychotics. Consequently, due to the adverse drug effects of mood stabilizers and anti-psychotics and the previous poor audit figures, there is a substantial need of new audits on blood monitoring. Therefore, the present audit aimed to conduct, compare and assess the adherence of BD patients with NICE guidelines in SQUH Department of Behavioral Medicinewill give a clearer view of adherence to medications. Hence, give recommendations to reduce the complications and further improve the quality of treatment of bipolar disorder.

## Aim of the Study

- Evaluate the performance and determine the adherence to the NICE guidelines in the Department of Behavioral Medicine, SQUH.
- Provide recommendations to improve adherence. Therefore, the standard of care.

## Specific Objectives

- To conduct the Audit to look at long-term blood monitoring of both typical and atypical anti-psychotics in bipolar disorder.
- To conduct the Audit to look at long-term blood monitoring of Mood Stabilizers in bipolar disorder.

# METHODS

***Study design and Data Collection:*** This retrospective clinical audit study was done in the Department of Behavioral Medicine at the Sultan Qaboos University Hospital (SQUH). The extent of adherence was concerning in regards to the NICE Blood Monitoring guidelines for Antipsychotics and Mood Stabilizers in Bipolar Disorder (BD) patients. The audit included patients from all age groups with BD that were admitted to the department from the 1st of January 2018 to the end of December 2018, who received the medications for 6 months or longer. Patients who stopped the medications within 6 months were excluded. The study included a total of 250 patients. This study looked at prescribed medications which were atypical antipsychotics such as (Olanzapine, Risperidone, Quetiapine and Aripiprazole). Typical Antipsychotic (Haloperidol) and Mood Stabilizers (Lithium, Sodium Valproate and Carbamazepine). The data was collected from the TrakCare System Electronic Patient Records. Ethical approval for this study was obtained through the Medical Research Committee at the College of Medicine and Health Sciences at Sultan Qaboos University in August 2019 (MERC #2171).

**Analysis:** Patient records were analyzed individually and compared to the NICE guidelines. Each recorded required test was compared to the NICE guidelines' recommendations. The guidelines state that patients on Antipsychotics should have their blood glucose monitored at the start of the treatment and after every 6 months. Antipsychotic patients should also have their lipid profile measured at the start and every 12 months and the prolactin levels at the start. For Lithium, Thyroid Function, Urea and Electrolytes and Plasma Drug Levels should be measured every 6 months. For Sodium Valproate, Liver Function should be measured Every 12 months and CBC every 6 months. Finally, for Carbamazepine, Plasma Drug Level 2 weeks after initiation, Urea and electrolytes in addition to CBC every 6 months. The method of analysis was descriptive statistics to obtain the percentage of adherence in accordance with the NICE guidelines, and it was categorized into two arms, mainly followed, and not followed. The data was then interpreted into Frequency and Bar Charts in terms of percentages. Result interpretations were noted, and recommendations and reasoning were made. The data obtained was then analyzed using the Statistical Package for Social Science (SPSS) version 23.

# RESULTS

***Baseline:*** A total of 249 number of cases of patients with bipolar disorder (BD) with mood stabilizers and antipsychotics were admitted and studied in the Department of Behavioral Medicine, Sultan Qaboos University hospital. The patients were reviewed and audited to determine the adherence to standard of care for their blood monitoring. Most of the bipolar patients in the audit group were administered with Antipsychotics (219), followed by, Sodium Valproate (144), Lithium (39) and then Carbamazepine (12). Out of the 249 patients most were females (56.6%) followed by Males (43.4%). The mean age of the patients in this study was (40.87). Performance against standards in the sub-group of bipolar disorder patients prescribed with anti-psychotics. A total of 219 patients with BD had been prescribed with anti-psychotics. 9.1%(20) hadadequate and regular monitoring regarding Lipid levels (every x months?), while every 29.7%(65) had adequate and regular monitoring of Prolactin levels and 18.6 %(40) had adequate monitoring of Blood Glucose levels. The number and percentage of patients who received adequate blood monitoring as per NICE guidelines are represented in (Table 1).

**Table 1. Number and Percentage of patients with adequate and non-adequate monitoring of parameters recommended by the NICE guidelines for antipsychotics in terms of followed and not followed**

| % (n) | Lipid | Prolactin | Glucose |
|---|---|---|---|
| Followed | 9.1% (20) | 29.7% (65) | 18.6%(40) |
| Not Followed | 90.9% (199) | 68.9%(151) | 81.4%(175) |

Performance against standards in the sub-group of bipolar disorder patients prescribed with Sodium Valproate. A total of 144 patients with BD had been prescribed with Sodium Valproate, of which 31.7 %(97) had adequate and regular monitoring of the Complete Blood Count and 32.6 %(45) hadadequate monitoring of the Liver Function. The number and percentage of patients who received adequate blood monitoring as per NICE guidelines are shown in (Table 2).

**Table 2. Number and Percentage of patients with adequate and non-adequate monitoring of parameters recommended by the NICE guidelines for Sodium Valproate mood stabilizer in terms of followed and not followed**

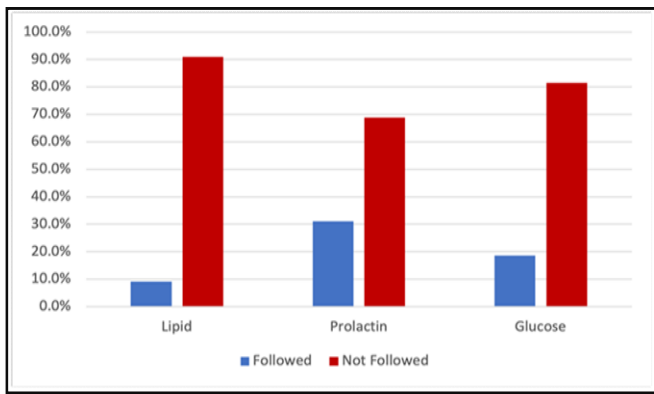| % (n) | Lipid | Prolactin | Glucose |
|---|---|---|---|
| Followed | 9.1% (20) | 29.7% (65) | 18.6%(40) |
| Not Followed | 90.9% (199) | 68.9%(151) | 81.4%(175) |

**Figure 1. Percentage of patients with adequate and non-adequate monitoring of parameters recommended by the NICE guidelines for antipsychotics**
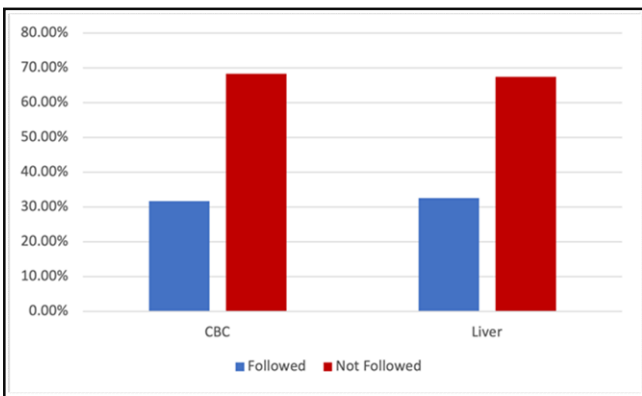


**Figure 2. Percentage of patients with adequate and non-adequate monitoring of parameters recommended by the NICE guidelines for Sodium Valproate mood stabilizer**

Performance against standards in the sub-group of bipolar disorder patients prescribed with Lithium A total of 41 patients with BD had been administered with Lithium, of which 61.5%( 24) of the sample had adequate regular monitoring of serum urea, 51.2 %(21) had adequate monitoring of the Thyroid Function and 57.5 %(23) had adequate monitoring of the Plasma Drug Levels. The number and percentage of patients who received adequate blood monitoring as per NICE guidelines are shown in (Figure 3).
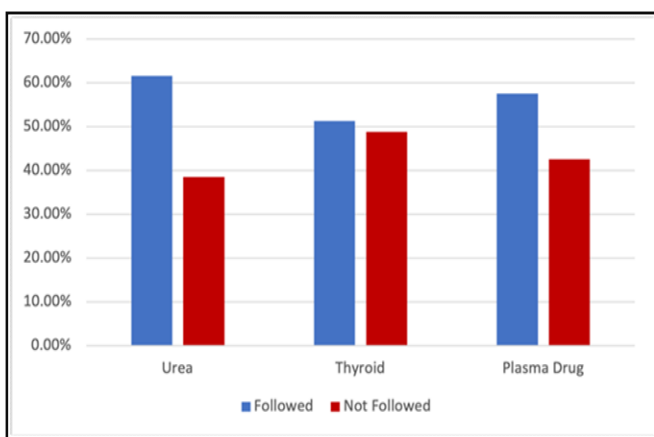


**Figure 3. Percentage of patients with adequate and non-adequate monitoring of parameters recommended by the NICE guidelines for Lithium mood stabilizer**

Performance against standards in the sub-group of bipolar disorder patients prescribed with Carbamazepine. A total of 12 patients with BD were administered with Carbamazepine, of which 8.3%(1)

hadadequate and regular urea serum level monitoring, 25%(3) hadadequate and regular complete blood count monitoring and 8.3%(1) had regular plasma drug level monitoring. The number and percentage of patients who received dequate blood monitoring as per NICE guidelines are shown in (Figure 4).
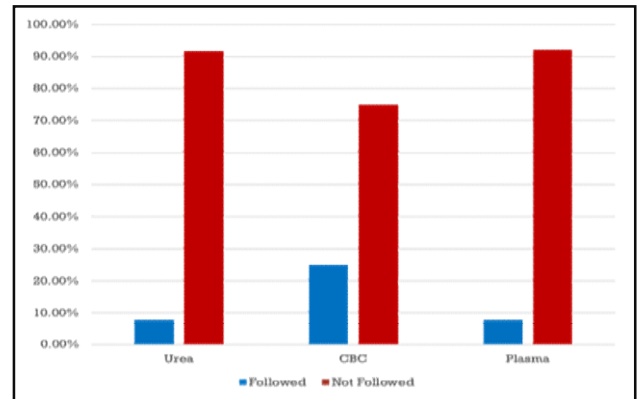


**Figure 4.Percentage of patients with adequate and non-adequate monitoring of parameters recommended by the NICE guidelines for Carbamazepine**

# DISCUSSION

This audit is the second audit conducted at the Sultan Qaboos University Hospital (SQUH) for blood monitoring of patients with bipolar disorder (BD), administered with Lithium (Al Senawi et al, 2016). The first audit for the blood monitoring of patients administered with Carbamazepine, Sodium Valproate and both typical and a-typical antipsychotics according to the NICE guidelines. The results of this audit show that the adherence to monitoring Lithium was the highest of the medications analyzed in this audit with an adequate monitoring of (57.5%) of the Plasma Drug Level, compared to the (30%) adequate monitoring deduced in the first clinical audit conducted on the Blood Monitoring in Patients on Lithium (Al Senawi et al, 2016). This shows a decent improvement following the previous audit. This pattern is similarly deduced with both thyroid and renal function, where the percentages increased from (10%) and (10%) adequate monitoring to (51.2%) and (61.5%) adequate monitoring respectively. However, we can conclude that the blood monitoring of lithium, still, falls short of recognized best practice in our center. The results of the other medications analyzed in this study in our center also show a low standard of care for their blood monitoring. It seems that the monitoring for Lithium was the highest, followed by Sodium Valproate, then Antipsychotics and finally Carbamazepine.

However, the difference between lithium and the other drugs monitoring remains significant. In our opinion, this high variance between the monitoring of lithium and the other drugs may be attributed to high toxicity and side effects profile of Lithium, as well as, that a pervious clinical audit was conducted on the monitoring of lithium, highlighting it, and causing physicians to attribute higher attention to it. However, it must be noted, that even with an increased monitoring of lithium in our center, it remains fairly low. A plausible reason for the monitoring falling short of best evidence is the appointment system in our center, SQUH, where patients find it very difficult to find appointments. This could be attributed to the short 7-hour workday, causing a heavy workload and a congested schedule. Another likely reason for the low adherence is that the patients themselves sometimes skip or miss appointments either due to unwillingness or negligence. Other probable reasons could be the low awareness and lack of continuous training on the regular safety monitoring of the drugs, particularly, Sodium valproate, Carbamazepine and Anti-psychotics. Additionally, the lack of continuous and regular follow-up audits for Lithium and any audits for the other drugs which consecutively means, no audit-based quality improvement processes to rectify the issue.

Additionally, the lack of an internal guideline or standard could contribute to this issue. We believe, in SQUH, there is an excellent infrastructure to meet the required sufficient monitoring, according to the NICE guidelines' recommendations. All the required tests, sufficient staff and necessary resources are available, and all tests are done free of charge for all patients. Allthis indicating that the system is ready to meet the recommendations of the guidelines. However, we believe this would need an increased commitment from both the physicians and patients, which would ultimately lead to a better standard of care for the patient. The blood monitoring system and practice needs to be modified in our setting to provide better care, either by placing a strong reminder system for the patients and increasing their awareness, or by introducing several systems, as well as improvement programs for staff. More audits are required to determine the effectiveness of improvement programs put in place, as well as provide feedback supplemented with improved systems to improve the therapy of patients with bipolar disorder and their blood monitoring.

**Recommendations for improvements are mentioned below.**

**Recommendations**

- Conduction of further and repeated clinical audits to improve safety monitoring and follow the audits up with audit-based quality improvement programs.
- Training and awareness programs/seminars for physicians and staff on the NICE guidelines and the importance of effective safety monitoring for lithium and increasingly alternative mood stabilizers (Sodium Valproate and Carbamazepine), as well as Antipsychotics. This is due to their extremely low adherence rates compared to lithium.
- Improve the appointment system and ensure follow-up appointments for monitoring are set up at correct timings according to guidelines, as well as, setting a reminder system in place for when the next test is due.
- Inform every patient on the importance of the blood monitoring to increase willingness to get tested and overcome patient barriers.
- Continuous feedback system to improve the monitoring
- Development of a set standard for the monitoring of Mood Stabilizers and Anti-Psychotics.

**Limitations:** One of the limitations of this study is the small sample size. Additionally, the study only included bipolar patients from Department of Behavioral Medicine, SQUH. Thus, this study cannot be generalized and extrapolated in other centers in Oman and is limited to SQUH. Additionally, another limitation is that some tests have been performed, but not recorded in the main record. It could be found in the patient notes, but there is a chance that was not recorded in the system.

# CONCLUSION

Safety blood monitoring according to NICE guidelines of patients with bipolar disorder falls short of best practice. Monitoring of Lithium is greater in comparison to other drugs and has showed a slight improvement compared to previous audits. Monitoring of carbamazepine, sodium valproate and antipsychotics are extremely poor.

The poor monitoring could be credited to both physician organizational and patient factors. As the infrastructure is available, meaning that standards can be met if correct actions are taken. Thus, it is important for actions to be taken in accordance with the guidelines and further audits are initiated.

Conflict of interest: **None.**

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