A Retrospective Study on Therapeutic Drug Monitoring of Mood Stabilizers in Real-life Clinical Scenario

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Background: Therapeutic drug monitoring (TDM) is the widely used tool in neuropsychiatric disorders. It is a valuable tool for tailoring the dose, preventing adverse drug reactions, and testing the drug adherence, therapeutic nonresponse, pharmacokinetic, and drug–drug interactions. TDM is most useful for individualized pharmacotherapy in bipolar disorders. But there exists a death of information on TDM of mood stabilizers in real-life scenario. Hence, this study aimed to assess the use and indication of TDM for mood stabilizers in a university hospital. Materials and Methods: A descriptive, retrospective, study was carried in a university teaching hospital in Dammam metropolitan region of Saudi Arabia. Patients were included in the study if they had a mood stabilizer with serum level drawn between January 2017 to December 2018. The patient list was collected from “QuadraMed” health information system. TDM details such as values of each TDM, reason for the TDM, and number of TDM for 1 year have been documented. Result: A total of 200 patients received 242 mood stabilizers during the study period. Gender distribution was almost equal in the study population male (52%) versus female (48%). Average age of the patients was 40 years (range = 17–87 years). A total of 41.5% (n = 83) patients were diagnosed with bipolar type 1. Valproic acid (n = 139 [57.9%]) and lithium (n = 54 [22.3%]) were the most commonly used mood stabilizers. Majority (80%) of the bipolar patients were managed with single mood stabilizers. A total of 613 TDM was ordered for the 200 patients during the study period. The average number of TDM per patient during the study period was 3 (range = 1–39). Validation of the therapeutic level (n = 140), lack of clinical response (n = 51), and change in the dose (n = 34) are the documented reasons for TDM. Conclusion: This study highlights the common and specific reasons for TDM of mood stabilizers in routine clinical practice. More extensive study on a larger sample size in the prospective basis is required to find out the rationality of TDM orders and its outcome for the development of the polices.

KEYWORDS: Bipolar disorders, mood stabilizers, therapeutic drug monitoring

INTRODUCTION

Bipolar affective disorder (BPAD) is a chronic and recurrent disease characterized by occurrences of mania and depression with a longitudinally diverse course.[1] Pharmacological management of psychiatric disorders has observed major advances in the last...
century. However, genetic variability in the metabolism of medications has doomed practical applications. One means of minimizing such problems has been the use of therapeutic drug monitoring (TDM).\[3\] It is a valuable tool for tailoring the dose, preventing adverse drug reactions, and testing the drug adherence, therapeutic nonresponse, pharmacokinetic, and drug–drug interactions. In psychiatry, TDM has been used to optimize medication therapy with antidepressants, mood stabilizers, and antipsychotics. In the developing and underdeveloped countries, the use of TDM is limited to few antiepileptics and mood stabilizers, especially drugs that have a narrow therapeutic index.\[3\]

In neuropsychiatric disorders, specific indications and distinct problems can make TDM most useful for individualized pharmacotherapy.\[3,4\] If the TDM is integrated into the clinical treatment process, the potential benefits can accelerate patient improvements. In psychiatric clinical practice, the advantages of using TDM for tricyclic antidepressants, antipsychotic drugs, and mood-stabilizing drugs have been reported.\[3,4,5\]

Currently in neuropsychiatry, TDM has converted as a standard of care and improvement. Hence, it reduces the phases of suffering in terms of patient medical benefits and reduces the cost of the health system.\[4\]

The psychiatric health-care services are expanding over the past several years in the Kingdom of Saudi Arabia. However, a literature survey conducted concerning mental illness in Saudi Arabia indicates the lack of an accurate estimate for the prevalence of such problems among the Saudi population. However, a few studies have been conducted in relation to specific mental disorders or populations and age groups.\[6,7\] There is a dearth of information on TDM of mood stabilizers in Saudi Arabia.\[8\] Hence, this study aimed to assess the use and indication of TDM for mood stabilizers in a university hospital.

**Materials and Methods**

**Study design and population**

This descriptive, retrospective, study was carried over the period of 6 months. The study site was a university teaching hospital in Dammam metropolitan region of Saudi Arabia. Data were collected from a hospital database. The data were collected on services provided between January 2017 and December 2018. The data file included detailed patients’ diseases condition, prescription, and dispensing status. All the laboratory data included TDM, patient’s progress notes, and admission details of clinic visits. It also included the patient’s primary and secondary diagnoses at the time of service as well as the information on the brand and dose of medication for filled prescriptions. Patient demographic information, including age, sex, and zip code, was also available.

Patients were included in the study if they had a mood stabilizer serum level drawn between January 2017 and December 2018. All the patients irrespective of the age and gender were included. All the diagnosis was carried out by the consultant psychiatrist based on 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) diagnosis. A patient is considered a mood stabilizer user, if they have a lithium/valproic acid/carbamazepine prescription filled at least three of the four quarters during the study year. All prescriptions were filled on either inpatient or outpatient basis. Patients who are withdrawn the treatment from the study site or lost follow-up or change the diagnosis were excluded from the study.

Initially, list of all the patients prescribed with mood stabilizer were reviewed. Later the collected list was checked for the inclusion–exclusion criteria. Once they included the study, all the study specific details such as patient demographic information regarding the mood stabilizers such as name, dose, frequency, and duration of each drug prescribed were noted. Then the TDM details such as values of each TDM, reason for the TDM, and number of TDM for 1 year have been documented. The numbers of mood stabilizers, prescriptions, and TDM measurements for mood stabilizers were counted by year. We sought to determine the patient demographic, diagnostic, and service use variables associated with TDM for bipolar disorder.

**Statistical analysis**

By using Raosoft (Raosoft Inc., Gary Trujillo, WA, USA) that is an online sample size calculator, the minimum recommended sample size is 199, which is calculated using the following equation: 

\[
n = \frac{Z^2 P (1-P)}{E^2}
\]

where \(n\) is the sample size, \(Z\) is standard normal deviation that is 99% and the confidential level is 2.04, \(E\) is the sampling error at ±1% = (0.01), and \(P\) is the percentage picking a response at 50%, which is 0.5. All the collected information was categorized on mean mode and percentage.

**Results**

A total of 283 patients were screened for the eligibility, of which 83 were excluded due to the several reasons such as new diagnosis, no documentation on TDM value, not having complete information, and a change in the diagnosis. Only 200
patients were included and analyzed for the further part of the study.

A total of 242 mood stabilizers were prescribed for 200 patients with BPAD during the study period. Gender distribution was almost equal in the study population ($n = 104$ [52%]) of male versus ($n = 96$ [48%]) female. Average age of the patients was 40 years (range = 17–87 years). The median number of medications received by the patients was 3 (range = 1–16). Hypertension, diabetes, and cardiovascular disorders are the common comorbidities presented in the study population. A total of 41.5% ($n = 83$) patients were diagnosed with bipolar type 1, whereas 11.5% ($n = 23$) of the patients were bipolar type 2. The details of the diagnosis are given in Figure 1.

Pattern of mood stabilizer use
Of the total 242 mood stabilizers prescribed during the study period, valproic acid (VA) ($n = 139$ [57.9%]), Lithium (Li) ($n = 54$ [22.3%]), carbamazepine (CBZ) ($n = 29$ [11.9%]), and lamotrigine ($n = 20$ [8.2%]) were available mood stabilizers in the study site. As shown in Figure 2, Majority (80%) of the bipolar patients were managed with single mood stabilizers.

Coprescribed psychotropic medications
Olanzapine ($n = 53$ [26.5%]), quetiapine ($n = 46$ [23%]), and risperidone ($n = 44$ [22%]) are most commonly received antipsychotics [Figure 3].

Therapeutic drug monitoring
A total of 613 TDMs were ordered for the 200 patients during the study period. Average number of TDM per patient during the study period was 3 (range 1–39). The details were serum level drawn for the individual mood stabilizers given in Table 1.

Documented indications of therapeutic drug monitoring
Of the 613 TDM orders, 404 (65.9%) order result was within the normal limit, whereas 209 (34.09%) have

![Figure 1: Types of bipolar disorders](image1)
![Figure 2: Number of mood stabilizers versus bipolar subtype](image2)
![Figure 3: Details of the psychotropic](image3)

| Medication | Frequency of TDM |
|------------|------------------|
|            | Minimum | Maximum | Sum | Mean | Standard deviation |
| VA         | 1       | 30      | 369 | 2.56 | 3.128               |
| CBZ        | 1       | 11      | 57  | 2.19 | 2.384               |
| Li         | 1       | 21      | 187 | 3.07 | 3.511               |
| All TDM    | 1       | 39      | 613 | 3.07 | 4.680               |

VA = valproic acid, CBZ = carbamazepine, TDM = therapeutic drug monitoring, Li = lithium
an abnormal outcome. Documented indications of the TDM included validation of the therapeutic level ($n = 140$), lack of clinical response ($n = 51$), and change in the dose ($n = 34$) [Figure 4].

**DISCUSSION**

Bipolar type 1 was predominantly diagnosed over bipolar type 2. Epidemiological studies also suggested a little high prevalence of bipolar type 1 as compared with bipolar type 2.$^{[9-11]}$ The reasons behind that may be related to severity of manic symptoms, which are more severe and are usually require hospitalization.$^{[12]}$ According to American Psychiatric Association (APA),$^{[13]}$ VA and Li are the drugs of choice in bipolar type 1 in managing manic episodes and this is what we observed in this study. A similar trend was observed in the world literature too.$^{[14-16]}$ However, in comparison with Li, VA was more preferred to be prescribed and this is correlated to previous studies.$^{[17]}$ Even though the efficacy of Li and VA in preventing recurrence and relapse among BPAD patients is equal, we found that VA was more prescribed than Li (58% vs. 22%), respectively. This may refer to narrow therapeutic index and severe side effects that are related to Li, which requires more drug monitoring. Over three-quarter of patients were prescribed a single mood stabilizer. Major guidelines$^{[13]}$ on BPAD preferred a single mood stabilizer; a correlating result was observed in the other research also. Similarly, 20% of the patients were prescribed a combination of two to three mood stabilizers. This highlighted the importance of practicing polypharmacy with mood stabilizers in the management of bipolar disorder. The dose of mood stabilizers varies; it is more related to target therapeutic drug concentration, which may differ because of genetic variabilities, comedication used, liver enzyme, and renal function.

In the last few decades the use of TDM in the clinical practice becomes a routine monitoring. As shown in Figure 4 there exist a multiple reasons for TDM. Toxicity of mood stabilizers, ruling out toxicities of other medications, sample hemolysis are the few reported one in the study site. We also observed that the TDM increased in patients suffering from acute illness included upper respiratory tract infections, pneumonia, seizure attack, and during recurrent BPAD episodes. For patients who has an excessive consumption of mood stabilizer, TDM was performed very frequently until the patient is stable or the TDM values reach to the normal limit. However, some of the patients whose drug level was abnormal, especially low level, the TDM was not repeated for them. In general, the frequency of indication TDM was not calculated, because it varies between patients and the study site has specific guideline for TDM procedure.

**Limitation:** This study was conducted in retrospectively, so the reason for TDM and its effect on therapeutic decision and improvement on patient conditions are not studied.

**CONCLUSION**

TDM plays an important role in the development of safe and effective therapeutic medications and individualization of these medications. This study overviews the common and specific reasons for TDM of mood stabilizers in routine clinical practice. In future, it will help to audit and improving of TDM in a more optimal way. More extensive study on a larger sample size in the prospective basis is required to find out the rationality of TDM orders and its outcome and development of the polices. Similarly a detailed pharmacoeconomic studies can assess the economic burden of TDM on patient, provider, and health-care system.

**Financial support and sponsorship**

Nil.
Conflicts of interest
There are no conflicts of interest.

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