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Comparative Efficacy of Introducing Mood Stabilizers in Acute or Maintenance Treatment of Bipolar Disorder: An Observational Prospective Study

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Abstract: Bipolar disorder is a severe chronic psychiatric disorder characterized by recurrent fluctuations in mood, energy, and behavior. The study determined the comparative efficacy of introducing mood stabilizers in the acute or maintenance treatment of bipolar disorder (BD). The study was conducted at the Psychiatry Unit of the Komfo Anokye Teaching Hospital, Kumasi-Ghana. Fifty-five (55) bipolar patients aged 14-77 years were recruited for the study through a convenience sampling technique. The Medication Adherence Rating Scale (MARS), which was a clinician-led tool, asked patients to respond to statements in the questionnaire by circling the answer (yes or no) that best described their behavior toward their medications over a time period; the Young Mania Rating Scale (YMRS), which was a clinician-administered tool, was used for measuring symptoms severity and monitoring resolution; the Insight and Treatment Attitude Questionnaire (ITAQ), which was a clinician-led tool for measuring patients' insight into their condition; and a structured questionnaire, which was a clinician-led tool for measuring patients' demographics, were adapted for the study. Statistical Package for Social Sciences (SPSS) version 25 was used to analyze the data. Most of the respondents were between 25-36 years (54.6%). Females constituted 58.6% of the sample. Most of the respondents had had education up to the Senior High School level (40.0%). The majority of the respondents were self-employed (36.5%). There was no difference in the duration of symptom resolution between given mood stabilizers within 0-3 days (Median=2, N=33) and 4- 16 days (Median=2 N=20). The test statistics were (U=309.00, Z=0.440, r=0.06, P=.660) using the Mann-Whitney test. However, there was an association between insight and religion ($X^2(4)=14.69$, p=.005) and black ethnicity (X^2 (2)=4.79, p=.002).Also, insight was associated with adherence ($X^2(2)=44.21$, p=<.001). Sodium valproate had a faster onset of mood stabilizing effect (less than 7 days) than carbamazepine (7-14 days) and the psychiatrist considered medication effectiveness and client history as the most important factors in the choice of a mood stabilizer for BD. Impaired insight is a predictor for non-adherence. Mood stabilizers can be started at any time in the acute

treatment of bipolar disorder. Sodium valproate must be given a priority in the acute treatment of bipolar disorder, except in women of reproductive age.

Keywords: mood stabilizer, insight, adherence, bipolar disorder

1.0 INTRODUCTION

Bipolar disorder (BD) is one of the most common of the severe chronic psychiatric disorders. The disorder is characterized by recurrent fluctuations in mood, energy, and behavior enveloping the extremes of human experience (Grande et al., 2016; Simone et al., 2019). Bipolar disorder differs from recurrent major depression (or unipolar depression) in that a manic, hypomanic, or mixed episode occurs during the illness (Grande et al., 2016). Bipolar disorder is a lifelong illness with a variable course and requires both non-pharmacologic and pharmacologic treatments for mood stabilization (Young, 2020). This disorder, according to the World Health Organization, affects about 45 million people worldwide. (WHO, 2019). Bipolar disorder treatment is largely individualized due to the large individual variation in patients' clinical presentation, episode frequency, and severity (Salagre, 2020). According to Saragre (2020), the type of episode a patient is having can affect how their bipolar disorder is treated. Pharmacotherapy is crucial for the acute and maintenance treatment of bipolar disorder and includes lithium, valproate, carbamazepine, lamotrigine, first- and second-generation antipsychotics, and adjunctive agents such as antidepressants and benzodiazepines (Young, 2020). Clozapine use in patients receiving treatment for resistant mood disorders appears to be the first observational study of antipsychotics for maintenance treatment (Zarate et al., 1995). One benefit of the second-generation antipsychotics (SGAs) over the first-generation antipsychotics (FGAs) was the latter's tendency to cause movement disorders less frequently. According to a 2017 meta-analysis, there was a statistically significant difference in the prevalence of tardive dyskinesia between classes (about 20% versus 30%), with a lower prevalence (about 7%) in subjects who had never taken flu shots. (Carbon et al., 2017). SGAs are more likely to cause additional side effects, such as metabolic effects. One 4-year observational study and fifteen RCTs ranging in length from six months to two years were included in a 2017 systematic review and meta-analysis of SGAs in the maintenance treatment of BD (Lindström et al., 2017). Based on the pharmacology of clozapine the first antipsychotic that was found to not cause catalepsy in rodents and to cause a movement disorder that was clinically significant—the second-generation antipsychotics, also referred to as "atypical" antipsychotics, are a heterogeneous group (Nucifora et al., 2017). Although there is little evidence to suggest a correlation between their affinity for receptor sites like the 5HT2A receptor and their effectiveness, they typically have greater affinity for these receptor sites than first-generation antipsychotics like haloperidol (amisulpride being the exception). There is a paucity of research on the neurobiology of mania.

A positron emission tomography (PET) study (Yatham et al., 2022) revealed that, mania had a higher capacity for dopamine synthesis than controls, but there was also an increase in mania associated with psychotic symptoms (Jauhar et al., 2019). Because different mechanisms are at work when medications are used long-term during an illness, they behave differently when given acutely for brief periods of time (Atagun, 2021). According to Malhi et al. (2022) an ideal mood stabilizer should be able to treat acute mania and depression as well as have minimal side effects and long-term prophylactic efficacy against both mania and depression. Currently, the U.S. Food and Drug Administration (FDA) has approved lithium, valproate (or divalproex sodium), extended-release carbamazepine, aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone for the treatment of mania in bipolar disorder. For the maintenance treatment of bipolar disorder however, only lithium, divalproex sodium, aripiprazole, olanzapine, and lamotrigine are approved. Quetiapine, Lurasidone, Cariprazine, and Lumateperone are the only monotherapy antipsychotics that are FDA-approved for bipolar depression (Levenberg et al.,2022). Lithium is the drug of choice for bipolar disorder with euphoric mania, whereas valproate has better efficacy for mixed states, irritable/dysphoric mania, and rapid cycling compared with lithium (Robert, 2019). According to the International Journal of Psychopharmacology, on acute and maintenance treatment with mood stabilizers, it was reported that, in the management of manic episodes, patients who were randomized to receive haloperidol (or an alternative antipsychotic) with valproate had a significantly greater improvement than those who received haloperidol (or an equivalent antipsychotic alone), but antipsychotics were superior in the management of manic episodes compared with classical mood stabilizers (Kendell et al., 2014). The atypical antipsychotics have shown superior efficacy in mania than the first-generation antipsychotics due to their additional effect on serotonin receptors. Serotonin receptors (5HT1A, 1B, 2A, 2C) are the mechanism of action for relief of mania and

depression in Bipolar Affective Disorder (BAD). Quetiapine, Lurasidone, and olanzapine are effective antipsychotics for bipolar depression (Kadakia et al., 2021).

In regions across Africa, including Ghana, there exists a notable gap in data regarding the ideal timing for initiating mood stabilizer therapy in the treatment of Bipolar Affective Disorder (BAD). This lack of information is critical, as it impacts the effectiveness of treatment outcomes. A significant number of BAD patients, even those who have achieved remission, continue to struggle with substantial functional impairments.

This is evident from the elevated Disability-Adjusted Life Years (DALY) rates associated with the disorder. Given this context, it becomes imperative to thoroughly examine how the timing of mood stabilizer administration particularly during the acute phase of the disorder and its subsequent continuation into the maintenance phase can influence patient outcomes. Such research is vital for the creation of tailored guidelines at both local and national levels. These guidelines would aim to provide clear recommendations on the most effective timing for introducing mood stabilizers, thereby optimizing patient outcomes. The primary objective of this study is to pinpoint the most beneficial period for introducing mood stabilizers in the management of BAD. To achieve this, the study sets out specific goals: firstly, to determine the optimal timing for beginning mood stabilizer treatment in BAD; secondly, to identify the pharmaceutical care challenges and adherence issues faced by BAD patients in relation to mood stabilizers; and thirdly, to explore the factors that most significantly influence psychiatrists in their choice of mood stabilizers for treating BAD. Through addressing these aims, the study seeks to contribute valuable insights and practical recommendations for the effective management of BAD in Ghana and similar contexts across Africa.

2.0 MATERIALS AND METHODS

2.1 Study Site

Data for the study were collected at KATH (Psychiatric Department). The KATH is located in Kumasi, the capital of Ashanti Region with a total projected population of 5, 440,463(GSS, 2021). The geographical location of the 1,200-bed capacity hospital is accessible to all areas that share boundaries with the Ashanti Region and others that are further away. Referrals are received from all northern regions (namely, Northern, Upper East and Upper West Regions), Bono East, Region, Bono Region, Ahafo Region, Western Region, Western North Region, Eastern Region and parts of the Volta Region. The hospital has a Psychiatric Unit which was founded in 1981.

2.2 Sample Size and Sampling Technique

The minimum sample size was determined using the Raosoft online sample calculator (Raosoft, 2021). Based on an average clinic size of 55 BAD clients per month (2022 Annual Performance Review), an estimated sample proportion of 50% (0.5), a 95% confidence interval, a 5% margin of error, a power of 80% and a non-response rate of 10%, the minimum sample size for this study was 49, but it was increased to 55. Sampling was done by convenient sampling method. The participants were recruited from the inpatient and outpatient Psychiatric clinic of the Komfo Anokye Teaching Hospital (KATH), Kumasi. The sample included participants with both relapse and BAD presenting with acute episodes and newly diagnosed BAD. Participants were recruited continually until the sample size was attained.

2.5 Data Collection

Data were collected at the Psychiatric Unit of KATH by reviewing patients' electronic folders to confirm their diagnosis of BAD and administering the appropriate tools. Patients on Mood Stabilizers in the acute phase were assessed at different times. In practice, some patients were started on Mood Stabilizers within the following different times of presentation: three (0-3 days), (4-16 days). Different responses depend on when a Mood Stabilizer was introduced within these specified times.

The comparison was made on which time phase better improved patients' symptoms when Mood Stabilizers were introduced during the Acute Phase. Mood Stabilizers were continued in the maintenance phase and their effectiveness (efficacy, adherence, and tolerability) was assessed. The effectiveness of Mood Stabilizers in the maintenance phase was compared regarding their ability to prevent relapse, adverse effects, and adherence. Medication therapy management for patients diagnosed with bipolar disorder and who were on antipsychotics and mood stabilizers was conducted to assess the specific drugs of patients and their side effect profile. The interview was conducted either physically or via phone. The method for assessing

the medicine utilization of the patient was by patient adherence measures. Patient adherence measures are most frequently measured for chronic conditions where patients are expected to remain on medicine long-term. It was to identify the extent to which utilization, refill or supply rates were consistent with expected utilization. The medications that were dispensed over a specific time were calculated as well as the time the patient was without treatment (Young, 2020).

The patient-level indicator was also used to assess medication utilization. It was used to assess the appropriateness of medication at the patient level. It was conducted with regards to age, gender, dosage used, or prescribed. It assessed adherence, duration of use, number of medicines used, and co-administration of recommended therapy. The clinical interview was conducted for the clinician to know their experience with mood stabilizers. After commenting on existing guidelines, clinicians were allowed to explore their experience with mood stabilizers and explicate what factors were most important in choosing a mood stabilizer using the data collection tool on Psychiatrist ranking of factors involved in choosing a mood stabilizer. It is a 7-item tool that assesses factors such as effectiveness, client history, physician knowledge of the drug, previous non-compliance, societal pressure to protect the client, client preference, and cost that influence psychiatrists' choice of mood stabilizers. Each item was rated 1-8, with 1-most important and 8-least important. A factor is considered important if 50% or more of clinicians selected it as a determinant in the choice of a mood stabilizer. The interview also assessed reasons for the preference for particular mood stabilizers in the management of bipolar patients. Figure 1 depicts a total of 63 participants with BAD who were enrolled in the study, among which 55 (87.73%) were eligible and completed the 12-week follow-up. Four (4) participants were excluded due to cor-morbid substance use and one participant had the diagnosis changed to schizo-affective (Manic type) disorder, while three (3) participants were lost to follow-up as they defaulted reviews and their contacts were unreachable.

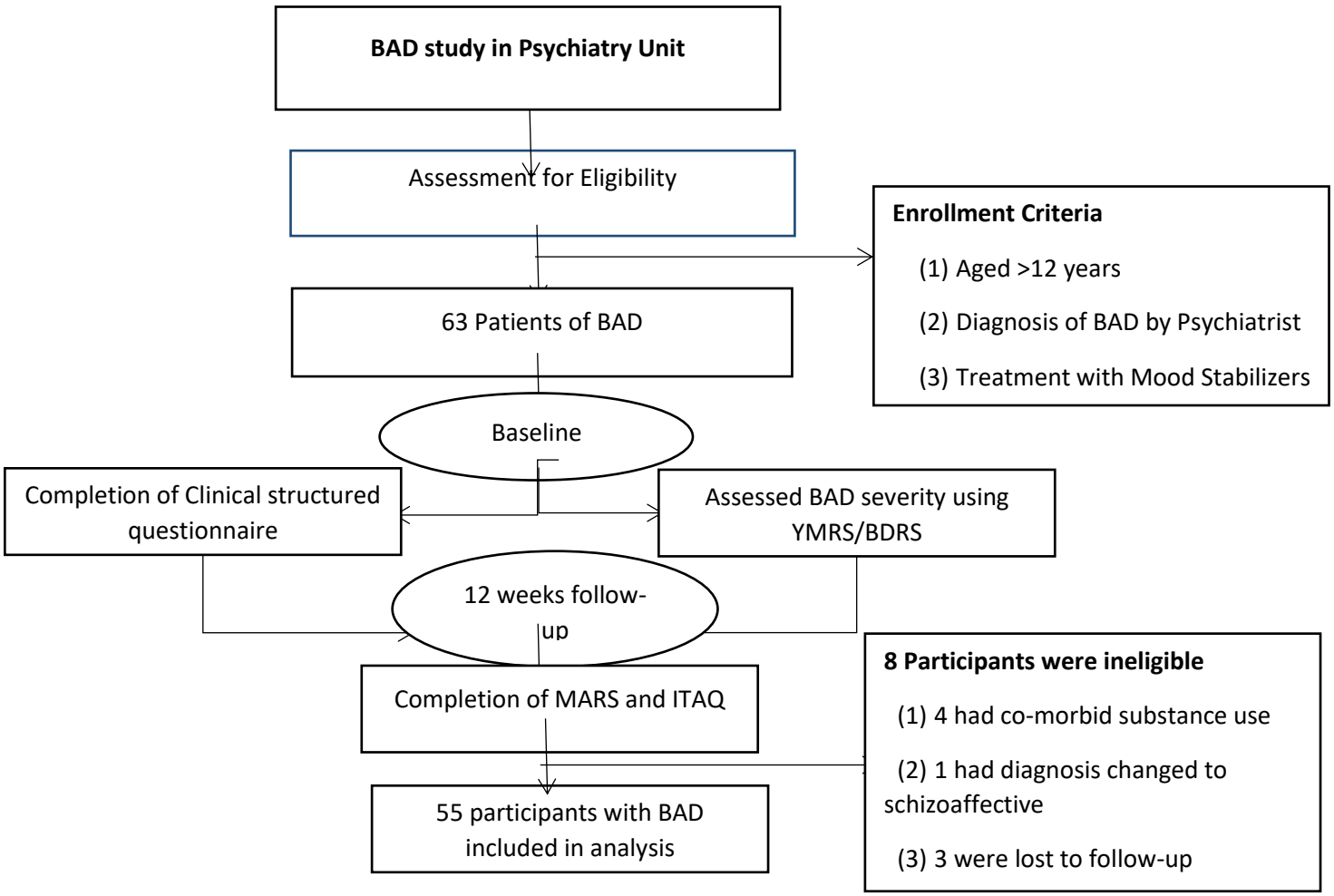

Figure 1. Study flow chart

2.6 Survey Instruments

A modified questionnaire was adapted from the questionnaire used by the Journal of Clinical and Diagnostic Research on the Pharmacotherapy of Bipolar Disorder (Banerjee, 2014). The questionnaire assessed sections such as i. Socio-demographic details including age, gender, occupation, ethnicity, employment, and monthly income. ii. Medical information that addressed the diagnosis and date it was made, medication the patient was put on after diagnosis and symptom resolution

The medication Adherence Rating Scale: Thompson et al. (2000) developed the medication Adherence Rating Scale, a ten-item yes/no self-report tool. The 30-item Drug Attitude Inventory (Hogan et al., 1983) and the 4-item Medication Adherence Questionnaire (Morisky et al., 1986) were the two existing scales from which it was developed to create a more valid and reliable tool. A score of (0-3), (4-6), and (7-10) were used to categorize patients into non-adherence, partial adherence, and adherence to their medications. (Wang et al.,2020). In this study, it was used to assess patient compliance with medications and identify any pharmaceutical care issues that enhance non-adherence.

The Young Mania Rating Scale: A psychiatric instrument, created to rank the intensity of manic symptoms (Young, 1978). The instrument is frequently used to check for manic symptoms, track the intensity of manic symptoms, and assess how well interventions are working (Nketiah et al., 2022). It is an 11-item scale assessing mood, motor activity/energy levels, interest in sex, sleep, irritability, rate and frequency of speech, flight of ideas, grandiosity, aggressive behavior, appearance, and insight into the current presentation. A score of <13 is considered normal, a score of 13-19 is considered minimal severity, a score of 20-26 is considered mild, a score of 27-38 is considered moderate and that of >38 is considered severe. The purpose of the scale in this study was to quantify the severity of mania and to monitor patients' progress while on medication.

The Bipolar Depression Rating Scale is an observer-rated, semi-structured, validated measure used in clinical settings to evaluate bipolar depression. Berk et al. created it (Berk et al., 2017). The scale consists of items that assess the clinical characteristics, such as atypical symptoms and mixed phenomenology, linked to the depressive phase of bipolar disorder. This measure can be used to measure the symptomatology of depression as well as the efficacy of therapeutic interventions for bipolar depression.

McEvoy and associates created the semi-structured Insight and Treatment Attitude Questionnaire (McEvoy et al., 1989). It is intended to gauge one's awareness of having a mental illness or its symptoms, as well as one's awareness of the need for medication or hospitalization for treatment. The validated interview consists of 11 semi-structured questions, with scores ranging from 0 (no insight) to 22 (maximum insight). The entire score is divided into three categories: fair insight (8–14), poor insight (0–7), and good insight (15–22). It was applied to assess how well therapeutic agents worked in treating bipolar disorder.

Data Collection Tool for Assessing Psychiatrist Experience with Mood Stabilizers is a validated tool adopted and modified from the Psychiatrist's attitude towards psychotropics prescribing guideline, and the Texas Medication Algorithm Project (TMAP) algorithm (Daniel, 2004). The purpose of this tool was to assess psychiatrists' ranking of factors that are important in the selection and prescribing of mood stabilizers and to determine which mood stabilizers would be considered first-line or frequently prescribed with reasons in the management of bipolar disorder patients considering their years of practice. The factors that are considered on the scale include a 7-item, namely; effectiveness, client history, physician knowledge of the drug, previous non-compliance, societal pressure to protect citizens, client preference, and cost. These are graded from 1-8, with 1-most important, 8-least important. A factor is considered important if 50% or more of clinicians selected it as a determinant in the choice of a mood stabilizer.

2.7 Data Analysis

Initial entry and organizing of the data were done using Microsoft Office 2016 Excel Spreadsheet. The data entry was performed by using IBM Statistical Package for Social Sciences (SPSS) version 25. Descriptive Statistics including total frequency and charts were used. Regression analysis (Time Series Regression Analysis) was used to test the associations between different points in time within a single series, as well as the importance of the predictors to the relationship. A p-value less than 0.05 was considered significant.

3. RESULTS

3.1 Participants sociodemographic characteristics

Table 1 presents the results of participants' socio-demographic data. About fifty-five (55) patients with BAD participated in the study with a 100% response rate. Most of the participants were between the ages of less than 25 (27.3%) and 26-35 (27.3%). Females constituted 58.2% of the sample. Regarding marital status, more than half of the participants were single (56.4%). A larger proportion of the participants had had education up to the senior high level (40.0%). Christians constituted more than two-thirds (94.5%) of the sample. The majority of the participants were self-employed (36.5%) with about 34.5% of the total sample receiving income less than 500 cedis. More than half of the participants (60%) were in a rented house with a larger proportion of them (76.4%) fluent in both English and Twi. The majority of the participants (52.7%) had their diagnosis made at the in-patient department.

Table 1. Demographic Characteristics of Participants

Characteristics	N	Valid (%)
Age groups (Yrs)		
≤25	15	27.3
26-35	15	27.3
36-45	12	21.8
≥46	13	23.6
Gender		
Male	23	41.8
Female	32	58.2
Education		
JHS	17	30.9
SHS	22	40
Tertiary	16	29.1
Nationality		
Ghanaian	54	98.2
Non-Ghanaian	1	1.8
Religion		
Christian	52	94.5
Muslim	2	3.6
Traditionalist	1	1.8
Marital Status		
Single	31	56.4
Married	21	38.2
Divorced	2	3.6
Widowed	1	1.8
Employment		
S. Employed	20	36.4
Retired	2	3.6
C.Servant	8	14.5
Student	7	12.7
Unemployed	14	25.5
Others	4	7.3
Income		
<500	19	34.5

500-999	16	29.1
1000-1999	8	14.5
2000-3999	11	20
>4000	1	1.8
Housing		
Tenant	33	60
Owner	13	23.6
Family H	9	16.4
Language		
Twi &English	42	76.4
English only	6	10.9
Twi only	7	12.7
Place of Dx		
OPD	26	47.3
IPD	29	52.7

Junior High School (JHS) and Senior High School (SHS) *; OPD: Outpatient Department; IPD: Inpatient Department; S. Employed: Self-Employed; C. Servant: Civil Servant;*

3.2 **Medication Adherence**

From the analysis, the majority of the participants 80% (n=44) were adherent to their medication, more than one-third of the participants16.4% (n=9) were partially adherent to their medication while 3.6% (n=2) were non-adherent to their medications. Table 2 presents descriptive statistics of medication adherence (MARS). The scale has good psychometric reliability with a Cronbach alpha of 0.81 (pallet 2016). The Mean (standard deviation), median, and modal scores for medication adherence were 8.72(±2.273), 10, and 10. The minimum and maximum scores for MARS were 2 (non-adherence) and 10 (adherence), respectively.

Table 2 Medication adherence

Descriptive Statistics	**MARS**
Mean	8.72
S. D	2.273
Median	10
Mode	10
Minimum	2
Maximum	10

*Note: MARS=medication adherence rating scale; S.D=standard deviation;*Multiple modes exist, the smallest value is shown.*

3.3 Insight and Treatment Attitude Questionnaire

From the analysis, the majority of the participants 76.4%(n=42) had good insight, less than one-third of the participants, 16.4%(n=9) had partial insight and 7.3% (n=4) had poor insight. Table 3 presents descriptive statistics of the insight and treatment attitude questionnaire. Cronbach alpha for the scale is 0.87, indicating good psychometric reliability (Naeimi, 2019). The insight and treatment attitude scores were 17.38 (±5.77), 20, and 20 for the mean (standard deviation), median, and modal scores, respectively. For the ITAQ, the lowest possible score was 4 (poor insight) and the highest possible score was 21 (good insight).

Table 3 Insight and Treatment Attitude Questionnaire

Descriptive Statistics	ITAQ
Mean	8.72
T. D	2.273
Median	10
Mode	10
Minimum	2
Maximum	10

*Note: Insight and treatment attitude questionnaire (ITAQ); S. D=standard deviation; *Multiple modes exist, the smallest value is shown.*

3.4 Association Between Adherence and Socio-demographic Characteristics

A chi-square test was performed to determine the association between medication adherence and various socio-demographic characteristics. The analysis performed showed no association between any of the socio-demographic characteristics and medication adherence as shown by the statistics: Language: Insight ($x^2(2)=0.83$, p=.659), Age: Insight ($x^2(3)=0.673$, p=.880), Housing: Insight ($x^2(2)=0.23$, p=.891), Income: Insight ($x^2(4)=2.38$, p=.660), Employment: Insight ($x^2(2)=8.71$, p=.121), Marriage: Insight ($x^2(3)=0.891$, p=.828), Education: Insight ($x^2(2)=0.354$, p=.838), Gender: Insight ($x^2(1)=0.075$, p=1.000), Religion: Insight ($x^2(2)=5.36$, p=.069), Nationality: Insight ($x^2(1)=4.07$, p=.20) Table 4.

Table 4-Association between Adherence and Demographics

Characteristics	Non-Adherent	Partial Adherent	Adherent	*P-Value*
Age groups (Yrs)				
≤25	1(50.0)	2(22.2)	12(27.3)	*0.918*
26-35	1(50.0)	3(33.3)	11(25.0)	
36-45	0(0.0)	2(22.2)	10(22.7)	
≥46	0(0.0)	2(22.2)	11(25.0)	
Gender				*0.341*
Male	0(0.0)	5(55.6)	18(40.9)	
Female	24(57.1)	4(44.4)	26(59.1)	
Education				*0.738*
JHS	1(50.0)	2(22.2)	14(31.8)	
SHS	1(50.0)	3(33.3)	18(40.9)	
Tertiary	0(0.0)	4(44.4)	12(27.3)	
Nationality				*0.074*
Ghanaian	2(100.0)	8(88.9)	44(100.0)	
Non-Ghanaian	0(0.0)	1(11.1)	0(0.0)	
Religion				*0.130*
Christian	2(100.0)	7(77.8)	43(97.7)	
Muslim	0(0.0)	1(11.1)	1(2.2)	
Traditionalist	0(0.0	1(11.1)	0(0.0)	
Marital Status				*0.982*

Single	1(50.0)	6(66.7)	24(54.4)	
Married	1(50.0)	3(33.3)	17(38.6)	
Divorced	0(0.0)	0(0.0)	2(4.6)	
Widowed	0(0.0)	0(0.0)	1(2.3)	
Employment				*0.281*
S. Employed	1(50.0)	1(11.1)	18(40.9)	
Retired	0(0.0)	0(0.0)	2(4.6)	
C.Servant	0(0.0)	4(44.4)	4(9.1)	
Student	0(0.0)	0(0.0)	7(15.9)	
Unemployed	1(50.0)	3(33.3)	10(22.7)	
Others	0(0.0)	1(11.1)	3(6.8)	
Income				*0.852*
<500	1(50.0)	3(33.3)	15(34.1)	
500-999	0(0.0)	2(22.2)	14(31.8)	
1000-1999	1(0.0)	2(22.2)	5(11.4)	
2000-3999	0(0.0)	2(22.2)	9(20.5)	
>4000	0(0.0)	0(0.0)	2(2.3)	
Housing				*0.808*
Tenant	2(100.0)	5(55.6)	26(59.1)	
Owner	0(0.0)	2(22.2)	11(25.0)	
Family H	0(0.0)	2(22.2)	7(15.9)	
Language				*0.292*
Twi &English	1(50.0)	7(77.8)	34(77.3)	
English only	0(0.0)	2(22.2)	4(9.1)	
Twi only	1(50.0)	0(0.0)	6(13.6)	
Place of Dx				*0.990*
OPD	2(100.0)	2(22.2)	22(50.0)	
IPD	0(0.0)	7(77.8)	22(50.0)	

Junior High School (JHS) and Senior High School (SHS); OPD: Outpatient Department; IPD: Inpatient Department; S. Employed: Self-Employed; C. Servant: Civil Servant;

3.5 Association between Medication Adherence and Other Factors

A chi-square test was performed to determine the association between medication adherence and the time of starting mood stabilizers on presentation, duration of symptom resolution, and cumulative side effects. The analysis performed as displayed in Table 5, showed no association between any of the above factors and medication adherence as shown; tsmsp: mars($x^2(8)$ =11.364,p=.182),dsre: mars($x^2(3)$=4.12, p=.249), c.s. effect: mars($x^2(1)$=0.764, p=.382).

Table 5-Association between Adherence and Factors

Characteristics		Non-Adherence	Partial Adherence	Adherence	P-Value
DSRe					
	<7days	0(0.0)	3(33.3)	10(22.7)	*0.086*
	7-14days	0(0.0)	4(44.4)	28(63.6)	
	15-21days	1(50.0)	1(11.1)	2(4.6)	
	22-30days	1(50.0)	1(11.1)	4(9.1)	
TSMSP					*0.438*
	0-3days	2(100.0)	5(71.4)	26(59.1)	
	4-16days	0(0.0)	2(28.6)	18(40.9)	
					0.990
C.S. Effect					
	No	2(100.0)	6(66.7)	37(84.1)	
	Yes	0(0.0)	3(33.3)	7(15.9)	

DSRe: Duration of Symptoms Resolution; TSMSP: Time of Starting Mood Stabilizer; C.S. Effect: Cumulative Side-effect

3.6 Association between ITAQ and Socio-demographic Characteristics

A chi-square test of independence showed that there was a significant association between religion, nationality, and insight of participants with BAD as evidenced by the statistics: ($x^2(4)=14.69$, p=.005) and ($x^2(2)=4.79$, p=.002) respectively. No association was found between the following socio-demographic characteristics and insight of participants into their condition; Language: Insight ($x^2(4)=8.16$, p=.086), Age: Insight ($x^2(6)=7.36$, p=.289), Housing: Insight ($x^2(4)=1.04$, p=.904), Income: Insight ($x^2(8)=5.99$, p=.648), Employment: Insight ($x^2(10)=11.81$, p=.298), Marriage: Insight ($x^2(6)=1.47$, p=.961), Education: Insight ($x^2(4)=4.79$, p=.310), Gender: Insight ($x^2(2)=0.40$, p=.821) (Table 6).

Table 6-Association between Insight and Demographics

Characteristics		Good Insight	Partial Insight	Poor Insight	*P-Value*
Age groups(Yrs)					
	≤25	10(23.8)	3(75.0)	2(22.2)	*0.289*
	26-35	11(26.2)	0(0.0)	4(44.4)	
	36-45	10(23.8)	0(0.0)	10(22.7)	
	≥46	11(26.2)	1(25.0)	11(25.0)	
Gender					*0.821*
	Male	18(42.9)	2(50.0)	3(33.3)	
	Female	24(57.1)	2(50.0)	6(66.7)	
Education					*0.310*
	JHS	11(26.3)	3(75.0)	3(33.3)	
	SHS	18(42.9)	0(0.0)	4(44.4)	

Tertiary	13(31.0)	1(25.0)	2(22.2)	***0.020***
Nationality				
Ghanaian	42(100.0)	3(75.0)	9(100.0)	
Non-Ghanaian	0(0.0)	1(25.0)	0(0.0)	
Religion				***0.005***
Christian	41(97.6)	3(75.0)	8(88.9)	
Muslim	1(2.4)	0(0.0)	1(11.1)	
Traditionalist	0(0.0	1(25.0)	0(0.0)	
Marital Status				*0.961*
Single	23(54.8)	3(75.0)	5(55.6)	
Married	16(38.1)	1(25.0)	4(44.4)	
Divorced	2(4.8)	0(0.0)	0(0.0)	
Widowed	1(2.4)	0(0.0)	0(0.0)	
Employment				*0.298*
S. Employed	17(40.5)	1(25.0)	2(22.2)	
Retired	2(4.8)	0(0.0)	0(0.0)	
C.Servant	5(11.9)	4(9.1)	3(33.3)	
Student	7(16.7)	0(0.0)	0(0.0)	
Unemployed	8(19.0)	3(75.0)	3(33.3)	
Others	3(7.1)	0(0.0)	1(11.1)	
Income				*0.648*
<500	12(28.6)	4(36.4)	4(344.4)	
500-999	14(33.3)	1(25.0)	1(11.1)	
1000-1999	6(14.3)	0(0.0)	2(22.2)	
2000-3999	9(21.4)	0(0.0)	2(22.2)	
>4000	1(2.4)	0(0.0)	0(0.0)	
Housing				*0.904*
Tenant	25(59.5)	3(75.0)	5(55.6)	
Owner	10(23.8)	1(25.0)	2(22.2)	
Family H	7(16.7)	0(0.0)	2(22.2)	
Language				*0.086*
Twi &English	34(81.0)	1(25.0)	7(77.8)	
English only	3(7.1)	2(50.0)	1(11.1)	
Twi only	5(11.9)	1(25.0)	1(11.1)	
Place of Dx				*0.622*
OPD	21(50.0)	1(25.0)	4(44.4)	
IPD	21(50.0)	3(75.0)	5(55.6)	

Junior High School (JHS) and Senior High School (SHS); OPD: Outpatient Department; IPD: Inpatient Department; S. Employed: Self-Employed; C. Servant: Civil Servant; Family H: Family House; I Insight And Treatment Attitude Questionnaire (ITAQ)

3.7 Association between ITAQ and other Factors

Results from chi-square analysis to determine the association between the duration of symptom resolution, medication adherence, and insight, found no statistically significant association between the time it takes for symptoms to resolve and patients' insight into their condition with statistic values as shown; ($x^2(6)=7.20$,

p=.303). However, there was a statistically significant association between patients' insight and attitude to the condition and management with medication adherence as shown; ($x^2(2)=44.21$, p=<.001) (Table 7).

Table 7. Association Between ITAQ and Factors

Characteristics	Good Insight	Partial Insight	Poor Insight	*P-Value*
DSRe				
<7days	10(23.8)	2(50.0)	1(11.1)	*0.289*
7-14days	25(61.9)	2(50.0)	4(44.4)	
15-21days	2(4.8)	0(0.0)	2(22.2)	
22-30days	4(9.5)	0(0.0)	2(22.2)	
Adherence				***<0.001***
Non-Adherence	0(0.0)	0(0.0)	2(22.2)	
Partial Adherence	1(2.4)	1(25.0)	9(81.9)	
Adherence	41(97.6)	3(75.0)	0(0.0)	

DSRe: Duration of Symptoms Resolution; ITAQ: Insight and Treatment Attitude Questionnaire

3.8 Comparison of the mood stabilizing effect between sodium valproate and carbamazepine

Figure 2 shows the onset of the mood stabilizing effect of sodium valproate comparatively to carbamazepine. The Sodium valproate group had symptoms of mania resolved in less than 7 days (*41.7%: n=5*) more than in the Carbamazepine group (*13.7%, n =7*). The Carbamazepine group had more symptoms resolved within 7-14days (*62.9%, n=22*) than Sodium valproate group within the same duration (*41.8%, n=5*). The results showed the Carbamazepine group with a gradual onset of mood stabilizing effect within 7days, followed by a sharp increase in its effect from 7-14days, compared to Sodium valproate group, that had a sharp increase in mood stabilizing effect within 7days, followed by a gradual decline in this effect after 7days to 14days. This finding showed sodium valproate to be more effective and faster in onset of anti-manic effect compared to carbamazepine.

Note: S.V =sodium valproate, Carba=Carbamazepine, b/n=between

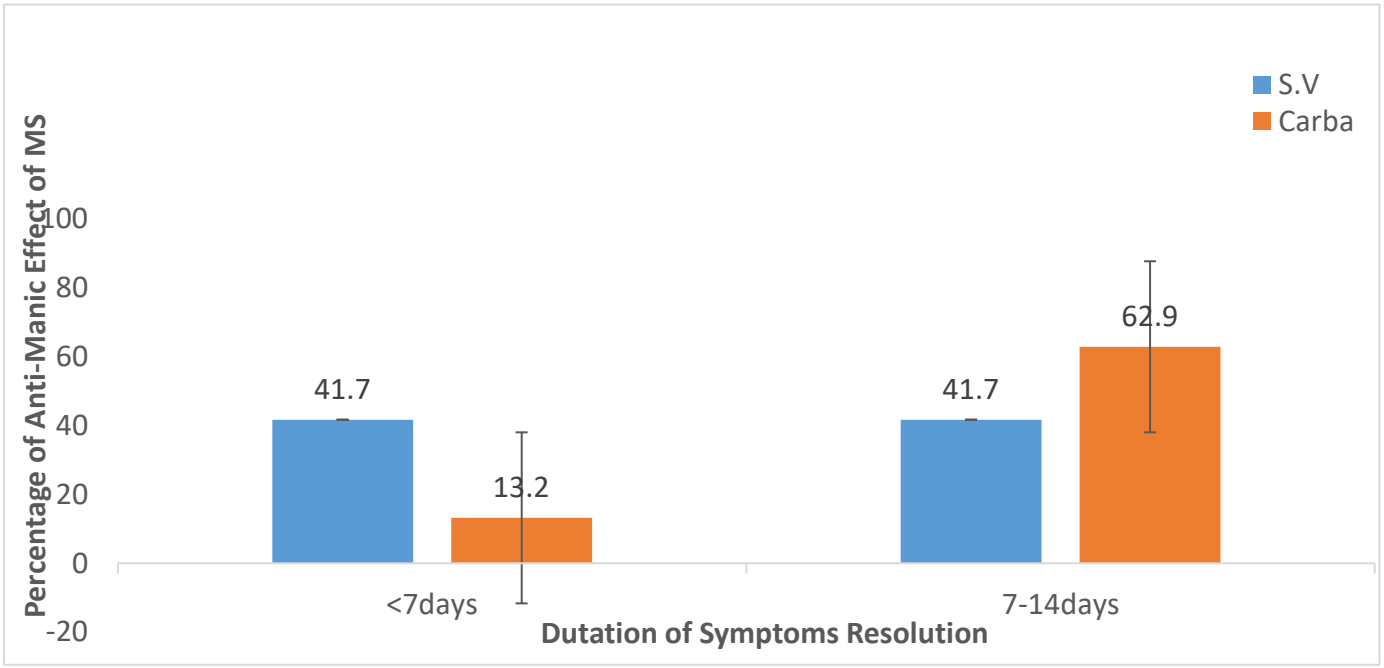

Fig 2. Comparison of the antimanic effect of sodium valproate and carbamazepine

3.9.2 **Comparison of the Time of Starting Mood Stabilizers and Duration of Symptom Resolution**
Figure 3 shows a box plot analysis of starting mood stabilizers within 0-3days and 4-16days. It can be inferred that, both groups had the same median, represented by the black line in the middle of the box, with evenly distributed outliers. The significance of the same median shows no difference in efficacy between the two groups of starting mood stabilizers.

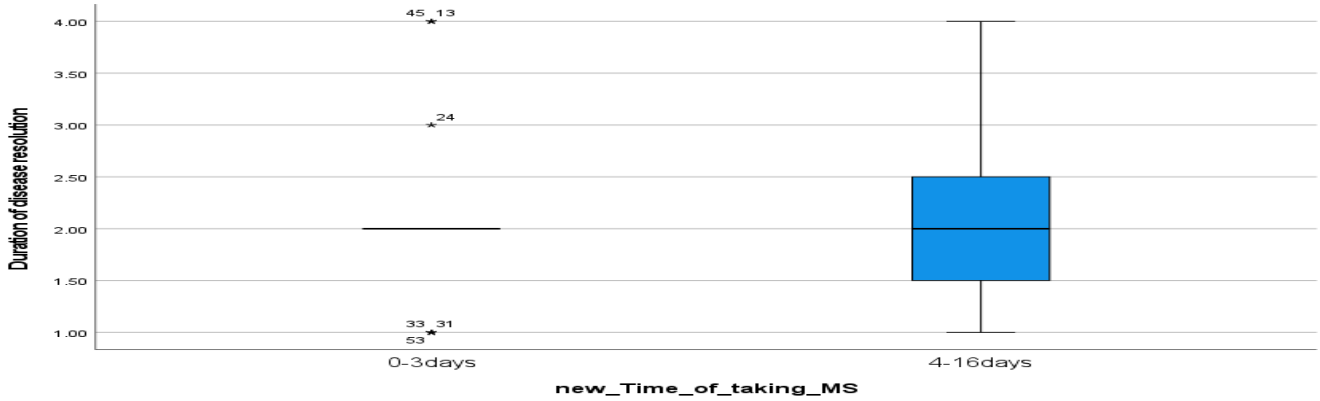

Figure 3- Box plot showing the overlap of duration of symptom resolution
Note: MS: Mood Stabilizer

Table 8-Statistics for Mann-Whitney U-test

	Values
Mann-Whitney U	309.00
Wilcoxin W	870.00
Z	-.440
Asymptomatic Significance (2tailed)	.660

A Mann-Whitney U test was performed to evaluate whether starting a patient on a mood stabilizer within 0-3 days differed from starting it within 4-16 days regarding the duration of symptom resolution. Mann-Whitney U test was selected because the data measured were ordinal and not normally distributed. Moreover, the sample size was small and there was a difference between the two groups in variance. Figure 4 shows a box plot analysis which in the Mann-Whitney test provides a measure of how great the overlap between the two groups being compared is. The black bars in the center of each plot value represent the median. From the box plot analysis, the two groups had the same median (median=2), and an interquartile range of 1.5-2.5. Hence, Ho: $Median_1$=$Median_2$. The test revealed a statistically not significant difference in the duration of symptom resolution between given mood stabilizers within 0-3 days (Median=2, n=33) and 4- 16 days (Median=2, n=20). The test statistic as shown in Table 8 was (U= 309.000, z= 0.440, p=.660). The effect size(r) was calculated to be 0.06, which according to Cohen et al (34) represents a small effect size, indicating there is no substantive significant difference between the starting patient on a mood stabilizer within (0-3days) and (4-16days) of presentation and their effect on the duration of symptom resolution.

3.10 Factors Influencing Clinician Choice of Mood Stabilizer

	1	***2***	***3***	***4***	***5***	***6***	***7***	***8***
Effectiveness	8	1	1					
Client History	5	4	1					
Prescriber's Knowledge of Drug	4	2	4					
Previous non-compliance	3	3	2	1			1	
Societal pressure to protect citizen		1	4	1				4
Client preferences	2	1	5			1	1	
Cost	3	2	4		1			

Table 11, Factors influencing Clinician choice of Mood Stabilizer

In a recent survey conducted at the Komfo Anokye Teaching Hospital (KATH), about 10 of the 13 clinicians participated, representing a diverse group with equal numbers of male and female professionals. These respondents are experienced, each having practiced for a minimum of two years, specifically in the field of psychiatry. Their expertise is particularly concentrated in the Psychiatry Unit of KATH. When asked about their preferences and considerations in prescribing Mood Stabilizers, a significant 80% (equating to 8 clinicians) identified medication effectiveness as the primary factor influencing their decision-making. This highlights the importance placed on the therapeutic efficacy of the medications in managing mood disorders. Following medication effectiveness, Client History emerged as the second most critical factor in the decision process for these clinicians, with half of them (50%, n=5) emphasizing its importance. This indicates a balanced approach to treatment, where both the efficacy of the medication and the individual history and needs of the client are taken into account in clinical decision-making. Such insights from the survey underscore the multifaceted considerations clinicians at KATH take into account while choosing appropriate treatment options, balancing both scientific evidence and individual patient factors to provide optimal care.

4. DISCUSSION

The study aimed to assess the best time to introduce mood stabilizers in acute or maintenance treatment of BAD, considering pharmaceutical care issues affecting medication adherence. Given its chronic, relapsing and remitting nature as well as attendant disability, comorbidity, and frequent negative therapeutic outcomes, BD is expected to be characterized by higher rates of treatment non-adherence. The study herein used the MARS as the adherence measure, focusing on medication behavior, beliefs and negative side effects of taking medication. A minimum percentage of the respondents (20%) reported having partial/poor adherence to medication. This is consistent with findings from previous studies on medication adherence among bipolar patients, where according to the majority of studies, non-adherence rates ranged from 20% to 50% (Miasso et al., 2011; Montes et al., 2013). This is similar to the estimates of several reviews on the subject, which concluded that on average about 40% to 50% of patients with BD (range of 9%-66%) do not take their medications regularly. (Leclerc, 2014; Chakrabarti, 2016). Our results showed a high rate of adherence (80%) of bipolar patients to their medications. This could be due to the integration of psycho-education and adherence counseling in the management of bipolar disorder at the Komfo Anokye Teaching Hospital's psychiatry department in Kumasi. This is consistent with a review done by Jaishri, where psycho-education was integrated into the management of bipolar disorder with impaired adherence to medication with most of the participants in the experimental group having 100% adherence (Jaishri et al., 2021).

Our study assessed socio-demographic variables, and related them to factors such as side effects, duration of symptom resolution, time of starting mood stabilizer on presentation, and medication adherence. Although among individual demographic attributes, there has been some evidence for an association of non-adherence in BD with younger age (Stephen et al., 2019), minority ethnicity (Sajatovic et al., 2006), and social disadvantage (Okasha et al.,2023), but evidence for such links is either limited or often contradictory (Chakrabarti, 2016). The role of sex and gender in adherence has been explored by Sajatovic and colleagues in a cross-sectional study of BD patients. Overall, there appeared to be no significant difference in adherence between men and women (Sajatovic et al., 2020). Our study found no association between medication adherence and socio-demographic variables and related factors. This is consistent with a recent meta-analysis that reported that demographics and treatment-related factors are equivocally linked to medication adherence (Chakrabarti, 2016). Furthermore, non-adherence to certainty is not predicted by demographics, illness, or treatment-related factors, according to a systematic review of studies (Chakrabarti, 2017).

Regarding the relationship between socio-demographic characteristics and insight level: An Italian nationwide study found an association between age (earlier or younger age onset and insight) (Alfredo et al., 2019). Age and insight did not appear to be correlated in our research. This was supported by a prospective study by Fredrick Cassidy, 2010, where he found age to be unrelated to insight (Fredrick, 2010). The majority of the studies that established a relationship between age and insight had an association with younger age group participants (14-16 years) (Stephen et al., 2019). The major reason for our study not having an association could be the age groups, mainly adults and not younger patients. Only 5.4% (n=3) of participants were within the stipulated age range. Employment; unemployed BD patients had an association with insight in previous studies (Alfredo et al., 2019). The unemployment rate for those with BD is higher than the general population (40-60%) (Marwaha et al., 2013). Study reviews of employment outcomes in adults with BD

experienced a decline in job status and income (Marwaha et al., 2013). Moreover, adults with newly diagnosed BD were less likely to be employed compared to well-matched healthy controls (Marwaha et al., 2013). Our study found no association between employment and insight. This could be due to the majority of our participants being self-employed (36.4%) compared to unemployed (25.5%). Again, previous studies found an association between marital status (never married/partnered) and poor insight (Alfredo et al., 2019). Our study found no association between marital status and insight level. This was consistent with a study review by Ramachandran, where no association was found between marital status and insight (Ramachandran et al., 2016). Our study also showed an association between insight and religion. This was consistent with the study conducted by Adams and colleagues among Christians with mental illness, which mirrored the findings from the Life-way Research Group 2014 study. They discovered that the Christian community lacked understanding of mental health disorders (BD) (Adams et al., 2018). The Pew Research Center (2017) reports that understanding of mental illness, including BD, was impacted by the religious phenomenon that permeates many African and African-American communities. According to the study, among all racial or ethnic groups, Africans and African Americans are among the most religious. As such, prayer and faith are often seen as a salve for mental health illness and may be favored over formal medical treatment (Pew Research, 2014). Our study also found an association between nationality (black ethnicity) and insight. This was consistent with a study by Earlise Ward, where seeking mental health among Africans and African Americans is often seen as a weakness (Ward et al., 2013). All other demographic variables and related factors were not associated with insight. This was consistent with a review study by Kevin A. et al, where insight was not strongly associated with any socio-demographic variable. Better insight was weakly but significantly associated with white ethnicity, being employed, and younger age (Kevin et al., 2021).

The current study's findings indicated a relationship between insight and drug adherence. This is consistent with a previous study by Luis Gutierrez-Rojes et al, where medication adherence in BD patients was independently and directly associated with insight (Gutierrez-Rojas et al., 2008). Consistent with this, again, non-adherent BD patients have lower levels of insight compared to adherent patients (Novick, 2019), with better insight associated with higher adherence (Novick, 2019). The study assessed the onset of the mood-stabilizing effect between sodium valproate and carbamazepine. In the study, sodium valproate showed a faster onset of mood stabilizing effect (less than 7 days) compared to carbamazepine (7-14 days). This is consistent with a study carried out by Vasudev et al (Vasudev, 2015), where 73% of the valproate-treated patients showed favorable clinical responses, while 53% of the patients had a clinical response to carbamazepine, with the demonstrated onset of anti-manic effect of sodium valproate around 3-4days (less than 7days). This finding also confirmed a report by a growing body of well-conducted clinical research that indicated sodium valproate had a faster onset of action in acute mania (2-5days) compared to carbamazepine (7-14days), lithium (10-20days) (Ogawa et al.,2014). The onset of the mood-stabilizing property of carbamazepine was further confirmed by Kelty Mental Health Research Center to be 1-2 weeks (Kelty Mental Health, 2022). The long-term effect of valproate in BD, a study by Fatima E et al, has shown valproate to be more effective than carbamazepine (Fatime, 2013). This finding was mirrored in our study as more of the participants on sodium valproate (41.7%) had a shorter duration of symptom resolution than those on carbamazepine (13.7%).

The optimal time to begin taking a mood stabilizer and its impact on the length of time symptoms resolve were the subjects of our investigation. To the best of our knowledge, research has been done on the effectiveness of antipsychotics in comparison to mood stabilizers in acute mania and the comparative effectiveness of augmentation therapy and monotherapy of either medication in acute bipolar disorder (Chakrabarti, 2022; Tajika et al., 2022). However, no study has looked at the variations in the length of time that mood stabilizers are taken to resolve symptoms in bipolar disorder. The present study revealed no difference between starting a mood stabilizer within (0-3 days) and (4-16 days) of presentation regarding the time both take to resolve symptoms in acute bipolar disorder. This was evidenced by the same median for each group (M=2) and a p-value of .660 (p=.660), using the Mann-Whitney U test. The effect size was 0.06, which represents a small effect size (74), indicative of no substantive significance difference between the starting patient on a mood stabilizer within (0-3 days) and (4-16 days) of presentation and their effect on the duration of symptoms resolution. Although the expectation was a linear relationship between starting a mood stabilizer earlier with early resolution of symptoms. This was not the case in this novel study due to significant reasons such as; firstly, the influence of antipsychotics. Reviews and meta-analyses have established the effectiveness of augmentation therapy (AP+MS) compared with MS or AP monotherapy (Lim et al., 2019).

Previous studies as shown the antipsychotic to be superior to classical mood stabilizers in the management of manic episodes (Kendell et al., 2014). Although the patient varied considerably in their response to the same anti-manic drug, dose and treatment period (Kishi et al.,2022; Yildiz et al., 2015), generally a uniform efficacy existed for every patient. An anti-manic agent can either have high variability or low variability, with low variability antipsychotics producing a homogeneous response despite subtle differences (Hsu et al., 2022). Anti-manic drug with better efficacy and lower variability is preferable for acute mania to produce a more stable response from a clinical perspective (Hsu et al., 2022). Based on a previous study, anti-manic drugs showed significantly lower variability in improving manic symptoms than placebo: Risperidone (0.51), Haloperidol (0.54), Olanzapine (0.59), Quetiapine (0.65) (Hsu et al., 2022). Improvement in manic symptoms also showed the antipsychotics with the higher efficacy to be: Risperidone (0.64), Haloperidol (0.57), and Olanzapine (0.44 (Yildiz et al., 2015). This is consistent with our study where the mean DSRe for the most used antipsychotics were; Risperidone (5.8), Haloperidol (5.8), Olanzapine (8.4) and Quetiapine (9.4). These findings clearly show the role of antipsychotics in the outcome of BAD and how the different antipsychotics affect the treatment outcome. Additionally, there could be adherence issues. In a prospective cohort study, it was found that partial/poor adherence to medications adversely affected remission and symptom resolution in bipolar disorder (Vedanarayanan et al., 2019). Our study revealed non-adherent participants starting their mood stabilizers within (0-3 days) to presentation with mean DSRe (8.4 days). This could have affected the lack of differences, due to the high number of partial/poor adherent participants in the (0-3 days) group not complying with their medications.

Our present study also assessed the factors clinicians considered in the selection of mood stabilizers in the treatment of bipolar disorder. Clinicians rated medication effectiveness as the most important factor in deciding which Mood Stabilizer to choose with a percentage response of 80% (n=8), followed by clients' history (50%). This was consistent with a study by Daniel J et al where clinicians rated medication effectiveness and client history as the two most important factors in deciding which mood stabilizer to choose (Daniel, 2004). Societal pressure to protect citizens was the least factor clinicians considered in the choice of Mood Stabilizers with a response rate of 40% (n=4). This was also mirrored in the same study by Daniel J et al with societal pressure to protect citizens being the least considered (Daniel, 2004). These findings are important in clinical practice as they will positively influence patient acceptability, improve rates of adherence across various phases of the condition and intervention types and further ensure faster patient;s recovery, prevent relapse and reduce adverse effects (Baryakova et al., 2023).

5. CONCLUSION

Our observational study proved that there was no difference between the time of starting a mood stabilizer in augmentation therapy regarding the duration of symptom resolution in acute bipolar disorder and that poor insight was significantly associated with medication non-adherence in either acute or maintenance treatment of bipolar disorder. Moreover, the most important factors psychiatrists consider in the choice of a mood stabilizer are medication effectiveness and client history, with the least important being societal pressure to protect citizens.

In clinical settings, this calls for psychiatrists, mental health professionals, and mental health advocates to liaise with churches and faith-based healers to ensure adequate education among these groups, and religious practitioners to improve patient awareness, acceptance of the condition and readiness to comply with recommended treatments. Again, there is a need for public education on mental health illness, especially bipolar disorder, to educate the masses about the condition and treatment available as black ethnicity has been demonstrated to have poor insight to white ethnicity. Additionally, psychological interventions (insight therapy) need to be strengthened to improve the understanding of our patients on their conditions and adherence. Again, both local and national guidelines for the treatment of BD should be able to account for medication effectiveness and client history as prime factors in the choice of mood stabilizers. The results of the present study should be evaluated taking into account its limitations. First of all, the sample size is relatively small and may limit the generalization of the findings. Data was collected from only one psychiatric clinic; hence future studies are recommended to collect data from multiple clinics. Moreover, the samples were not randomized into groups, as this could have also reduced selection and treatment biases. While we believe these limitations have not impacted the primary outcome of the study, future work may include additional controls.

Availability of Data and Materials

Databases and other relevant documents concerning the research can be made available upon request by the journal. Databases can be sent through the email of the corresponding author or contact details

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