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CLINICAL PHARMACIST ASSESSMENT OF MONITORING AND RESOLVING THE DRUG-RELATED PROBLEMS IN BIPOLAR DISORDER PATIENTS: A PROSPECTIVE, OBSERVATIONAL STUDY AT TERTIARY CARE TEACHING HOSPITAL

Ashish Singh Parihar [*1], Madiwalayya S. Ganachari [1], Bheemsain V. Tekkalaki [2] and Sandeep C. Patil [2]

Department of Pharmacy Practice [1], KLE College of Pharmacy, KLE Academy of Higher Education and Research (Deemed to be University), Belagavi - 590010, Karnataka, India.
Department of Psychiatry [2], Jawaharlal Nehru Medical College, KLE Academy of Higher Education and Research, Belagavi - 590010, Karnataka, India.

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Correspondence to Author:
Ashish Singh Parihar

Research Scholar,
Department of Pharmacy Practice,
KLE College of Pharmacy, KLE Academy of Higher Education and Research (Deemed to be University), Belagavi - 590010, Karnataka, India.

E-mail: ashishsinghparihar@klepharm.edu

ABSTRACT: Background: Bipolar disorder is a chronic mental illness due to a different interval of manic and depressive phase, the patient may become more prone to DRP, which interfere with the patients' health outcome. Hence, clinical pharmacist can contribute to managing the DRP through proper pharmaceutical care intervention. **Method/Design:** A prospective, observational study had been done with 286 participants to assess, monitor, and resolve the DRP through Clinical Pharmacist intervention. Patients with Bipolar disorder, aged 18 to 65, included in the study except for the patient with other comorbid condition, lactating mothers, and pregnant women. **Results:** DRP in between, all the patients were observed, of which 70.9 % were drug-drug interaction followed by 29.1% ADR. The two major causes of DRP were at drug/dose selection level 95.5%, followed by a drug use process level 4.5%. Pharmacist intervention has been proposed at prescriber level, of which majority of interventions 52.7% had been accepted by the prescriber. **Conclusion:** In our study, the majority of DRP 64.7%, had been resolved due to the clinical pharmacist intervention, which shows that participation of clinical pharmacist in psychiatric setting may help to resolve the DRP and integrate the health care delivery system.

INTRODUCTION: The drug-related problems (DRPs) are the major public health concern because of its consequence on morbidity, mortality, and burden on the patient's pocket [1]. As per PCNE and SFPC classification, DRP is the event or circumstances involving drug therapy that actually or potentially interfere with the desired therapeutic outcome [2, 3].

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There are several studies reported the incidence of DRP is approximately 1.7% to 25.1% of which only 5% of studies had been reported hospital admission [4]. As per the Pharmacy Today report, the DRPs are raising the cost of healthcare expenditure around $177.4 Billion. They estimated that 40% of the cost and 120,000 deaths due to DRP could be preventable through clinical pharmacist effort to assure the proper pharmacological treatment [5].

Almost all the psychiatry diseases or disorders have a temporary cure and long-term pharmacological treatment. Due to their psychiatry condition and long-term treatment, psychiatry patient's population are most susceptible to the DRP [6]. As Bipolar disorder is a severe mental as well as a life-

long long co-morbid disorder, which is responsible for premature mortality from suicide [7]. Which implies the patients quality of life through mood swings, personal suffering. Uneven sociological behavior and distinguished family relationship [8]. In India, there is 200 bipolar disorder sufferer per 100,000 population [9]. Indeed, bipolar disorder is a severe chronic mental illness which is represented by the mood swing, dysthymia, depression, cyclothymia, euphoria, and mania at a different time interval [10].

Lack of follow-up and reassessment of therapeutic outcome may also contribute toraising the number of DRPs. Clinical pharmacist assists care with other health professional offers to improve health outcome [11]. DRP is a challenge for the healthcare professionals because of its health-related burden on patients, especially psychiatry population like bipolar disorder patient. As a patient with bipolar disorder may undergo through the various phases of mania and depression, in such condition, there are more chances of a drug-related problem.

Aim of the Study: To Identified, Resolve and Report and percentage of DRP of the patient with bipolar disorder (as per DSM-V) at tertiary care hospital.

Ethics Approval: The study was reviewed and approved by the institutional ethics committee (KLEU/Ethics/2015-16/D-93) the study related documents, including study Protocol, Patent data collection form, patient information sheet (PIS), informed consent form (ICF) and patient information leaflets (PIL's) which were prepared in local language (Kannada, Marathi and Hindi) and submitted prior to study presentation. The study protocol and procedure were explained orally to the IEC.

Method:

Study Design and Patient Recruitment: The study was initiated in 2,400 bedded tertiary care teaching hospitals at the Department of Psychiatry. It was prospective, observational study with 286 enrolled patients out of 314 patients, those were fulfilled the study inclusion criteria like aged between 18 to 65 years of either gender and diagnosed with the bipolar disorder as per DSM- V. Patient with other comorbid psychiatry problem, lactating mothers and pregnant women were excluded out from the study.

Study Protocol: Patient those were fulfilled; the above-cited criteria were admitted. In the study, patient demographic data, the chief complaint, past medical and medication history, a current treatment plan with a subscription, inscription, and signature were collected at the time of enrollment. The drug-related problems (DRP's) have been identified through clinical discussion with the psychiatrist.

The type of DRP's, Brief description of DRP's, clinical suggestions, causes, and outcome of DRP's has been collected in the data collection form and pharmacist intervention form.

PCNE Classification: DRP's has been monitored, identified, assessed, and analyzed daily as per the PCNE classification of the drug related problem's version 5.01. This classification is used to assess the nature, prevalence; the incidence of DRP's and also acts as an indicator of pharmaceutical care outcome. As per this classification, DRP's are classified into six major categories [2].

1. **Adverse Reaction (P1):** the Patients those who are suffering or are going to suffer from an adverse drug event such as an ADR or toxicity. This problem might occur due to prescribing error. The ADRs may also immerge at fixed dosages of the appropriate drug. It consists of three major problems; P1.1 Side effect suffered (Non-allergic), P1.2 Side effect suffered (Allergic), and P1.3 Toxic effect suffered.

2. **Drug Choice Problem (P2):** under this domain Patients comes those are getting or are going to get a wrong drug for their disease condition. This may occur due to a prescribing error. It's covered six major problems; P2.1 Inappropriate drug (not most appropriate for indication), P2.2 Inappropriate drug form (not most appropriate for indication), P2.3 Inappropriate duplication of therapeutic group or active ingredient, P2.4 Contra-indication for drug (include Pregnancy/breastfeeding), P2.5 No clear indication for drug use and P2.6 No drug prescribed but clear indication.

3. **Dosing Problem (P3):** Patient may get a low or high dose of a drug which is not meet with their therapy requires. It can be due to prescribing error or drug use error. This is classified in four categories; P3.1 Drug dose too low or dosage regime not frequent enough, P3.2 Drug dose too high or dosage regime too frequent, P3.3 Duration of treatment too short and P3.4 Duration of treatment too long.

4. **Drug Use Problem (P4):** Under this domain, willingly or unwillingly Patient uses to take a wrong drug or no drug. Such a problem may occur because of drug use or administration errors and filling error in the pharmacy. It consists; P4.1 Drug not taken/administered at all and P4.2 Wrong drug took/administered.

5. **Interactions (P5):** Under this domain, mild, moderate, and major drug-drug or drug-food interaction covered. This may occur because of prescribing or drug use error. Under this P5.1 Potential interaction and P5.2 Manifested interaction comes.

6. **Others (P6):** Problems like P6.1 Patient dissatisfied with therapy despite taking the drug(s) correctly, P6.2 Insufficient awareness of health and diseases (possibly leading to future problems), P6.3 Unclear complaints. Further, clarification necessary and P6.4 Therapy failure (reason unknown) falls under this domain.

The causes of DRP's, intervention and outcome of intervention have been assessed with the help of PCNE V.05.1 classification.

For the suspected DRP's proper interventions are made by the clinical pharmacist. The proposed interventions were provided at Prescriber level (I1), Patient/care level (I2) and Drug level (I3)

1. **At Prescriber Level (I1):** Intervention proposed through the prescriber, under this some of the intervention include Prescriber informed only (I1.1), Prescriber asked for information (I1.2), Intervention proposed, approved by Prescriber (I1.3), Intervention proposed, not approved by Prescriber (I1.4) and Intervention proposed, outcome unknown (I1.5).

2. **At Patient / Care Level (I2):** Intervention at patient level mainly focus on the patient-related issue, and it proposed to the patients, these are Patient counseling (medication) (I2.1), Written information provided only (I2.2), Patient referred to prescriber (I2.3) and Spoken to family member/LAR (I2.4).

3. **At Drug level (I3):** The Intervention directly by altering/substituting the drug or frequency change in the use of the drug. Under this domain proposed intervention was drug change (I3.1), dosage change (I3.2), substitute drug (I3.3), instruction for use (I3.4), drug withdraw (I3.5) and new drug start (I3.6).

During the treatment period, patient data like current medication, altered dose or medication, lab investigation value, and ECG report was collected daily, latter collected data was segregated and analyzed with the help of IBM SPSS V.20.

Causality Assessment: The probability of DRP's was being assessed by Naranjo adverse drug reaction probability scale that is an adverse event (AE) related list of questionnaires, which consist information of drug administration and event occurrence, alternative causes for the event, drug levels, dose-response relationships and previous patient experience with the medication [12].

Statistical Analysis: The sample size of the conducted study was calculated with the help of the prevalence of DRP in previous studies. The probability value (p) was considered p 0.05 as a significant value with the 95% confidence interval (CI). The collected data were analyzed with the help of IBM-SPSS Version 20 software.

RESULTS: The study was conducted at the Department of Psychiatry of tertiary care hospital. Total 314 patients were screened out of which 286 patients were included in the study after their and family member writing signed consent.

The patient related demographic data are mentioned below **Table 1**.

TABLE 1: DEMOGRAPHIC DATA OF THE PATIENTS

Category		Frequency	Percent %
Sex	Male	175	61.2
	Female	111	38.8
Age	Under 30	87	30.4
	30 To 39	78	27.3
	40 To 49	71	24.8
	50 To 65	50	17.5
Religion	Hindu	266	93.0
	Muslim	19	6.6
	Christian	1	0.3
Marital Status	Single	67	23.4
	Married	217	75.9
	Divorcee	1	0.3
	Widow	1	0.3
Occupation	Government	8	2.8
	Private	61	21.3
	Daily Basis	4	1.4
	Homemaker	86	30.1
	Student	44	15.4
	Unemployed	11	3.8
	Farmer	66	23.1
	Retired	6	2.1
Family History	Nothing Significant	248	86.7
	Paternal	29	10.1
	Maternal	9	3.1
Childhood Adversity	Neglect	23	8.0
	Physical Health	2	0.7
	Sexual Abuse	1	0.3
	Loss Of Parents	2	0.7
	Absent	258	90.2
Smoking Habit	Yes	77	26.9
	No	209	73.1
Alcoholic	Yes	52	18.2
	No	234	81.8
BMI	Under Weight	16	5.6
	Normal Weight	176	61.5
	Over Weight	63	22.0
	Obese	31	10.8
Other Comorbidity	Nil	251	87.8
	Hypothyroidism	16	5.6
	Hypertension	6	2.1
	CVS Disease	1	0.3
	Diabetes mellitus	9	3.1
	Respiratory Disease	3	1.0

TABLE 2: ADVERSE DRUG REACTIONS (ADR)

Drug	ADR	No. of AE's
Lithium	Hypothyroidism	06
	Hand Tremor	13
	Muscle Twitching	02
	Dry mouth	01
Valproate	Hand Tremor	02
	Thrombocytopenia	01
Trifluoperazine	Bradykinesia	01
Alprazolam	Impaired coordination	01

All the selected patients were receiving their treatment as per DSM-V, of which 9.7% (43) Valproate; 50% (223) Lithium; 0.9% (04) Sertraline; 1.3% (06) Chlorpromazine; 2.0% (09) Aripiprazole; 20.7% (92) Olanzapine; 13.0% (58) Quetiapine; 9.2% (41) Trifluoperazine; 10.8% (48) Trihexyphenidyl; 3.6% (16) Haloperidol; 2.9% (13) Divalproex; 4.2% (19) Respiridon; 15.5% (69) Lorazepam and 0.4% (02) were with Alprazolam.

DRP's had been assessed through PCNE classification. In our study, among the DRP's, we had found 29.1% (27) ADR and 70.9% (66) Drug-Drug Interaction. Of which, 88.8% (24) ADR were reported non-allergic side effects suffered and

11.1% (03) ADR were reported allergic side effect suffered. Whereas, among all drug-drug interactions, minor drug interactions were reported 22.7%; significant drug interaction 87.8% (58) and serious drug interaction 4.5% (3). Drug-related ADR and Interactions have been mentioned in below cited **Table 2** and **Table 3**.

TABLE 3: DRUG-DRUG INTERACTIONS

Drug-Drug interaction		Causality		No. of AE's
		Probable	Suspected	
Minor drug interaction	Haloperidol + chlorpromazine	0	1	1
	Sertraline + lithium	1	2	3
	Sertraline + chlorpromazine	1	0	1
	Total	2	3	5
significant drug interaction	Trihexphenedyl + trifluoperazine	3	1	4
	Lorazepam + trifluoperazine	3	6	9
	Lorazepam + haloperidol	1	3	4
	Lorazepam + quetiapine	1	3	4
	Lorazepam + aripiprazol	0	1	1
	Trihexphenedyl + chlorpromazine	2	0	2
	Lorazepam + olanzapine	7	7	14
	Haloperidol + quetiapine	0	1	1
	Haloperidol + olanzwpine	1	0	1
	Lithium + trifluoperazine	4	5	9
	Lithium + haloperidol	1	0	1
	Quetiapine + trihexyphenidyl	1	1	2
	Sertraline + lithium	1	0	1
	Aripiprazole + quetiapine	1	0	1
	Olanzapine + trifluoperazine	1	0	1
	Olanzapine + quetiapine	2	1	3
	Total	29	29	58
serious drug interaction	Trifluoperazine + chlorpromazine	1	2	3
	Total	1	2	3

DISCUSSION: Globally, there are 140,000 hospitalizations due to DRP's every year. It indicates the problem in current medical practices and service delivery system, which leads the drug-related morbidity and mortality [13]. In this contest for assessment of DRP's, Dahal P *et al*., have assessed the clinical pharmacist intervention in 49 patients with DRP's, of which most were related to inappropriate drug dosing problem (25.3%) followed by drug selection (23.9%). As per the result of their study, an acceptance rate of the proposed intervention was 70.5%. As per their conclusion, clinical pharmacist interventions are helpful to monitor, resolve, and prevent the DRP's [14]. In the same type of study, Vijayalakshmi *et al*., has been found 598 DRP's, of which 55.5% due to drug interactions and 12.7% drug choice problem. The intervention has been proposed by them at prescriber and drug administration level with an 88.5 % acceptance rate [15]. Khoda DA *et al*. has monitored and reported the AE's of 32 psychiatric patients. Of which they have found a 79.31% incidence in AE's among the psychiatric population. As per result, the author concluded that effective monitoring by a clinical pharmacist could help to minimize the incidence of AE's [16].

In our study, cause of DRP had to be found at Drug/Dose selection level 95.5% (85) and Drug use process level 4.4% (4). The majority of DRP cases were at the drug/dose selection level in which 74.1% (63) due to pharmacokinetics problems with the drug, including aging/deterioration in organ function and interactions, 3.5% (3) due to Synergistic/preventive drug required, but not given, 9.4% (8) due to the new symptom or indication revealed/presented and 12.9% (11) due to manifest side effect. Rest of cases were at a drug use process level in which 4 cases were associated with un-monitored therapeutic drug level. As per the assessed causes, we framed our intervention for the patients. The intervention has been proposed at the prescribed level. Total 91 interventions have been proposed, out of which a large number of intervention, *i.e.*, 72.5% (66) has been accepted and 27.4% (25) were not accepted by the prescriber. The number of proposed intervention has been cited in **Table 4**.

TABLE 4: PHARMACIST INTERVENTIONS

Pharmacist intervention		No. of proposed intervention
At prescriber level	Prescriber informed only	3 (3.2%)
	Prescriber asked for information	8 (8.7%)
	The intervention proposed, approved by Prescriber	48 (52.7%)
	The intervention proposed, not approved by Prescriber	25 (27.4%)
	The intervention proposed outcome unknown	7 (7.6 %)

The outcome of the intervention has been assessed of which, 35.2% (31) were not known, 28.4% (25) were solved, 36.3% (32) were partially solved, and 1.1% (1) was not solved.

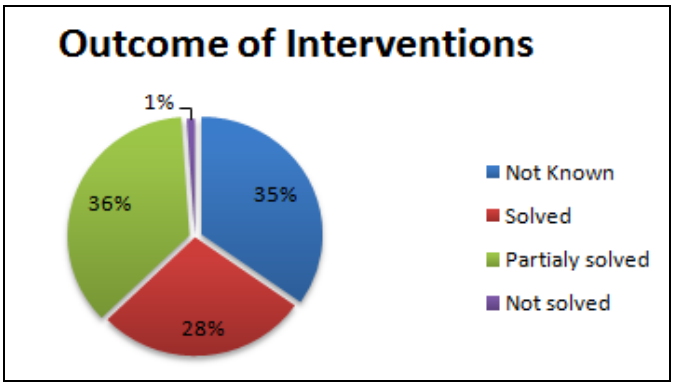

FIG. 1: OUTCOME OF THE PROPOSED PHARMACIST INTERVENTION

For good quality of data, we used PCNE classification for the drug-related problem (V5.01). In the same, we participated in ward round daily basis as well as, we were in contact with the patients during the study period so that we could provide better quality care to the patients. As we also had some limitation during the study of which patient-related barrier was more common. As most of the bipolar affective patients may fall into mania or depression at that time, there may be chances of subjective as well as information related bias. Another challenge was to make them adhere to the medication, as bipolar is a mood disorder so it was difficult to make them agree to adhere to their medication plan. The majority of suggestions has been accepted by the prescriber which helped to resolve the patient's DRP and enhancement of their quality of life.

CONCLUSION: The study result has given us the insight that clinical pharmacist lead a collaborative approach with the Psychiatrist and other health care professionals can help to minimize the DRP's associated with the patient's pharmacotherapy. The result shows that clinical pharmacist intervention is very important in maximizing the beneficiary effect & minimizing the side effect or DRP which ultimately promotes the better quality of life.

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CONFLICT OF INTEREST: There are no conflicts of interest.

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