A CROSS-SECTIONAL STUDY ON THE PREVALENCE OF ADVERSE DRUG REACTIONS OF SODIUM VALPROATE USED AS A MOOD STABILIZER IN PATIENTS WITH BIPOLAR AFFECTIVE DISORDER IN A TERTIARY CARE HOSPITAL.

Nisha V[1], Rakhi Krishnan[1], Nagendra R [2], M S Narendra Kumar [3], Charan C S[4] Prashanth L Naik[5], Hanumanthachar Joshi[6].

[1]Pharm D 5th year students, Sarada Vilas College of Pharmacy, Mysuru, Karnataka, India.

[2]Professor, Department of Pharmacy Practice, SVCP, Mysuru, Karnataka, India.

[3]Assistant professor, Department of psychiatry, K R Hospital, Mysuru

[4]Head of the Department, Department of Pharmacy Practice, SVCP, Mysuru, Karnataka, India

[5]Assistant Professor, Department of Pharmacy Practice, SVCP, Mysuru, Karnataka, India

[6]Principal, Sarada Vilas College of Pharmacy, Mysuru, Karnataka, India *Corresponding Author: Rakhi krishnan, Sarada Vilas College of Pharmacy, Krishnamurthy Puram, Mysuru-570004. Karnataka, India.

ABSTRACT:

Objectives: To determine the prevalence of ADRs and to analyse the causality, severity and preventability of ADRs associated with sodium valproate in BPAD patients.

Methods: A cross-sectional study was carried out in KR Hospital, Mysuru for a period of 6 months. After taking the consent the patients were interviewed to gather ADRs of sodium valproate, which were then recorded using the UKU SERS scale. ADRs associated were evaluated for causality, severity, and preventability using Naranjo's Algorithm, Modified Hartwig and Siegel scale, and Modified Shumock and Thornton scale respectively and recorded.

Results: Our study included 142 study population. Male preponderance (65.49%) was observed. A total of 368 ADRs were identified using UKU-side effect rating scale among the study population. The most common ADRs observed were increased

sleep (11.41%), weight gain (8.69%), sexual dysfunction (8.69%), headache (7.33%). 69.57% of reactions were possible, 75.27% of ADRs were assessed as mild and 94.29% of ADRs were definitely preventable. Prevalence of ADRs was found to be 85.91%.

Conclusion: ADRs are a frequent occurrence in patients with BPAD who are taking sodium valproate which is mild in most cases. Early detection and management can reduce the frequency of ADRs, increase compliance, and enhance patient quality of life.

INTRODUCTION:

Sodium valproate is a well-established anticonvulsant medication that has been repurposed for the management of mood disorders, particularly bipolar disorder. Like any medication, it can cause ADRs in some individuals. So through this study, we are making an attempt to access knowledge about ADRs.

World Health Organization (WHO) defines an ADR as "A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function. ADRs have been traditionally divided into two categories: Type A reactions, also known as Augmented reactions, are 'dose-dependent' and Type B reactions, often known as Bizarre reactions.

Bipolar disorder is a serious mental health condition characterized by recurrent episodes of depression, hypomania, and/or mania, which are typically interspersed with periods of relatively normal mood and functioning.

According to a global study on mental health, bipolar disorders were prevalent across all cultures and racial/ethnic groups, with lifetime prevalence rates of 0–6% for bipolar I disorder, 0–4% for bipolar II disorder, 1–4% for subthreshold bipolar disorder, and 2–4% for the full spectrum of bipolar disorders.

There are three types of bipolar disorder. Bipolar I disorder, Bipolar II disorder Cyclothymic disease. Manic Episode: A manic episode is a period of at least one week during which a person has more energy than normal, is extremely elated or agitated most of the time. Symptoms include reduced need for sleep, larger or more rapid speech, when speaking, have erratic or uncontrollably rushing thoughts or change topics quickly, Distractibility, Increased activity, such as restlessness or juggling multiple tasks at once a rise in dangerous behaviour (such as reckless driving and shopping binges). Hypomanic Episode: Less intense manic symptoms that just need to persist for four days.Episode of Major Depression: Extreme melancholy or despair, Loss of interest in once-enjoyed hobbies; feelings of shame or unworthiness, Fatigue, Either more or less sleep, Decreased appetite, Pacing or agitation, or slowed speech or movement, difficulty in paying attention, recurring suicidal or death thoughts.

Sodium valproate: Among the various drugs used for mood stabilization, sodium valproate has emerged as a prominent and effective treatment option. It is a well-established anticonvulsant medication that has been repurposed for the management of mood disorders, particularly Bipolar disorder.

MATERIALS AND METHOD:

Study site: Krishna Rajendra Hospital, a tertiary care hospital attached to Mysore Medical College & Research Institute, Mysuru.

Study design: The study was designed to be a cross sectional observational study. The sample size of the study was 142 patients.

Study period: The study was carried out for a period of six months.

Ethical approval: Institutional Human Ethical Committee of Mysore Medical College and Research Institute, Mysuru approved the study.

Study criteria:

Inclusion criteria:

1. Patients of age group 18 years – 75 years.
2. Patients of either gender.
3. Patients diagnosed with bipolar disorder according to International Classification of Diseases (ICD-11) criteria.
4. Patients taking sodium valproate for Bipolar Affective Disorder.

Exclusion criteria:

1. Those patients not willing to give informed consent.
2. Pregnant women
3. Lactating women

Source of data: All the relevant and necessary data will be collected from Interviewing patients and caretakers, Prescription of the patient, Communicating with concerned clinicians and health care professionals, Medical and Medication records of the patient

Study procedure: The study involved the following steps: -

1. Preparation of informed consent form (ICF): An appropriate ICF was created in both English (Annexure 1) and Kannada (Annexure 2) to gain patients' informed consent to participate in the study for those who are fulfilling the study criteria. A committee charged with upholding institutional Ethics evaluated and approved the ICF. The patient was fully informed about the study in their regional languages, and their consent was obtained by taking their signature or thumb impression.

2. Preparation of data collection form (DCF): For the study, a specially created data collection form (Annexure 3) was developed. The form included demographic details like name, age, gender, family history of psychiatric illness, education, occupation, income, diet, social habits, residence, and contact information. Clinical information such as the diagnosis, co-morbidities, adverse drug reactions and therapeutic information such as the name of the prescribed drug, dose, frequency, route, and duration of administration, as well as the use of concurrent drugs also were considered. To document the ADRs due to Sodium Valproate Udvalg for Kliniske Undersøgelser (UKU) side effect rating scale (Annexure 4) was used. assessment the Causality, Severity and Preventability of recorded ADRs were done using Naranjo's algorithm (Annexure 5), Modified Hartwig and Seigel scale (Annexure 6), Modified Shumock and Thornton scale(Annexure 7) respectively.

3. Patient enrollment: Patients who met the criteria for the study were included once their Informed Consent was obtained and translated into their regional or preferred language. Enrolment took place during OPD visits of patients.

4. Data collection: First and foremost, patients were interviewed in their regional languages. All relevant details of the enrolled patients were obtained from the aforementioned data sources and documented in the Data collection form (Annexure 3). The patients were interviewed once when they are attending OPD to gather ADRs of sodium valproate, which were then recorded using the UKU scale (Annexure 4). ADRs associated with sodium valproate were evaluated for causality, severity, and preventability using Naranjo's Algorithm, Modified Hartwig and seigel scale, and Modified Shumock and Thornton scale respectively and recorded.

5**. Statistical analysis:** A descriptive statistics was presented in terms of frequency and percentages for

categorical value. Mean, was used to describe the general characteristics of the study sample. An inferential statistic was be done by using chi-square test. In chi-square test p value ≤0.005 is considered as significant.

RESULTS:

A total of 142 study participants from the Psychiatry OPD who met our inclusion criteria were analysed.

Demographic Data:

The study population comprised of 65.49%(n=93) of males and 34.50% (n=49) females. Maximum patients belongs to the age group of 26-35 years(n=41).

PREVALENCE OF ADRs:

The prevalence of ADRs was found to be 85.91%. The prevalence of psychiatric and metabolic ADRs was found to be same (51.40%).Least prevalent ADRs were Blood related (1.40%), and vision related(3.52%).

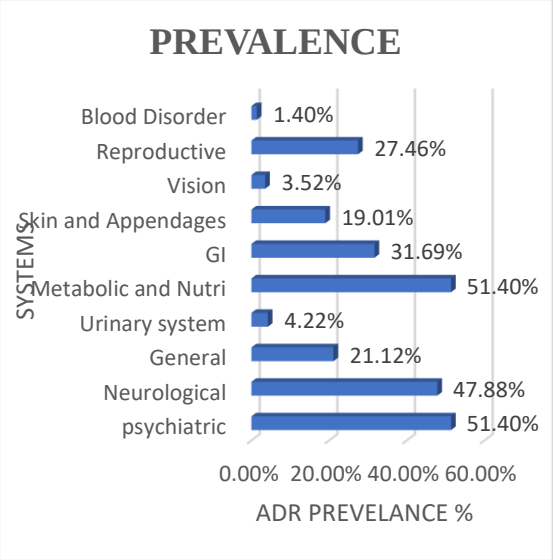

Figure 1: ADR Prevalence percentage distribution

Distribution of ADRs:

Out of 142 patients, 122(85.91%) patients developed one or more ADRs. The percentage of patients developing ADRs was slightly more in males (86.02%; n=80) as compared to females (85.71%; n=42). The most common ADR observed was Increased Sleep comprising 11.41%(n=42) of total ADRs. The other frequently seen ADRs included weight gain(n=32;8.69%), sexual dysfunction(n=32;8.69%), Xerostomia(n=27;7.33%), Headache(n=27;7.33%), Tremors(n=23;6.25%), Photosensitivity(n=23;6.25%), Anorexia(n=21;5.70%), weightloss(n=20;5.43%), Myalgia(n=17;4.61%) as depicted in figure 1.

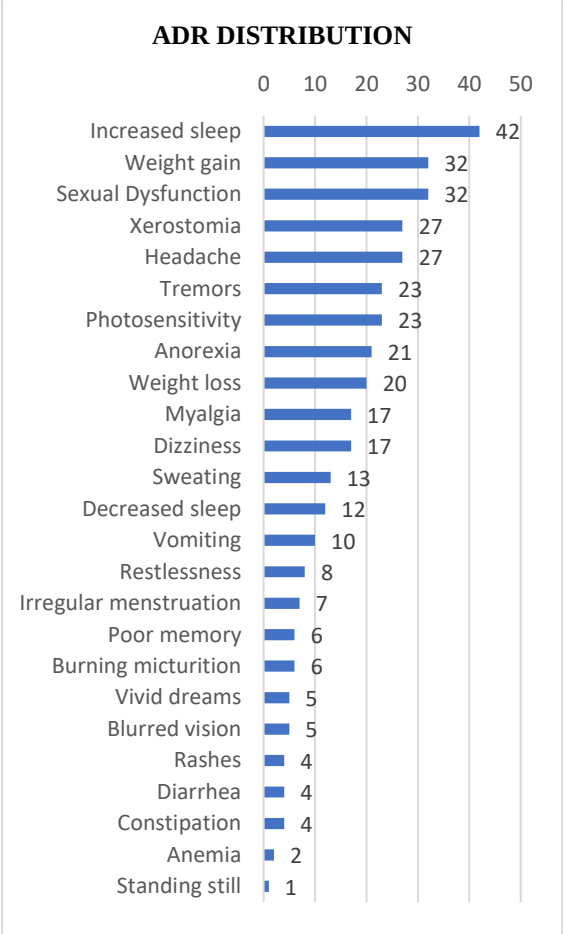

Figure 2: ADR Distribution among the study population.

According to the UKU side effect rating scale ADRs belonging to the group of other side effects (n=115; 33.23%)like Erectile dysfunction, Ejaculatory dysfunction, Menstrual irregularities, Weight gain, and Photosensitivity etc.were most common followed by Autonomic side effects(n=87;25.14%) like orthostatic dizziness, micturition disturbances, accomodation disturbances, xerostomia etc. 75 were psychic side effects(21.67%) like decreased and increased sleep, vivid dreams, failing memory etc. and 69 were neurological side effects(19.94%) like tremors, dystonia, headache etc. as shown in figure 3.

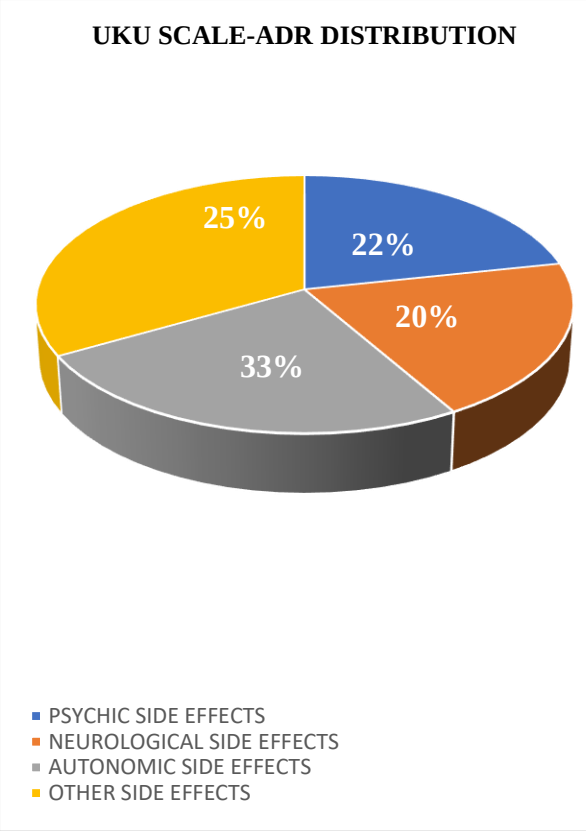

Figure 3: Distribution of ADRs according to UKU-Scale(n=346). (*Anemia and Anorexia were not included in this evaluation as they are not a part of the standard UKU Side effect rating scale.)

According to the UKU Side effect rating scale, most of the ADRs belong to Degree 1(n=250;72.25%) followed by Degree 2(n=95;27.45%) and Degree 3(n=1; 0.28%) based on the degrees specified in the UKU scale which is depicted in the figure 4.

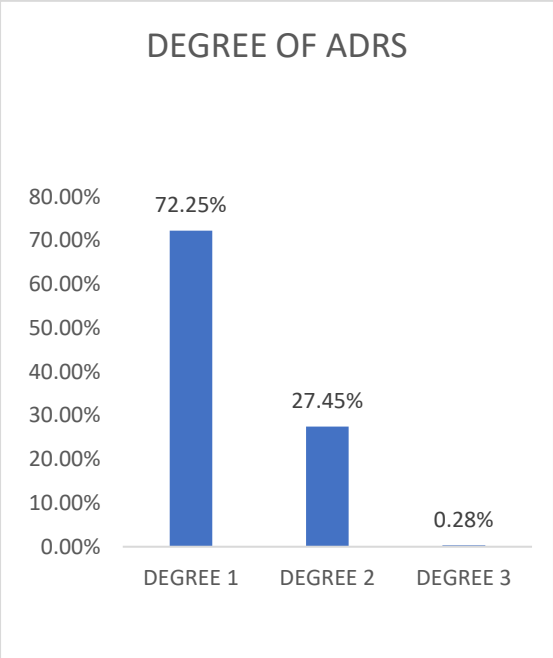

Figure 4:Degree of ADRs according to UKU Scale(n=346).
(*Anemia and Anorexia were not included in this evaluation as they are not a part of the standard UKU Side effect rating scale.)

The below table gives the various organ system affected by ADRs to WHO- adverse reaction terminology.

Sl. No	SOC(WHO-ART SOC Code)	Percentage of ADRs (n=368)	Adverse Drug reactions (No.of patients affected)
1.	Psychiatric disorders (0500)	19.83% (n=73)	Filing memory(6), Decreased sleep(42), increased sleep(12), vivid dreams(5), Restlessness(8),
2.	Neurological Disorders (0400)	18.47% (n=68)	Myalgia(17), Headache(27), Tremor(23), Standing still(1)
3.	Body as a whole- general disorders (1810)	8.15% (n=30)	Sweating(13), Dizziness(17)
4.	Urinary system disorders (1300)	1.63% (n=6)	Micturition disturbances(6)
5.	Metabolic and Nutritional disorders (0800)	19.83% (n=73)	Weight gain(32), Weight loss(20), Anorexia(21)
6.	Gastrointestinal disorders (0600)	12.22% (n=45)	Vomiting(10), Diarrhea(4), Constipation(4), Xerostomia(27)
7.	Skin and appendages disorders (0100)	7.33% (n=27)	Photosensitivity(23), Rashes(4)

8.	Vision disorders (0431)	1.35% (n=5)	Blurred vision(5)
9.	Reproductive disorders (1400)	10.59% (n=39)	Sexual dysfunction(32), Menstrual irregularities(7)
10.	Blood disorders (1200)	0.54% (n=2)	Anemia(2)

Table I: ADR distribution according to organ system.

CAUSALITY ASSESSMENT:

Causality Assessment of ADRs was done using Naranjo's Algorithm (Annexure 5). Out of 368 ADRs identified from the study population, majority of the ADRs were found to be Possible (n=256; 69.57%). Around 26.90% (n=99) of ADRs were found to be Probable and n=13; 3.53% of ADRs were identified as Unlikely. No ADRs belonged to Definite.

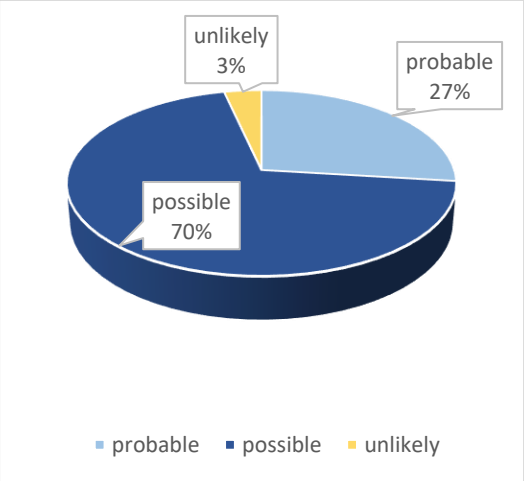

Figure 5: Causality distribution according to Naranjo's Algorithm.

SEVERITY ASSESSMENT:

Severity assessment of ADRs were done using Modified Hartwig and Siegel Scale (Annexure 6). Out of 368 ADRs 277 were found to be mild (n=277;75.27%). Among mild ADRs Level 1 ADRs were found to be 201 (54.62%) followed by Level 2 (n=76;20.65%). In Moderate ADRs Level 3 ADRs were found to be 91(24.72%). No ADRs belonged to Level 4(a), Level 4(b) and Severe.

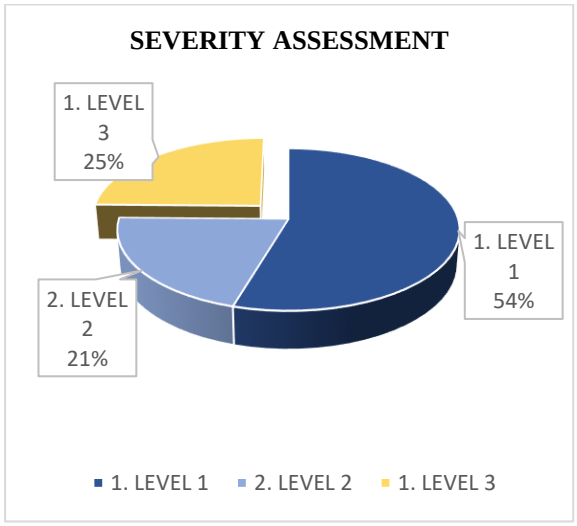

Figure 6: Severity distribution according to Modified Hartwig and Siegel Scale.

PREVENTABILITY ASSESSMENT

Preventability of ADRs among the study participants was assessed by using Modified Shumock and Thornton Scale (Annexure 7). Out of 368 ADRs 347 (94.29%) were Definitely preventable and 21 (5.70%) were probably preventable.

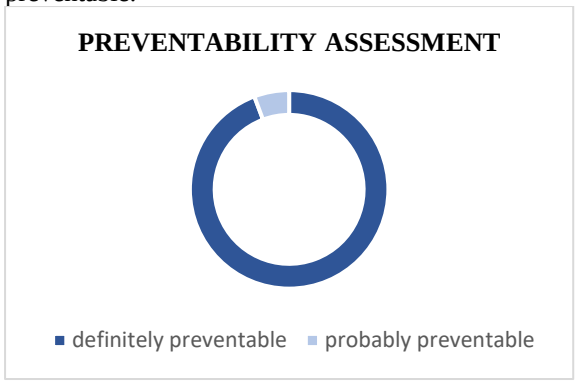

Figure 7: Preventability Distribution according to Modified Shumock and Thornton Scale

RISK FACTOR ASSOCIATION WITH ADRs:

Factors		ADRs		Chi-square value	p-value
		Yes	No		
Age	≤35 years (n=67)	60	7	1.3862	0.2389

	>35 years(n=75)	62	13		
Gender	Male(n=93)	80	13	0.0025	0.9600
	Female(n=49)	42	7		
Education	Illiterate (n=27)	25	2	1.2283	0.2677
	Literate(n=115)	97	18		
Employment Status	Employed (n=59)	51	8	0.02300	0.8794
	Unemployed (n=83)	71	12		
Diet	Veg(n=41)	35	6	0.0143	0.9045
	Non veg(n=101)	87	14		
Family Hx of psychiatric illness	Family Hx(n=35)	35	0	7.6145	0.0057*
	NoFamily Hx(n=107)	87	20		
Other medical illness	Present(n=31)	27	4	0.0457	0.8306
	absent(n=111)	95	16		
Marital Status	Single(n=45)	36	9	1.9050	0.1675
	Married (n=97)	86	11		
Substance Abuse (Alcohol)	Alcoholics (n=38)	34	4	0.5428	0.4612
	Non alcoholics (n=104)	88	16		
Substance Abuse (smoking)	Smokers(n=25)	23	2	0.9282	0.3353
	Non smokers (n=117)	99	18		
Substance Abuse (Others)	Users(n=2)	2	0	0.3325	0.5641
	Non users(n=140)	120	20		
Disease State	BPAD I(n=104)	91	13	0.8063	0.3692
	BPAD II(n=38)	31	7		
Treatment	Monotherapy(n=22)	19	3	0.0043	0.9475
	Polytherapy(n=120)	103	17		

Table II: Risk factor association with ADRs

ACKNOWLEDGEMENT:

The authors are thankful to our mentor **Dr. Nagendra R**, Professor, Department of Pharmaceutics, SVCP, and all the faculty members of the Department of Pharmacy Practice, SVCP, Mysuru. We also thank **Dr. Hanumanthachar Joshi, Principal, SVCP, Mysuru**, and **Mr. Charan C S**, Head of the department, Department of Pharmacy practice, SVCP, Mysuru. We unfeignedly appreciate our cherished lecturer and institutional co-guide**, Dr. Prashanth L Naik,** Assistant Professor, Department of Pharmacy Practice, Sarada Vilas College of Pharmacy, Mysuru for his precious guidance. Special thanks to **Dr. Ravindra P Choudhary** for his support and guidance which helped us complete our project work. Our special thanks to all my friends for their moral support and suggestion which helped us complete our project work.

REFERENCES:

1. World Health Organization. International drug monitoring: The

2. role of national centres. Report of a WHO meeting. World Health Organ Tech Rep Ser. 1972;498:1-25.
3. Sriram S, Ghasemi A, Ramasamy R, Devi M, Balasubramanian R, Ravi TK, et al. Prevalence of adverse drug reactions at a private tertiary care hospital in south India. J Res Med Sci. 2011;16(1):16–25.
4. Ejeta F, Aferu T, Feyisa D, Kebede O, Siraj J, Hammeso WW, et al. Adverse drug reaction and its predictors among psychiatric patients taking psychotropic medications at the Mizan-tepi university teaching hospital. Neuropsychiatr Dis Treat. 2021;17:3827–35.
5. Coleman JJ, Pontefract SK. Adverse drug reactions. Clin Med 2016;16(5):481–5.
6. Smith DJ, Whitham EA, Ghaemi SN. Bipolar disorder. Aminoff MJ, Boller F, Swaab DF, editors. Handb Clin Neurol. 2012;106:251–63.
7. Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder. Lancet. 2016;387(10027):1561–72.
8. Bipolar disorder. National Institute of Mental Health (NIMH).
9. Vieta E, Salagre E, Grande I, Carvalho AF, Fernandes BS, Berk M, et al. Early intervention in bipolar disorder. Am J Psychiatry. 2018;175(5):411–26.
10. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5 (R)). 5th ed. Vol. 5. Arlington, TX: American Psychiatric Association Publishing; 2013.
11. Impact of the DSM-IV to DSM-5 changes on the national survey on drug use and health. 2016.
12. Perugi G, Hantouche E, Vannucchi G. Diagnosis and treatment of cyclothymia: The "primacy" of temperament. Curr Neuropharmacol. 2017;15(3):372–9.
13. Bipolar disorder. Nami.org.
14. Stahl SM. Prescriber's guide: Stahl's essential psychopharmacology. 7th ed. Cambridge, England: Cambridge University Press; 2020.
15. Perugi G, Medda P, Toni C, Mariani M, Socci C, Mauri M. The role of electroconvulsive therapy (ECT) in bipolar disorder: Effectiveness in 522 patients with bipolar depression, mixed-state, mania and catatonic features. Curr Neuropharmacol. 2017;15(3):359–71.