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Clinical use of mood stabilizers beyond treatment for bipolar disorder: The REAP-MS study

Chih-Ken Chen [a], Shu-Yu Yang [b], Seon-Cheol Park [c,d], Ok-Jin Jang [e], Xiaomin Zhu [f], Yu-Tao Xiang [g], Wen-Chen Ouyang [h,i,j], Afzal Javed [k], M. Nasar Sayeed Khan [l], Sandeep Grover [m], Ajit Avasthi [m], Roy Abraham Kallivayalil [n], Kok Yoon Chee [o], Norliza Chemi [p], Takahiro A. Kato [q], Kohei Hayakawa [q], Pornjira Pariwatcharakul [r], Margarita Maramis [s], Lakmi Seneviratne [t], Kang Sim [u], Wai Kwong Tang [v], Tin Oo [w], Norman Sartorius [x], Chay-Hoon Tan [y], Mian-Yoon Chong [z,aa], Yong Chon Park [c], Naotaka Shinfuku [ab], Shih-Ku Lin [ac,ad,*]

[a] Department of Psychiatry, Keelung Chang Gung Memorial Hospital and School of Medicine, Chang Gung University, Taiwan
[b] Department of Pharmacy, Taipei City Hospital, Taipei, Taiwan
[c] Department of Psychiatry, Hanyang University College of Medicine, Seoul, the Republic of Korea
[d] Department of Psychiatry, Hanyang University Guri Hospital, Guri, the Republic of Korea
[e] Department of Psychiatry, Bugok National Hospital, Changyeong, the Republic of Korea
[f] Department of Psychiatry, Suzhou Guangji Hospital, the Affiliated Guangji Hospital of Soochow University, Suzhou, China
[g] Unit of Psychiatry, Department of Public Health and Medicinal Administration, Faculty of Health Sciences & Centre for Cognitive and Brain Sciences, University of Macau, Macao SAR, China
[h] Department of Geriatric Psychiatry, Jianan Psychiatric Center, Tainan, Taiwan
[i] Department of Psychiatry, Kaohsiung Medical University, Kaohsiung, Taiwan
[j] Department of Nursing, Shu-Zen Junior College of Medicine and Management, Kaohsiung, Taiwan
[k] Pakistan Psychiatric Research Centre, Fountain House, Lahore, Pakistan
[l] Department of Psychiatry, Services Hospital, Lahore, Pakistan
[m] Department of Psychiatry, Post Graduate Institute of Medical Education and Research, Chandigarh, India
[n] Pushpagiri Institute of Medical Sciences, Tiruvalla, India
[o] Department of Psychiatry & Mental Health, Tunku Abdul Rahman Institute of Neurosciences, Kuala Lumpur Hospital, Kuala Lumpur, Malaysia
[p] Department of Psychiatry and Mental Health, Hospital Kajang, Selangor, Malaysia
[q] Department of Neuropsychiatry, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
[r] Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
[s] Department of Psychiatry, Dr. Soetomo Hospital - Faculty of Medicine, Airlangga University, Surabaya, Indonesia
[t] Department of Psychiatry, University of Sri Jayewardenepura, Sri Lanka
[u] Institute of Mental Health, Buangkok Green Medical Park, Singapore
[v] Department of Psychiatry, Chinese University of Hong Kong, Hong Kong, China
[w] Mental Health Hospital, Yangon University of Medicine, Yangon, Myanmar
[x] Association for the Improvement of Mental Health Programs, Geneva, Switzerland
[y] Department of Pharmacology, National University of Singapore, Singapore
[z] Health Management International, Singapore
[aa] Regency Specialist Hospital, Johor, Malaysia
[ab] School of Human Sciences, Seinan Gakuin University, Fukuoka, Japan
[ac] Department of Psychiatry, Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan
[ad] Department of Psychiatry, Taipei City Hospital and Psychiatric Center, Taipei, Taiwan

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ABSTRACT

Objective: Mood stabilizers are psychotropic drugs mainly used to treat bipolar disorder in the acute phase or for maintenance therapy to prevent relapse. In clinical practice, mood stabilizers are commonly prescribed for conditions other than bipolar disorder. This study investigated the distribution of mood stabilizer prescriptions

* Corresponding author at: Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan.
E-mail address: sklin@tpech.gov.tw (S.-K. Lin).

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Schizophrenia
REAP

for different psychiatric diagnoses and studied differences in the drugs, dosage, and plasma concentration in 10 Asian countries including Taiwan, South Korea, Malaysia, China, Thailand, India, Pakistan, Singapore, Indonesia, and Myanmar.

Methods: Patients prescribed mood stabilizers (lithium, carbamazepine, valproic acid, or lamotrigine) for a psychiatric condition other than bipolar disorder (codes F31.0–F31.9 in the *International Classification of Diseases, 10th Edition, Clinical Modification*) were recruited through convenience sampling. A website-based data entry system was used for data collection.

Results: In total, 1557 psychiatric patients were enrolled. Schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders (F20-F29, 55.8 %) was the most common diagnosis, followed by non-bipolar mood disorders (F30, F31- F39, 25.3 %), organic mental disorder (F00-F09, 8.8 %), mental retardation (F70-F79, 5.8 %) and anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders (F40-F48, 4.4 %). The most frequently targeted symptoms (>20 %) were irritability (48 %), impulsivity (32.4 %), aggression (29.2 %), anger (20.8 %), and psychosis (24.1 %). Valproic acid was the most frequently used medication.

Conclusions: Clinicians typically prescribe mood stabilizers as empirically supported treatment to manage mood symptoms in patients with diagnoses other than bipolar disorders, though there is on official indication for these disorders. The costs and benefits of this add-on symptomatic treatment warrant further investigation.

1. Introduction

Mood stabilizers, though there is no clear definition (Ghaemi, 2001), it is generally accepted that they are the psychotropic drugs mainly used to treat bipolar disorder in the acute phase (either manic or depressive) or prevent relapse (maintenance therapy). Lithium, a prototype mood stabilizer, was the first medication reported to be effective for mania (Cade, 1949; Malhi et al., 2017). Anticonvulsants such as carbamazepine, valproic acid, and lamotrigine are also considered mood stabilizers and are used to treat bipolar disorder (Fountoulakis et al., 2017; Grunze et al., 2018; Yatham et al., 2018). Mood stabilizers are sometimes prescribed as treatment for other psychiatric disorders, including schizoaffective disorder (Baethge et al., 2004; Kantrowitz and Citrome, 2011; Keck et al., 1996), major depressive disorder (Rajaratnam et al., 2017; Tundo et al., 2015; Wang et al., 2017), schizophrenia (Glick et al., 2009; Xiang et al., 2012), posttraumatic stress disorder (Jain et al., 2012), autism spectrum disorder (Canitano, 2015), and personality disorders (Belli et al., 2012; Ingenhoven et al., 2010), as an adjunct or add-on medication. There are no rigorous controlled clinical trials in this kind of clinical application, or even it was proved no effects on schizophrenia in a small scale study (Glick et al., 2009), it is still widely prescribed in clinical practice. For instance, in a large scale survey from 30908 patients with schizophrenia, the rate of anticonvulsants or lithium prescription was 16.2 % (Toto et al., 2019). A US study conducted more than two decades prior (Citrome et al., 1998) reported that 28 % of patients with schizophrenia were prescribed valproic acid. It is generally believed that the purposes of mood stabilizers are to mitigate symptoms of irritability, aggression, anger, impulsivity, disruptiveness, and severe anxiety as well as reduce autonomous overreactions to stress and mood swings.

The Research on Asian Prescription Patterns (REAP), which investigates prescription patterns of psychotropics across Asian countries, is an international collaboration between psychiatrists and pharmacologists (http://reap.asia/index.html). The objectives of this study, entitled the REAP–Mood Stabilizer (REAP-MS) Study, are to examine prescription patterns of mood stabilizers in patients with psychiatric diagnoses other than bipolar disorder, analyze the distribution of mood stabilizer prescriptions for specific psychiatric diagnosis and targeted symptoms, and determine the differences in the type and dosage of mood stabilizers prescribed and (if available) their plasma concentration. Primary and concomitant medications were also analyzed to be compared between countries.

2. Methods

Ten Countries including Taiwan, South Korea, Malaysia, China, Thailand, India, Pakistan, Singapore, Indonesia, and Myanmar were involved to enroll patients in this study. The participants of this study were recruited through convenience sampling. Patients prescribed mood stabilizers (lithium, carbamazepine, valproic acid, or lamotrigine) who were diagnosed as having a psychiatric condition other than bipolar disorder (codes F31.0–F31.9 in the *International Classification of Diseases, 10th Edition, Clinical Modification*) were included. A website-based data entry system was used for data collection. The research protocol can be accessed at http://www.reap.asia/pdf/reap_ms_protocol.pdf. In brief, data on the daily medications prescribed to inpatients or outpatients, including mood stabilizers, antipsychotics, antidepressants, anxiolytics, hypnotics, and other concomitant medications, were collected, along with the participants' demographic and laboratory data.

To compare the dosage of various mood stabilizers, the Anatomical Therapeutic Chemical (ATC) Classification System—that is, the ATC/Defined Daily Dose [DDD] Index 2016 developed by the World Health

Table 1
Demographic characteristics of the study population by country.

	Taiwan	South Korea	Malaysia	China	Thailand	India	Pakistan	Singapore	Indonesia	Myanmar	Total
n	**374**	**283**	**278**	**277**	**88**	**79**	**70**	**46**	**45**	**17**	**1557**
Gender											
Male	215	154	175	152	36	46	63	21	27	6	897
Female	159	129	103	125	52	33	7	25	18	11	659
Age (years)											
mean	46.2	41.6	43.3	38.2	47.7	40.1	32.6	47.5	33.7	33.9	42.1
SD	12.3	16.5	12.9	16.0	21.2	15.6	9.9	12.3	12.8	9.4	15.1
Weight (Kg)											
mean	69.1	70.7	68.2	67.5	63.0	69.7	63.8	70.2	66.2	54.4	68.1
SD	16.4	15.2	16.0	13.2	13.7	11.0	9.3	15.6	14.0	9.1	14.8
BMI											
mean	25.9	25.8	25.5	23.7	23.7	25.7	23.1	26.1	25.9	24.3	25.1
SD	5.2	4.8	5.5	3.7	4.2	4.2	2.6	5.3	5.2	3.0	4.8

Abbreviation: BMI, body mass index

Table 2
Comparison of the use of different mood stabilizers by country.

	Taiwan	South Korea	Malaysia	China	Thailand	India	Pakistan	Singapore	Indonesia	Myanmar	Total	Mean ± SD Daily dose (mg)
n (%)	**374**	**283**	**278**	**277**	**88**	**79**	**70**	**46**	**45**	**17**	**1557**	
Valproic Acid												
n	238	187	239	208	59	50	62	39	36	15	1133	751.0
(%)	(63.6)	(66.1)	(86.0)	(75.1)	(67.0)	(63.3)	(88.6)	(84.8)	(80.0)	(88.2)	(72.8)	± 370.7
Lithium												
n	87	73	17	59	11	22	0	5	9	0	289	656.8
(%)	(23.3)	(25.8)	(6.1)	(21.3)	(12.5)	(27.8)	(0.0)	(10.9)	(20.0)	(0.0)	(18.6)	± 249.9
Lamotrigine												
n	23	16	5	17	22	5	0	2	0	0	90	126.8
(%)	(6.1)	(5.7)	(1.8)	(6.1)	(25.0)	(6.3)	(0.0)	(4.3)	(0.0)	(0.0)	(5.8)	±82.4
Carbamazepine												
n	33	24	27	4	2	4	8	0	0	2	104	499.5
(%)	(8.8)	(8.5)	(9.7)	(1.4)	(2.3)	(5.1)	(11.4)	(0.0)	(0.0)	(11.8)	(6.7)	±252.6

Organization—[accessed 1, May 2021]) (http://www.whocc.no/atc_ddd_index/?code=N03AG01). For statistical analyses, the SPSS for Windows (version 20; IBM Corp., Armonk, NY, USA) was applied for computing study data. Here, the samples are reported as numbers and percentages as well as means ± standard deviations (SDs).

The study was sponsored by the Taiwan Ministry of Science and Technology (106–2314-B-532-009) and the Taipei City Government. The study protocol was approved by the Taipei City Hospital Research Ethics Committee. All participated sites had their own IRB approval.

3. Results

In total, 1557 psychiatric patients prescribed mood stabilizers (60.1 % outpatients; 57.6 % male) from 10 countries were enrolled. The demographic characteristics of the participants from each country are presented in Table 1, listed in order of the number enrolled. The use of different mood stabilizers and their total mean dosage are compared by country in Table 2. The mean plasma concentrations of valproic acid, lithium, and carbamazepine were 69.0 ± 25.0 ug/mL, 0.65 ± 0.22 mEq/L, and 6.5 ± 2.8 ug/mL (n = 417, 153, and 15), respectively.

Schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders (F20-F29, 55.8 %) was the most common diagnosis, followed by non-bipolar mood disorders (F30, F31- F39, 25.3 %), organic mental disorder (F00-F09, 8.8 %), mental retardation (F70-F79, 5.8 %) and anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders (F40-F48, 4.4 %). In descending order, the targeted symptoms of mood stabilizers were irritability (48 %), impulsivity (32.4 %), aggression (29.2 %), anger (20.8 %), psychosis (24.1 %), elevated mood (17.9 %), depressed mood (17.8 %), sleep disturbance (17.6 %), talkativeness (15.8 %), disruptiveness (13.0 %), mood swimming (10.1%), anhedonia (9.9%), increased energy (9.1 %), loss of energy (9.2 %), indecisiveness or reduced concentration (9.1 %), grandiosity (8.9 %), psychomotor agitation or retardation (7.0%), flight of ideas (6.7 %), feelings of worthlessness or guilt (6.2 %), suicidal ideation or attempt (6.2 %), increased risk taking (6.0 %), reduced need for sleep in mania-like episodes (6.0 %), significant body weight changes (3.6 %), and autonomous overreactions to stress (1.8 %).

Table 3 presents the statistics on the concomitant use of psychotropics by participants in each country. Antipsychotics were the most frequently used (83.2 ± 12.3 %).

4. Discussion

To the best of our knowledge, this is the first study to explore the clinical use of mood stabilizers for psychiatric conditions other than bipolar disorder in Asian countries. As mentioned, 55.8 % of mood stabilizers were prescribed for schizophrenia and related psychotic disorders. Exacerbation of schizophrenic symptoms is typically accompanied by irritability, impulsivity, aggression, anger, and psychosis, explaining the use of mood stabilizers, especially valproic acid, as add-on medications in patients with this condition. Although the precise pharmacological mechanism of mood stabilizers remains unclear, they are widely used for symptom amelioration in clinical practice beyond mood disorders. In a study of 3557 patients with schizophrenia in Asian countries, 13.6 % were prescribed mood stabilizers (Lim et al., 2020), with sodium valproate (11.1 %), lithium (1.94 %), carbamazepine (1.04 %), and lamotrigine (0.34 %), respectively. Factor analysis revealed significant associations between being female and current hospitalization with any use of adjunctive mood stabilizers. For these patients, multiple psychiatric hospitalizations, no illness remission, disorganized speech, higher sedation score and body mass index, verbal or physical aggression, affective symptoms, and social–occupational dysfunction were noted. They were also taking higher daily chlorpromazine-equivalent doses of antipsychotics.

Valproic acid was the most often used mood stabilizer in our study subjects with schizophrenia. Toto et al. (2019) reported that the

Table 3
Comparison of concomitant use of psychotropics by country.

	Taiwan	South Korea	Malaysia	China	Thailand	India	Pakistan	Singapore	Indonesia	Myanmar	Total
In n (%)	**374**	**283**	**278**	**277**	**88**	**79**	**70**	**46**	**45**	**17**	**1557**
Antipsychotics											
n	350	223	249	213	47	58	62	40	36	16	1294
(%)	(93.6)	(78.8)	(89.9)	(77.7)	(53.4)	(73.4)	(88.6)	(87.0)	(80.0)	(94.1)	(83.1.)
Antidepressants											
n	99	92	31	85	41	35	6	15	12	0	416
(%)	(26.5)	(32.5)	(11.2)	(31.0)	(46.6)	(44.3)	(8.6)	(32.6)	(26.7)	(0.0)	(26.7)
Anxiolytics											
n	196	124	33	104	46	4	50	12	13	6	588
(%)	(52.4)	(43.8)	(11.9)	(38.0)	(52.3)	(5.1)	(71.4)	(26.1)	(28.9)	(35.3)	(37.8)
Hypnotics											
n	173	12	5	24	0	0	0	4	0	1	219
(%)	(46.3)	(4.2)	(1.8)	(8.8)	(0.0)	(0.0)	(0.0)	(8.7)	(0.0)	(5.9)	(14.1)

Table 4
Mood stabilizers used as treatment for depressive episodes or recurrent depressive disorder in 270 patients.

	n	%
Valproic Acid	163	60.3
Lithium	57	21.1
Lamotrigine	35	13.0
Carbamazepine	15	5.6

proportion of individuals concomitantly using anticonvulsants and lithium in a cohort of 30,908 inpatients with schizophrenia in Germany was 14 % and 2.1 %, respectively. A US study conducted more than two decades prior, Citrome et al. (1998) reported that 28 % of patients with schizophrenia were prescribed valproic acid in a large scale study. In a comparative effectiveness study conducted by (Stroup et al., 2019) using US Medicaid data of 81,921 adult outpatients with schizophrenia, the authors suggested that initiating adjunctive treatment with an antidepressant was associated with reduced risk of psychiatric hospitalization and emergency department visits. The effects of initiating the use of a mood stabilizer did not differ significantly from those of initiating the use of another antipsychotic. Their data even showed that initiating a mood stabilizer was associated with an increased risk of mortality.

Notably, in a review of randomized controlled trials investigating the effectiveness of valproic acid as a treatment for schizophrenia including seven studies with a total of 519 participants by Schwarz et al. (2008), the authors found that no evidence supports or refutes the efficacy of using valproate as an adjunct to antipsychotic medication on the participants' global state or the general mental state at the endpoint. Also in a recent review article, Baandrup (2020) found no solid evidence of the benefits of combining an antipsychotic with an antiepileptic in the treatment of schizophrenia.

In a systematic review by Gardea-Resendez et al. (2020), the results indicated that valproate and lithium may induce broad epigenetic changes through various mechanisms, primarily DNA demethylation, and histone acetylation, leading to the amelioration of psychiatric symptoms. No definitive conclusions were drawn for the use of lamotrigine or carbamazepine because of the relative lack of evidence. Taken together, the benefits of cotreatment with mood stabilizers in patients with schizophrenia are controversial and require further investigation.

As mentioned, the second most common diagnosis for which mood stabilizers were prescribed in the present study was non-bipolar mood disorders (F30, F31- F39, 25.3 %), in which depressive episode or recurrent depressive disorder was 17.3 %. In most treatment guidelines, mood stabilizers, especially lithium, are suggested for use in refractory depressive patients (Bschor, 2014). Our results indicate that valproic acid was the dominant medication used for these conditions (60.3 %; Table 4). No solid evidence supports the use of valproic acid for this purpose; its common prescription may be due to clinicians regarding it as safer than lithium with respect to the risk of overdose.

The mean plasma concentrations of the mood stabilizers examined in the present study were all within the suggested therapeutic range, but with a DDD much lower than that recommended by the WHO (valproic acid: 751.0 vs. 1500 mg, lithium: 656.8 vs. 900 mg, lamotrigine 126.8 vs 300 mg, and carbamazepine: 542.9 vs. 1000 mg). This might be attributable to the fact that valproic acid and carbamazepine are indicated for seizure disorders. For lithium, although the DDD was lower than suggested, the mean plasma concentration of 0.65 ± 0.22 mEq/L was within the suggested optimal concentration range of 0.6–0.75 mEq/L (Severus et al., 2008). In concomitant medications, the use of anxiolytics and hypnotics was much more common in Taiwan than in other countries. This is consistent with results from a survey of patients with schizophrenia in Asian countries (Yang et al., 2018).

The limitations of this study are as follows. It was a cross-sectional survey, data from different clinical settings (outpatients and inpatients) were used, convenience sampling was applied, and the number of participants from each country was uneven.

In conclusion, although there were no evidence-based studies to support the use of mood stabilizers, especially valproic acid, clinicians typically prescribe mood stabilizers as an empirically supported treatment to manage mood symptoms in patients with conditions other than bipolar disorder, such as schizophrenia, schizoaffective disorder, major depressive disorder, and organic mental disorders. The costs and benefits of this add-on treatment warrant further investigation.

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Declaration of Competing Interest

The authors declare no conflict of interest in reporting this study.

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