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RESEARCH ARTICLE

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Coprescription of mood stabilizers in schizophrenia, dosing, and clinical correlates: An international study

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Abstract

Objective: Studies examining coprescription and dosages of mood stabilizers (MSs) with antipsychotics for psychotic disorders are infrequent. Based on sparse extant data and clinical experience, we hypothesized that adjunctive MS use would be associated with certain demographic (e.g., younger age), clinical factors (e.g., longer illness duration), and characteristics of antipsychotic treatment (e.g., multiple or high antipsychotic doses).

Methods: Within an Asian research consortium focusing on pharmaco-epidemiological factors in schizophrenia, we evaluated rates of MS coprescription, including high doses (>1000 mg/day lithium-equivalents) and clinical correlates.

Results: Among 3557 subjects diagnosed with schizophrenia in 14 Asian countries, MSs were coprescribed with antipsychotics in 13.6% ($n = 485$) of the sample, with 10.9% ($n = 53$) on a high dose. Adjunctive MS treatment was associated (all $p < 0.005$) with demographic (female sex and younger age), setting (country and hospitalization), illness (longer duration, more hospitalizations, non-remission of illness, behavioral disorganization, aggression, affective symptoms, and social–occupational dysfunction), and treatment-related factors (higher antipsychotic dose, multiple antipsychotics, higher body mass index, and greater sedation). Patients given high doses of MSs had a less favorable illness course, more behavioral disorganization, poorer functioning, and higher antipsychotic doses.

Conclusions: Schizophrenia patients receiving adjunctive MS treatment in Asian psychiatric centers are more severely ill and less responsive to simpler treatment regimens.

KEYWORDS
adjunctive treatment, Asia, mood stabilizers, schizophrenia

1 | INTRODUCTION

Schizophrenia is a severe mental illness associated with life-long disability, high social burden, excess mortality, and major costs and has proven to be difficult to treat successfully (GBD, 2017; Owen, Sawa, & Mortensen, 2016). Contemporary treatment of schizophrenia involves antipsychotic drugs and rehabilitative methods (Owen et al., 2016), as well as the use of adjunctive psychotropic medications. Mood stabilizers (MSs) have been used to augment the effects of antipsychotic drugs for schizophrenia, at rates ranging from 7% to 28% especially in Europe and North America (Buchanan, Kreyenbuhl, Zito, & Lehman, 2002; Haro & Salvador-Carulla, 2006; Sim et al., 2011; Szkultecka-Debek et al., 2016; Xiang et al., 2012). However, evidence that such adjunctive interventions are effective and safe is limited and inconsistent. Sodium valproate has been specifically studied, with some unfavorable observations regarding its efficacy as an adjunctive treatment for schizophrenia (Casey et al., 2009; Glick, Bosch, & Casey, 2009), but other findings were more favorable, including in comparisons with placebo, especially for patients with prominent aggression and impulsive behavior (Horowitz et al., 2014) and to supplement clozapine treatment (Siskind et al., 2018; Zheng, Xiang, Yang, Xiang, & de Leon, 2017). Other adjunctive MSs, including lithium carbonate (Leucht, Kissling, & McGrath, 2004) and carbamazepine (Leucht, Helfer, Dold, Kissling, & McGrath, 2014), have been found to be ineffective in the treatment of schizophrenia. Evidence for lamotrigine has been mixed and includes both unfavorable findings (Goff et al., 2007), but some evidence of efficacy in schizophrenia with obsessive-compulsive features (Poyurovsky, Glick, & Koran, 2010) and in clozapine resistant schizophrenia (Tiihonen, Wahlbeck, & Kiviniemi, 2009).

Despite evidently widespread international use of MSs for the treatment of patients with schizophrenia, there are cogent reasons to further evaluate their clinical use and value, especially in Asia, where such studies have been rare, geographically limited, and usually without consideration of drug doses and related factors (Sim et al., 2011; Xiang et al., 2012).

Given these circumstances, we aimed to examine the rate of adjunctive use of MSs for patients with schizophrenia across Asia, including drug doses and factors associated with such treatment.

Studies of effects of doses of MSs can be facilitated by the availability of methods for estimating lithium equivalents or doses equivalent to typical clinical daily mg-doses of lithium carbonate (Baldessarini, 2013; Rajaratnam et al., 2017). We hypothesized that adjunctive treatment with MSs would be associated with indicators of illness severity (such as hospitalization and nonremission), particular types of psychopathology (such as aggression and affective features), and use of multiple antipsychotic agents, and at relatively high total daily chlorpromazine-equivalent (CPZ-eq) doses.

2 | METHODS

2.1 | Study subjects and locations

This study examined data collected in the Research on Asian Psychotropic prescription patterns in Schizophrenia (REAP-SZ) project, a pharmaco-epidemiological study started in 1999 (Chong et al., 2004) and fourth round of the REAP-AP survey was done in 2016. Data collected include the nature of adjunctive use of MSs for schizophrenia patients across 14 Asian countries and regions (Bangladesh, Hong Kong, India, Indonesia, Japan, Malaysia, Myanmar, Pakistan, PR China, RO Korea, Singapore, Sri Lanka, Taiwan, Thailand, and Vietnam). Data collection follows the same protocol at each site. Consecutive subjects diagnosed with schizophrenia received antipsychotic drug on the day in various hospital and ambulatory, and inpatient settings were recruited. Data recorded included subject age, sex, diagnosis, setting of treatment (outpatient or inpatient), clinical features, and all medications and doses prescribed by clinicians responsible for their care. Diagnoses were confirmed by at least two research psychiatrists at each site, following ICD-10 (World Health Organization, 1992) or Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria (American Psychiatric Association (APA), 2013). The study protocol was approved by an institutional Ethics Review Committee at each collaborating site. All participants were fully informed of the aims of the study and provided written, informed consent for anonymous and aggregate reporting of their findings. The study was conducted in accordance with the Declaration of Helsinki. Based on the concomitant use of lithium or an anticonvulsant with mood stabilizing properties, the study sample was divided into those receiving MSs and those not receiving MSs.

2.2 | Drug doses

We estimated lithium carbonate-equivalent (Li-eq) mg/day doses of agents with mood stabilizing properties (carbamazepine, lamotrigine, lithium carbonate, and sodium valproate; Rajaratnam et al., 2017). Based on clinical impressions, high-dose MS use was defined as adjunctive MS prescription of >1000 Li-eq mg/day. Doses of antipsychotic agents are reported as CPZ-eq mg/day, as described previously (Baldessarini, 2013).

2.3 | Data analyses

Averages are reported as means + standard deviation (SD), and relative rates of factors among patients cotreated with MSs or not are reported as odds ratios (OR) with their 95% confidence intervals (CI). Statistical analyses were based on the Statistical Package for the Social Sciences (IBM Corp, 2015). Normality of distributions of continuous measures was tested with the Kolmogorov–Smirnov one-sample test before further analysis. Differences between groups receiving versus not receiving MSs were tested by analysis of variance (ANOVA; *t*-test) for normally distributed continuous data and nonparametric Mann–Whitney *U*-tests for non-normally distributed continuous data; contingency tables (χ^2) were used for categorical variables. Multivariate logistic regression modeling was used to adjust for relevant covariates and to determine factors associated significantly and independently with adjunctive MS treatment.

3 | RESULTS

3.1 | Subjects and treatments

The study sample included 3557 adult subjects, of whom 59.0% (n = 2099) were men; mean age (±SD) was 39.9 ± 12.8 years (Table 1). Adjunctive treatment with MSs at any dose was found in 485 (13.6%) subjects: 457 (12.8%) received one, 27 (0.76%) received two, and 1 subject (0.03%) received three MSs. The use of MSs was most prevalent in PR China, Japan, and Pakistan and was least in Bangladesh, Malaysia, Indonesia, and India (Table 1). Among MSs prescribed, usage ranked: sodium valproate (n = 396; 11.1%) > lithium (n = 69; 1.94%) > carbamazepine (n = 37; 1.04%) > lamotrigine (n = 12; 0.34%). The overall mean ± SD Li-eq dose of MSs was 613 ± 456 mg/day.

Treatment with second-generation antipsychotics (SGAs) was twice as prevalent as with older, first-generation agents (FGAs): 80.0% versus 39.8% (χ^2 = 1199, $p < 0.0001$). Use of more than one antipsychotic agent was noted in 40.1% of subjects, and such polytherapy was somewhat more prevalent with MS cotreatment (46.2%) than without (39.1; χ^2 = 8.36, p = 0.004). The mean total daily CPZ-eq antipsychotic dose was 428 ± 358 mg/day overall for the entire sample, and antipsychotic dose was significantly greater when MSs cotreatment was used (521 ± 432 vs. 413 ± 343 CPZ-eq mg/day; t = 6.20, $p < 0.0001$).

3.2 | Factors associated with MS use

Factors significantly associated with any use of adjunctive MSs included female sex and current hospitalization, but not current age (Table 2). MS-cotreated subjects also had multiple psychiatric hospitalizations, nonremission of illness, disorganized speech, verbal or physical aggression, affective symptoms, social–occupational dysfunction, as well as higher daily CPZ-eq doses of antipsychotics,

TABLE 1 Characteristics of study sample ($N = 3557$)

Country	Subjects (*n*)	Age ± SD (years)	Men (%)	Hospitalized (%)	First-admission (%)	In remission (%)	Adjunctive MS use (%)	Relative MS use (OR [CI])
PR China	152	40.9 ± 16.0	65.1	90.8	36.2	48.7	36.2	27.8 [3.73–207]
Japan	219	46.6 ± 14.3	62.1	58.4	14.1	35.2	28.8	19.5 [2.63–144]
Pakistan	287	37.2 ± 11.9	55.1	47.7	20.4	36.9	26.1	17.3 [2.35–128]
Thailand	319	39.4 ± 12/3	66.5	42.9	32.1	60.2	19.4	11.8 [1.60–87.3]
Hong Kong	31	38.8 ± 13.9	58.1	100	9.70	71.0	19.4	11.8 [1.34–103]
Singapore	160	47.9 ± 13.5	35.6	73.1	11.1	24.4	16.3	9.51 [1.26–72.0]
Vietnam	270	39.1 ± 11.7	67.4	100	33.3	16.7	13.7	7.78 [1.04–58.1]
Taiwan	392	47.5 ± 11.8	45.7	56.6	7.20	52.6	13.0	7.33 [0.99–54.2]
Myanmar	163	37.7 ± 11.2	65.6	55.2	42.2	37.4	9.80	5.33 [0.69–41.3]
Sri Lanka	96	40.6 ± 13.5	60.4	52.1	34.0	30.2	7.30	3.85 [0.46–32.2]
RO Korea	112	39.4 ± 12.1	44.6	5.40	33.3	42.0	7.10	3.77 [0.46–31.0]
India	475	36.0 ± 10.4	66.5	31.2	55.6	65.7	6.10	3.19 [0.43–23.9]
Indonesia	539	36.2 ± 10.4	64.0	50.5	45.6	59.7	5.90	3.19 [0.43–23.8]
Malaysia	292	39.2 ± 12.1	51.5	34.2	24.0	66.8	5.80	3.03 [0.39–233]
Bangladesh	50	33.4 ± 10.1	58.0	0.00	-	30.0	2.00	1.00 (index)
Totals	3557	39.9 ± 12.8	59.0	51.9	29.8	49.0	13.6	-

Note: MS use = adjunctive treatment with mood stabilizers. Data are in rank order of prevalence of MS use.
Abbreviations: CI, confidence interval; MS, mood stabilizer; OR, odds ratio.

use of more than one antipsychotic agent, and with higher body mass index, and more sedation (Table 2).

Logistic regression modeling designated any adjunctive use of MSs as the dependent variable and found several significantly and independently associated factors. These included the country (greatest use in PR China and least in Taiwan), current hospitalization, female sex, relatively young age, longer duration of illness, disorganized speech, verbal or physical aggression, social–occupational dysfunction, and lack of hallucinations (Table 3).

Subjects given high doses of MSs (>1000 mg/day Li-eq) differed significantly from those given lower MS doses in several ways. Between these MS-cotreated subgroups, mean doses of MSs differed highly significantly and were 3.32 times greater if a high dose of MS was used: 1625 ± 619 versus 489 ± 215 Li-eq mg/day. In addition, subjects given high doses of MSs were more likely to be treated with an older FGA, to have social–occupational dysfunction, disorganized speech, to be given a 1.33-fold higher mean dose of antipsychotics (670 ± 547 vs. 504 ± 414 CPZ-eq mg/day), and were less likely to be in remission currently.

4 | DISCUSSION

In this large, descriptive, pharmaco-epidemiological study of 3557 adult patients diagnosed with schizophrenia in 14 Asian countries or regions, there were several notable findings. Use of cotreatment with lithium or an anticonvulsant MS varied markedly among study sites, ranging from 36.2% of subjects in PR China to 2.00% in Bangladesh—regional variance that remains unexplained. The overall mean rate of MS use, at 13.6% accords well with reports from Europe and North America, ranging from 7% to 27% (Buchanan et al., 2002; Haro & Salvador-Carulla, 2006; Szkultecka-Debek et al., 2016), but is somewhat lower than rates of 20.4%–27.7% in previous Asian surveys (Sim et al., 2011; Xiang et al., 2012). Accordingly, these findings add to the impression that use of MSs is quite prevalent in the treatment of patients with schizophrenia throughout the world. Off-label or adjunctive use of MS has been described in other studies where there is incomplete response to antipsychotic monotherapy, but efficacy studies of the individual MSs have been inconclusive (Buchanan et al., 2010). Pharmacokinetic interactions between antipsychotics and MSs could lead to increased effective dose of antipsychotics which should be borne in mind (Schoretsanitis et al., 2016). The potential significance of preferential use of valproate among MSs is not clear, although the preference accords with previous reports of some success in its use in schizophrenia, even when clozapine has proved to be unsatisfactory (Horowitz et al., 2014; Siskind et al., 2018; Zheng et al., 2017). Clinicians could consider the use of MS in those with aggression and affective symptoms, but should review response to MS and individualize therapy.

Adjunctive treatment with an MS was significantly associated with indications of more severe illness and less successful treatment by antipsychotic drugs alone. These included multiple hospitalizations, current hospitalization, more dysfunction,

TABLE 2 Comparison of patients given adjunctive mood stabilizers or not

Factors	Mood stabilizers		*t*-score (df) or OR (95% CI)	*p*-value
	Present ($n = 485$)	Absent ($n = 3072$)		
Antipsychotic dose (CPZ-eq mg/day [SD])	521 (432)	413 (343)	5.17 (3556)	**<0.001**
Hospitalized (*n* [%])	344 (70.9)	1502 (48.9)	2.55 (2.07–3.14)	**<0.001**
Affective symptoms (*n* [%])	80 (16.5)	317 (10.3)	1.72 (1.32–2.24)	**<0.001**
Disorganized speech (*n* [%])	200 (41.2)	838 (27.3)	1.87 (1.54–2.28)	**<0.001**
Social–occupational dysfunction (*n* [%])	284 (58.6)	1326 (43.2)	1.86 (1.53-–0.26)	**<0.001**
Verbal aggression (*n* [%])	161 (33.2)	726 (23.6)	1.61 (1.31–1.97)	**<0.001**
Physical aggression (*n* [%])	135 (27.8)	596 (19.4)	1.60 (1.29-–0.99)	**<0.001**
First admission (*n* [%])	62 (18.0)	489 (32.5)	0.460 (0.340–0.610)	**<0.001**
BMI (kg/m^2 [SD])	24.6 (4.85)	23.9 (4.66)	3.09 (3055)	**0.002**
Multiple antipsychotics (*n* [%])	224 (46.2)	1204 (39.2)	1.33 (1.10–1.61)	**0.004**
In remission (*n* [%])	209 (43.1)	1533 (49.9)	0.760 (0.630–0.92)	**0.005**
Sedated (*n* [%])	63 (13.7)	296 (10.1)	1.42 (1.06–1.90)	**0.018**
Male sex (*n* [%])	263 (54.2)	1834 (59.7)	0.800 (0.660–0.97)	**0.023**
Second-generation antipsychotics (*n* [%])	405 (83.5)	2442 (79.5)	1.31 (1.01–1.69)	**0.040**
Weight gain (*n* [%])	74 (16.6)	366 (13.2)	1.31 (1.00–1.72)	0.052
Negative symptoms (*n* [%])	190 (39.2)	1081 (35.2)	1.19 (0.970–1.44)	0.089
Delusions (*n* [%])	222 (45.8)	1284 (41.8)	1.18 (0.970–1.43)	0.100
Disorganized/catatonic behavior (*n* [%])	95 (19.6)	528 (17.2)	1.17 (0.920–1.50)	0.197
Hallucinations (*n* [%])	219 (45.2)	1426 (46.4)	0.950 (0.780–1.15)	0.604
Age (years [SD])	40.2 (12.8)	39.8 (12.8)	0.470 (3556)	0.638
First-generation antipsychotics (*n* [%])	191 (39.4)	1225 (39.9)	0.980 (0.80–1.19)	0.836

Note: Statistics are based on ANOVA for continuous factors (*t* score with df); or contingency analysis for categorical factors (OR with [95% CI]). Data are listed in order of *p*-value (with significant differences indicated in bold).

Abbreviations: ANOVA, analysis of variance; BMI, body mass index; CI, confidence interval; CPZ-eq, chlorpromazine-equivalent; df, degrees of freedom; OR, odds ratio.

and nonremission with unresolved psychotic symptoms that included aggressive behaviors and disorganized speech and behavior. MS-treated subjects also were receiving higher CPZ-eq doses of antipsychotic drugs, including preferential use of modern SGAs, as well as treatment with multiple different antipsychotics. In addition to unsatisfactory responses to more conservative treatments, it may be that clinical features related to mood or affect, including aggressive behaviors that may have encouraged addition of a MS. These included affective features and aggressive behaviors (Tables 2 and 3). Of note, affective features in schizophrenia patients were previously reported to be associated with MS cotreatment (Horowitz et al., 2014; Wang, Xia, Helfer, Li, & Leucht, 2016). The MS cotreatment was also helpful in the reduction of patient hostility (Citrome et al., 2004). In addition, relatively high doses of MSs were used in association with the use of older antipsychotic drugs, greater social–occupational dysfunction, disorganized speech, and lack of illness remission, as well as with relatively high doses of antipsychotics—all suggesting relatively challenging or treatment-resistant illness.

These clinical findings identify a subgroup of patients who are in need of closer attention and more intensive management and rationalization of pharmacotherapy management, including antipsychotic polytherapy and high daily antipsychotic dose. Clinicians should monitor for response before and after MS augmentation and individualize treatment for their patients. Further follow-up studies on the efficacy of MSs as adjunctive treatments in schizophrenia are proposed to shed more light on this matter.

4.1 | Limitations

This study has several important limitations. Although the sample size is relatively large and involved a broad cross section of Asian nations, the numbers of subjects in some sites was small (Table 2) and the data collected are cross sectional without longitudinal follow-up or details or previous and future illness course. Efforts were made to standardize methods of diagnosis, clinical assessment, and data

TABLE 3 Factors significantly associated with adjunctive use of mood stabilizers

Factor	OR	95% CI	Wald test	*p*-value
Country (vs. Malaysia)	-	-	174	<0.001
PR China	7.48	3.97–14.1	38.8	<0.001
Japan	6.72	3.63–12.4	36.9	<0.001
Thailand	5.82	3.20–10.6	33.4	<0.001
Pakistan	3.46	1.87–6.40	15.7	<0.001
Singapore	2.74	1.39–5.40	8.44	0.004
Taiwan	2.01	1.10–3.64	5.22	0.022
Months ill (vs. >20 years)			27.6	<0.001
3–6	0.214	0.081–0.570	9.52	0.002
7–12	0.356	0.181–0.700	8.96	0.003
13–60	0.427	0.284–0.644	16.5	<0.001
61–120	0.676	0.467–0.978	4.31	0.038
Hospitalized	1.80	1.38–2.36	18.4	<0.001
Younger age	0.978	0.967–0.988	17.4	<0.001
Social–Occupational dysfunction	1.49	1.17–1.89	10.6	0.001
Affective symptoms	1.98	1.47–2.67	20.2	<0.001
Verbal aggression	1.49	1.10–2.00	6.76	0.009
Disorganized speech	1.36	1.06–1.75	5.81	0.016
Less hallucinations	0.764	0.602–0.969	4.91	0.027
Fewer men	0.806	0.652–0.997	3.95	0.047

Abbreviations: CI, 95% confidence interval; OR, odds ratio (based on logistic regression modeling).

recording across sites, but some heterogeneity of findings across sites was unavoidable. A very important limitation in this descriptive, survey study is the lack of systematic data by which to evaluate the added value and safety of MS cotreatment in Asian schizophrenia patients. Indeed, the status of this form of treatment supplementation remains inadequately evaluated as regards the efficacy and safety of particular MSs and doses.

5 | CONCLUSION

In conclusion, prescription of adjunctive MSs to treat schizophrenia patients not responding satisfactorily to antipsychotic drugs alone is not uncommon in Asia and its prevalence is consistent with rates reported from Europe and North America. Psychotic disorder patients who were treated with MSs, especially with high doses, appeared to have relatively severe illnesses and poor daily functioning, as well as exposure to relatively high doses and combinations of antipsychotics. The observations of elevated risks of excessive sedation and weight gain in patients so treated encourage close monitoring for adverse effects of complex and aggressive pharmacotherapies as well as continued efforts to advance novel pharmacological and nonpharmacological strategies to improve symptomatic and functional outcomes in patients with chronic psychotic disorders.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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