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ARTICLE

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Adjunctive mood stabilizer treatment for hospitalized schizophrenia patients: Asia psychotropic prescription study (2001–2008)

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Abstract

Recent studies indicate relatively high international rates of adjunctive psychotropic medication, including mood stabilizers, for patients with schizophrenia. Since such treatments are little studied in Asia, we examined the frequency of mood-stabilizer use and its clinical correlates among hospitalized Asian patients diagnosed with schizophrenia in 2001–2008. We evaluated usage rates of mood stabilizers with antipsychotic drugs, and associated factors, for in-patients diagnosed with DSM-IV schizophrenia in 2001, 2004 and 2008 in nine Asian regions: China, Hong Kong, India, Korea, Japan, Malaysia, Taiwan, Thailand, and Singapore. Overall, mood stabilizers were given to 20.4% ($n=1377/6761$) of hospitalized schizophrenia patients, with increased usage over time. Mood-stabilizer use was significantly and independently associated in multivariate logistic modeling with: aggressive behaviour, disorganized speech, year sampled (2008 *vs.* earlier), multiple hospitalizations, less negative symptoms, younger age, with regional variation (Japan, Hong Kong, Singapore > Taiwan or China). Co-prescription of adjunctive mood stabilizers with antipsychotics for hospitalized Asian schizophrenia patients increased over the past decade, and was associated with specific clinical characteristics. This practice parallels findings in other countries and illustrates ongoing tension between evidence-based practice *vs.* individualized, empirical treatment of psychotic disorders.

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Key words: Adjunctive, clinical, treatment, mood stabilizers, schizophrenia.

Introduction

Recent pharmacoepidemiological studies evaluating use of psychotropic drugs by patients with schizophrenia have found substantial rates of co-treatment with adjunctive mood stabilizers, at rates ranging from 7% to 50% of patients in various countries, with evidence of increasing use over time (Buchanan *et al.* 2002; Haro & Salvador-Carulla, 2006). In turn, use of adjunctive mood stabilizers has been associated with variance in the use of antipsychotic drugs, including their number, doses, and duration (Centorrino *et al.* 2010; Galletly & Tsourtos, 1997; Mallinger & Lamberti, 2007). In some samples, use of mood stabilizers has

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been associated particularly with aggression or irritability (Kingsbury *et al.* 2001; Littrell *et al.* 2004), persistent positive symptoms (Citrome, 2009), or as supplementation of antipsychotics tolerated only at moderate doses or with unsatisfactory responses (Basan *et al.* 2004; Centorrino *et al.* 2010; Stahl, 2004).

Studies of psychotropic treatment practice in schizophrenia are important to document changes in the use of specific treatments over time, and to investigate the basis of such trends. Associations of adjunctive mood-stabilizer use with particular clinical or demographic factors may support rational selection of such treatments even without formal, prospective and controlled trials, which remain rare (Buchanan *et al.* 2010; Gorwood, 2006). In addition, such studies may identify relevant adverse effects or drug interactions. Such information can guide consideration of such treatments for other patients and encourage specific hypotheses to be tested prospectively.

We were unable to identify any large-scale pharmacoepidemiological studies of adjunctive mood-stabilizer use for patients diagnosed with schizophrenia in Asia, despite the huge burden of this severe mental illness in this most populous part of the world. Accordingly, we sought to: (1) elucidate the prevalence of adjunctive mood-stabilizer use among Asian in-patients diagnosed with schizophrenia in 2001, 2004, and 2008, and (2) identify clinical and other selected correlates of this practice. Based on clinical impressions and reports from other parts of the world, we hypothesized that use of adjunctive mood stabilizers (such as lithium, sodium valproate, carbamazepine, topiramate) would be relatively common, might have increased in recent years, and be associated with specific clinical or demographic features.

Methods

Study design and participants

The Research on East Asia Psychotropic Prescription (REAP) study originated in 2001 as a pharmacoepidemiological project surveying trends regarding the use of psychotropic drugs in schizophrenia in-patients in six East Asian countries and regions (China, Hong Kong, Japan, Korea, Singapore, Taiwan). Such studies are rare, although there have been some comparisons of treatments for hospitalized schizophrenia patients between culturally dissimiler countries (Dollfus *et al.* 1996; Kiivet *et al.* 1995). Studies of schizophrenia patients in Asia are supported by widespread acceptance of DSM-IV (APA, 1994) and ICD-10 (WHO, 1992) as international standards for the diagnosis of psychotic disorders. Methods of case ascertainment, diagnosis, and treatment assessment used in this study have been detailed previously (Sim *et al.* 2004*a*, *b*) and are summarized here.

In 2001, this project conducted a cross-sectional study on a sample of 2399 consecutive adult (age $\geqslant$18 yr) in-patients diagnosed with DSM-IV schizophrenia (in PR China, SAR Hong Kong, Japan, RO Korea, Singapore, Taiwan), based on a standardized protocol. In 2004, we considered an independent replication sample of 2136 consecutive in-patients with schizophrenia not included in the earlier study in 2001 in these six regions using the same procedures. In 2008, three other countries (Malaysia, India, Thailand) joined this international project. Consensus meetings were held at participating sites before the present study to coordinate and standardize data acquisition and management.

The study protocol and consent form were approved by the Institutional Research Boards of each of the collaborating centres within the nine Asian countries and territories, and all patient participants provided written, informed consent for participation and for anonymous and aggregate presentation of study findings. Study patients fulfilled DSM-IV diagnostic criteria for schizophrenia (APA, 1994) and were considered clinically stable by their primary psychiatrists when recruited to participate. Patients with clinically significant medical illnesses or psychiatric symptoms considered to be secondary to substance-use disorders were excluded.

Data collected included basic sociodemographic information, salient clinical features, and the names and total daily doses of all psychotropic medicines prescribed, including depot intramuscular injections within 30 d of the index psychiatric hospitalization. Daily doses of antipsychotic drugs, including depot preparations, were converted to approximate chlorpromazine equivalents (CPZ-eq) based on established guidelines (Baldessarini & Tarazi, 2005; Centorrino *et al.* 2010; Gardner *et al.* 2010; Kane *et al.* 1998).

Statistical analysis

Averages are reported as means $\pm$ standard deviations (S.D.), and relative risks (among patients co-treated with mood stabilizers or not) are reported as odds ratios (OR) with their 95% confidence intervals (CI), based on the Statistical Package for Social Sciences (SPSS Windows version 13.0; SPSS Inc., USA). Normality of distributions of continuous measures was tested with the Kolmogorov–Smirnov one-sample test before further analysis. Differences between groups

Table 1. Comparison of demographic and clinical features *vs.* years sampled

Measures	2001 ($n=2399$)	2004 ($n=2136$)	2008 ($n=1906$)	Statistics[a]	p value
Current age, yr (S.D.)	43.6 (13.5)	43.1 (14.2)	45.5 (13.5)	16.5	<0.001
Proportion of men, *n* (%)	1340 (55.9)	1220 (57.2)	1167 (61.7)	15.4	0.001
First lifetime hospitalization, *n* (%)	387 (16.4)	443 (21.1)	343 (18.5)	15.8	<0.001
First-generation antipsychotics, *n* (%)	1627 (61.8)	1109 (51.9)	763 (40.3)	338	<0.001
Second-generation antipsychotics, *n* (%)	1092 (45.5)	1382 (64.7)	1460 (76.6)	449	<0.001
Depot antipsychotics, *n* (%)	384 (16.01)	205 (9.67)	192 (10.1)	54.3	<0.001
Dose CPZ-eq, mg/d (S.D.)	633 (616)	558 (505)	559 (458)	14.7	<0.001
Antipsychotic polytherapy, *n* (%)	1122 (46.8)	818 (38.3)	817 (42.9)	33.1	<0.001
Mood stabilizer use, *n* (%)	484 (20.2)	417 (19.5)	451 (23.7)	11.9	0.003

CPZ-eq, Chlorpromazine-equivalent total daily dose (mg).

[a] Statistics are χ^2 (categorical) or F value from ANOVA (continuous measures).

(patients receiving *vs.* not receiving mood stabilizers) were tested by ANOVA (t test) for normally distributed data, non-parametric Mann–Whitney U tests for non-normally distributed continuous data. Contingency tables (χ^2) were used for categorical variables. Analyses of changes over years (2001–2008) excluded data from Malaysia, India, and Thailand, which only joined the project in 2008. Multivariate logistic regression analyses were performed to adjust for relevant covariates and to determine the factors associated significantly and independently with adjunctive mood-stabilizer treatment. Statistical significance required two-tailed $p<0.01$ to adjust for multiple comparisons.

Results

Demographic and clinical factors associated with mood-stabilizer treatment

Salient demographic and clinical features of the study populations sampled in 2001, 2004 and 2008 are shown (Table 1). For the entire sample ($N=6761$), mean age (with S.D.; all $\geqslant$18 yr) was 43.5 (13.8) yr, including 3910 (57.8%) men and 2851 (42.2%) women. Of all cases, 1310 (19.4%) represented first-lifetime psychiatric hospitalizations. A total of 1377 (20.4%) patients received an adjunctive mood stabilizer in addition to one or more antipsychotic drugs.

For the six regions sampled in all three years (as noted above), there was a significant increase in the prescription of mood stabilizers from 2001 to 2008 ($\chi^2=11.9$, $p=0.003$). The inclusion of data from the three countries added in 2008 made little difference in this trend. However, for the six original countries, there were larger increases in 2008 compared to either 2004 (23.7% *vs.* 19.5%; OR 1.28, 95% CI 1.10–1.49, $p=0.001$) or 2001 (23.7% *vs.* 20.2%; OR 1.23, 95% CI 1.10–1.42, $p=0.007$). The most striking increases were found with valproate, use of which more than doubled between 2001 and 2008 (OR 2.43, 95% CI 2.00–2.94, $p<0.001$), and increased by 28% between 2004 and 2008 (OR 1.28, 95% CI 1.10–1.49, $p=0.001$) in the six original Asian countries. In contrast, use of lithium salts (2008 *vs.* 2001: OR 0.74, 95% CI 0.57–0.95, $p=0.02$) and carbamazepine (OR 0.37, 95% CI 0.28–0.50, $p<0.001$) declined by 26% and 63%, respectively, in the same era. Overall, the most commonly prescribed adjunctive mood stabilizers were valproate (11.1%) > lithium (5.6%) = carbamazepine (5.6%) > lamotrigine (0.1%) = topiramate (0.1% of cases). This ranking differed somewhat between 2008 (valproate > lithium > carbamazepine > lamotrigine > topiramate) and 2001 (carbamazepine > valproate > lithium) (Table 2).

The gains in the use of valproate were associated with a decline in the total daily dose of antipsychotic drugs. The mean (S.D.) daily total CPZ-eq antipsychotic dose was approximately 580 (534) mg overall, and 633 (616) mg/d in 2001, 558 (505) mg/d in 2004, and 559 (458) mg/d in 2008.

Clinical correlates of adjunctive mood stabilizer use in preliminary bivariate analyses

Patients who were prescribed adjunctive mood stabilizers in 2008 as well as in the entire 3-yr sample were significantly associated with relatively similar demographic, clinical, and treatment factors (Tables 3 and 4). Overall, patients receiving mood stabilizers were younger compared to those not given such drugs, whereas sex distribution was similar in both subgroups. Patients who received mood stabilizers were more likely to have had multiple previous psychiatric hospitalizations, and more likely to have

Table 2. Commonly prescribed adjunctive mood stabilizers *vs.* years sampled

Mood stabilizers	2001[a] ($n=2399$)	2004[a] ($n=2136$)	2008[a] ($n=1906$)	χ^2	p value
Valproate	183 (7.63)	232 (10.9)	318 (16.7)	87.2	<0.001
Lithium	163 (6.80)	117 (5.55)	97 (5.09)	6.42	0.04
Carbamazepine	205 (8.54)	107 (5.00)	64 (3.36)	56.0	<0.001
Topiramate	0 (0.00)	0 (0.00)	6 (0.31)	14.3	0.001
Lamotrigine	0 (0.00)	2 (0.09)	4 (0.21)	5.03	0.081

[a] Values are *n* (%).

Table 3. Correlates of adjunctive mood-stabilizer use in all 6441 cases

Factors	MS ($n=1352$)	No MS ($n=5089$)	Statistics[a]	p value
Current age, yr (S.D.)	42.8 (12.6)	44.3 (14.0)	3.41 (6420)	0.001
Current body-weight, kg (S.D.)	63.8 (13.8)	62.0 (12.7)	4.45 (6307)	<0.001
CPZ-eq dose, mg/d (S.D.)	755 (680)	541 (483)	13.2 (6439)	<0.001
Proportion of men, *n* (%)	789 (58.4)	2938 (57.7)	1.02 (0.90–1.15)	0.78
First-lifetime hospitalization, *n* (%)	148 (10.9)	1140 (22.4)	0.48 (0.40–0.58)	<0.001
Delusions, *n* (%)	832 (61.5)	2908 (57.1)	1.20 (1.06–1.36)	0.004
Hallucinations, *n* (%)	692 (51.2)	2362 (46.4)	1.20 (1.07–1.36)	0.002
Disorganized speech, *n* (%)	446 (33.0)	1243 (24.4)	1.50 (1.30–1.70)	<0.001
Negative symptoms, *n* (%)	626 (46.3)	2844 (55.9)	0.68 (0.60–0.81)	<0.001
Aggression, *n* (%)	253 (18.7)	417 (8.20)	2.60 (2.20–3.10)	<0.001
Weight gain, *n* (%)	110 (8.14)	369 (7.25)	0.88 (0.71–1.10)	0.27
Excess sedation, *n* (%)	75 (5.55)	172 (3.38)	1.70 (1.3–2.20)	<0.001
Depot antipsychotics, *n* (%)	207 (15.31)	574 (11.3)	1.40 (1.20–1.69)	<0.001
First-generation antipsychotics, *n* (%)	826 (61.1)	2673 (52.5)	1.42 (1.2–1.61)	<0.001
Second-generation antipsychotics, *n* (%)	814 (60.2)	3120 (61.3)	1.05 (0.93–1.18)	0.47
Antipsychotic polytherapy, *n* (%)	709 (52.4)	2048 (40.2)	1.64 (1.45–1.85)	<0.001

CPZ-eq, Chlorpromazine-equivalent; MS, mood stabilizer.

[a] Statistics are based on: Student's *t* test for continuous factors with *t* value (degree of freedom); or χ^2 test for categorical factors with odds ratio (95% confidence interval) for patients who did *vs.* did not receive an adjunctive mood stabilizer with antipsychotics.

positive psychotic symptoms (notably, delusions), disorganized speech, or aggression, and less likely to have negative symptoms. In addition, patients given mood stabilizers were more likely to receive first-generation neuroleptics, more than one antipsychotic agent, and a higher total daily dose of antipsychotics than those not given a mood stabilizer. Not surprisingly, they also were more likely to have higher body-weight, and to experience adverse effects such as excessive sedation (Tables 3 and 4).

Multivariate modelling of factors associated with adjunctive mood-stabilizer use

Based on multivariate logistic regression modelling, with adjunctive mood-stabilizer use as the dependent factor, associated factors, in descending order of OR, were: (*a*) *aggression* (OR 1.89, 95% CI 1.58–2.27, $p<0.001$); (*b*) *disorganized speech* (OR 1.43, 95% CI 1.25–1.65, $p<0.001$); (*c*) *year sampled* (2008 *vs.* 2001: OR 1.37, 95% CI 1.16–1.61, $p<0.001$; or 2008 *vs.* 2004 (OR 1.41, 95% CI 1.20–1.67, $p<0.001$); (*d*) *younger age* (OR 0.98, 95% CI 0.97–0.98, $p<0.001$); (*e*) *less likelihood of negative symptoms* (OR 0.80, 95% CI 0.69–0.92, $p=0.002$); and (*f*) *less likelihood of first-hospitalization* (OR 0.53, 95% CI 0.43–0.64, $p<0.001$); with (*g*) significant *regional variation*: less likely in China (OR 0.36, 95% CI 0.28–0.46, $p<0.001$) and more likely in Japan (OR 1.73, 95% CI 1.40–2.10, $p<0.001$), Hong Kong (OR 1.51, 95% CI 1.12–2.03, $p=0.006$), or Singapore (OR 1.45, 95% CI 1.08–1.96, $p=0.014$) – all compared to Taiwan (Table 5).

Table 4. Correlates of adjunctive mood stabilizer use in 2008 ($N = 2226$)

Factors	MS ($n = 476$)	No MS ($n = 1750$)	Statistics[a]	p value
Age, yr (S.D.)	43.1 (13.5)	44.1 (13.8)	−1.44 (2206)	0.15
Body-weight, kg (S.D.)	65.4 (15.6)	62.7 (13.8)	3.54 (2109)	<0.001
CPZ-eq dose, mg/day (S.D.)	664 (535)	512 (425)	6.53 (2224)	<0.001
Proportion of men, *n* (%)	292 (61.3)	1058 (60.4)	1.02 (0.83–1.25)	0.92
First hospitalization, *n* (%)	72 (15.1)	419 (23.9)	0.46 (0.34–0.62)	<0.001
Delusions, *n* (%)	342 (71.8)	1055 (60.3)	1.68 (1.35–2.10)	<0.001
Hallucinations, *n* (%)	270 (56.7)	916 (52.3)	0.84 (0.68–1.03)	0.09
Disorganized speech, *n* (%)	125 (26.3)	385 (22.0)	1.26 (1.01–1.59)	0.05
Negative symptoms, *n* (%)	196 (41.2)	879 (50.2)	0.69 (0.56–0.85)	<0.001
Aggression, *n* (%)	96 (20.2)	221 (12.6)	1.75 (1.34–2.78)	<0.001
Weight gain, *n* (%)	49 (10.3)	168 (9.6)	0.93 (0.66–1.30)	0.66
Excess sedation, *n* (%)	42 (8.8)	109 (6.2)	1.46 (1.01–2.11)	0.046
Depot antipsychotics, *n* (%)	64 (13.4)	220 (12.6)	0.93 (0.69–1.25)	0.64
First-generation antipsychotics, *n* (%)	221 (46.4)	708 (40.5)	1.28 (1.04–1.56)	0.019
Second-generation antipsychotics, *n* (%)	368 (77.3)	1273 (72.7)	1.28 (1.01–1.62)	0.045
Antipsychotic polytherapy, *n* (%)	236 (49.6)	730 (41.7)	1.37 (1.1–1.68)	0.002

CPZ-eq, Chlorpromazine-equivalent dose (mg/d); MS, mood stabilizer.
[a] Statistics are based on: Student's t test for continuous factors with t value (degree of freedom); or χ^2 test for categorical factors with odds ratio (95% confidence interval) for patients who did *vs.* did not receive an adjunctive mood stabilizer with antipsychotics.

Other factors that were associated with mood-stabilizer use in preliminary bivariate comparisons were no longer associated in multivariate modelling. These included: sex, presence of delusions or hallucinations, use of first-generation antipsychotics, antipsychotic polytherapy, or use of a depot antipsychotics.

Discussion

There were several notable findings in this study. First, there was a significant trend of increased use of adjunctive mood stabilizers in the treatment of Asian patients with schizophrenia over the past decade. Second, use of mood stabilizers was associated with multiple hospitalizations, certain psychopathology (aggressive behaviour, more positive than negative symptoms, disorganized speech), younger age, and certain features of antipsychotic treatment (including use of older neuroleptics, antipsychotic polytherapy, higher total daily dose of antipsychotics, and more adverse, treatment-associated effects including higher body-weight). Third, in the multivariate logistic regression analyses, adjunctive mood-stabilizer use was significantly associated with younger age, multiple hospitalizations, disorganized speech, aggression, country, and more recent time-point. Some of these clinical and treatment characteristics strongly suggest unsatisfactory treatment responses that may well have encouraged empirical addition of mood stabilizers.

Table 5. Factors associated with adjunctive mood-stabilizer use (multivariate logistic regression modelling)

Factor	OR	95% CI	Wald test	p value
Age, yr	0.98	0.9–0.98	35.3	<0.001
First admission	0.53	0.43–0.64	41.2	<0.001
Disorganized speech	1.43	1.25–1.65	25.8	<0.001
Negative symptoms	0.80	0.69–0.92	9.91	0.002
Aggression	1.89	1.58–2.27	46.8	<0.001
Year (*vs.* 2008)				
2001	0.73	0.62–0.86	14.3	<0.001
2004	0.71	0.60–0.83	17.5	<0.001
Country (*vs.* Taiwan)			165	<0.001
China	0.36	0.28–0.46	64.2	<0.001
Japan	1.73	1.40–2.10	26.9	<0.001
Hong Kong	1.51	1.12–2.03	7.49	0.006
Singapore	1.45	1.08–1.96	6.09	0.014

OR, Odds ratio; CI, confidence interval.

In this study, we found increased use of mood stabilizers over time particularly with valproate and in association with some decrease in use of lithium or carbamazepine. Similar trends have been noted by investigators in other countries (Buchanan *et al.* 2002;

Centorrino *et al.* 2010; Citrome *et al.* 2000; Haro & Salvador-Carulla, 2006). Buchanan *et al.* (2002) found that up to 50% of their patients with schizophrenia were prescribed an adjunctive medication including mood stabilizers. More recently, Haro & Salvador-Carulla (2006) examined in their naturalistic study more than 10 000 patients with schizophrenia in 10 European countries and found that adjunctive mood stabilizers were prescribed in 7–19% of patients. With regard to longitudinal changes in mood-stabilizer use, Citrome *et al.* (2000) reported an increase of adjunctive mood stabilizer use from 26.2% to 43.4% after an interval of 4 yr (1998 *vs.* 1994) in the treatment of in-patients with schizophrenia, and specifically for sodium valproate with a tripling of its use over the same time period. Centorrino *et al.* (2010) similarly observed an increase in adjunctive mood-stabilizer use within hospitalized patients with schizophrenia over a 5-yr period from 2004 to 2009.

The basis of such striking growth in the use of valproate in Asia is not readily explained, although its popularity as a mood stabilizer in other countries may reflect its relative ease of use, and the impact of advertising and clinical, word-of-mouth support, as well as a simply empirical step in response to the typically limited impact of treatment of patients with chronic psychotic disorders (Baldessarini & Tarazi, 2005; Basan *et al.* 2004; Citrome, 2009; Citrome *et al.* 2004; Kreyenbuhl *et al.* 2007; Ventriglio *et al.* 2010). In addition, there may be specific indications for mood stabilizers, including their effectiveness in the control of agitation, aggressive behaviours (Huband *et al.* 2010) or affective features (Ventriglio *et al.* 2010). However, the pharmacodynamics of these mood stabilizers such as sodium valproate do not provide ready explanations for its recent popularity (Baldessarini & Tarazi, 2005; Ichikawa *et al.* 2005; Wassef *et al.* 2003; Winterer & Hermann, 2000). Moreover, there are very few controlled studies of its use alone or as an adjunct to antipsychotic drugs in the treatment of schizophrenia patients (Buchanan *et al.* 2010; Schwarz *et al.* 2008). Most reported trials have been small, brief, and do not support the efficacy of valproate for psychotic symptoms. In addition, evidence of the effectiveness of lithium (Collins *et al.* 1991; Terao *et al.* 1995; Wilson, 1993) or carbamazepine (Dose *et al.* 1987; Leucht *et al.* 2007), and other mood-stabilizing agents in the treatment of psychotic disorder patients is also limited and unconvincing.

The lack of specific, evidence-based treatment recommendations regarding mood-stabilizer use for schizophrenia patients leaves open the option of empirical clinical trials of such treatments for individual patients, particularly when standard antipsychotic treatments are unsatisfactory or poorly tolerated (Buchanan *et al.* 2010; Ventriglio *et al.* 2010). At the same time, sound clinical practice calls for close consideration of possible explanations of unsatisfactory treatment responses, including poor adherence to recommended treatment (Jónsdóttir *et al.* 2009), as well as specific clinical monitoring for additional adverse effects or unfavourable drug–drug interactions (Kelly *et al.* 2006).

There are several limitations to this study. The heterogeneity of the healthcare systems in the different sites and the focus on hospitalized patients, and only those diagnosed with DSM-IV schizophrenia, limit generalizability of the findings. Further, only three years of the past decade were sampled, and three of the nine countries or regions involved were sampled only in 2008. It is also not always clear how the decision was made to supplement antipsychotic treatment with mood stabilizers for individual patients, and clinically and individually decided treatment preclude analysis of the clinical effects of treatment options with current data. In addition, assays of serum concentration of drugs in order to evaluate the adequacy of antipsychotic dosing or potential pharmacokinetic interactions, particularly between antipsychotic agents and some anticonvulsants would have been of interest, but were not available (Baldessarini & Tarazi, 2005).

In conclusion, this study found that prescription of adjunctive mood stabilizers is a prevalent practice in the management of schizophrenia in Asia that has increased in recent years, especially regarding empirical use of valproate. Adjunctive mood-stabilizer use was associated with relative youth, and the presence of aggression, positive symptoms, and disorganized speech, as well as a history of multiple hospitalizations and relatively aggressive antipsychotic treatment. In addition, its association with use of first-generation neuroleptics, antipsychotic polytherapy, greater bodyweight and sedation all suggest that a mood stabilizer was particularly likely to be added when aggressive antipsychotic treatment was proving to be unsatisfactory or poorly tolerated. Prudence calls for particularly close clinical monitoring of patients treated with multiple psychotropic agents in whom the efficacy and safety of such applications remain poorly studied.

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Statement of Interest

None.

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