

# 15. Clinical Use of Mood Stabilizers With

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# Clinical Use of Mood Stabilizers With Antidepressants in Asia

## Report From the Research on Asian Psychotropic Prescription Patterns for Antidepressants (REAP-AD) Projects in 2004 and 2013

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### Abstract:

**Objective:** As most reports concerning treatment with combinations of mood stabilizer (MS) with antidepressant (AD) drugs are based in the West, we surveyed characteristics of such cotreatment in 42 sites caring for the mentally ill in 10 Asian countries.

**Methods:** This cross-sectional, pharmacoepidemiologic study used 2004 and 2013 data from the REAP-AD (Research Study on Asian Psychotropic Prescription Patterns for Antidepressants) to evaluate the rates and doses of MSs given with ADs and associated factors in 4164 psychiatric patients,

using standard bivariate methods followed by multivariable logistic regression modeling.

**Results:** Use of MS + AD increased by 104% (5.5% to 11.2%) between 2004 and 2013 and was much more associated with diagnosis of bipolar disorder than major depression or anxiety disorder, as well as with hospitalization > outpatient care, psychiatric > general-medical programs, and young age (all  $P < 0.001$ ), but not with country, sex, or AD dose.

**Conclusions:** The findings provide a broad picture of contemporary use of MSs with ADs in Asia, support predictions that such treatment increased in recent years, and was associated with diagnosis of bipolar disorder, treatment in inpatient and psychiatric settings, and younger age.

**Key Words:** antidepressant, anxiety, bipolar disorder, major depression, mood stabilizer

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examined such treatments for association with country, types of treatment settings, clinical diagnosis, and other potentially relevant factors, including potential changes over time. Based on available data and clinical experience, we hypothesized that use of such combination treatment would be largely limited to persons with a diagnosis of bipolar disorder, but with possible differences in types of drug combinations and doses among Asian countries, and in association with the type of clinical setting, and possibly also with patient age and sex. We also tested specifically the hypothesis that such combination treatment has increased over the past decade in Asia.

## METHODS

### Participants

Study data are from the REAP-AD (Research on Asian Psychotropic Prescription Pattern for Antidepressants) project, a long-standing pharmacoepidemiologic study that currently evaluates AD prescription patterns in psychiatric patients at 42 collaborating sites in 10 Asian countries. Data collection follows the same protocol at each site. To be included, study subjects with any psychiatric disorder were required to be prescribed an AD on the day of surveys involving consecutive patients in various hospital and ambulatory settings. Data recorded included subject age, sex, diagnosis, setting of treatment (outpatient vs inpatient settings, psychiatric vs general medical services, public vs private facilities), and all medicines prescribed and their doses, as prescribed by clinicians responsible for their care. Diagnoses were confirmed by at least 2 research psychiatrists at each site, following *International Classification of Diseases: Mental and Behavioral Disorders: Clinical Descriptions and Diagnostic Guidelines, 10th Revision*<sup>17</sup> or *Diagnostic and Statistical Manual of Mental Disorders, Fourth Revision, Text Revision* criteria (American Psychiatric Association, 2000). 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 or informed consent for anonymous and aggregate reporting of their findings.

### Treatments

Names and doses of all medicines given to study participants were recorded. Types of ADs and their approximate imipramine-equivalent (IMI-eq) total daily doses are detailed in Appendix

Table A1, Supplemental Digital Content 1, <http://links.lww.com/JCP/A420>.<sup>18,19</sup> In addition, we estimated lithium carbonate-equivalent (Li-eq) mg/d doses of other agents with mood-stabilizing properties (carbamazepine, lamotrigine, and sodium valproate, as well as lithium), as summarized in Appendix Table A2, Supplemental Digital Content 2, <http://links.lww.com/JCP/A421>.

### Statistical Analyses

Data are presented as means  $\pm$  SD or with 95% confidence interval (CI). Categorical differences were compared for subjects given an MS + AD or not by contingency tables ( $\chi^2$ ) and continuous measures by analysis-of-variance methods (*t* test). Factors found to be associated with MS + AD treatment in preliminary bivariate analyses were then entered, stepwise in descending order of significance, into multivariable logistic regression modeling to generate odds ratios with CI and controlling for age, sex, and year of sampling. Analyses used commercial statistical software (Statistical Package for the Social Sciences 23 [IBM SPSS Inc, Chicago, Ill] or Stata 13 [StataCorp, College Station, Tex] with spreadsheets prepared in Excel [Microsoft Corp, Redmond, Wash] and StatView 5 [SAS Institute, Cary, NC]).

## RESULTS

### Subjects

The study sample included 4164 AD-treated subjects (2292 [55.0%] in 2004; 1872 [45.0%] in 2013) from a total of 42 study sites in 10 Asian countries (Table 1). Overall, ages averaged 43.4 years (CI, 43.0–43.8 years), and 2373 subjects (57.0%) were women. Diagnoses ranked overall as follows: unipolar major depressive disorder (46.6%) > anxiety and disorders (39.7%) > bipolar disorder (13.7%). Most subjects were treated as hospital outpatients (68.4%), in public-sector programs (66.2%), and in general medical rather than psychiatric programs (60.5%). All study subjects were treated with ADs, at IMI-eq doses that averaged 124 mg/d (CI, 120–129 mg/d).

### MS Treatment

Of the 4164 subjects, 334 (8.0%) also received an MS, use of which ranked as follows: sodium valproate > lithium carbonate > carbamazepine > lamotrigine = combinations with lithium > anticonvulsant combinations (Table 2). Usage of MS with ADs differed highly significantly across countries, but MS doses

TABLE 1. Distribution of Subjects and Use of MSs

Country	Subjects	No. (%) Receiving MS	MS Dose
Thailand	245	44 (18.0)	546 $\pm$ 401
Hong Kong	74	9 (12.2)	644 $\pm$ 296
Japan	633	77 (12.2)	631 $\pm$ 347
Taiwan	476	50 (10.5)	657 $\pm$ 372
Indonesia	222	14 (6.3)	309 $\pm$ 192
India	272	17 (6.3)	603 $\pm$ 259
Republic of Korea	415	26 (6.3)	758 $\pm$ 534
Malaysia	133	8 (6.0)	691 $\pm$ 477
People's Republic of China	695	38 (5.5)	360 $\pm$ 362
Singapore	999	51 (5.1)	582 $\pm$ 478
Total/mean	4164	8.0	612 $\pm$ 396

Dose is in Li-eq mg/d.

Across countries, MS usage rates varied highly significantly ( $\chi^2 = 57.3, P < 0.0001$ ), but MS doses did not ( $t = 1.28, P = 0.11$ ).

**TABLE 2.** Types of MSs Used With ADs in Asia

MSs	Rate of Use, %
Sodium valproate	46.7
Lithium carbonate	29.9
Carbamazepine	10.0
Lamotrigine	6.22
Lithium + anticonvulsant	6.22
Anticonvulsant combinations	0.48

These distributions did not vary significantly by country.

were similar across sites, averaging 612 Li-eq mg/d (CI, 603–621 Li-eq mg/d) (Table 1).

### Factors Associated With Use of MSs

Cotreatment with an MS + AD was most strongly associated with diagnosis of bipolar disorder and far less with unipolar major depressive disorder or anxiety disorders (Table 3). There also was a strong association of MS use with younger age, but not with sex. Between 2004 and 2013, such combination treatments increased by 104% (from 5.5% to 11.2%;  $P \leq 0.0001$ ). Largest increases were found in Japan and least in the Republic of Korea. Mood stabilizer use with ADs was significantly associated with hospitalization and with treatment in psychiatric settings, but did not differ between publicly and privately funded programs. Finally, there was some trend association between use of MS + AD combinations with higher IMI-eq daily doses of ADs, although doses of MSs were not greater with higher doses of ADs ( $r = 0.018$ , slope = +0.096 [CI, -0.49 to +0.67],  $t = 0.33$ ,  $P = 0.74$ ).

### Multivariate Modeling

Factors found to be associated with MS cotreatment in preliminary bivariate analyses were then entered, stepwise in descending order of preliminary significance, into multiple-variable, logistic regression modeling. In descending order by significance, factors remaining independently and significantly associated with MS use were bipolar disorder diagnosis, inpatient treatment, psychiatric versus general medical service, and younger age (Table 4).

### DISCUSSION

Rates of concurrent treatment of psychiatric patients with an MS plus an AD varied markedly among Asian countries: they were highest in Thailand and lowest in Singapore and increased over the past decade. The most frequently used MSs were valproate and lithium, whereas lamotrigine was least common. Not surprisingly, such combination treatment was associated with bipolar disorder, hospitalization, and specialized psychiatric settings, as well as younger age. There was no difference in AD dose with or without an MS, or with MS dose.

The recent secular increase (2013 vs 2004) in use of MS + AD combination treatments found in the present Asian samples accords with earlier studies in Europe,<sup>20</sup> as well as in the United Kingdom from 1995–2009.<sup>21</sup> As expected, concurrent MS use was associated far more with bipolar disorder than with unipolar depression or anxiety disorders.<sup>22,23</sup> Such practices are in line with current expert treatment guidelines, which recommend routine use of MSs for all phases of bipolar disorder and consideration of their application in the treatment of relatively severe unipolar depression that proves refractory to AD monotherapy, but not for anxiety disorders unassociated with a mood disorder.<sup>2-4,24-27</sup> However, even in bipolar disorder, there is a notable lack of consensus as to whether adding an AD improves

**TABLE 3.** Comparison of Subjects Treated With ADs With Versus Without an MS in Asia

Factor	Given MS	No MS	<i>t</i> Score or $\chi^2$	<i>P</i>
Cases, n (%)	334 (8.0)	3830 (92.0)	—	—
Diagnosis, %			533	<0.0001
Bipolar disorder	61.5	38.5		
Major depression	5.95	94.1		
Anxiety disorders	3.85	96.2		
Clinical setting, %			28.3	<0.0001
Inpatient	15.0	85.0		
Outpatient	8.79	91.2		
Service setting, %			13.3	0.0003
Psychiatric	13.2	86.8		
General medical	9.17	90.8		
Age, y	41.5 ± 11.5	43.6 ± 12.4	3.35	0.0008
Year, %			7.26	<0.0001
2004	5.50	94.5		
2013	11.2	88.8		
AD dose, IMI-eq mg/d	128 ± 74.8	120 ± 79.3	1.98	0.05
Sex			2.51	0.11
% Women	46.6	57.4		
% Men	53.4	42.6		
Financial setting, %			0.32	0.57
Public	11.0	89.0		
Private	10.4	89.6		

Ranked by statistical significance.

**TABLE 4.** Multivariable Logistic Regression Modeling of Factors Associated With Use of MSs With ADs in Asia

Factors	Odds Ratio (95% CI)	P
Bipolar disorder	22.6 (16.4–31.2)	<0.0001
Inpatient setting	1.69 (1.30–2.19)	<0.0001
Psychiatric service	1.61 (1.24–2.08)	0.0004
Younger age	1.02 (1.01–1.03)	0.0009
Higher AD dose	1.00 (0.99–1.01)	0.08

Additional factors not associated with use of MSs included sex, year, country, and public versus private setting.

treatment of bipolar depression more than with an MS or atypical antipsychotic, but broader agreement that an MS should be given if an AD is used, particularly in patients with bipolar I disorder.<sup>2–4,28</sup> Caution in the use of ADs to treat bipolar depression probably is implicit in the lack of unusually high doses of AD when an MS was used.

In the present findings in Asia, concurrent MS + AD treatment was more likely among hospitalized patients and psychiatric rather than general medical settings. These findings probably reflect the relative severity of illnesses for which combination treatments are given and preferential use where there are expertise and experience to support such treatment. This conclusion accords with other findings that patients with bipolar depression tend to have complex illnesses that are not easily treated and often encounter hospitalization and empirical trials of off-label treatments and combinations.<sup>29</sup>

There are several limitations in this study. The numbers of subjects in total (N = 4164) was substantial, but limited in the face of major international variance in the use of MS + AD combination treatments among the 42 sites involved. Despite the inclusion of 10 Asian countries within this study, it is still not representative of the entire Asian population. The present cross-sectional evaluations would be improved by prospective follow-up of subjects over time to allow for better assessment of implications of associations found with the use of MS + AD treatment, particularly those related to clinical changes over time. In particular, this study was unable to address the important question of whether combination treatments were more effective or less well tolerated than monotherapies with either type of agent alone, and this basic question requires further study.

In conclusion, the present findings provide a broad picture of contemporary usage of MSs with ADs in Asia, encourage future studies adopting and comparing equivalent MS doses, and support the impression that such treatment increased in recent years, as well as supporting expectations that such combination treatment was strongly associated with bipolar disorder diagnoses, treatment in inpatient and psychiatric settings, and younger age.

#### 23 AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

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# 15. Clinical Use of Mood Stabilizers With

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## GRADEMARK REPORT

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FINAL GRADE

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GENERAL COMMENTS

**Instructor**

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