Trends of Polypharmacy and Prescription Patterns of Antidepressants in Asia

Cho-Yin Huang, MD, Shu-Yu Yang, PhD,† Ramin Mojtabai, MD, PhD, MPH,‡ Shu-Ku Lin, MD,*§ Yan-Ling He, MD,|| Mian-Yoon Chong, MD, PhD,¶ Gabor Ungvari, MD, PhD,# Chay-Hoon Tan, MD, PhD,** Yu-Tao Xiang, MD, PhD,†† Norman Sartorius, MD, PhD,‡‡ Naotaka Shinfuku, MD, PhD,§§ and Lian-Yu Chen, MD, PhD*||||*

Abstract:

Purpose: Little is known regarding the trend of polypharmacy in Asia. We used data from 5 Asian countries to examine the patterns of antidepressant (AD) prescription and trends of psychotropic polypharmacy over time.

Methods: We used the cross-sectional, pharmacoepidemiological data from 2004 and 2013 REAP-AD (Research on Asian Psychotropic Prescription Patterns for Antidepressants) to examine the patterns of AD prescriptions in clinical settings in China, Japan, Korea, Singapore, and Taiwan. We compared the trend in polypharmacy (ie, concomitant use of ≥2 classes of psychotropic) among individuals receiving AD prescriptions in 2004 and 2013 using multivariable logistic regression models in different diagnostic categories.

Results: The proportion of patients with psychotropic polypharmacy decreased from 2004 to 2013 in all 3 diagnostic categories, including mood disorders (adjusted odds ratio [aOR], 0.44 [0.35–0.56]; $P < 0.001$), anxiety disorders (aOR, 0.58 [0.36–0.94]; $P = 0.028$), and psychotic disorders (aOR, 0.18 [0.05–0.60]; $P = 0.006$). Among individuals with AD prescriptions, concomitant use of anxiolytics (including sedative-hypnotics) decreased in patients with mood disorders (aOR, 0.34 [0.27–0.42]; $P < 0.001$) and anxiety disorders (aOR, 0.43 [0.27–0.67]; $P < 0.001$). In contrast, concomitant use of antipsychotics in patients with mood disorders increased (aOR, 1.43 [1.15–1.77]; $P = 0.001$), and concomitant use of mood stabilizers in patients with psychotic disorders also increased (aOR, 3.49 [1.50–8.14]; $P = 0.004$).

Conclusions: This is the first study examining trends in psychotropic polypharmacy in East Asia. We found a generally decreasing trend of psychotropic polypharmacy in contrast to the increasing trend reported from Western countries. These findings could offer significant implications for health system reform or policy making.

Key Words: antidepressant use, polypharmacy, prescription pattern

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Antidepressants (ADs) have become one of the most widely prescribed psychotropic medications with an escalating trend of prescription in recent decades.[1–4] There are several possible reasons behind the phenomenon, including a wider range of approved indications,[2,5,6] increased access to care for mental disorders, and growing public acceptance of psychiatric medications,[7] as well as increased off-label use in poorly defined mental conditions.[8] In the United States, the prevalence of prescriptions of AD increased from 6.8% to 13% from 1999 to 2012 in a national survey.[9] In addition, increased trends of psychotropic polypharmacy in the United States[10] and Australia[11] were observed. Such increased trend of psychotropic polypharmacy was also noted in the child and adolescent populations.[12] Concerns with psychotropic polypharmacy include not only possibilities of possible accumulating adverse drug effects and drug-drug interactions,[10] but also adherence issues that emerge with increasing regimen complexity.[13]

Several studies have supported an increasing trend of polypharmacy in Western countries. For instance, a US study showed that prescription drug use went up as polypharmacy of the majority of drug classes went up from 1999 to 2012.[9] Among all drug classes, psychotropic polypharmacy is a common phenomenon both in the general population and in routine psychiatric care.[14] Mojtabai and Olfson[10] found a significant increase in psychotropic polypharmacy involving ADs and antipsychotics (APs) between 1996 and 2006 in office-based psychiatry in the United States. Psychotropic polypharmacy was also found to be increasingly common in outpatient services in child and adolescent population in the United States.[12] However, studies investigating this issue in Asian countries are sparse. We found 1 study that showed that the prevalence of AP polypharmacy in schizophrenic patients has increased[15]; another study in Taiwan showed anxiolytics-hypnotics polypharmacy went up from 2002 to 2009.[14] Within our knowledge, there is no study examining the trend of polypharmacy involving ADs in Asia.

The present study sought to address this limitation in past research.[1] The Research on Asian Psychotropic Prescription Patterns for Antidepressants (REAP-AD) project had conducted 2 waves of surveys on AD prescriptions in several Asian countries in 2004 and 2013, respectively.[16] More specifically, by using data

From the Departments of *Addiction Psychiatry and †Pharmacy, Taipei City Psychiatric Center, Taipei City Hospital, Taipei, Taiwan; ‡Mental Health Department, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; §Department of Psychiatry, College of Medicine, Taipei Medical University, Taiwan; ||Department of Psychiatric Epidemiology, Shanghai Mental Health Center, Shanghai, China; ¶Department of Psychiatry, Kaohsiung Chang Gung Memorial Hospital-Kaohsiung Medical Center and School of Medicine, Chang Gung University, Taiwan; #School of Psychiatry & Clinical Neurosciences, University of Western Australia, Australia; **Department of Pharmacology, National University of Singapore, Singapore; ††Faculty of Health Sciences, University of Macau, Macao SAR, China; ‡‡Association for the Improvement of Mental Health Programmes, Geneva, Switzerland; §§International Center for Medical Research, Kobe University Graduate School of Medicine. Kobe, Japan; and ||||Institute of Epidemiology and Preventive Medicine, National Taiwan University, Taiwan.

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Reprints: Lian-Yu Chen, MD, PhD, Addiction Psychiatry Department, Taipei City Psychiatric Center, Taipei City Hospital, No. 309, Songde Road, Xinyi District, Taipei City, Taiwan (e-mail: lianyu0928@gmail.com).

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C.-Y.H. and S.-Y.Y. share first authorship equally.

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from 2 waves of REAP-AD, we aimed to examine trends in psychotropic polypharmacy in those with AD prescriptions based on their major diagnoses in Asian countries. In addition, we aimed to identify the factors associated with newer AD prescriptions from 2004 to 2013, as compared with Sim and colleagues'[17] previous work using REAP data from 2003 only.

Several past reports have utilized and analyzed the data from REAP study.[1,16–18] For instance, prescriptions of newer ADs in East Asia were found to be associated with sociodemographic characteristics such as younger age, country, and treatment settings rather than clinical diagnoses in the 2004 survey.[17] Rajaratnam et al[1] have found that average daily doses of ADs had increased by 12% from 2004 to 2013, and higher dosage was associated with hospitalization and having a diagnosis of major depressive disorder. Furthermore, significant increase in concurrent use of mood stabilizers (MSs) and ADs from 2004 to 2013 was noted, with risk factors being younger age, hospitalization, and having a diagnosis of bipolar disorder.[18] In our study, we aimed to examine the trend of polypharmacy in Asia utilizing data from these 2 waves of surveys.

METHODS

Study Population and Assessments

Research on Asian Psychotropic Prescription Pattern is a long-standing international, pharmacoepidemiological project that aims to examine the prescription patterns of psychotropics in Asia, starting in 2001. Six large scale multinational surveys have been done so far by the REAP project, 4 of which focused on patients receiving APs (REAP-AP), whereas the remaining 2 surveys (REAP-AD1 and REAP-AD2) involved patients receiving ADs in 2004 and 2013, respectively. In order to examine the trend of polypharmacy across time, we included 5 countries (in total 33 sites) that participated in both surveys including People's Republic of China, Japan, Republic of Korea, Singapore, and Taiwan. Data collection followed the same protocol at each site. All recruited study subjects with any psychiatric diagnosis were required to be prescribed an AD (62 agents classified as AD in Anatomical Therapeutic Chemical classification system-Defined Daily Dose) on the day of surveys involving consecutive patients at all participating sites.

Information was recorded systemically including patients' age, sex, and treatment setting (outpatient vs inpatient setting, public vs private facilities, psychiatric vs general medical services), as well as doses of all prescribed medications. Older ADs, developed prior to 1990, included tricyclic antidepressants, tetracyclics, and irreversible monoamine oxidase inhibitors, as well as a reversible irreversible monoamine oxidase inhibitor. Newer ADs included selective serotonin reuptake inhibitors, serotonin and noradrenaline reuptake inhibitors, and noradrenergic and specific serotonin antidepressants. Psychiatric diagnoses were confirmed by at least 2 psychiatrists at each site based on the *International Statistical Classification of Diseases, 10th Revision* (*ICD-10*)[19] or *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria (American Psychiatric Association, 1994). Protocols and consent forms were approved by the individual institutional review boards of the survey centers. Informed consents were obtained from all study subjects prior to participation in each survey.

Statistical Analysis

Contingency analyses were performed to examine the sociodemographic and clinical characteristics of participants from 2 waves. We used multivariable logistic regression models to (1) identify factors of newer AD prescriptions and to (2) examine the polypharmacy trends of psychotropic medications from REAP-AD1 (2004) to REAP-AD2 (2013). We examined the proportion of concurrent use of multiple classes of psychotropic medications (ie, polypharmacy) including ADs, APs, MSs, and anxiolytics in patients with different diagnoses, including psychotic disorders (F2), mood disorders (F3), and anxiety disorders (F4) based on *ICD-10* diagnostic categories. We used logistic regression models to examine the trend of polypharmacy from 2 waves,

TABLE 1. Sociodemographics of Patients Treated With ADs in REAP-AD1(2004) and REAP-AD2 (2013), by Country

	REAP-1 (n = 1898)					REAP-2 (n = 1189)				
	China (n = 537)	Japan (n = 602)	Korea (n = 293)	Singapore (n = 71)	Taiwan (n = 387)	China (n = 350)	Japan (n = 246)	Korea (n = 259)	Singapore (n = 135)	Taiwan (n = 199)
Sex (%)										
Male	43.1	36.5	37.5	41.7	47.0	40.3	45.1	42.1	43.0	49.2
Female	56.9	63.5	62.5	58.3	53.0	59.7	54.9	57.9	57.0	50.8
Age (%)										
<18	3.7	1.5	1.4	0.0	1.6	2.6	1.6	0.8	4.4	0.0
18–34	34.3	22.4	21.8	31.0	22.5	29.7	20.3	18.5	27.4	13.6
35–54	33.9	36.0	35.8	46.5	47.3	30.6	36.2	32.0	41.5	44.7
55–74	23.3	32.1	37.9	22.5	23.0	32.6	32.5	39.0	22.2	32.2
≥75	4.8	8.0	3.1	0.0	5.7	4.6	9.3	9.7	4.4	9.5
Diagnosis (%)										
ICD-10 F2	12.3	8.0	4.1	47.2	22.5	4.3	3.7	9.3	23.7	28.6
ICD-10 F3	56.2	63.4	80.2	27.8	58.7	77.1	67.5	71.8	37.8	58.8
ICD-10 F4	22.7	21.0	13.0	18.1	6.2	15.7	20.3	9.7	32.6	4.5
ICD-10 others	8.8	7.6	2.7	6.9	12.7	2.9	8.5	9.3	5.9	8.0
AD used type										
Older only	16.8	24.5	4.4	11.1	9.8	0.3	11.8	2.7	3.0	3.5
Newer only	76.5	65.7	76.1	86.1	88.9	96.3	83.7	90.7	94.1	93.0
Older + newer	6.7	9.9	19.5	1.4	1.3	3.4	4.5	6.6	3.0	3.5

with adjusted models accounting for age, sex, treatment setting, and country. Statistical significance was set at 2-tailed $P < 0.05$. All analyses were performed using the Statistical Package for Social Sciences, version 21.0(SPSS Inc, Chicago, Ill).[20] To avoid false-positive results due to multiple testing, we used Bonferroni correction to adjust the results in the analysis of identifying factors associated with newer AD prescriptions.[21] On the other hand, in order to focus on the trend of psychotropic polypharmacy in 2 waves, we did not adjust for multiple testing in this model, as supported by previous literature.[21,22]

RESULTS

Sociodemographic and Clinical Characteristics

Sociodemographic and clinical characteristics of the participants by country are shown in Table 1. There were 1898 participants in REAP-AD1 and 1189 in REAP-AD2. Overall, their mean age was 46.7 (±16.9) in REAP-AD1 and 47.6 (±17.1) in REAP-AD2; 40.9% of participants in REAP-AD1 were male, whereas 43.5% of participants in REAP-AD-2 were male. Overall, the proportion of newer AD prescriptions increased over time in all 5 countries. Furthermore, we found the proportion of combination use of older and newer ADs decreased in China, Japan, and Korea from 2004 to 2013. Further analysis has confirmed that the decrease was statistically significant ($P < 0.05$, data not shown in Table 1).

Antidepressants Prescription Patterns in 2 Waves

The factors associated with greater use of newer ADs are shown in Table 2. Sociodemographic data such as age and sex were not associated with higher number of prescriptions of newer ADs. Being in year 2013 was much more likely to receive newer AD prescriptions compared with being in year 2004 (odds ratio [OR], 5.08 [3.57–7.22]; $P < 0.0001$). Compared with Japan, all the other countries were more likely to have newer AD prescriptions (China: OR, 3.79 [2.53–5.68]; Korea: OR, 4.53 [2.77–7.41]; Taiwan: OR, 4.88 [3.05–7.80]; all $P < 0.0001$; Singapore: OR, 4.25 [1.47–12.25]; $P = 0.0299$). In addition, patients from private institutions were more likely to be prescribed newer ADs compared with those from public institutions (OR, 2.18 [1.58–3.01]; $P < 0.0001$).

Trends of Polypharmacy

We examined the trend of polypharmacy among participants with AD prescriptions in 3 different diagnostic categories including mood disorders, anxiety disorders, and psychotic disorders (Table 3). In the group of mood disorders, we found the trend of polypharmacy decreased from 79.1% to 66.2% between 2004 and 2013 (adjusted OR [aOR], 0.44 [0.35–0.56]; $P < 0.001$). The concurrent prescription of anxiolytics decreased from 72.4% to 50.0% (aOR, 0.34 [0.27–0.42]; $P < 0.001$), and the concurrent prescription of APs increased from 26.6% to 36.1% (aOR, 1.43 [1.15–1.77]; $P = 0.001$).

In the group of anxiety disorders, we also observed a downward trend of psychotropic polypharmacy. The percentage of multiclass psychotropic prescriptions decreased from 77.8% to 62.8% (aOR, 0.58 [0.36–0.94]; $P = 0.028$). Likewise, the percentage of concurrent prescriptions with anxiolytics decreased from 72.3% to 53.0% (aOR, 0.43 [0.27–0.67]; $P < 0.001$), whereas no significant trend was noted on the prescriptions of APs and MSs.

In the group of psychotic disorders, the trend of polypharmacy decreased from 96.0% to 92.7% (aOR, 0.18 [0.05–0.60]; $P = 0.006$). However, the percentage of concurrent prescriptions

TABLE 2. Multivariate Logistic Regression Values for Factors Associated With Greater Use of Newer* Versus Older ADs in Asian Countries Between 2004 and 2013 (n = 2795)

Factor	*B*	SE	Wald	Bonferroni-Corrected *P*	OR (95% Confidence Interval)
Constant	0.67	0.29	5.26	0.0218	
Male	−0.13	0.13	1.03	0.3103	0.88 (0.69–1.13)
Age	−0.01	0.00	8.17	0.0043	0.99 (0.98–1.00)
Regions/countries					
China	1.33	0.21	41.45	<0.0001	3.79 (2.53–5.68)
Japan					Reference
Korea	1.51	0.25	36.09	<0.0001	4.53 (2.77–7.41)
Singapore	1.45	0.54	7.16	0.0299	4.25 (1.47–12.25)
Taiwan	1.58	0.24	43.80	<0.0001	4.88 (3.05–7.80)
Year of survey					
2004					Reference
2013	1.62	0.18	81.38	<0.0001	5.08 (3.57–7.22)
Institution type					
Public					Reference
Private	0.78	0.16	22.47	<0.0001	2.18 (1.58–3.01)
Hospital type					
Psychiatric					Reference
General	−0.31	0.23	1.84	0.5239	0.73 (0.47–1.15)
University affiliated—psychiatric	0.41	0.33	1.55	0.6397	1.50 (0.79–2.84)
University affiliated—general	0.33	0.17	3.59	0.1740	1.39 (0.99–1.96)
Treatment settings					
Outpatient					Reference
Inpatient	0.15	0.14	1.08	0.2984	1.16 (0.88–1.53)

TABLE 3. Trends in Multiclass Psychotropic Prescriptions Between REAP-AD1(2004) and REAP-AD2 (2013)

Multiclass Psychotropic Prescriptions	REAP-AD1 (n = 1170)		REAP-AD2 (n = 790)		Trend Statistics		
Mood Disorders (F3)	**n**	**%**	**n**	**%**	**aOR**	**95% Confidence Interval**	***P***
Any ≥2 psychotropic medication classes	926	79.1%	523	66.2%	0.44	0.35–0.56	<0.001
Antipsychotics	311	26.6%	285	36.1%	1.43	1.15–1.77	0.001
Mood stabilizers	134	11.5%	89	11.3%	0.93	0.68–1.27	0.653
Anxiolytics	847	72.4%	395	50.0%	0.34	0.27–0.42	<0.001
	REAP-AD1 (n = 325)		**REAP-AD2 (n = 183)**		**Trend Statistics**		
Anxiety Disorders (F4):	**n**	**%**	**n**	**%**	**aOR**	**95% Confidence Interval**	***P***
Any ≥2 psychotropic medication classes	253	77.8%	115	62.8%	0.58	0.36–0.94	0.028
Antipsychotics	97	29.8%	49	26.8%	1.25	0.79–1.98	0.345
Mood stabilizers	15	4.6%	10	5.5%	2.01	0.82–4.92	0.128
Anxiolytics	235	72.3%	97	53.0%	0.43	0.27–0.67	<0.001
	REAP-AD1 (n = 248)		**REAP-AD2 (n = 137)**		**Trend Statistics**		
Psychotic Disorders (F2)	**n**	**%**	**n**	**%**	**aOR**	**95% Confidence Interval**	***P***
Any ≥2 psychotropic medication classes	238	96.0%	127	92.7%	0.18	0.05–0.60	0.006
Antipsychotics	227	91.5%	126	92.0%	0.48	0.18–1.31	0.151
Mood stabilizers	26	10.5%	31	22.6%	3.49	1.50–8.14	0.004
Anxiolytics	167	67.3%	80	58.4%	0.63	0.35–1.15	0.133

The adjusted models were adjusted for age, sex, hospital type, and country.

with MSs increased from 10.5% to 22.6% (aOR, 3.49 [1.50–8.14]; $P = 0.004$). No significant change was observed in the proportion of concurrent prescriptions with APs and anxiolytics.

DISCUSSION

There are 3 major findings in our study. First, we found an increasing trend of newer AD prescriptions over time with the associated factors being receiving care in private institutions and residing in countries other than Japan. Second, we found a decreasing trend of psychotropic polypharmacy in AD users across all 3 diagnostic categories including mood disorders, anxiety disorders and psychotic disorders, which is the opposite of the increasing trend of psychotropic polypharmacy observed in Western countries. Third, despite that we found a decrease in concurrent prescriptions of anxiolytics in patients with mood disorders and anxiety disorders, higher proportion of AP prescriptions in mood disorders and higher proportion of MS prescriptions in psychotic disorders were noted in this study.

Preferential use of newer ADs with an increasing trend of prescriptions has been reported in many Western countries.[9,23,24] Our study showed similar trend in Asian countries. The growing acceptability of newer ADs could be attributed to several factors including better tolerability, more favorable safety profiles, and, particularly, widening range of clinical indications.[5,25,26] This part of our study could be viewed as a continuum from a previous study, which examined factors associated with newer AD prescriptions using REAP-AD1 data.[17] Compared with this study, we found Japan has consistently remained the country in which the participants would least likely to receive newer ADs, with 83.7% of Japanese participants in 2013. Overall, more than 90% of participants in other 4 countries were recorded as receiving newer ADs. Japan has been known for its strict regulations of approving new drugs via the Food and Drug Administration, which might explain the consistency of this finding over multiple years.[27] Although Japan has also shown an increasing trend of newer AD prescriptions, physicians in Japan continued to have relatively fewer options than other Asian countries.[16]

Our data from 5 East Asian countries revealed an opposite trend of polypharmacy as compared with the increasing prevalence of psychotropic polypharmacy in Western countries.[10–12] For example, a national survey in the United States has shown a marked increase in psychotropic polypharmacy in office-based psychiatric visits, with prescriptions of 2 or more medications increasing from 42.6% to 59.8% from 1996 to 2006 and 3 or more medications increasing from 16.9% to 33.2%.[10] Another study using National Ambulatory Medical Care Survey revealed that multiclass psychotropic polypharmacy increased from 14.3% to 20.2% of child psychotropic visits from 1996 to 2007, with ADs being the most common coprescribed medication class. More recently, Brett et al[11] showed a significant increase in psychotropic polypharmacy using national pharmaceutical claim data in Australia from 2006 to 2015.

As abundant evidence revealed the phenomenon of increasing psychotropic polypharmacy, its risk and benefits have not been clear.[11] On the one hand, polypharmacy could be driven by insufficient response from monotherapy and by patients reporting better perceived outcome with polypharmacy.[28] On the other hand, polypharmacy may cause cumulative toxicity and increased vulnerability to adverse events.[29] For instance, 1 study showed that psychotropic polypharmacy was linked to increased mortality in patients with dementia, especially in co-use of benzodiazepines.[30] Possible explanations behind the increasing trend of psychotropic polypharmacy include increasing disease severity, more identified psychiatric comorbidities,[10] a growth of off-label prescriptions of certain psychotropics,[31] and poor communication between health care professionals.[11] Thus, to our knowledge, this is the first study that examined trend of psychotropic polypharmacy in Asia, which in contrast to Western countries demonstrated a generally decreasing trend of psychotropic polypharmacy among patients receiving AD treatment.

The reason behind this opposite trend in these Asian countries was unclear. However, it is postulated that the effect of a national health insurance system in these Asian countries to curtail polypharmacy may play a central role. All the participating countries in our study have established national health insurance systems for decades and have made several policy reforms in recent years in order to curtail unnecessary health costs.[14,32–36] For example, the Taiwanese National Health Insurance program, as a single payer system, covers more than 96% of the Taiwanese population. In this system, a monitoring mechanism promoting rational medical practice has been implemented in every contracted medical facility. Thus, overlapping prescriptions or polypharmacy without reasonable medical indications would not be reimbursed.[14,32] Similar monitoring systems are implemented in South Korea, Japan, and China, to ensure appropriate prescription and to avoid escalating medical expenditure.[33–36] This mechanism might help explain the downward trend of psychotropic polypharmacy in these countries.

Despite the decreasing trend of psychotropic polypharmacy, we found higher concurrent AP prescriptions in mood disorders and higher concurrent MS prescriptions in psychotic disorders in patients receiving ADs. This finding could be the product of more updated treatment guidelines of mood disorders. For instance, both the World Federation of Societies of Biological Psychiatry and the Canadian Network for Mood and Anxiety Treatments suggested combination treatment of ADs and APs for treatment-refractory depression, psychotic depression,[37,38] and bipolar depression.[39–41] More specifically, augmentation of AD with quetiapine or aripiprazole is recommended in treatment of unipolar depression if monotherapy fails[38]; combination use of olanzapine and selective serotonin reuptake inhibitor is also a first-line treatment option for bipolar depression.[40,41] A growing body of research supporting the increased off-label use for APs as sedating agents may also contribute to this phenomenon.[31] As our finding is consistent with the growing prevalence of AP-AD combination use in Western countries,[10,42] the increased risk of drug-drug interaction involving cytochrome P450 system should be emphasized.[43]

Higher prevalence of combination use of MS-AD in psychotic disorders could also be explained by increased off-label use of MSs. One report utilizing data from 2 waves of REAP-AD revealed a general trend of increasing use of MS-AD[18]; our study further showed that such increase was in individuals with psychotic disorders, not in those with mood or anxiety disorders. A previous study showed off-label use of sodium valproate in psychiatric patients with schizophrenia or schizoaffective disorder is extensive, especially in younger patients or those with schizoaffective disorder.[44] Another study showed adding valproic acid to atypical APs is effective for treating excitement and impulsiveness in schizophrenic patients.[45] Nevertheless, we should be cautious about the complex pharmacokinetic drug-drug interactions of MS and AP while using such combination treatment regimen.[46]

The global trends of anxiolytics-hypnotics prescriptions are mixed. While US and Taiwanese national studies showed an increasing trend of anxiolytics-hypnotics prescriptions,[10,14] some others have shown a steady or downward trend.[11,47,48] Some possible explanations should be considered. First, because of safety concerns and abuse potential of these medications, physicians may become more cautious about their prescription patterns.[49] Second, countries such as South Korea and Taiwan have set limits on the durations of prescription of these medications to reduce overprescriptions and to save medical costs, which showed prominent effects on cutting down prescriptions of these medications.[47,50] Third, combination use with MS or AP, which has sedating effects, might contribute to the decreased use of anxiolytics-hypnotics, which was supported by our other study finding of increasing AP use in mood disorders and increasing MS use in psychotic disorders. However, further investigations to delineate such a correlation should be conducted.

Several limitations of this study should be addressed. First, our definition of polypharmacy involved only concomitant use of different classes of psychotropics. Intraclass polypharmacy was not included in our analysis, which may underestimate the proportion of polypharmacy. Second, possible confounding factors such as illness severity were not considered, which might lead to residual confounding. It is possible that more combination use is due to higher illness severity. Third, the participating sites were mainly major hospitals in large cities of these countries. These results could not be interpreted as national representative findings. Fourth, we have utilized 2 waves of data across 10 years, which may not capture the dynamic changes during the time gap. Nevertheless, the study included more than 3000 subjects from a broadly representative sampling of countries, treatment settings, and diagnoses. Furthermore, we utilized data across 10 years to examine the general prescription trend, which augments the literature gap of polypharmacy study in Asian countries.

CONCLUSIONS

To our knowledge, this is the first international study examining trends of psychotropic polypharmacy in Asian countries. We found a general declining trend of polypharmacy among individuals with AD prescriptions. However, higher proportion of AP prescriptions in mood disorders and higher proportion of MS prescriptions in psychotic disorders were observed. As polypharmacy may cause more adverse effects from cumulative toxicity or complex drug-drug interaction, this study could offer insight and reflections to health professionals and policy makers regarding how psychotropic prescription patterns might differ. In addition, these results could fill the knowledge gap of psychotropic polypharmacy in Asia and provide a basis for international comparison.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

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