Xiang Yu-Tao (Orcid ID: 0000-0002-2906-0029)

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Concurrent antipsychotic use in older adults treated with antidepressants in Asia

Running head: Antipsychotics in older adults

1# Min Dong, MD
2# Liang-Nan Zeng, MD
3# Qinge Zhang, MD
4, 5 Gabor S. Ungvari, MD, PhD
6 Chee H. Ng, MBBS, MD
7 Helen F. K. Chiu, FRCPsych,
8 Tian-Mei Si, MD PhD
9 Kang Sim, MD,
10 Ajit Avasthi, MD,
10 Sandeep Grover, MD,
11 Mian-Yoon Chong, MD, PhD,
12 Kok-Yoon Chee, MD
13 Shigenobu Kanba, MD PhD,
14 Min-Soo Lee, MD,
15 Shu-Yu Yang, PhD,
16 Pichet Udomratn, MD,
17 Roy A. Kallivayalil, MD,
18 Andi J. Tanra, MD,
19 Margarita M. Maramis, MD, PhD,
20 Winston W. Shen, MD,
21 Norman Sartorius, MD,
22 Rathi Mahendran, MBBS, MMed (Psych)
23 Chay-Hoon Tan, MD
24 Naotaka Shinfuku, MD PhD
1*Yu-Tao Xiang, MD, PhD,

1. Unit of Psychiatry, Faculty of Health Sciences, University of Macau, Macao SAR, China;
2. The Affiliated Hospital of Southwest Medical University, Luzhou, China;

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3. The National Clinical Research Center for Mental Disorders, China &Center of Depression, Beijing Institute for Brain Disorders & Mood Disorders Center, Beijing Anding Hospital, Capital Medical University, Beijing, China
4. The University of Notre Dame Australia / Marian Centre, Perth, Australia
5. Graylands Hospital, Perth, Australia
6. Department of Psychiatry, University of Melbourne, Melbourne, Victoria, Australia
7. Department of Psychiatry, Chinese University of Hong Kong, Hong Kong, China
8. Peking University Institute of Mental Health (the sixth Hospital) & National Clinical Research Center for Mental Disorders & the key Laboratory of Mental Health, Ministry of Health (Peking University), Beijing, China
9. Institute of Mental Health, Buangkok View, Buangkok Green Medical Park, Singapore
10. Department of Psychiatry, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India
11. Department of Psychiatry, Kaohsiung Chang Gung Memorial Hospital-Kaohsiung Medical Center and School of Medicine, Chang Gung University, Taiwan
12. Department of Psychiatry & Mental Health, Tunku Abdul Rahman Institute of Neurosciences, Kuala Lumpur Hospital, Kuala Lumpur, Malaysia
13. Department of Neuropsychiatry, Kyushu University, Fukuoka, Japan
14. Department of Psychiatry, College of Medicine, Korea University, Seoul, Korea
15. Department of Pharmacy, Taipei City Hospital, Taipei, Taiwan
16. Department of Psychiatry, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand
17. Department of Psychiatry, Pushpagiri Institute of Medical Sciences, Thiruvalla, India
18. Department of Psychiatry, Hasanuddin University Faculty of Medicine, Makassar, Sulawesi Selatan, Indonesia
19. Dr. Soetomo Hospital – Faculty of Medicine, Airlangga University, Jawa Timur, Indonesia
20. Departments of Psychiatry, TMU-Wan Fang Medical Center and School of Medicine, Taipei Medical University, Taiwan
21. Association for the Improvement of Mental Health Programmes, Geneva, Switzerland
22. Department of Psychological Medicine, National University of Singapore, Singapore
23. Department of Pharmacology, National University of Singapore, Singapore
24. International Center for Medical Research, Kobe University School of Medicine, Kobe, Japan

# These authors contributed equally to this work.

*Address correspondence to Dr. Yu-Tao Xiang, 3/F, Building E12, Faculty of Health Sciences, University of Macau, Avenida da Universidade, Taipa, Macau SAR, China. Fax: +853-2288-2314; Phone: +853-8822-4223; E-mail: xyutly@gmail.com

Abstract

Background: Depressive disorders are common in old age. Antipsychotics (APs) are often used as an adjunctive treatment with antidepressants (ADs) in this population but its patterns of use in Asia are not known. This study explored the rate of combination of APs and ADs in older adult psychiatric patients in Asia.

Methods: This is a secondary analysis of the database of a multicenter study which recorded participants' basic demographical and clinical data in standardized format in ten Asian countries and territories. The data were analyzed using univariate and multivariate logistic regression analyses.

Results: A total of 955 older adult psychiatric in- and outpatients were included in this study. The proportion of concurrent AP and AD use was 32.0%, ranging from 23.3% in Korea to 44.0% in Taiwan. Multivariate logistic regression analysis

found that younger age, inpatient status and diagnosis of schizophrenia were significantly related to a higher proportion of concurrent use of APs and ADs.

Conclusion: Around a third of older adult psychiatric patients had concurrent AP and AD use in the Asian countries/regions surveyed. Considering the uncertain effectiveness and questionable safety of the APs and ADs combination in this patient population, this type of polypharmacy should be used cautiously.

Key words adjunctive treatment, antidepressants, antipsychotics, Asia, older adults

Introduction

Depressive disorders are frequent in older adults. For example, one survey found that the prevalence of major depression was up to 16% in old people living in private households or institutions.[1] Another study reported that the prevalence of major depressive disorder, minor depression and clinically relevant depressive symptoms in old people living in the community were 1.8%, 9.8% and 13.5%, respectively.[2] Compared to younger adults, older adults suffering from depression have an increased risk of physical and psychological comorbidities, more disability and social isolation,[3-6] greater economic cost,[7,8] and higher mortality.[1,9]

Psychotropic medications are prescribed for old people up to 7-18 times more frequently than for middle-aged adults.[10] Of the psychotropic medications, antidepressants (ADs) are one of the most widely prescribed ones.[11,12] For example, one study found that 51.8% of nursing homes residents suffered from depression, of whom 82.8% received ADs.[13] Antipsychotics (APs), such as aripiprazole, quetiapine and olanzapine, are often used augmenting ADs for depression.[14] Over half of older adults who received ADs are also prescribed other psychotropic drugs, particularly benzodiazepines (BZDs) and APs.[15] Compared to younger adults, due to their poorer general health status and age-related physiological changes, older adults are more likely to experience

medication-induced adverse events.[16,17] Therefore, polypharmacy with psychotropic medications in older adults, if indicated at all, should be prescribed cautiously.

Regular surveys of prescription patterns are useful to examine the appropriateness of pharmacotherapy.[18] Although APs and ADs combinations are often used, the frequency of such co-prescription patterns are unknown in older adult psychiatric patients in Asia. This study set out to examine the concurrent use of APs and ADs in older adult psychiatric patients in several Asian countries and territories in, and explore its independent demographic and clinical correlates.

Methods

Study design and sample

The Research on Asian Psychotropic Prescription Patterns for Antidepressants (REAP-AD) project is an international, multicenter survey on the use of ADs,[19] which was conducted between March and June 2013 in 42 centers and hospitals in ten Asian territories and countries, including China, Malaysia, Hong Kong, India, Indonesia, Japan, Thailand, Korea, Singapore and Taiwan. Patients with any mental disorder treated with ADs on the day of data collection were consecutively screened and enrolled in the survey. The data were collected with

a standardized protocol in all participating hospitals. Patients who were eligible for the study were aged 50 years or above and were either in- or outpatients. In many Asian countries, patients aged 50 years or older are defined as 'old people'. This cut-off is in line with some other studies.[20-22] The study protocol was approved by the Institutional Review Boards at each participating center and hospital. When the survey involved retrospective anonymous medical chart review, informed consent was waived. However, when patients were interviewed, they provided written informed consent.

Assessment

Patients' demographical and clinical data were retrieved by reviewing medical records, or during a clinical interview supplemented by a review of medical records. Diagnoses were established according to ICD-10[23] or DSM-IV.[24] For the sake of comparison in the statistical analysis, doses of ADs were transformed into imipramine equivalent (IMI-eq) doses.[25]

Statistics

Data analyses were performed with the SPSS statistical package, Version 20. The demographical and clinical data were compared between patients treated with APs plus ADs and on ADs only with Mann-Whitney *U*-test, independent sample

t-test or χ^2 test, if applicable. Independent associations between demographical and clinical characteristics (independent variables) and the combination of APs and ADs (dependent variable) were explored with binary logistic regression analysis. The variables that significantly differed in univariate analysis were entered as independent variables, and the combination of APs and ADs was the dependent variable. Statistical significance was set at 0.05 (two-sided).

Results

A total of 955 older adult patients who received antidepressants were enrolled in the study. The rate of combination of APs and ADs in the whole sample was 32.0% ranging from 23.3% in Korea to 44.0% in Taiwan (Table 1). Table 2 shows the demographic and clinical data for the whole sample and separately for the ADs and the combination groups. In the whole sample, the mean age was 62.6 years and 375 patients (39.3%) were men; the proportion of mood disorders, anxiety disorders, schizophrenia and other diagnoses was 70.3%, 13.6%, 8.3% and 7.9%, respectively. The mean dose of ADs in IMI-eq was 131.2 mg/day.

Concurrent APs and ADs use was significantly associated with younger age, male gender, less number of ADs, inpatient treatment, in psychiatric or public hospitals, more frequent use of mood stabilizers (MS) and BZDs, and psychiatric diagnoses (Table 2). Binary logistic regression analyses found that concurrent

APs and ADs prescription was independently related to younger age, inpatient treatment and diagnosis of schizophrenia, anxiety and other mental disorders (Table 3).

Discussion

This was the first survey of the pattern of concurrent use of APs and ADs in older adult psychiatric patients in Asia. The proportion of concurrent prescription was 32.0% in the whole sample but it varied markedly across countries/territories, with the highest in Taiwan (44.0%) and lowest in Korea (23.3%). These figures are much higher than the corresponding ones in the USA (13.9%) and Europe (12.3%).[26] The discrepancy across study sites could be related to the diversity of socio-cultural factors, local clinical practices, healthcare polices, medication cost, and insurance coverage.[27] For example, there is a widely held view in Asia that combination of medications of different pharmacological activities has better efficacy in clinical practice.[28] In addition, the co-existence of psychotic and depressive symptoms occurring in various psychiatric disorders are frequent in elderly patients, increasing the likelihood of concurrent use of APs and ADs. As the risk of side effects of psychotropic drugs may increase due to the age-related changes in pharmacokinetic and pharmacodynamics responses in older

patients,[17] the safety of APs and ADs combination should be taken into consideration in clinical practice.

Concurrent use of APs and ADs was associated with psychiatric diagnoses (particularly schizophrenia), younger age and inpatient treatment in this study. ADs were often prescribed in schizophrenia for negative and depressive symptoms and even lessening cognitive impairment.[29] Negative and depressive symptoms improve in around a third of schizophrenia patients receiving ADs [30,31] and adjunctive ADs.[32-34] This may be related to the effect of ADs in modifying serotonergic (5-HT) dysfunction that is thought to be involved in the pathophysiology of psychotic symptoms.[14,35,36]

Although AD monotherapy has been recommended in treating depressive disorders,[37] adjunctive APs are often used as an augmentation strategy for treatment-resistant depression.[38] Second generation antipsychotics (SGAs) are frequently co-prescribed with ADs [39,40] given that SGAs improve depressive symptoms[42] by enhancing monoaminergic transmission[14,41] . A meta-analysis demonstrated that adjunctive SGAs have significant effects on the severity of major depression, resulting in improved quality of life and less functional deficit.[43]

In this survey, inpatients were more likely to be treated with APs and ADs combination, probably due to the more severe psychiatric symptoms.[44] Previous

studies in the US and Europe found that depressed patients prescribed with APs present with more severe comorbid psychotic symptoms.[26] The finding that younger age was associated with concurrent APs and ADs use is perhaps due to the better tolerance of polypharmacy in younger age. Conversely, the higher risk of medication-induced adverse events in older patients may discourage psychiatrists to prescribe combinations of psychotropic medications.

Several limitations of the study should be acknowledged. First, the sample size in several countries/territories was small, therefore analyses could not be performed separately in each study site. Second, as only 10 Asian countries/territories were included in the study, the findings are not representative of the whole Asian patient population. Third, due to the cross-sectional study the causality between variables could not be explored. Fourth, due to logistical reasons the severity of depressive and psychotic symptoms was not measured, hence their associations with prescription patterns could not be analyzed. Fifth, the study mainly focused on prescription of ADs in psychiatric hospitals or psychiatric units at general hospitals. Patients with other psychiatric and medical diagnoses treated with ADs, such as dementia or other neuropsychiatric disorders, rarely treated in psychiatric hospitals/units in most Asian countries, thus they were not covered in this study. Finally, several relevant factors of prescription patterns, such as cost of treatment, were not recorded.

In conclusion, around a third of older adult psychiatric patients in ten Asian countries and territories received concurrent ADs and APs. Given the increased age-related risks of psychotropic medication-induced side effects, the combination of ADs and APs should be used with caution in this population.

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Disclosure statement

We declare that the authors have no competing interests related to this study.

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Table 1. Prescription of psychotropic medication for olderadult psychiatric patients by country/territory

Country/territory	China (n=158)		Hong Kong (n=39)		Japan (n=119)		RO Korea (n=150)		Singapore (n=48)		Taiwan (n=109)		India (n=63)		Malaysia (n=67)		Thailand (n=128)		Indonesia (n=74)		Overall (n=955)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
APs	51	32.3	17	43.6	40	33.6	35	23.3	17	35.4	48	44.0	16	25.4	20	29.9	30	23.4	32	43.2	306	32.0
TCAs	6	3.8	3	7.7	15	12.6	18	12	1	2.1	8	7.3	7	11.1	1	1.5	33	25.8	7	9.5	99	10.4
Tetracyclics	0	0	0	0	7	5.9	0	0	0	0	0	0	0	0	1	1.5	19	14.8	0	0	27	2.8
SSRIs	103	65.2	21	53.8	52	43.7	101	67.3	30	62.5	57	52.3	44	69.8	47	70.1	71	55.5	67	90.5	593	62.1
SNRIs	42	26.6	7	17.9	24	20.2	35	23.3	3	6.3	22	20.2	10	15.9	4	6	8	6.3	0	0	155	16.2
NaSSAs	31	19.6	6	15.4	40	33.6	36	24	12	25	11	10.1	6	9.5	13	19.4	8	6.3	0	0	163	17.1
Other drugs	12	7.6	6	15.4	16	13.4	39	26	5	10.4	23	21.1	2	3.2	2	3	22	17.2	0	0	127	13.3
BZDs	64	40.5	19	48.7	71	59.7	40	26.7	16	33.3	76	69.7	18	28.6	31	46.3	50	39.1	38	51.4	423	44.3
MS	5	3.2	1	2.6	15	12.6	5	3.3	4	8.3	11	10.1	6	9.5	0	0.0	12	9.4	4	5.4	63	6.6

AP=antipsychotics; BZD=benzodiazepine; MS=mood stabilizer; NaSSA=noradrenergic and specific serotonergic antidepressant; TCA=tricyclic antidepressant; SSRI=selective serotonin reuptake inhibitor; SNRI=serotonin/norepinephrine reuptake inhibitor

Table 2. Basic demographic and clinical characteristics of the study sample

	The whole sample (n=955)		**No APs (n=649)**		**On APs (n=306)**		**Statistics**		
	Mean	SD	Mean	SD	Mean	SD	***t /z***	***df***	***P***
Age (years)	62.6	9.5	63.3	9.7	60.9	8.7	3.7	953	**<0.001**
AD dose, IMIeq (mg/d)	131.2	112.5	126.5	109.1	141.1	118.8	-1.9	---	0.051
Number of ADs	1.2	0.5	1.27	0.51	1.21	0.53	-2.1	---	**0.029**
Number of depressive symptoms	3.4	2.0	3.4	2.0	3.5	2.1	-0.8	---	0.38
	N	%	N	%	N	%	***Ç²***	***df***	***P***
Age (years)							9.1	1	**0.002**
50-64	615	64.4	397	61.2	218	71.2			
65 and older	340	35.6	252	38.8	88	28.8			
Male	375	39.3	238	36.7	137	44.8	5.7	1	**0.017**
Psychiatric hospital	351	36.8	201	31.0	150	49.0	29.1	1	**<0.001**
Outpatients	722	75.6	544	83.8	178	58.2	74.1	1	**<0.001**
General hospital psychiatric unit	687	71.9	448	69.0	239	78.1	8.4	1	**0.004**
Country/ territory							25.2	9	**0.003**
Income							3.1	2	0.21
High income	465	48.7	308	47.5	157	51.3			
Upper middle income	353	37.0	252	38.8	101	33.0			
Lower middle income	137	14.3	89	13.7	48	15.7			
Major medical conditions	421	44.1	281	43.3	140	45.8	0.5	1	0.47
Use of antidepressants									
TCAs	99	10.4	75	11.6	24	7.8	3.0	1	0.07
Tetracyclics	27	2.8	21	3.2	6	2.0	1.2	1	0.26
SSRIs	593	62.1	407	62.7	186	60.8	0.3	1	0.56
SNRIs	155	16.2	104	16.0	51	16.7	0.06	1	0.80
NaSSAs	163	17.1	109	16.8	54	17.6	0.1	1	0.74
Other ADs	127	13.3	85	13.1	42	13.7	0.07	1	0.79
Use of MS	63	6.6	31	4.8	32	10.5	10.8	1	**0.001**
Use of BZDs	423	44.3	268	41.3	155	50.7	7.3	1	**0.007**
Principal psychiatric diagnosis							93.5	3	**<0.001**
Mood disorders	671	70.3	479	73.8	192	62.7			
Anxiety disorders	130	13.6	109	16.8	21	6.9			
Schizophrenia	79	8.3	19	2.9	60	19.6			

Other diagnoses	75	7.9	42	6.5	33	10.8			

Bolded values: <0.05; AD=antidepressant; AP=antipsychotic; BZD=benzodiazepine; TCA=tricyclic antidepressants; NaSSA=noradrenergic and specific serotonergic antidepressant; SSRI=selective serotonin reuptake inhibitor; SNRI=serotonin/norepinephrine reuptake inhibitor; IMI-eq=imipramine-equivalent; MS=mood stabilizer

Table 3. Independent demographic and clinical correlates of concurrent antipsychotics and antidepressants use

Variables	*P* value	Odds Ratio	95% CI
Age (years)	**0.026**	0.98	0.963-0.998
Number of ADs	0.97	1.006	0.727-1.392
Male	0.301	0.181	0.861-1.619
Psychiatric hospital	0.424	1.183	0.783-1.787
Outpatients	**<0.001**	0.305	0.213-0.438
General hospital psychiatric unit	0.307	1.309	0.781-2.192
Use of MS	0.253	1.41	0.783-2.539
Use of BZDs	0.519	1.112	0.806-1.533
Principal psychiatric diagnosis			
Mood disorders	---	1	---
Anxiety disorders	**0.01**	0.493	0.289-0.842
Schizophrenia	**<0.001**	6.284	3.432-11505
Other diagnoses	**0.004**	2.265	1.296-3.957
Country/territory			
China	0.395	1	0
Hong Kong	0.271	1.586	0.698-3.606
Japan	0.276	1.408	0.761-2.609
South Korea	0.554	1.238	0.611-2.509
Singapore	0.951	1.028	0.429-2.463
Taiwan	0.367	1.360	0.698-2.651
India	0.325	1.456	0.689-3.075
Malaysia	0.541	1.265	0.596-2.688
Thailand	0.391	0.765	0.415-1.411
Indonesia	**0.039**	2.004	1.035-3.878

Bold values: <0.05; participating country/territory has been controlled for as a covariate. AD=antidepressants; BZD=benzodiazepine; IMI-eq=imipramine-equivalent; MS=mood stabilizer; SGA=second-generation antipsychotic