Source details

nternational Psychogeriatrics

Scopus coverage years: from 1989 to Present

Publisher: Cambridge University Press

SSN: 1041-6102 E-ISSN: 1741-203X

Subject area: Nursing: Gerontology | Psychology: Clinical Psychology | Medicine: Geriatrics and Gerontology | Medicine: Psychiatry and Mental Health

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Nursing
- Gerontology

Psychology
- Clinical Psychology

PUBLISHER

Cambridge University Press

H-INDEX

91

PUBLICATION TYPE

Journals

ISSN

1741203X, 10416102

COVERAGE

1989-2020

INFORMATION

Homepage

How to publish in this journal

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A highly respected, multidisciplinary journal, International Psychogeriatrics publishes high quality original research papers in the field of psychogeriatrics. The journal aims to be the leading peer reviewed journal dealing with all aspects of the mental health of older people throughout the world. Circulated to over 1,000 members of the International Psychogeriatric Association, International Psychogeriatrics also features important editorials, provocative debates, literature reviews, book reviews and letters to the editor.

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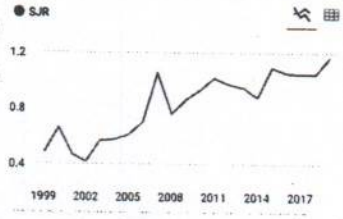

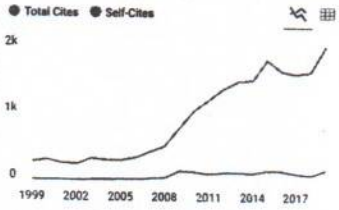

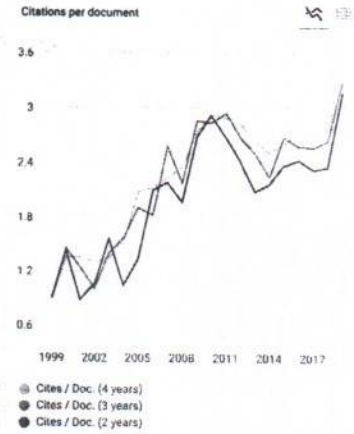

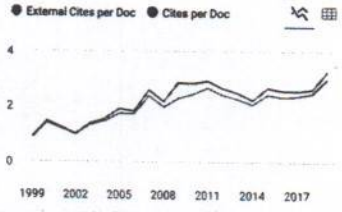

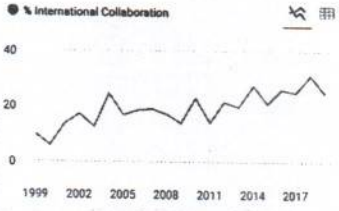

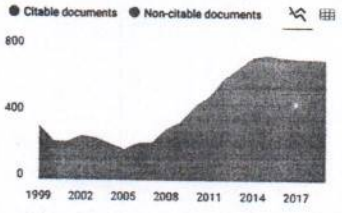

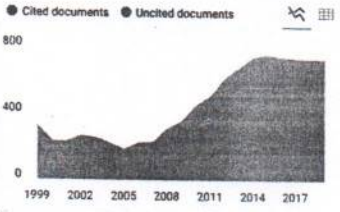

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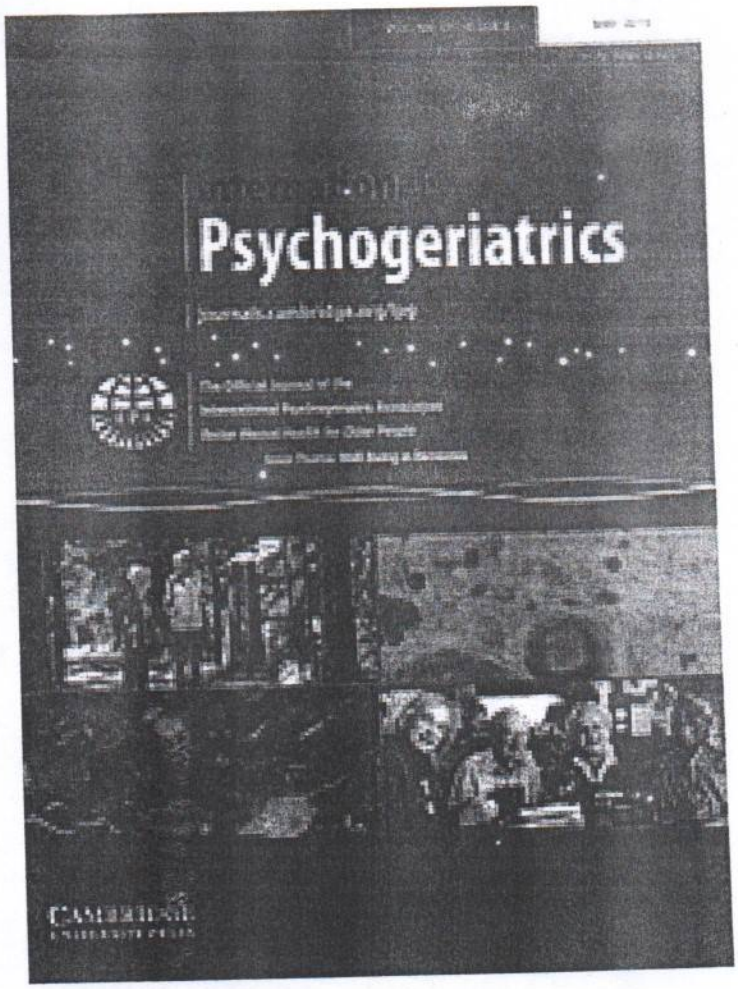
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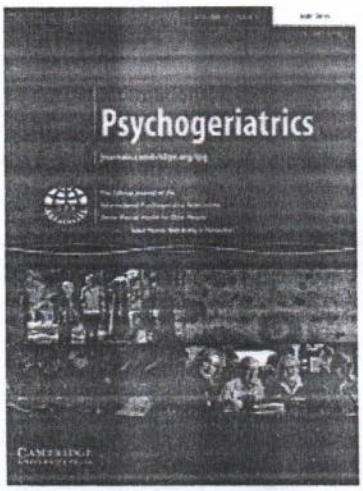

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Published online by Cambridge University Press: 18 June 2019, pp. f1-f2

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International Psychogeriatrics: page 1 of 7 © International Psychogeriatric Association 2017
doi:10.1017/S1041610217002563

Concurrent benzodiazepine use in older adults treated with antidepressants in Asia

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

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ABSTRACT

Background: Little is known about the combined use of benzodiazepines and antidepressants in older psychiatric patients. This study examined the prescription pattern of concurrent benzodiazepines in older adults treated with antidepressants in Asia, and explored its demographic and clinical correlates.

Methods: The data of 955 older adults with any type of psychiatric disorders were extracted from the database of the Research on Asian Psychotropic Prescription Patterns for Antidepressants (REAP-AD) project. Demographic and clinical characteristics were recorded using a standardized protocol and data collection procedure. Both univariate and multiple logistic regression analyses were performed.

Results: The proportion of benzodiazepine and antidepressant combination in this cohort was 44.3%. Multiple logistic regression analysis revealed that higher doses of antidepressants, younger age (<65 years), inpatients, public hospital, major comorbid medical conditions, antidepressant types, and country/territory were significantly associated with more frequent co-prescription of benzodiazepines and antidepressants.

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[#] These authors contributed equally to this work.

Conclusions: Nearly, half of the older adults treated with antidepressants in Asia are prescribed concurrent benzodiazepines. Given the potentially adverse effects of benzodiazepines, the rationale of benzodiazepines and antidepressants co-prescription needs to be revisited.

Key words: antidepressant, benzodiazepines, older adults, Asia

Introduction

Psychiatric disorders are common in older adults. For example, the prevalence of depression was 5.7% in Singapore (Kua, 1992) and 5.9% in Taiwan (Chong *et al.*, 2001). A survey conducted in China found that the prevalence of insomnia was 7.6% in older adults (Dai *et al.*, 2013). Due to the high rates of both conditions, benzodiazepines and antidepressants are often prescribed for this population. For example, 10% older adults with depression in the USA received benzodiazepines and antidepressants simultaneously between 2001 and 2014 (Bushnell *et al.*, 2017).

In older adults, antidepressant use has increased in the past decades (Soudry *et al.*, 2008; Parabiaghi *et al.*, 2011; Aarts *et al.*, 2014). In one survey, 38% of older adults living in nursing homes received as least one antidepressant (Manthey *et al.*, 2011). Benzodiazepines are commonly used in older adults primarily for sleep problems and anxiety (Smith and Tett, 2009), but chronic use of benzodiazepines is problematic because of common side effects, such as dependence, excessive sedation, falls, and cognitive impairment (Volz *et al.*, 2007). In Japan, 20–50% of older persons with psychiatric patients are prescribed benzodiazepines (Uchida *et al.*, 2009). Another survey in Asia found that 20.7% of older patients with schizophrenia received benzodiazepines (Xiang *et al.*, 2012).

Compared to younger people, older adults are more likely to have poorer general health and more frequent medication-induced adverse events (Meyers and Jeste, 2010). The latter is related to pharmacokinetic changes with advanced age affecting drug absorption, metabolism and excretion (Masand, 2000). In addition, older adults have age-related changes in pharmacodynamic response to benzodiazepines (Kruse, 1990), which increases the risk of adverse effects. As a consequence, prescription of benzodiazepines for older adults may often be harmful (Manthey *et al.*, 2011).

Regular cross-sectional surveys of prescription patterns are an efficient and quick method to assess the appropriateness of pharmacotherapy (Ungvari *et al.*, 1997). Several surveys have examined the combined use of benzodiazepines and antidepressants for psychiatric disorders, with the percentage ranging from 20.5% to 57% (van Dijk *et al.*, 2002; Leggett *et al.*, 2015; Fulone *et al.*, 2016; Bushnell *et al.*, 2017). However, very little is known about the co-prescription of these two groups of medications in Asian older psychiatric patients (Xiang *et al.*, 2014a).

This study examined the prescribing patterns of concurrent benzodiazepines and antidepressants in older psychiatric patients in Asia, and explored their associated demographic and clinical features.

Methods

Study sample and sites

This study was a secondary analysis of the database of the Research on Asian Psychotropic Prescription Patterns for Antidepressants (REAP-AD) project, which is a pharmaco-epidemiological study on antidepressant prescription patterns in psychiatric patients at 42 hospitals in 10 Asian countries/territories, including China, Hong Kong, Japan, Korea, Singapore, Taiwan, India, Malaysia, Thailand, and Indonesia. Patients who received antidepressants on the day of the survey were consecutively included in the REAP-AD study. Data collection followed the same standardized protocol and collection procedure at all study sites. Due to different local conventions, the cut-off age for older adults across the participating countries/territories ranged from 50 to 65 years. To ensure a homogeneous sample for the analysis, patients aged $\geq$50 years in the REAP-AD project were defined as "older adults." The same age cut-off was also used in other studies (Dassori *et al.*, 2011; Xiang *et al.*, 2014a) and in a World Health Organization report (WHO, 2001).

Assessments

Basic demographic and clinical characteristics were collected by a review of medical records verified by members of the research team at each site. Benzodiazepines were listed according to the World Health Organization Anatomical Therapeutic Chemical (ATC) classification system (WHO Collaborating Centre for Drug Statistic Methodology, 2002). Doses of antidepressants were converted into imipramine equivalent (IMIeq) mg/d doses (Rajaratnam *et al.*, 2016).

The study protocol was approved by the clinical research and ethics committee at each study site. Because the survey was anonymous and posed no

https://doi.org/10.1017/S1041610217002563

risk to patients, informed consent was waived at some study sites according to the requirements of the local ethics committee (Shinfuku and Tan, 2008), if only medical records was reviewed. All patients receiving interview provided consent according to the requirements of the ethics committee in the respective study sites.

Data analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 22.0 (IBM SPSS, Chicago, IL, USA). Comparisons of the demographic and clinical characteristics between patients on benzodiazepines plus antidepressants and those on antidepressants only were conducted using χ^2 test, independent sample *t*-test and Mann–Whitney *U*-test, as appropriate. Multiple logistic regression analysis with the "Enter" method was used to identify the demographic and clinical variables independently influencing benzodiazepines and antidepressants combination. The variables showing significant group difference in univariate analysis were independent variables, while benzodiazepines and antidepressants combination was the dependent variable. The level of significance was set at 0.05 (two-tailed).

Results

Of 955 patients treated with antidepressants included in the study, 44.3% were prescribed a combination of benzodiazepines and antidepressants (Table 1). Table 2 presents the basic demographic and clinical characteristics of the whole sample and separately for the combined benzodiazepine/antidepressant group. Younger age, higher dose of antidepressants, being treated in psychiatric hospitals, inpatient treatment, country/territory, major comorbid medical conditions, antidepressant type, and use of second-generation antipsychotics (SGAs) were significantly associated with co-prescription of benzodiazepines and antidepressants. Table 3 shows the independent demographic and clinical correlates of the combination treatment: higher doses of antidepressants, younger age (<65 years), inpatients, public hospital, major comorbid medical conditions, antidepressant types, and country/territory were significantly associated with more frequent co-prescription of benzodiazepines and antidepressants. The most commonly prescribed benzodiazepines were lorazepam (27%) and clonazepam (24%). The most common physical comorbidities were diabetes mellitus (27.5%), followed by cerebrovascular diseases (11.4%) and peptic ulcer (5.7%).

Discussion

This was the first large-scale, international survey of concurrent prescription of benzodiazepines and antidepressants in older adults. The proportion of combination treatment was 44.3% in Asia, which is lower than the figure (52%) in patients with major depression (mean age: 52.1 years) in Brazil (Fulone *et al.*, 2016), but higher than the 20.5% found in older veterans with depression (mean age: 64.9 years) in the USA (Leggett *et al.*, 2015).

The common use of antidepressants together with benzodiazepines could be due to several reasons. Depression with comorbid anxiety and insomnia is common in older adults (Biderman *et al.*, 2002; Johnson *et al.*, 2006; Neckelmann *et al.*, 2007), which justifies this practice. In addition, concerns about benzodiazepine withdrawal may contribute to the long-term use of these medications (Xiang *et al.*, 2012). In general, the combination of psychotropic medications with different pharmaceutical properties is common medical practice in Asian countries (Binder *et al.*, 1987). There was considerable variation in the combination treatment across different countries/territories that ranged from 26.7% in Korea to 59.7% in Japan. The variability in prescribing could be due to different insurance coverage, healthcare policies, psychopharmacological traditions, and medication costs (Xiang *et al.*, 2013).

In this study, the combined use of benzodiazepines and antidepressants was associated with younger age, inpatients, and being treated in public hospitals. These associations are probably related to the severity of psychiatric symptoms. Such combinations are usually prescribed for severe symptoms of depression, anxiety, and insomnia (Millan, 2014; Xiang *et al.*, 2014a). Relatively younger patients are more prone to present with severe psychiatric symptoms that are more likely to necessitate hospitalization in public psychiatric wards (White *et al.*, 1995; Zhang *et al.*, 2004; Xiang *et al.*, 2014a).

Insomnia, anxiety, and depressive symptoms are common in older adults with major medical conditions (Manthey *et al.*, 2011; Xiang *et al.*, 2014b), which could explain the high rate of polypharmacy. Antidepressant types and countries/territories were also associated with co-prescription of benzodiazepines and antidepressants. Socio-cultural factors, prescription traditions, access to psychotropic drugs, insurance coverage, costs and healthcare policies might contribute to the combined prescription (Xiang *et al.*, 2007). Higher antidepressant doses were significantly associated with more frequent combined treatment, but the minor difference

https://doi.org/10.1017/S1041610217002563

Table 1. Distribution of patients by study sites

	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)	
COUNTRY/ TERRITORY	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Receiving 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
Receiving 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
Receiving 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
Receiving 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
Receiving 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
Receiving 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
Receiving 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

Notes: BZD = bendiazepines; TCA = tricyclic antidepressants; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin/norepinephrine reuptake inhibitor; NaSSA = noradrenergic and specific serotonergic antidepressant.

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

	TOTAL SAMPLE (N = 955)		NO BZDs (N = 532)		ON BZDs (N = 423)		STATISTICS		
	MEAN	SD	MEAN	SD	MEAN	SD	*T*/*Z*	DF	*p*
Age (years)	62.6	9.5	63.6	9.9	61.2	8.8	3.9	953	**<0.001**
AD dose, IMIeq (mg/d)	131.2	112.5	123.5	107.8	140.9	117.4	–3.6	–	**<0.001**
	N	%	N	%	N	%	χ^2	*df*	*p*
Age (years)							11.1	1	**0.001**
50–64	615	64.4	318	59.8	297	70.2			
65 and older	340	35.6	214	40.2	126	29.8			
Female	580	60.7	325	61.1	255	60.3	0.06	1	0.80
Psychiatric hospital	351	36.8	181	34.0	170	40.2	3.8	1	**0.049**
Inpatients	233	24.4	96	18.0	137	32.4	26.2	1	**<0.001**
Public hospital	687	71.9	363	68.2	324	76.6	8.1	1	**0.004**
Country/territory							71.7	9	**<0.001**
Income group							4.3	2	0.112
High income	465	48.7	243	45.7	222	52.5			
Upper middle income	353	37.0	208	39.1	145	34.3			
Lower middle income	137	14.3	81	15.2	56	13.2			
Major medical conditions	421	44.1	213	40.0	208	49.2	7.9	1	**0.005**
Use of antidepressants									
TCAs	99	10.4	57	10.7	42	9.9	0.1	1	0.69
Tetracyclics	27	2.8	14	2.6	13	3.1	0.1	1	0.68
SSRIs	593	62.1	338	63.5	255	60.3	1.0	1	0.30
SNRIs	155	16.2	90	16.9	65	15.4	0.4	1	0.51
NaSSAs	163	17.1	89	16.7	74	17.5	0.09	1	0.75
Other antidepressants	127	13.3	59	11.1	68	16.1	5.0	1	**0.02**
Use of FGAs	83	8.7	41	7.7	42	9.9	1.4	1	0.22
Use of SGAs	238	24.9	117	22.0	121	28.6	5.5		**0.019**
Use of MS	63	6.6	28	5.3	35	8.3	3.4		0.06
Principal psychiatric diagnosis							0.4	3	0.92
Mood disorders	671	70.3	374	70.3	297	70.2			
Anxiety disorders	130	13.6	72	13.5	58	13.7			
Schizophrenia	79	8.3	42	7.9	37	8.7			
Other diagnoses	75	7.9	44	8.3	31	7.3			

Bolded values: <0.05; AD = antidepressants; BZD = bendiazepines; TCA = tricyclic antidepressants; NaSSA = noradrenergic and specific serotonergic antidepressant; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin/norepinephrine reuptake inhibitor; IMI-eq = imipramine-equivalent; FGA = first-generation antipsychotic; SGA = second-generation antipsychotic; MS = mood stabilizer.

(OR: 1.002) is not clinically relevant in clinical practice.

There are several limitations to this study. First, due to the cross-sectional design, the causality between benzodiazepines and antidepressants co-prescription and variables, such as change of psychotropic medications, could not be examined. Second, the sample size was very small in some countries/territories, therefore, their associations with benzodiazepine prescription could not be examined by countries/territories. The whole sample size was also relatively small compared to the huge number of patient population in the ten Asian countries/territories, which constitutes a probable ascertainment bias. Third, the efficacy and side effects of the benzodiazepine-antidepressant combination were not measured. Fourth, relevant contributing factors, such as treatment costs and health insurance policy could not be examined. Fifth, due to logistic reasons, the presence of depressive and anxiety symptoms and insomnia were not assessed using standardized tools. Finally, only patients who received antidepressants on the day of the survey were included in the REAP-AD project. The sample in this study could not represent all patients attending medical treatment in the participating countries/territories.

In conclusion, nearly half of older adults treated with antidepressants in Asia were prescribed concurrent benzodiazepines. Considering the age-related risk of drug-induced adverse effects in

https://doi.org/10.1017/S1041610217002563

Table 3. Independent demographic and clinical correlates of the benzodiazepines and antidepressants combination

VARIABLES	*p* VALUE	ODDS RATIO	95% CI
AD dose, IMI-eq (mg/d)	**0.010**	1.002	1.0–1.003
65 years and older	**0.001**	0.591	0.4–0.8
Psychiatric hospital	0.74	0.940	0.6–1.3
Outpatients	**0.001**	0.544	0.3–0.7
Public hospitals	**0.003**	2.077	1.2–3.3
Use of SGAs	0.74	0.945	0.6–1.3
Major medical conditions	**0.03**	1.380	1.03–1.8
Use of other antidepressants	**0.016**	1.6	1.1–2.5
Country/territory			
China	**<0.001**	1	0
Indonesia	**0.007**	2.273	1.2–4.1
Hong Kong	0.45	1.321	0.6–2.7
Japan	**<0.001**	3.206	1.8–5.6
South Korea	0.86	1.058	0.5–2.0
Singapore	0.46	0.766	0.3–1.5
Taiwan	**<0.001**	5.837	3.1–10.9
India	0.92	0.968	0.4–1.9
Malaysia	0.18	1.551	0.8–2.9
Thailand	0.58	1.160	0.6–1.9

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

this population, the rationale of benzodiazepines and antidepressants co-prescription needs to be revisited.

Conflict of interest

All authors declare no conflicts of interest concerning this article.

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Acknowledgments

This study was supported by the Taipei City Hospital (10201-62-077), Taipei, Taiwan and the University of Macau (SRG2014-00019-FHS; MYRG2015-00230-FHS; MYRG2016-00005-FHS). The authors thank all clinicians involved in the REAP-AD project.

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