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Clinical Characteristics and Psychotropic Prescribing Patterns Associated with impaired Concentration in Asians with Depressive Disorders: The REAP-AD Study

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The Research on Asian Psychotropic Prescription Patterns for Antidepressants (REAP-AD) study aimed to survey and review antidepressant prescribing patterns in different clinical settings in Asian countries/areas. The REAP-AD study collected comprehensive data for psychiatric patients prescribed antidepressants in 10 Asian countries/areas during the period from March to June 2013. Depressive disorders have been an important issue closely associated with ill-health and disability in the realm of mental health. Impaired concentration was found to be a consistent symptom in depressive disorders regardless of clinical course, and a predictor of poor treatment outcome. In this work we aimed to identify clinical characteristics independently associated with impaired concentration in patients with depressive disorders, using data from the REAP-AD study. A total of 336 depressive disorder patients with impaired concentration and 786 depressive disorder patients without impaired concentration were recruited from 40 centers in 10 Asian countries/areas. A binary logistic regression model was fitted to identify the independent correlates of impaired concentration in patients with depressive disorders. After adjusting the effects of covariates, the binary logistic model showed that impaired concentration was independently associated with higher rates of loss of interest ($P < 0.0001$), fatigue ($P < 0.0001$), low self-confidence ($P < 0.0001$) and appetite disturbance ($P < 0.0001$) and with a lower rate of adjunctive antipsychotic prescription ($P = 0.007$). Our findings suggest that impaired concentration and its associated depressive symptom profiles constitute a unitary depressive symptom cluster that is also an intervening variable for poor social function.

Keywords: Asian; depressive disorders; impaired concentration; social function; symptom cluster
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Introduction

Depressive disorders have been closely associated with ill-health and disability and often defined in a socio-cultural context (Joensuu et al. 2016; Kato et al. 2016). There is evidence that cognitive dysfunction is related to poor social functioning in patients with depressive disorders (Kim et al. 2016; Woo et al. 2016). It has been reported that cognitive dysfunction is already present at an early stage of depressive disorders and is maintained even in remission (Woo et al. 2016). Impaired concentration or indecisiveness has been proposed as a predictor of poor

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antidepressant treatment outcome (Ulher et al. 2012). Regarding psychiatric taxonomy, impaired concentration has been a symptom of depression, although it is also a criterion for other disorders (Zimmerman et al. 2006). It was also one of the specific depressive symptoms found for ruling in major depressive disorder (MDD) among 1,523 psychiatric outpatients (Mitchell et al. 2009) and as a predictive factor for late-onset depression in 664 healthy elderly individuals (Hein et al. 2003). Moreover, the prefrontal cortex and hippocampus are sites of structural abnormalities associated with the impaired concentration in patients with depressive disorders (Trivedi and Greer 2014), and the cognitive dysfunction in patients with depressive disorders is linked to functional cerebral asymmetries involving a hyperactive right-hemisphere coupled to a hypoactive left-hemisphere (Hecht 2010).

Despite the substantial clinical significance of impaired concentration, its overall clinical correlates have been little studied in large cohorts of patients with depressive disorders. Hence, using data from the Research on Asian Psychotropic Prescription Patterns for Antidepressants (REAP-AD) study (Park et al. 2015), we aimed to examine depressive symptom profiles, psychotropic prescription patterns and other clinical characteristics related to impaired concentration in a large sample of patients with depressive disorders from 40 survey centers in 10 Asian countries/areas, namely China, Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Singapore, Taiwan and Thailand.

Materials and Methods

Study overview and subjects

A total of 2,470 patients who had used antidepressants were recruited from psychiatric settings in 40 survey centers in 10 Asian countries/areas from March to June 2013 in the REAP-AD study (Park et al. 2015). The objects of the REAP-AP study were to survey and review antidepressant prescribing patterns in different clinical settings in Asian countries/areas. The institutional review boards of Taipei City Hospital, Taipei, Taiwan and the other hospitals participating in survey approved the study protocol. Patients who had used antidepressants in a medical or surgical setting were excluded. The consistency of data collection and diagnosis among the centers were established by consensus conference before the initiation of the REAP-AD study.

For our study, a sub-sample of the subjects aged 18 to 80 years old, with a diagnosis of depressive episode (F32) or recurrent depressive episode (F33) according to the International Classification of Diseases and Related Health Problems, 10th revision (ICD-10) (World Health Organization 1992) was selected. The diagnosis of depressive episode (F32) or recurrent depressive episode (F33) was made by survey center psychiatrists. Exclusion criteria were (i) co-diagnosis as organic mental disorder, schizophrenia spectrum disorder, bipolar disorder, or intellectual disability and (ii) neurological co-diagnosis as seizure disorder or other neurological disease. Finally, 1,122 patients with depressive disorders were included in the study.

Baseline characteristics

The 10 Asian countries/areas were transformed into dummy variables based on geographic region (United Nations classification) and income level (World Bank income designation). China, Hong Kong, Japan, Korea, and Taiwan were grouped as East Asia. India, Indonesia, Malaysia, Singapore, and Thailand as South/South-East Asia (Park et al. 2015). Hong Kong, Japan, Korea, Singapore and Taiwan were grouped as high-income countries/areas, and China, India, Indonesia, Malaysia and Thailand as upper- and lower-middle income. In addition, treatment setting (public or private) and hospital setting (psychiatric, general, university-affiliated psychiatric or university-affiliated general) were defined.

Impaired concentration and other depressive symptom profiles

The presence/absence of impaired concentration and other depressive symptom profiles (persistent sadness, loss of interest, fatigue, insomnia, low self-confidence, poor appetite, suicidal thoughts/acts, agitation/retardation and guilt/self-blame) was assessed in accordance with the 10 depressive symptoms listed in the National Institute for Health and Clinical Excellence guidelines for depressive disorders. The degree of depression was defined by the number of depressive symptom profiles as follows: 0-3 for subthreshold depression, 4 for mild depression, 5-6 for moderate depression and 7-10 for severe depression (National Institute for Health and Clinical Excellence 2009). The severity of each of the depressive symptom profiles was not evaluated. However, it has been reported that the clinical significance criterion for major depression does not reduce false positives in the National Comorbidity Survey Replication (Wakefield et al. 2010). Furthermore, it was found that, in 71 patients with major depression, the specific depressive symptom patterns were consistently presented over the clinical course (Minor et al. 2005). Hence, the accuracy of identification of the presence/absence of depressive symptom profiles (for the survey period) is ensured.

Also, psychiatric co-morbidity including psychoactive substance abuse (F1) and neurotic, stress-related, and somatoform disorders (F4) were evaluated as well as physical co-morbidity including chronic obstructive pulmonary disease, rheumatic disease, peptic ulcer disease, diabetes mellitus, renal disease, liver disease, malignancy and AIDS/HIV.

Psychotropic prescription patterns

The newer class of antidepressants comprised selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), norepinephrine and dopamine reuptake inhibitors (NDRIs), mixed noradrenergic-serotonergic antidepressants, selective norepinephrine reuptake inhibitors and serotonin receptor antagonists as defined by the Anatomical Therapeutic Chemical Classification index of the World Health Organization Collaborating Center for Drug Statistics Methodology (Sim et al. 2007); the older class was defined as tricyclic antidepressants and monoamine oxidase inhibitors. Antipsychotics were divided into first- and second-generations based on the definition of previous study (Park et al. 2014).

Statistical analysis

Baseline characteristics, depressive symptom profiles, psychotropic prescription patterns and other clinical variables were compared in subjects with and without impaired concentration using independent t-tests for continuous variables and χ^2 tests for discrete variables. In addition, the potential effects of confounding factors were controlled using logistic regression analyses for discrete vari-

ables. A binary logistic model was fitted to identify the independent clinical correlates of impaired concentration with adjustment for the effects of confounding factors. We used a goodness-of-fit test to select and validate the final model. Statistical significance was set at $P < 0.01$ (two-tailed) for all tests to reduce the familywise error rate in multiple comparisons. IBM SPSS for Windows, Version 21.0 (IBM Corp. Released 2012. Armonk, NY: IBM Corp.) was used for all statistical analyses.

Results

Baseline characteristics of depressive disorder patients with and without impaired concentration

As shown in Table 1, 29.9% (n = 336) of the total patients had impaired concentration. These patients included a significantly higher proportion of East Asians ($\chi^2 = 32.308$, $P < 0.0001$), a lower proportion of high income level countries/areas ($\chi^2 = 26.662$, $P < 0.0001$), and were more often located in public treatment settings ($\chi^2 = 37.856$, $P < 0.0001$) and enrolled as outpatients ($\chi^2 = 12.740$, $P < 0.0001$) than those without impaired concentration. However, there were no significant differences in gender ($\chi^2 = 0.186$, $P = 0.666$) or diagnosis ($\chi^2 = 0.450$, $P = 0.502$) between the two groups. Hence, to mitigate the potential influences of confounding variables, the depressive symptom profiles, clinical characteristics and psychotropic prescription patterns in those with and without impaired concentration were compared with adjustment for the effects of age, geographic classification, income level classification, treatment setting and outpatient enrollment.

Depressive symptom profiles and clinical characteristics in patients with and without impaired concentration

As shown in Table 2, patients with impaired concentration had significantly higher rates of persistent sadness (adjusted odds ratio [aOR] = 2.099, $P < 0.0001$), loss of interest (aOR = 3.044, $P < 0.0001$), fatigue (aOR = 3.077, $P < 0.0001$), sleep disturbance (aOR = 1.628, $P = 0.001$), low self-confidence (aOR = 2.825, $P < 0.0001$), appetite disturbance (aOR = 2.592, $P < 0.0001$), suicidal thoughts/acts (aOR = 1.522, $P = 0.010$), psychomotor disturbance (aOR = 1.479, $P = 0.015$) and guilt/self-blame (aOR = 1.997, $P < 0.0001$) than those without impaired concentration. Using multinominal logistic regression analysis and defining subthreshold depression as the reference category, those with impaired concentration were characterized by a significantly lower frequency of mild depression (aOR = 0.225, $P < 0.0001$) and higher frequencies of moderate (aOR = 0.095, $P < 0.0001$) and severe (aOR = 0.028, $P < 0.0001$) depression than those without impaired concentration.

In addition, they had significantly higher rates of co-diagnosis of neurotic, stress-related, and somatoform disorders (F4) (aOR = 2.060, $P = 0.004$). There were no significant differences in co-morbid substance abuse (F1) (aOR = 0.882, $P = 0.805$) and physical disease (aOR = 0.869, $P = 0.376$) between the two groups.

Psychotropic prescription patterns in those with and without impaired concentration

As shown in Table 2, patients with impaired concentration received significantly fewer antipsychotic prescriptions (aOR = 0.578, $P < 0.0001$) than those without

Table 1. Baseline characteristics of Asian depressive disorder patients with and without impaired concentration.

	Total sample (n = 1,122)	Impaired concentration		Statistical coefficient	Unadjusted *P*-value	Adjusted *P*-value†
		Present (n = 336)	Absent (n = 786)			
Age, mean (SD) years	48.1 (15.6)	45.7 (15.7)	49.1 (15.5)	t = -3.282	0.001	-
Female, n (%)	672 (59.8)	198 (58.9)	474 (60.3)	$\chi^2 = 0.186$	0.666	0.494
Country/Area				$\chi^2 = 110.764$	< 0.0001	-
China, n (%)	234 (20.9)	65 (19.3)	169 (21.5)			
Hong Kong, n (%)	37 (3.3)	7 (2.1)	30 (3.8)			
India, n (%)	126 (11.2)	69 (20.5)	57 (7.3)			
Indonesia, n (%)	98 (8.7)	14 (4.2)	84 (10.7)			
Japan, n (%)	133 (11.9)	24 (7.1)	109 (13.9)			
Korea, n (%)	168 (15.0)	40 (11.9)	128 (16.3)			
Malaysia, n (%)	104 (9.3)	61 (18.2)	43 (5.5)			
Singapore, n (%)	37 (3.3)	11 (3.3)	26 (3.3)			
Taiwan, n (%)	47 (4.2)	6 (1.8)	41 (5.2)			
Thailand, n (%)	138 (12.3)	39 (11.6)	99 (12.6)			
East Asian,‡ n (%)	619 (55.2)	142 (42.3)	477 (60.7)	$\chi^2 = 32.308$	< 0.0001	-
High income level country/region,§ n (%)	422 (37.5)	88 (20.9)	334 (42.5)	$\chi^2 = 26.662$	< 0.0001	-
Treatment setting				$\chi^2 = 37.856$	< 0.0001	-
Public, n (%)	842 (75.0)	293 (87.2)	549 (69.8)			
Private, n (%)	280 (25.0)	43 (12.8)	237 (30.2)			
Hospital setting				$\chi^2 = 37.192$	< 0.0001	-
Psychiatric, n (%)	419 (37.3)	127 (37.8)	292 (37.2)			
General, n (%)	119 (10.6)	63 (18.8)	56 (7.1)			
University-affiliated psychiatric, n (%)	77 (6.9)	17 (5.1)	60 (7.6)			
University-affiliated general, n (%)	507 (45.2)	129 (38.4)	378 (48.1)			
Diagnosis				$\chi^2 = 0.450$	0.502	0.331
Depressive episode (F32), n (%)	843 (75.1)	248 (73.8)	595 (75.7)			
Recurrent depressive episode (F33), n (%)	279 (24.9)	88 (26.2)	191 (24.3)			
Outpatient enrollment, n (%)	806 (71.8)	266 (79.2)	540 (68.7)	$\chi^2 = 12.740$	< 0.0001	-

†Adjusted for the effects of age, geographic classification, income level classification, treatment setting, and outpatient enrollment.

‡Defined by United Nations classification, including China, Hong Kong, Japan, Korea and Taiwan.

§Defined by World Bank designation, including Hong Kong, Japan, Korea, Singapore and Taiwan.

Table 2. Depressive symptom profiles and psychotropic prescription patterns of depressive disorder patients with and without impaired concentration in Asia.

	Total sample (n = 1,122)	Impaired concentration		Statistical coefficient	Unadjusted *P*-value	Adjusted *P*-value†
		Present (n = 336)	Absent (n = 786)			
Depressive symptom profile						
Persistent sadness, n (%)	822 (73.3)	278 (82.7)	544 (69.2)	χ^2 = 21.987	< 0.0001	< 0.0001
Loss of interest, n (%)	600 (53.5)	241 (71.7)	359 (45.7)	χ^2 = 64.211	< 0.0001	< 0.0001
Fatigue, n (%)	514 (45.8)	218 (64.9)	296 (37.7)	χ^2 = 70.263	< 0.0001	< 0.0001
Insomnia/hypersomnia, n (%)	725 (64.6)	247 (73.5)	478 (60.8)	χ^2 = 16.599	< 0.0001	0.001
Low self-confidence, n (%)	263 (23.4)	124 (36.9)	139 (17.7)	χ^2 = 48.454	< 0.0001	< 0.0001
Decreased/increased appetite, n (%)	370 (33.0)	159 (47.3)	211 (26.8)	χ^2 = 44.653	< 0.0001	< 0.0001
Suicidal thoughts/acts, n (%)	259 (23.1)	99 (29.5)	160 (20.4)	χ^2 = 10.998	0.001	< 0.0001
Agitation/retardation, n (%)	257 (22.9)	85 (25.3)	172 (21.9)	χ^2 = 1.552	0.213	0.010
Guilt/self-blame, n (%)	179 (16.0)	74 (22.0)	105 (13.4)	χ^2 = 13.180	< 0.0001	< 0.0001
Degree of depression				χ^2 = 287.524	< 0.0001	
Subthreshold depression, n (%)	504 (44.9)	46 (13.7)	458 (58.3)			-‡
Mild depression, n (%)	197 (17.6)	54 (16.1)	143 (18.2)			< 0.0001‡
Moderate depression, n (%)	291 (25.9)	141 (42.0)	150 (19.1)			< 0.0001‡
Severe depression, n (%)	130 (25.9)	95 (28.3)	35 (4.5)			< 0.0001‡
Comorbid psychiatric disorder						
Substance abuse,§ n (%)	20 (1.8)	6 (1.8)	14 (1.8)	χ^2 < 0.0001	0.996	0.805
Anxiety and somatoform disorders,¶ n (%)	85 (7.6)	35 (10.4)	50 (6.4)	χ^2 = 5.529	0.019	0.004
Comorbid physical disease, n (%)	327 (29.1)	84 (25.0)	243 (30.9)	χ^2 = 3.989	0.046	0.376
Psychotrophic prescription pattern						
Newer antidepressant,†† n (%)	849 (75.7)	274 (81.5)	575 (73.2)	χ^2 = 9.004	0.003	0.136
Combination therapy, n (%)	283 (25.2)	79 (23.5)	204 (26.0)	χ^2 = 0.744	0.368	0.507
Augmentation therapy, n (%)	756 (67.4)	214 (63.7)	542 (69.0)	χ^2 = 2.970	0.085	0.049
Antipsychotic, n (%)	368 (32.8)	81 (24.1)	287 (36.5)	χ^2 = 16.438	< 0.0001	< 0.0001
Mood stabilizer, n (%)	229 (20.4)	72 (21.4)	157 (20.0)	χ^2 = 0.306	0.580	0.746
Anxiolytic, n (%)	333 (29.7)	100 (29.8)	233 (29.6)	χ^2 = 0.002	0.968	0.948
Hypnotic, n (%)	146 (13.0)	30 (8.9)	116 (14.8)	χ^2 = 7.067	0.008	0.177

†Adjusted for the effects of age, geographic classification, income level classification, treatment setting, and outpatient enrollment.

‡Multinomial logistic regression analysis (subthreshold depression defined as the reference category).

§Mental and behavioral disorders due to psychoactive substance abuse (F1).

¶Neurotic, stress-related and somatoform disorders (F4).

††Newer antidepressant includes the selective serotonin reuptake inhibitor, serotonin and norepinephrine reuptake inhibitor, mixed noradrenergic-serotonergic antidepressant, selective noradrenaline reuptake inhibitor and agents with serotonin receptor-antagonist and weak monoamine transport effects.

Table 3. Binary logistic regression model to identify the distinctive clinical correlates of impaired concentration in 1,122 patients with depressive disorders.

	Adjusted odds ratio†	95% confidence interval	Adjusted P-value†
Loss of interest	2.017	1.480 – 2.747	< 0.0001
Fatigue	2.040	1.509 – 2.760	< 0.0001
Low self-confidence	1.945	1.402 – 2.700	< 0.0001
Decreased/increased appetite	1.805	1.332 – 2.446	< 0.0001
Antipsychotic	0.640	0.463 – 0.884	0.007

†Adjusted for the effects of age, geographic classification, income level classification, treatment setting, and outpatient enrollment.

impaired concentration. However, there were no significant differences between the two groups in frequency of treatment with a combination strategy (aOR = 0.899, $P = 0.507$), augmentation strategy (aOR = 0.748, $P = 0.049$) or a newer antidepressant (aOR = 0.777, $P = 0.136$), mood stabilizer (aOR = 1.056, $P = 0.746$), anxiolytic (aOR = 1.028, $P = 0.948$) or hypnotic (aOR = 0.723, $P = 0.177$).

A binary logistic regression model to identify the independent clinical correlates of impaired concentration

In fitting a binary logistic model, the initial covariates were defined as persistent sadness, loss of interest, fatigue, insomnia/hypersomnia, low self-confidence, appetite/weight disturbance, suicidal thoughts/acts, psychomotor disturbance, guilt/self-blame, co-morbid neurotic, stress-related and somatoform disorders (F4) and adjunctive use of an antipsychotic, and adjustment was made for the potential effects of age, geographical classification, income level classification, treatment setting and outpatient enrollment. The model was validated with the Hosmer-Lemeshow goodness-of-fit test ($\chi^2 = 6.487$, df = 8, $P = 0.593$) and explained 25.1% (Nagelkerke R^2) of the variability of impaired concentration. To avoid multicollinearity, forward selection was performed. As shown in Table 3, the final model showed that impaired concentration was independently associated with loss of interest ($P < 0.0001$; aOR = 2.017, 95% confidence interval [CI] = 1.480-2.747), fatigue ($P < 0.0001$; aOR = 2.040, 95% CI = 1.509-2.760), low self-confidence ($P < 0.0001$; aOR = 1.945, 95% CI = 1.402-2.700) and appetite/weight disturbance ($P < 0.0001$; aOR = 1.805, 95% CI = 1.332-2.446), and was negatively associated with receipt of an adjunctive antipsychotic ($P = 0.007$; aOR = 0.640, 95% CI = 0.463-0.884).

Discussion

Our analysis has shown that patients with impaired concentration have higher rates of other depressive symptom profiles and of neurotic, stress-related, and somatoform

disorders (F4) than those without impaired concentration, and are less frequently prescribed antipsychotics. Also our binary logistic model indicates that loss of interest, fatigue, low self-confidence and appetite/weight disturbance and a lower likelihood of being prescribed adjunctive antipsychotics are independent clinical correlates of impaired concentration.

Indecisiveness and the other interest-activity depressive symptoms (including low interest, reduced activity, and lack of enjoyment) were proposed as predictors of poor treatment outcomes to escitalopram and nortriptyline in 811 adults with moderate to severe depression in the study Genome-based Therapeutic Drugs for Depression (GENDEP) (Ulher et al. 2009). Similar findings have been reported in 3,637 MDD adults treated with citalopram in Sequenced Treatment Alternatives to Relieve Depression (STAR*D) (Ulher et al. 2012). In addition, indecisiveness, guilt, ideas of reference, depressed mood, insomnia and other symptom dimension were proposed as predictors of depression that is resistant to escitalopram and nortriptyline in 793 adults with MDD (Iniesta et al. 2016). Hence, we suggest that impaired concentration and its depressive symptom correlates can be regarded as a unitary depressive symptom cluster that is associated with poor treatment response as well as being an intervening variable for poor psychosocial functioning. On the other hand, in a comparison of depressive symptoms in 156 depressed suicides and 81 MDD controls, the presence of impaired concentration or indecisiveness and fatigue, and of weight or appetite gain and hypersomnia, were associated with decreased risk of suicide (McGirr et al. 2007). Thus, impaired concentration or indecisiveness and other depressive symptom correlates may be regarded not only as intervening variables for poor psychosocial function but also as protective factors for suicidal risk.

Furthermore, significant associations were recently reported between sub-symptoms of depression and plasma metabolites in 26 medication-free patients with depressive mood. Loss of interest was positively associated with 2-oxobutyrate, acetylcarnitine, carbamoylphosphate, and 3-methylhistidine concentrations, and negatively associated with proline concentration (Setoyama et al. 2016). The unitary depressive symptom cluster containing impaired concentration, loss of interest, fatigue, low self-confidence and appetite/weight disturbance derived from our findings may be associated with the biological underpinnings of loss of interest reported by Setoyama et al. (2016).

A survey of 4,018 MDD patients in the USA and Europe has shown that psychotic symptoms, psychomotor agitation, hostility, irritability, impulsivity and bursts of anger are key symptoms leading to prescription of adjunctive antipsychotics (McIntyre and Weiller 2015). In addition, another survey of 3,655 MDD patients in China from 2002 to 2012 showed that lower treatment satisfaction on the part of patient and family is associated with prescription of adjunctive antipsychotics (Wang et al. 2015). Hence, we speculate that the lack of association with psychotic symptoms, psychomotor agitation, hostility, irritability, impulsivity, bursts of anger and other factors may partly explain the association between impaired concentration and the low level of prescription of adjunctive antipsychotics. Moreover, ethno-cultural variation can contribute to differences n prescription of antipsychotic in Asian patients with depressive disorders (Han and Pae 2013). However, the association between antipsychotic prescription and the depressive symptom cluster that includes impaired concentration cannot be explained in a straightforward manner and needs further investigation.

Our study has several limitations. First, the REAP-AD study was designed as an epidemiological study. Hence, extrapolation and/or generalization of our findings must be limited. Second, the REAP-AD study was not a longitudinal follow-up study but a cross-sectional study. Thirdly, impaired concentration can be influenced by medication effects, fatigability, other physical illnesses and others. However, the potential covariates were limitedly controlled in our study. Fourthly, depressive severity was measured not the assessment scale covering depressive symptoms but the number of depressive symptoms. Finally, impaired concentration was not defined by a specific scale covering the cognitive domains in depressive disorders. Despite these limitations, our study has the virtue of showing that impaired concentration, loss of interest, fatigue, low self-confidence and weight/appetite disturbance may be regarded as a unitary depressive symptom cluster and may play an intervening role in psychosocial dysfunction among the patients with depressive disorders in a large sample from 10 Asian countries/areas. However, since the association between impaired concentration and adjunctive antipsychotic prescription cannot be easily explained, further study is needed.

Acknowledgments

All members of the REAP-AD study are listed in the REAP homepage (http://reap.asia/).

Conflict of Interest

The authors declare no conflict of interest.

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