

# Newer antidepressant drug use in East Asian psychiatric treatment settings: REAP (Research on East Asia Psychotropic Prescriptions) Study

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## Aims

Antidepressant use in East Asia is poorly documented. We compared patients given newer and older antidepressants to test the hypothesis, suggested in the literature, that use of newer antidepressants is associated with treatment settings rather than specific diagnostic categories.

## Methods

We compared rates of use of older (pre 1990) vs. newer antidepressants among 1898 patients identified as antidepressant treated at 21 centres in five East Asian countries (China, Japan, Korea, Singapore, Taiwan) in 2003. Demographics, treatment setting and clinical factors associated with preferential use of newer drugs were tested in univariate and multivariate analyses.

## Results

Newer antidepressants were included in the treatment regimens of 67.5% ( $N = 1282/1898$ ) of study subjects. Prescription for newer antidepressants was significantly associated with younger age ( $z = -4.55$ , d.f. = 1888,  $P < 0.001$ ), hospitalization [odds ratio (OR) 1.32, 95% confidence interval (CI) 1.07, 1.64,  $P < 0.01$ ] and treatment within psychiatric hospitals (OR 1.59, 95% CI 1.27, 2.00,  $P < 0.001$ ). On multivariate analyses, treatment with newer antidepressants was independently associated with younger age ( $P < 0.001$ ), country ( $P < 0.001$ ) and treatment within private hospitals ( $P < 0.001$ ), but not with sex or diagnosis of affective or anxiety disorders (all  $P > 0.1$ ).

## Conclusion

Demographic factors and treatment settings appear to influence antidepressant choice more than clinical factors such as diagnosis.

## Introduction

Some population-based studies have found increased use of antidepressants in some countries or regions over the years [1, 2], particularly in primary-care settings [3] and following the introduction of modern antidepressants in the 1990s [4]. Increased use of modern antidepressants, including selective serotonin reuptake inhibitors (SSRIs), has been associated specifically with younger patient age [5], ethnicity [6], type of clinical setting, including the presence of counselling within surgery consultations [7], availability of treatment guidelines [8] and pharmaceutical promotional activity [9], whereas association of modern antidepressant use with particular psychiatric diagnoses has been inconsistent [10]. In addition, antidepressant selection within and between clinical settings has been highly variable [7, 11]. Overall, such findings indicate considerable clinical and sociological complexity in the selection of specific types of antidepressants, and that the choice may not necessarily be based on clinical indications.

There is increasing awareness of the potential value of documenting sometimes major disparities between clinical practice and recommended treatment guidelines based on research and expert opinion [12]. Antidepressant selection may affect the effectiveness of clinical treatment and patient outcome [13], but most reported research evidence suggests only minor differences in efficacy among dissimilar antidepressants, at least in major depressive disorder, leaving other factors to influence drug selection [14]. We perceive a need to clarify practice patterns with modern and older drugs in areas that have been little studied, particularly in East Asia.

Accordingly, in this study we examined differences between East Asian patients given newer antidepressants introduced after 1990 *vs.* older agents, in relation to demographic and clinical factors, and particular treatment settings. Based on the literature just cited, we hypothesized that preferential use of newer antidepressants is associated with treatment settings rather than specific diagnostic categories.

## Methods

### *Study sample and design*

We conducted an international, cross-sectional, case-record and drug-centred study using a standardized data collection procedure within a 1-month period in November 2003. The study sample involved 1898 consecutive patients treated with antidepressants and seen at 21 psychiatric centres in five East Asian countries (The People's Republic of China, Japan, Republic of Korea, Singapore and Taiwan), with no specific exclusion criteria applied in terms of age or diagnosis. We collected

data from representative psychiatric units serving defined populations within geographical catchment areas and which were affiliated with the Institute of Mental Health: Beijing Medical University (Beijing, China); the Department of Psychiatry, Kobe University School of Medicine (Kobe, Japan); the Seoul National Hospital (Seoul, Korea); the Institute of Mental Health (Singapore); and Department of Psychiatry, Kaoshiung University (Kaoshiung County, Taiwan). The study was approved by research and ethics committees of each of the collaborating sites.

Two consensus meetings were held before the study to discuss methodological details, including uniformity of case selection, data collection, arrangement and data-entry procedures to assure comparability across sites and countries. Socio-demographic and clinical information collected from medical records and held confidential included age, sex, ICD-10 diagnosis, treatment setting (inpatient *vs.* outpatient, public *vs.* private psychiatric hospital or clinic, psychiatric hospital *vs.* psychiatric units in general hospitals) and the type and dose of antidepressants prescribed.

Older antidepressants, developed prior to 1990, included tricyclic antidepressants (TCAs: amitriptyline, clomipramine, doxepin, imipramine, nortriptyline); tetracyclics (maprotiline, mianserin); irreversible monoamine oxidase (MAO) inhibitors (phenelzine, tranylcypromine) as well as a reversible MAO inhibitor (moclobemide). Newer antidepressants included SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline); a serotonin and noradrenaline reuptake inhibitor (venlafaxine); a mixed noradrenergic-serotonergic antidepressant (mirtazapine); a selective noradrenaline reuptake inhibitor (NRI; reboxetine); and agents with serotonin receptor-antagonist and weak monoamine transport effects (trazodone, nefazodone).

Diagnoses were grouped into the major, standard, ICD-10 categories: organic mental disorders (F1); primary psychotic disorders (F2: schizophrenia, schizotypal and delusional disorders); mood disorders (F3); neurotic, stress-related and somatoform disorders (anxiety-related conditions, F4); behavioural syndromes associated with physiological disturbance and physical factors (F5); disorders of adult personality and behaviour (F6); mental retardation (F7); disorders of psychological development (F8); behavioural and emotional disorders with onset in childhood and adolescence (F9).

### *Statistical analysis*

Averages are reported as means  $\pm$  standard deviation (SD) and relative risks are reported as odds ratios (OR) with 95% confidence intervals (95% CI). Normality of

distributions of continuous measures was checked with the Kolmogorov–Smirnov one-sample test. Differences between groups were tested by Student's *t*-test and one-way ANOVA for normally distributed data, nonparametric Mann–Whitney *U* and Kruskal–Wallis tests for non-normally distributed continuous data, and by contingency tables ( $\chi^2$ ) for categorical variables. Sociodemographic and clinical variables were included in the univariate analyses and significant variables in the initial analyses were then considered for multivariate analyses. Multiple logistic regression was carried out to adjust for relevant covariates and to determine predictors (age, gender, country, different treatment settings, ICD-10 diagnoses) of selecting newer antidepressants. Statistical significance was set at two-tailed  $P < 0.05$ . All analyses were performed using the Statistical Package for Social Sciences (SPSS®), version 11.0 (SPSS Inc, Chicago, IL, USA).

## Results

### Demographic and clinical characteristics

Medical records of 1898 adult subjects were examined for demographic and clinical characteristics of the sample (Table 1). Overall, age averaged  $46.7 \pm 16.9$  years, 59.1% were women, 68.9% were treated as outpatients and 73.3% of those hospitalized were admitted to a

psychiatric unit within a general hospital rather than to a psychiatric specialty hospital. Treatment settings varied considerably among countries sampled (Table 1). Antidepressant treatment was associated with either group F3 (mood disorders) or F4 (anxiety-associated disorders or neuroses) ICD-10 diagnoses in 78.8% of all subjects.

Newer antidepressants were included in the treatment regimens of 67.5% of the 1898 patients sampled. Preferential use of modern agents ranked: Taiwan  $\geq$  Singapore  $>$  China  $\geq$  Korea  $>$  Japan (Table 1). With Japan as reference, the use of newer antidepressants was greatest in Taiwan (OR 1.78, 95% CI 1.63, 1.95), followed by Singapore (OR 1.76, CI 1.56, 1.99), China (OR 1.44, CI 1.31, 1.59) and Korea (OR 1.42, CI 1.27, 1.59; all  $P < 0.001$ ).

The most commonly prescribed older antidepressants in specific countries were: China (amitriptyline, clomipramine, maprotiline); Japan (amitriptyline, clomipramine, mianserin); Korea (amitriptyline, imipramine); Singapore (clomipramine, imipramine); Taiwan (clomipramine, imipramine, moclobemide), making amitriptyline, clomipramine and imipramine the most employed older drugs across countries. The most commonly prescribed modern antidepressants, by country, were: China (fluoxetine, paroxetine, sertraline); Japan (fluvoxamine, paroxetine, trazodone); Korea (citalo-

**Table 1**

Characteristics of 1898 East Asian patients treated with antidepressants, by country

	Japan <i>n</i> = 609	Korea <i>n</i> = 293	China <i>n</i> = 536	Singapore <i>n</i> = 73	Taiwan <i>n</i> = 387	<i>P</i> -value
Age, years						
Mean	48.9	48.6	43.5	42.4	47.2	<0.001*
SD	17.1	15.9	18.3	12.3	15.4	
Gender						
Male (%)	36.5	37.5	43.2	42.5	47.0	0.009†
Female (%)	63.5	62.5	56.8	57.5	53.0	0.009†
Treatment settings						
Outpatient (%)	81.1	90.1	51.7	100.0	51.7	<0.001†
Inpatient (%)	18.9	9.9	48.3	0	48.3	<0.001†
Public hospital (%)	27.6	3.8	100.0	100.0	25.8	<0.001†
Private hospital (%)	72.4	96.2	0	0	74.2	<0.001†
Psychiatric hospital (%)	15.6	3.8	23.7	100.0	51.7	<0.001†
General hospital (%)	84.4	96.2	76.3	0	48.3	<0.001†
Diagnosis						
ICD-10 F3 (%)	63.4	80.2	56.2	28.8	58.7	<0.001†
ICD-10 F4 (%)	21.0	13.0	22.8	17.8	6.2	<0.001†
Newer antidepressants (%)	48.9	69.6	70.7	86.3	87.3	<0.001†

Columns in ascending rank order of usage of modern antidepressants. \**P*-values derived from Kruskal–Wallis test. †*P*-values derived from  $\chi^2$  test.

**Table 2**

Overall prescription numbers of antidepressants by class

	Japan <i>N</i> (%)	Korea <i>N</i> (%)	China <i>N</i> (%)	Singapore <i>N</i> (%)	Taiwan <i>N</i> (%)
Newer antidepressants	298 (48.9)	204 (69.6)	379 (70.7)	63 (86.3)	338 (87.3)
(1) SSRI	227 (37.2)	143 (48.8)	309 (57.6)	60 (82.2)	136 (35.2)
(2) SNRI	–	26 (8.9)	15 (2.8)	–	59 (15.2)
(3) NASSA	–	19 (6.5)	32 (6.0)	3 (4.1)	40 (10.3)
(4) SARI	71 (11.7)	16 (5.4)	23 (4.3)	–	103 (26.6)
Older antidepressants	311 (51.1)	89 (30.4)	157 (29.3)	10 (13.7)	49 (12.7)
(5) TCA	196 (32.2)	89 (30.4)	92 (17.2)	9 (12.3)	39 (10.1)
(6) Tetracyclics	115 (18.9)	–	65 (12.1)	–	3 (0.8)
(7) RIMA	–	–	–	1 (1.4)	7 (1.8)

SSRI, Selective serotonin reuptake inhibitor; SNRI, serotonin and noradrenaline reuptake inhibitor; NASSA, noradrenergic and specific serotonergic agent; SARI, serotonin antagonist reuptake inhibitor; TCA, tricyclic antidepressant; RIMA, reversible inhibitor of monoamine oxidase.

**Table 3**

Characteristics of East Asian patients given either older or newer antidepressants

	Older ( <i>n</i> = 616)	Newer ( <i>n</i> = 1282)	Test statistics <i>z</i> or OR (95% CI)	<i>P</i> -value
Age (mean ± SD, years)	49.3 ± 16.4	45.5 ± 17.0	<i>z</i> = -4.55	<0.001
Females ( <i>N</i> ,%)	364 (59.3)	755 (59.0)	1.00	>0.05
Treatment settings ( <i>N</i> ,%)*				
(a) Inpatients	167 (27.2)	423 (33.0)	1.32 (1.07, 1.64)	0.009
(b) Public units	288 (46.8)	600 (46.8)	1.00	>0.05
(c) General hospital	488 (79.2)	904 (70.5)	0.63 (0.50, 0.79)	<0.001
Diagnosis ( <i>N</i> ,%)				
ICD-10 (F3)	413 (67.0)	757 (59.0)	0.71 (0.58, 0.87)	<0.001
ICD-10 (F4)	105 (17.0)	220 (17.2)	1.00	>0.05
ICD-10 (Other)	98 (15.9)	305 (23.8)	1.65 (1.28, 2.12)	<0.001

\*Treatment setting comparisons involve 2 × 2 contrasts for drug type and: (a) inpatients vs. outpatients; (b) public vs. private settings; (c) general vs. psychiatric hospital sites for inpatients; unstated are the proportion of subjects in each contrasting setting (in each category, the difference between the stated proportion and 100%).

pram, paroxetine, sertraline); Singapore (fluoxetine, fluvoxamine, mirtazapine); and Taiwan (paroxetine, trazodone, venlafaxine), indicating that various SSRIs were, by far, the most popular modern drugs in 2003. Overall prescription numbers of separate antidepressants by class and country are shown in Table 2.

#### Correlates of antidepressant use

Patients given newer antidepressants were several years younger but included the same proportion of women as

were given older agents (Table 3). Patients given newer antidepressants were also more likely to be treated in a psychiatric institution when hospitalized, somewhat less likely to be diagnosed with a mood disorder, and more likely to have a disorder other than a neurotic or anxiety-related condition (Table 3).

Using multivariate logistic regression modelling with antidepressant type (newer/older) as the dependent outcome variable and adjusting for covariates (age, sex, country, treatment settings and ICD-10 diagnostic cat-

**Table 4**

Multivariate logistic regression values for factors associated with greater use of modern\* vs. older antidepressants in five East Asian countries

Factor	B	SE	Wald	P-value	OR	95% CI
Constant	0.26	0.25	1.12	0.29		
Age	-0.13	0.003	16.36	<0.001	0.99	0.98, 0.99
Females	0.16	0.11	2.14	0.14	1.17	0.95, 1.45
China†	1.28	0.18	53.20	<0.001	3.59	2.55, 5.07
Korea†	0.76	0.16	23.24	<0.001	2.13	1.57, 2.90
Singapore†	2.14	0.39	30.35	<0.001	8.49	3.97, 18.17
Taiwan†	1.96	0.19	111.13	<0.001	7.11	4.94, 10.24
Private institutions	0.56	0.16	12.22	<0.001	1.75	1.28, 2.40
Inpatients	-0.18	0.12	0.02	0.89	0.98	0.77, 1.25
Psychiatric hospitals	0.04	0.14	0.09	0.77	0.96	0.72, 1.27
ICD-10 F3/F4 diagnoses	-0.24	0.15	2.67	0.10	0.79	0.59, 1.05

B, logit estimate; SE, standard error of logit estimate; OR, odds ratio. \*Of the total of 1898 subjects, 1282 (67.5%) were given modern antidepressants. †Compared with Japan.

egory; Table 4), factors that were significantly associated with greater use of newer antidepressants were: younger age, country (Singapore > Taiwan > China > Korea) and treatment setting (private hospitals vs. public institutions).

## Discussion

This is the first large-scale, multicentre, international study of antidepressant use within psychiatric treatment settings in East Asia. Newer antidepressants, especially SSRIs, were prescribed in a majority of the treatment regimens in late 2003. However, despite wide availability of older and newer types of antidepressants in all 21 participating sites and five countries, we found major international variations in antidepressant selection. Use of modern antidepressants was more likely to occur in all four other East Asian countries studied compared with Japan. Based on multivariate analysis, selection of newer antidepressants was associated with younger patients, especially in private hospitals, whether general or psychiatric, as well as being less likely to occur in Japan compared with other countries. These relationships are consistent with our hypothesis that preferential use of newer antidepressants is associated with demographic profiles and treatment settings rather than specific diagnostic categories.

In this study, 67.5% of all antidepressant prescriptions were for modern agents, particularly the SSRIs. The only exception to this preference for modern antidepressants was Japan, which continued to prefer older antidepressants by a slight majority (51.1%; Table 1). Large international differences in antidepressant selection also

have been found recently between Australia, Brazil, Israel, Russia, Spain and the USA [11]. Even within a single country, there were sixfold variations in the types of antidepressants used recently in specific regions and healthcare settings within Denmark [7]. Preferential and increased use of modern antidepressants, and particularly the SSRIs, has been reported in recent studies conducted in countries as diverse as Australia [2] and Italy [4], as well as among elderly, young adult and juvenile patients [15, 16]. Reasons for this trend may include vigorous promotion of SSRIs and other newer antidepressants [15], improved safety and patient tolerability of modern agents [17] and a broadening range of approved and empirical indications for the versatile SSRIs [17], which are about as effective in a number of anxiety-related disorders as in major depression [18].

The lack of empirical support of superior efficacy of one antidepressant over another in major depression [18] suggests that factors associated with local preferences in specific treatment settings [19] may contribute to antidepressant selection. We found that selection of modern antidepressants was associated with hospitalization, especially in specialized psychiatric institutions as well as in private general and psychiatric hospitals. Reasons for such choices are not entirely clear, but social expectations of patients and physicians, access, affordability and economic factors may play a role, including whether relatively expensive modern drugs are allowed by managed-care policies and supported by third-party payments in particular settings [20].

Greater use of modern antidepressants by younger patients has been observed in some [21, 22] but not other

recent studies [4, 5]. The inconsistencies may be related to the region-specific demographic profile of patients involved, and whether they have been sampled since the early 1990s, during which world-wide preference for the newer antidepressants became established. Preferential use of modern antidepressants with younger age may also reflect apparent growth in the recognition and pharmacological treatment of children and adolescents with emotional problems in many countries [23], their preference for better-tolerated treatments [24] and the fact that only fluoxetine, and no older antidepressant, has been approved by some international regulatory bodies for use in juvenile depression [18].

Conversely, the association of older antidepressants with advanced age calls for critical re-evaluation of indications for these medications, and close medical monitoring during their use, especially long-term, in elderly patients owing to their potential toxicity. The TCAs, in particular, are associated with adverse cardiac depressant, hypotensive, central intoxicating and other anticholinergic autonomic effects. Such effects can compound existing medical or neurological problems, including cardiac disorders and even dementia [25, 26].

The lack of association of preferential use of modern antidepressants with gender which we found agrees with the findings of Olfson *et al.* [22]. In other reports [5, 12] women were over-represented among patients given all types of antidepressants, perhaps related to the higher prevalence of depressive disorders among women, their greater likelihood of seeking treatment for emotional distress and a proposed superiority of SSRIs over TCAs in depressed women compared with men [27].

Antidepressant use was not strongly associated with specific diagnoses and, indeed, preferential use of modern antidepressants was slightly less likely among patients diagnosed with mood disorders (ICD-10 F3 cluster). Lack of strong association of antidepressant use with affective disorder diagnoses seems paradoxical, but has been noted in other settings [10]. The lack of a strong and consistent preference for modern antidepressants for use in affective disorders in East Asian centres is not readily explained. As suggested by the data, it may be related to the use of antidepressants, especially SSRIs, in conditions other than purely affective disorders such as anxiety spectrum disorders, comorbid depression in chronic psychotic disorders, as well as in patients with alcohol or drug use disorders and coexisting depression [28]. In addition, clinician factors such as patient mix and experience may further influence antidepressant prescribing practices.

There are several limitations of this study. First, its cross-sectional sampling does not allow a longitudinal

comparison of expected recent changes of antidepressant use within and between countries over time. Second, some potentially highly relevant factors were not evaluated, particularly provider preferences and economic factors, including local reimbursement and funding policies. Third, as this is a drug-centred case record study, more elaborate assessment of individual patient variables using rating scales was not included. Fourth, the study population was restricted to patients attending psychiatric treatment centres, hence the findings may not be generalizable to primary healthcare settings.

In conclusion, we found that greater use of modern antidepressants in 21 centres in five East Asian countries was associated with being a relatively young adult patient and with particular treatment settings (especially psychiatric inpatient settings and in private hospitals), and in countries other than Japan, but not with psychiatric diagnosis or sex. These findings add to a growing international research literature on factors associated with selection of particular treatments in specific settings.

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