

Prevalence and Prescription of Antidepressants in Depression with Somatic Comorbidity in Asia: The Research on East Asian Psychotropic Prescription Patterns Study

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Abstract

Background: Depression is often comorbid with chronic somatic diseases. Few previous studies have investigated the prevalence of somatic diseases in depression or the prescription pattern of antidepressants in comorbidly depressed patients in Asia. This study aimed to investigate the prevalence of somatic comorbidity (SC) in depression and compared the prescriptions of antidepressants in depressed patients with and without SC.

Methods: A total of 2320 patients treated with antidepressants in 8 Asian countries were examined, and a diagnosis was based on the International Classification of Disease, 10th revision. We listed 17 common chronic somatic diseases. Patients' socio-demographic and clinical characteristics and psychotropic drug prescriptions were recorded using a standardized protocol and data collection procedure.

Results: Of the patients examined, 1240 were diagnosed with depression and 30% of them ($n = 375$) had SC. The most common comorbid condition was diabetes (23.7%). The patients with SC were more likely to seek help at a general hospital (74.7% vs. 47.2%), and had a higher incidence of symptoms involving sadness, disturbed sleep, and poor appetite. Noradrenergic and specific serotonergic antidepressant was prescribed more for patients with SC than for those without SC (30.4% vs. 22.9%).

Conclusions: SC is common in depressed Asian patients. It is important to strengthen the recognition of depression, especially in general hospitals and when patients report some somatic discomfort. It is also a matter of urgency to establish evidence-based guidelines for the use of new antidepressants in depressed patients with SC.

Key words: Asia; Depression; Prescription; Prevalence; Somatic Comorbidity

INTRODUCTION

Depression is a common mental disorder that is associated with functional impairment and high morbidity and mortality.

The World Health Organization (WHO) has reported that depression is the leading cause of disability in the world,^[1] and by 2020, it will be the second greatest public health concern.^[2]

One of the important issues to note is that depression has been shown to have a higher prevalence in patients

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with somatic diseases than in healthy people.^[3-5] A large, prospective, community-based study in Canada found that 4% (confidence interval [CI]: 3.3–4.7) of those with medical conditions versus 2.8% (CI: 2.2–3.4) of those without developed depression over a 2-year period.^[6] Another study performed a meta-analysis^[7] of studies investigating the prevalence of depression in coronary heart disease (CHD) in China, with the results showing that patients with CHD had a high prevalence of depression: 51% in hospitals and from 34.6% to 45.8% in the community. However, unrecognized rate of depression is high in clinical practice.^[8,9] Furthermore, it has been suggested that chronic somatic diseases might have a negative impact on the overall functioning,^[10] recognition rate, or treatment response^[11] of depressed patients, and that these patients are associated with a higher risk of recurrence or chronic course of depression.

Furthermore, studies have suggested that depression has a high comorbidity with chronic somatic diseases.^[12-14] For example, a meta-analysis of studies that tested the bi-directional relationship between depression and type 2 diabetes showed a high relative risk of 1.60 (CI: 1.37–1.88) for the incidence of diabetes associated with depression.^[14] Another meta-analysis of the impact of depression on various cardiovascular diseases (CVDs) showed that depression might be an independent risk factor for the onset of a wide range of CVDs.^[13] However, it is important to note that although a high comorbidity in depression and somatic diseases has been highlighted, few studies have comprehensively investigated and compared the socio-demographic characteristics, clinical symptoms, and antidepressant prescriptions of depressed patients with and without somatic comorbidity (SC).

Based on the above considerations, we conducted this study to investigate the prevalence of SC in depressed Asian patients, and to determine the differences in socio-demographic characteristics, depressive symptoms, and prescription patterns of psychotropic drugs of depressed patients with and without SC.

METHODS

Study sample

The study was a part of the Research on East Asian Psychotropic Prescription Patterns project, an international, cross-sectional, case record, and drug-centered study using a standardized data collection procedure in Asian countries and territories. The sample included 2320 outpatients or inpatients from 42 psychiatric centers in 8 Asian countries: China (including the Mainland, Hong Kong SAR, Taiwan), India, Indonesia, Japan, the Republic of Korea, Malaysia, Singapore, and Thailand. All the survey settings are psychiatric departments.

A consensus meeting was 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.

Each center used the same standardized protocol and data collection procedure. Briefly, patients were included if they (i) had been prescribed antidepressants on the day of the survey; (ii) could comprehend the aims of the study; and (iii) agreed to participate in this study, and provided written or oral consent according to the requirements of the clinical research ethics committees at the respective study sites. There were no specific exclusion criteria. The clinical research ethics committees of the respective centers granted approval for the study protocol.

Criteria of depression and somatic diseases

Diagnoses were made according to the major, standard, International Classification of Disease, 10th revision (ICD-10) categories. Depression was defined as the presence of F32 or F33 in the ICD-10 diagnostic system. Somatic diseases were self-reported diseases monitored by a healthcare professional and/or treated with medication. We listed 17 common physical disorders: Myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, mild liver disease, diabetes without chronic complications, diabetes with chronic complications, hemiplegia or paraplegia, renal disease, any malignancy, moderate or severe liver disease, metastatic solid tumor, and HIV/AIDS. Somatic disorders not included on the list were to be written down in detail. We classified somatic diseases into 9 categories, and the percentages of patients with each category are shown in Figure 1.

The 10 depressive symptoms in this study were selected based on the National Institute for Health and Care Excellence guidelines, the ICD-10 and the Diagnostic and Statistical Manual of Mental Disorders-IV. These are the core symptoms of depression that represent the mood and the vegetative and cognitive profiles of a depressive illness.

Classification of antidepressants

Fifty-six antidepressants in the Anatomical Therapeutic Chemical classification index by the WHO Collaborating

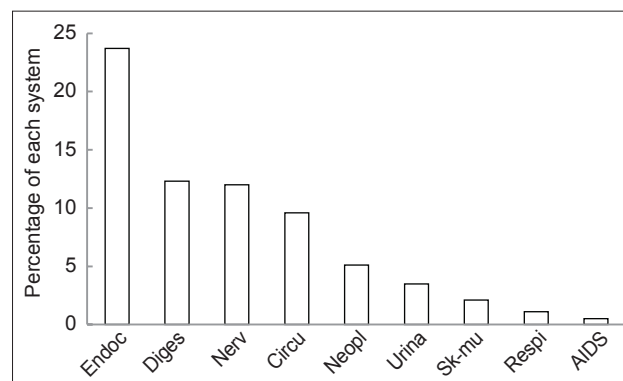


Figure 1: The percentages of each system of somatic diseases in depressed patients. Endoc: Endocrine system; Diges: Digestive system; Nerv: Nervous system; Circu: Circulatory system; Neopl: Neoplastic disease; Urina: Urinary system; Sk-mu: Musculoskeletal system; Respi: Respiratory system.

Center for Drug Statistics Methodology (Oslo) were listed. Based on which chemicals in the brain they affect, the antidepressants were classified into 7 classes including tricyclic antidepressants, tetracyclic, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), noradrenergic and specific serotonergic antidepressant (NaSSA), and other newer antidepressants. Other newer antidepressants mean that they cannot be included in the former classes.

Statistical analyses

All analyses were performed using the Statistical Package for Social Sciences (SPSS®), version 21.0 (SPSS Inc., Chicago, IL, USA). Comparisons of socio-demographic and clinical characteristics between the comorbidity group and the noncomorbidity group were performed with independent samples *t*-test or Pearson Chi-square tests, as appropriate. Statistical significance was set at a two-tailed $P < 0.05$.

RESULTS

Prevalence of somatic diseases in depression

Of all the patients, 1240 were diagnosed with depression; among them, 375 (30.2%) had SC. The most common somatic disease was diabetes ($n = 89$, 23.7%), followed by cerebrovascular disease ($n = 40$, 10.7%) and peptic ulcer ($n = 26$, 6.9%). The percentages of patients with each system of somatic diseases are shown in Figure 1.

Group differences in socio-demographic characteristics

As shown in Table 1, almost all of the patients were from psychiatric departments; the average age of patients with SC was older than that of patients without SC (55.3 vs. 45.2 years, $P < 0.001$), and patients with SC had a higher frequency of seeing doctors at general hospital (74.7% vs. 47.2%, $P < 0.001$). No significant differences were found between the two groups in gender distribution or current setting.

Group differences in depressive symptoms

The number of patients with each depressive symptom and the respective percentages is listed in Table 2. The two groups had different rates of four symptoms, with a higher frequency of persistent sadness and two vegetative symptoms (including disturbed sleep and poor appetite) in the SC group, but a higher frequency of cognitive symptoms (including poor concentration or indecisiveness) in the noncomorbidity group.

Group differences in psychotropic medication prescriptions

A total of 956 (76.7%) patients were prescribed one antidepressant. The three most commonly used antidepressants were sertraline ($n = 245$, 19.6%), escitalopram ($n = 232$, 18.6%), and mirtazapine ($n = 201$, 16.1%). SSRIs were the most commonly prescribed type of antidepressant ($n = 841$, 67.4%), followed by SNRIs ($n = 213$, 17.1%) and

Table 1: Demographic characteristics of depressed patients with or without SC

Parameters	Without SC ($n = 872$)	With SC ($n = 375$)	<i>P</i>
Age (years)	45.2 ± 16.1	55.3 ± 16.4	<0.001
Gender (n (%))			
Male	360 (41.3)	149 (39.7)	0.599
Female	512 (58.7)	226 (60.3)	
Current setting (n (%))			
Outpatient	627 (71.9)	269 (71.7)	0.951
Inpatient	245 (28.1)	106 (28.3)	
Hospital type (n (%))			
Psych	460 (52.8)	95 (25.3)	<0.001
Gene	412 (47.2)	280 (74.7)	
Department (n (%))			
Psych	872 (100.0)	375 (100.0)	1.000

SC: Somatic comorbidity; Psych: Psychiatric hospital/Psychiatry; Gene: General hospital.

Table 2: Differences in the frequency of each depressive symptom between the two groups

Symptoms (n)	Without SC (n (%))	With SC (n (%))	Statistics		
			χ^2	df	<i>P</i>
Sadness ($n = 918$)	626 (71.8)	292 (77.9)	4.987	1	0.026*
Loss of interest ($n = 660$)	476 (54.6)	184 (49.1)	3.208	1	0.073
Fatigue ($n = 570$)	386 (44.3)	184 (49.1)	2.435	1	0.119
Sleep ($n = 791$)	515 (59.1)	276 (73.6)	23.901	1	<0.001
Concentration ($n = 374$)	277 (31.8)	97 (25.9)	4.347	1	0.037*
Self-confidence ($n = 296$)	215 (24.7)	81 (21.6)	1.353	1	0.245
Appetite ($n = 409$)	266 (30.5)	143 (38.1)	6.924	1	0.009*
Suicide ($n = 287$)	188 (21.6)	99 (26.4)	3.468	1	0.063
Agitation ($n = 288$)	189 (21.7)	99 (26.4)	3.297	1	0.069
Guilt ($n = 200$)	131 (15.0)	69 (18.4)	2.221	1	0.136
Others ($n = 189$)	126 (14.4)	63 (16.8)	1.127	1	0.289

* $P < 0.05$. SC: Somatic comorbidity; Sleep: Disturbed sleep; n (%): The number and percentage of patients with such symptom.

NaSSA ($n = 201$, 16.1%). Others included agomelatine, trazodone, and bupropion.

The between-group differences in the number and rate of patients with each type of antidepressant and other types of medication like antipsychotics are listed in Table 3. As indicated, the SC group had a lower rate of patients prescribed SSRIs and anti-parkinsonian drugs and a higher rate of NaSSA and sedative hypnotics than the group without SC.

DISCUSSION

To the best of our knowledge, this is the first large-scale, multicenter, international study to survey the differences in demographic characteristics, symptoms, and prescriptions of depressed patients with and without SC in Asia. The main findings are that a high percentage of the surveyed depressed patients had SC, the comorbid depressed patients were more likely to seek help at general hospitals, three depressive

Table 3: Differences in prescription of psychotropic drugs between the two groups (n (%))

Classification	Without SC	With SC	Total	P
Antidepressants				
Monotherapy	669 (76.7)	287 (76.5)	956 (76.7)	0.943
Two or more	203 (23.3)	88 (23.5)	291 (23.3)	
TCAs	88 (10.1)	40 (10.7)	120 (9.6)	0.759
Tetracyclic	23 (2.6)	10 (2.7)	33 (2.6)	0.977
SSRIs	628 (72.0)	249 (66.4)	877 (70.3)	0.046*
SNRIs	144 (16.5)	69 (18.4)	213 (17.1)	0.417
NaSSA	118 (13.5)	83 (22.1)	201 (16.1)	<0.001*
Others	92 (10.6)	38 (10.1)	130 (10.4)	0.825
Antipsychotics	344 (39.4)	136 (36.3)	480 (38.5)	0.289
FGAs	90 (10.3)	27 (7.2)	117 (9.4)	0.083
SGAs	254 (29.1)	109 (29.1)	363 (29.1)	0.982
Mood stabilizers	183 (21.0)	68 (18.1)	251 (20.1)	0.249
Sedative hypnotics	296 (33.9)	171 (45.6)	467 (37.4)	<0.001*
Anxiolytics	20 (2.3)	12 (3.2)	32 (2.6)	0.353
APSS	63 (7.2)	14 (3.7)	77 (6.2)	0.019*

* $P < 0.05$. SC: Somatic comorbidity; FGAs: First-generation antipsychotics; SGAs: Second-generation antipsychotics; APSS: Antiparkinsonian drugs; TCAs: Tricyclic antidepressants; SSRIs: Selective serotonin reuptake inhibitors; SNRIs: Serotonin-norepinephrine reuptake inhibitors; NaSSA: Noradrenergic and specific serotonergic antidepressant.

symptoms had higher rates in the comorbidity group, and the rates of the prescription of NaSSA were different between the two groups.

Several studies have investigated the rate of SC in depression. One study^[15] reported that in 76 depressed patients in Croatia, 75% had SCs. Another study^[16] reported that in 1209 depressed patients in the Netherlands, 43% had at least one SC. The STAR*D study^[17] found that two-third of depressed patients had at least one concurrent general medical condition. In 1240 surveyed depressed patients in Asia, we found that 30% had SC, which is relatively lower than the previous studies. In our study, we surveyed the patients who were treated with antidepressants, which is different from other studies including all the patients with depression. Considering the higher patients were not recognized by clinicians and low rate of treatment for the patients with depression,^[8,9] the high rate of SC in depression is an important matter of public health concern in Asian countries and territories. In our study, another interesting finding was that 46.25% ($n = 1173$) of patients prescribed with antidepressants were not diagnosed with depression. We will analyze it further in another way.

Further, we found a higher rate of seeking help at general hospitals rather than psychiatric hospitals among depressed patients with SC (74.7% vs. 47.2%), and a higher prevalence of depressive symptoms, including depressed mood, disturbed sleep, and poor appetite. In line with our finding, a study conducted in China^[18] reported that the rate of SC was higher in depressed patients who first chose general hospitals. That phenomenon may not be hard to understand given that comorbidly depressed patients

predominantly report their somatic symptoms before any others.^[19] The strong illness stigma reported in patients with mental disorders may be another important reason, which would mean that depressive symptoms are less discussed in general clinics.^[20] These potential problems pose great challenges to clinicians in general hospitals, as several studies conducted in Chinese general hospitals have reported low rates of recognition and treatment of depression.^[8,21,22] Moreover, some studies have shown that comorbid somatic diseases could prolong the duration of depression and that higher rates of comorbidity were associated with treatment resistance among depressed patients.^[23] These findings, together with ours, suggest that it is important to identify and intervene in depression as early as possible in patients who have complaints of somatic discomfort. Specific examinations for symptoms such as depressed mood, disturbed sleep, poor or increased appetite, the latter two symptoms were recognized as the third factor of depression^[24,25], would be helpful for the recognition of depression.

As shown in this study, newer antidepressants, especially SSRIs, were still the most prescribed antidepressants for depressed patients, followed by other novel antidepressants, which is in accordance with the findings of previous studies conducted in Asia.^[26] Furthermore, we found significant differences in rates of prescribing NaSSA between the two groups (13.5% vs. 22.1%, $P < 0.001$). The reasons for this difference may be as follows. Because SC is associated with a higher frequency of treatment resistance in depressed patients,^[23] according to World Federation of Societies of Biological Psychiatry guidelines,^[27] a combination of an SSRI and mirtazapine is an evidence-based choice in depressed patients for whom monotherapy has failed. And it has special advantages over SSRIs in the treatment of certain symptoms, such as disturbed sleep, poor appetite,^[28-30] and sexual dysfunction.^[31,32] Therefore, higher rate of patients in SC group used mirtazapine. A meta-analysis showed that SSRIs, especially citalopram, were associated with a dose-dependent increase in QTc interval.^[33] A US Food and Drug Administration Safety Announcement advocated that citalopram should no longer be used at doses above 40 mg/d because in higher doses, the drug could unfavorably change the electrical activity of the heart without additional benefits in the treatment of depression.^[34] However, it should also be noted that studies addressing the risks of other novel antidepressants are limited, and evidence-based guidelines for depressed patients with SC are unavailable.^[35] It will thus be necessary to conduct large-scale clinical trials to test the advantages and disadvantages of other novel antidepressants and establish relevant guidelines for the use of these agents in depression with SC.

This study has several limitations. First and foremost is the sampling bias. The data were collected from eight different countries, and each center chose a certain day to collect data. Second, because the study was conducted

at hospitals or universities in major cities, the data may not be generalizable to rural areas and smaller cities. It is possible that second-generation antidepressants are used much less at smaller hospitals or in rural areas due to a lack of financial support. Third, because of nonrandomized sampling method, the findings of this study may not be generalizable to the entirety of Asia. Another limitation is the variation of sample size at each participating center, which might have influenced the overall results.

In conclusion, the findings of this study suggest a high rate of SC in depressed patients in Asia, which may pose great challenges for clinicians recognizing depression, especially those at general hospitals. For a more efficient recognition of depression, clinicians should routinely examine symptoms related to emotions, sleep, and appetite when patients have complaints of somatic discomfort. Depressed patients with SC are more likely to use other novel antidepressants; thus, large-scale clinical trials of the efficacy and side-effects of these agents are urgently needed to contribute to a final development of guidelines for their use in depression with SC.

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