Physical comorbidities in older adults prescribed with antidepressants in Asia

Running Head: Physical comorbidities in older adults

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ABSTRACT:

Background: This study explored the patterns of physical comorbidities and their associated demographic and clinical factors in older psychiatric patients prescribed with antidepressants in Asia.

Methods: Demographic and clinical information of 955 older adults were extracted from the database of the Research on Asian Psychotropic Prescription Patterns for Antidepressants (REAP-AD) project. Standardized data collection procedure was used to record demographic and clinical data.

Results: The proportion of physical comorbidities in this cohort was 44%. Multiple logistic regression analyses revealed that older age (OR=1.7, \( P < 0.001 \)), high number of depressive symptoms (OR=1.09, \( P = 0.016 \)), being treated in psychiatric inpatient units (OR=0.5, \( P=0.002 \)), living in high income countries/territories (OR=2.4, \( P=0.002 \)), use of benzodiazepines (OR=1.4, \( P=0.013 \)) and diagnosis of ‘other psychiatric disorders’ (except mood, anxiety disorders and schizophrenia) (OR=2.7, \( P<0.001 \)) were significantly associated with physical comorbidities.

Conclusions: Physical comorbidities in older patients prescribed with antidepressants were common in Asia. Integrating physical care into the treatment of older psychiatric patients should be urgently considered.

Key Words: antidepressant, Asia, older adults, physical comorbidity
INTRODUCTION

With decreasing birth rates and increasing life expectancy, the proportion of older adults has been growing globally. For example, the percentage of older adults in Europe is expected to rise to 44% by 2025. 1 Psychiatric disorders are very common in older adult population. In Europe, 47% older adults experienced at least one psychiatric disorder in their life-time, and nearly one fourth had a current psychiatric disorder. 2 The lifetime prevalence of any type of psychiatric disorder was 23% in older African Americans. 3

Use of antidepressants is becoming more prevalent in older adults in recent years, 4 particularly in developing countries. 5 This could be partly due to the increased identification of depressive symptoms, treatment initiation and maintenance treatment in depressed patients. 6 Another reason could be the increased off-label use of antidepressants for other conditions, such as chronic physical illness, mild cognitive impairment or functional limitation. 7

Aging is associated with increased risk of both chronic physical diseases and psychiatric disorders. Older adults with major psychiatric disorders including depression, schizophrenia and bipolar disorder have a particularly high risk of physical comorbidities, such as hypertension (83.1%), diabetes mellitus (43.1%), congestive heart failure (29.0%) and chronic obstructive pulmonary disease (27.5%). 8 Physical comorbidities with psychiatric disorders could result in poor
quality of life, increased risk of hospitalization and functional disability and worse treatment outcomes.

Due to pharmacokinetic changes in older adults that alter the absorption, metabolism and excretion of drugs, older people are more prone to drug-induced adverse events. Therefore, prescription of antidepressants in older adults, particularly those with physical comorbidities, should be done with caution. Surveys of prescription patterns are an efficient approach to appraise the appropriateness of psychopharmacotherapy. It is, thus, important to investigate the patterns of use of antidepressants in older adults with physical comorbidities.

This study examined the patterns of physical comorbidities and their associated demographic and clinical factors in older psychiatric patients prescribed with antidepressants in Asia. We hypothesized that physical comorbidities in older patients prescribed with antidepressants are common and independently associated with clinical risk factors.

METHODS

Study design and sample

The Research on Asian Psychotropic Prescription Patterns for Antidepressants (REAP-AD) project is a pharmaco-epidemiological survey of the antidepressant
prescription patterns in psychiatric patients across 42 psychiatric centers in 10 Asian countries / regions (China, Singapore, Hong Kong, Japan, Korea, Taiwan, India, Malaysia, Thailand and Indonesia). All patients treated with antidepressants on the day of the survey were enrolled without any exclusion criteria. Data were collected using a standardized protocol and procedure at all study sites.

The current study is a secondary analysis of the database of the REAP-AD 2013 that was conducted between March and June 2013. Data of all patients who were ≥50 years old were analyzed. In most Asian countries, patients aged ≥50 years were defined as ‘older adults’ in the REAP-AD project. This cut-off age is in line with other studies 17.

For logistical reasons, the presence of 10 core depressive symptoms selected from the National Institute for Health and Care Excellence (NICE) guidelines, ICD-10 18 and DSM-IV 19 that included insomnia, appetite change, agitation, fatigue, suicidal ideation, guilt/self-blame, lack of confidence, poor concentration, sadness and loss of interests 20 were recorded. The participating countries and territories were collapsed into high income (Hong Kong, Singapore, Japan, Korea, and Taiwan) and middle income sites (China, Malaysia, Thailand, India and Indonesia) according to the World Bank criteria (https://datahelpdesk.worldbank.org/knowledgebase/articles/906519).
Data collection

Demographic and clinical characteristics including physical comorbidities were collected either by a review of medical records only, or a review of medical records review that was supplemented by a clinical interview by the patients’ attending psychiatrists or by members of the research team. Principal psychiatric diagnoses were made according to the International Classification of Diseases, 10th Revision 21 or Diagnostic and the Statistical Manual of Mental Disorders, 4th edition. 19 Psychotropic medications were categorized according to the World Health Organization Anatomical Therapeutic Chemical (ATC) classification system 22. In this study, physical comorbidities included myocardial infarction, congestive heart failure, cerebrovascular diseases, peripheral vascular diseases, dementia, peptic ulcer, liver diseases, chronic pulmonary diseases, diabetes mellitus, renal diseases, rheumatic diseases, acquired immunodeficiency syndrome/ human immunodeficiency virus, malignancy, and other specified diseases.

The research and ethics committee at each study site approved the research protocol. When the study involved anonymous retrospective medical chart review, informed consent was waived at the study sites because it was considered low risk to patients. When patients were interviewed, they provided written informed
Data analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 22.0 (IBM SPSS, Chicago, IL, USA). Group differences were compared between older adults with physical comorbidities and those without using chi-square test, independent sample t-test and Mann–Whitney U-test, as appropriate. Multiple logistic regression analysis with the “Enter” method (i.e., all independent variables were entered into the model simultaneously) was performed to identify the independent associations with physical comorbidities. The presence of physical comorbidities was the dependent variable, while those that significantly differed between the two groups in univariate analyses were the independent variables. The level of significance was set at 0.05 (two-tailed).

RESULTS

Of the 954 older adults included in the analyses, 421 (44%) had at least 1 physical comorbidity (Table 1). The most common physical comorbidity was diabetes, followed by cerebrovascular diseases, peptic ulcer, malignancy and peripheral vascular diseases (Table 2).

The basic demographic and clinical characteristics of the whole sample and
separately by physical comorbidities are showed in Table 3. Older age, high number of depressive symptoms, being treated in general hospital psychiatric units, living in high income countries/territories, use of benzodiazepines (BZD), use of noradrenergic and specific serotonergic antidepressants (NaSSAs) and diagnosis of ‘other psychiatric disorders’ were significantly associated with physical comorbidities. Patients in higher income countries/territories were older than in middle income countries/territories (63.6±9.9 vs. 61.5±9.0 years, p <0.05). Multiple logistic regression analysis revealed that older age, high number of depressive symptoms, being treated in general hospital psychiatric units, living in high income countries/territories, use of BZD and diagnosis of ‘other psychiatric disorders’ were independently and significantly associated with physical comorbidities (Table 4).

DISCUSSION
To the best of our knowledge, this was the first large-scale, international survey of the patterns of physical comorbidities in older psychiatric patients prescribed with antidepressants. In this study, 44% of older psychiatric patients prescribed with antidepressants had at least one physical comorbidity. Given that we could not locate similar studies of this kind, no direct comparisons could be made with previous studies. In a study examining use of electroconvulsive therapy in older
psychiatric patients the proportion of physical comorbidities was 66.9% (1,604/2,339), which is higher than our results. The cut-off age for older patients in this study however was older (60 vs. 50 years), which could explain the differing frequency of physical comorbidities between the two studies.

Previous studies have found that the increased use of antidepressants in older adults was mainly driven by the introduction of selective serotonin reuptake inhibitors (SSRIs). This notion was partly supported by our study in that 62.1% of the whole sample received SSRIs. Apart from depressive symptoms, sleep disturbances and anxiety symptoms are also common in older adults. SSRIs are effective to relieve anxiety and anxiety-related insomnia with relatively few adverse events and good treatment adherence, which could also increase their use.

As benzodiazepines are also used commonly for anxiety and sleep disturbances, they are frequently used in older patients with physical diseases. Similarly, this study found that physical comorbidities could increase the likelihood and severity of depressive symptoms. As expected, older age was associated with higher risk of physical comorbidities in this study therefore patients with physical comorbidities were more likely to receive treatment in hospital settings.

In this multi-site study, older patients living in high-income
countries/territories were more likely to have physical comorbidities. Compared to middle income countries/territories, hospitals in high-income countries/territories usually have higher staff-patient ratio and better medical equipment and training, therefore, regular screening tests for physical diseases are more frequent. In addition, psychiatric patients in middle income countries/territories are more likely to be treated in psychiatric institutions in which general medical services are not easily accessible. As a result, physical comorbidities in psychiatric patients treated in high-income countries/territories are more likely to be identified.

Older patients with major psychiatric disorders utilize medical health services frequently due to physical diseases. However, in this study patients with other psychiatric disorders were more likely to have physical co-morbidities; 65.3% of other psychiatric disorders were organic mental disorders and 18.6% substance abuse disorders. This may explain why these patients had more physical co-morbidities.

The strengths of this study include its large sample size and the representative samples across Asia. However, there are several limitations. First, due to logistical reasons, the presence of physical comorbidities could not be confirmed by direct medical examination or investigations. Second, depressive symptoms were not assessed with standardized tools. Third, there was no control
group. Finally, due to the cross-sectional design, causality between physical comorbidities and other variables could not be examined.

In conclusion, nearly half of older adults treated with antidepressants in this cohort had physical co-morbidities. Considering the high prevalence of physical comorbidities, integrating physical care into the treatment of older psychiatric patients should be urgently considered.

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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. Distribution of patients with physical comorbidities across Asian countries / territories

<table>
<thead>
<tr>
<th>Country/territory</th>
<th>Patients</th>
<th>Physical comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=955</td>
<td>n=421</td>
</tr>
<tr>
<td>China</td>
<td>158</td>
<td>41</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>39</td>
<td>17</td>
</tr>
<tr>
<td>Japan</td>
<td>119</td>
<td>73</td>
</tr>
<tr>
<td>RO Korea</td>
<td>150</td>
<td>68</td>
</tr>
<tr>
<td>Singapore</td>
<td>48</td>
<td>26</td>
</tr>
<tr>
<td>Taiwan</td>
<td>109</td>
<td>56</td>
</tr>
<tr>
<td>India</td>
<td>63</td>
<td>26</td>
</tr>
<tr>
<td>Malaysia</td>
<td>67</td>
<td>41</td>
</tr>
<tr>
<td>Thailand</td>
<td>128</td>
<td>44</td>
</tr>
<tr>
<td>Indonesia</td>
<td>74</td>
<td>29</td>
</tr>
<tr>
<td>Overall</td>
<td>955</td>
<td>421</td>
</tr>
</tbody>
</table>
TABLE 2. Most common physical comorbidities in patients treated with antidepressants in Asia (n=421)

<table>
<thead>
<tr>
<th>Primary physical comorbidity</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>116</td>
<td>27.5</td>
</tr>
<tr>
<td>Cerebrovascular diseases</td>
<td>48</td>
<td>11.4</td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>24</td>
<td>5.7</td>
</tr>
<tr>
<td>Malignancies</td>
<td>24</td>
<td>5.7</td>
</tr>
<tr>
<td>Peripheral vascular diseases</td>
<td>21</td>
<td>4.9</td>
</tr>
</tbody>
</table>
TABLE 3. Basic demographic and clinical characteristics of patients with and without physical comorbidities

<table>
<thead>
<tr>
<th></th>
<th>Total sample</th>
<th>No physical comorbidities</th>
<th>Physical comorbidities</th>
<th>statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=955)</td>
<td>(n=534)</td>
<td>(n=421)</td>
<td></td>
</tr>
<tr>
<td>Mean (years)</td>
<td>62.6</td>
<td>61.0</td>
<td>64.5</td>
<td>-5.6</td>
</tr>
<tr>
<td>AD dose, IMI-eq (mg/d)</td>
<td>131.2</td>
<td>132.1</td>
<td>129.9</td>
<td>-0.3</td>
</tr>
<tr>
<td>Number of antidepressants</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
<td>-0.08</td>
</tr>
<tr>
<td>Number of depressive symptoms</td>
<td>3.4</td>
<td>3.3</td>
<td>3.6</td>
<td>-2.1</td>
</tr>
<tr>
<td>N %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years) 50-64</td>
<td>615</td>
<td>379</td>
<td>236</td>
<td>22.8</td>
</tr>
<tr>
<td>Age (years) 65 and older</td>
<td>340</td>
<td>155</td>
<td>185</td>
<td>1.3</td>
</tr>
<tr>
<td>Female</td>
<td>580</td>
<td>333</td>
<td>247</td>
<td>6.3</td>
</tr>
<tr>
<td>Psychiatric hospital</td>
<td>351</td>
<td>234</td>
<td>117</td>
<td>26.0</td>
</tr>
<tr>
<td>Inpatients</td>
<td>233</td>
<td>125</td>
<td>108</td>
<td>0.6</td>
</tr>
<tr>
<td>General hospital</td>
<td>687</td>
<td>388</td>
<td>299</td>
<td>0.3</td>
</tr>
<tr>
<td>Income group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High income</td>
<td>465</td>
<td>225</td>
<td>240</td>
<td>20.8</td>
</tr>
<tr>
<td>Middle income</td>
<td>490</td>
<td>309</td>
<td>181</td>
<td></td>
</tr>
<tr>
<td>Use of FGA</td>
<td>83</td>
<td>48</td>
<td>35</td>
<td>0.1</td>
</tr>
<tr>
<td>Use of SGA</td>
<td>238</td>
<td>127</td>
<td>111</td>
<td>0.8</td>
</tr>
<tr>
<td>Use of MS</td>
<td>63</td>
<td>33</td>
<td>30</td>
<td>0.3</td>
</tr>
<tr>
<td>Use of NaSSAb</td>
<td>163</td>
<td>78</td>
<td>49</td>
<td>7.9</td>
</tr>
<tr>
<td>Principal psychiatric diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mood disorders</td>
<td>671</td>
<td>386</td>
<td>285</td>
<td>14.9</td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td>130</td>
<td>76</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>79</td>
<td>46</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>75</td>
<td>26</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Use of antidepressants</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCA</td>
<td>99</td>
<td>60</td>
<td>39</td>
<td>0.9</td>
</tr>
<tr>
<td>Tetracyclic</td>
<td>27</td>
<td>18</td>
<td>9</td>
<td>1.3</td>
</tr>
<tr>
<td>SSRI</td>
<td>593</td>
<td>336</td>
<td>257</td>
<td>0.3</td>
</tr>
<tr>
<td>SNRI</td>
<td>155</td>
<td>85</td>
<td>70</td>
<td>0.08</td>
</tr>
<tr>
<td>NaSSA</td>
<td>163</td>
<td>78</td>
<td>85</td>
<td>5.1</td>
</tr>
</tbody>
</table>

Note: ^a indicates comparison to reference group.
**TABLE 4. Independent demographic and clinical correlates in patients with physical comorbidities**

<table>
<thead>
<tr>
<th>Variables</th>
<th>P value</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>65 years and older</td>
<td>&lt;0.001</td>
<td>1.7</td>
<td>1.3-2.3</td>
</tr>
<tr>
<td>Psychiatric hospital</td>
<td>0.002</td>
<td>0.5</td>
<td>0.4-0.8</td>
</tr>
<tr>
<td>High income group</td>
<td>0.002</td>
<td>2.4</td>
<td>1.3-4.2</td>
</tr>
<tr>
<td>Principal psychiatric diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mood disorders</td>
<td>---</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td>0.97</td>
<td>1.008</td>
<td>0.6-1.5</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>0.78</td>
<td>1.07</td>
<td>0.6-1.8</td>
</tr>
<tr>
<td>Others</td>
<td>&lt;0.001</td>
<td>2.7</td>
<td>1.5-4.6</td>
</tr>
<tr>
<td>Number of depressive symptoms*</td>
<td>0.016</td>
<td>1.09</td>
<td>1.01-1.1</td>
</tr>
<tr>
<td>On NaSSA</td>
<td>0.41</td>
<td>1.1</td>
<td>0.8-1.6</td>
</tr>
<tr>
<td>On BZD</td>
<td>0.013</td>
<td>1.4</td>
<td>1.08-1.9</td>
</tr>
</tbody>
</table>

Bolded values: <0.05; a: due to collinearity between the number of core depressive symptoms and the individual core depressive symptom, the individual core depressive symptom cannot be entered as independent variable. Participating country/territory has been controlled for as a covariate. Multiple logistic regression analysis with diagnosis of mood disorders as the reference group. NaSSA=noradrenergic and specific serotonergic antidepressant; BZD=benzodiazepines.

Others: 127 13.3 71 13.3 56 13.3 0 1 0.99

Bolded values: <0.05; a: Mann–Whitney U-test; b: NaSSAs were available in all countries/territories except Indonesia; AD=antidepressants; IMI-equiv=imipramine-equivalent; FGA=first-generation antipsychotic; SGA=second-generation antipsychotic; MS=mood stabilizer; BZD=benzodiazepines; TCA=tricyclic antidepressants; SSRI=selective serotonin reuptake inhibitors; SNRI=serotonin-norepinephrine reuptake inhibitors; NaSSA=noradrenergic and specific serotonergic antidepressant.
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