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Abstract. Objective: The aim of the study was to survey the frequency of tardive dyskinesia (TD) in patients with schizophrenia and its demographic and clinical correlates in selected Asian countries. Method: A total of 6,761 hospitalized schizophrenia patients in nine Asian countries and territories were examined from 2001 to 2009. TD was evaluated as “present” or “absent” according to the clinical judgment of experienced psychiatrists. The patients’ socio-demographic and clinical characteristics and the prescriptions of psychotropic drugs were recorded using a standardized protocol and data collection procedure. Results: The frequency of TD in the whole sample was 5.0% with wide variations between countries (0 – 14.9%). Multiple logistic regression analysis showed that the following variables were independently associated with TD: study time, study site, older age, male gender, more severe negative and extrapyramidal symptoms and less anticholinergic drugs. Conclusions: A generally low frequency of TD in Asian schizophrenia patients with inter-ethnic variations was recorded. It is unclear whether the low prevalence of TD compared with Western data is real or the result of it being insufficiently recognized.

Introduction

The frequency of tardive dyskinesia (TD) in schizophrenia ranges from 3% to 62% with an overall frequency of 24% [1]. Most surveys have found a lower frequency of TD in Asian patients [2, 3, 4, 5]. The consistently reported risk factors for TD are older age, female gender, use of first generation antipsychotics (FGA), extrapyramidal symptoms, and a host of genetic and cultural factors [4, 6, 7, 8, 9]. Recognition of TD has important implications in clinical practice. To date, however, there has been no comprehensive survey examining the prevalence of TD in Asian patients with schizophrenia. In this study, data from the Research on Asian Psychotropic Prescription Pattern (REAP) study, a large-scale observational study conducted in nine Asian countries and territories, were analyzed to determine the point prevalence of TD in schizophrenia in selected Asian countries, its trend over time, and associations with socio-demographic and clinical factors.
Methods

Settings, subjects and study design

The REAP study is an ongoing, pharmacoepidemiological survey of the treatment of schizophrenia patients in selected Asian countries and territories (China, Hong Kong, Japan, Korea, Singapore and Taiwan). Each study site examined a cohort of schizophrenia inpatients on three occasions in July 2001, July 2004, and October 2008 – March 2009, using a standardized protocol and data collection procedure. Centers in India, Malaysia, and Thailand joined the survey in 2009.

The details of the methodology of the REAP project have been described elsewhere [10, 11, 12]. Entry criteria were (1) diagnosis of schizophrenia according to ICD-10 and/or DSM-IV; (2) able to comprehend the aims of the study; and (3) willing to provide written or oral consent according to the requirements of the clinical research ethics committees in the respective study sites. Patients suffering from major medical conditions were excluded. The study was approved by the Institutional Review Boards of the respective centers.

Patients were examined and their basic socio-demographic and clinical data were recorded with the aid of a questionnaire designed by the authors. Doses of antipsychotic drugs used on census days were converted into chlorpromazine equivalent milligrams (CPZeq) [13, 14, 15].

Following the example of large-scale, multi-center, international studies [16, 17, 18], psychopathology and drug-induced side effects were evaluated with a selection of measures chosen for their simplicity and ease of use without requirement for training. In the REAP surveys psychiatrists rated TD as either “present” or “absent”. Before the REAP studies, consensus meetings were held but no formal inter-rater reliability exercises were conducted. All participating psychiatrists were fully qualified in their respective countries and had several years of clinical experience. Essentially identical, simple methods of identifying TD have been used in other pharmacoepidemiological studies [16, 17].

Statistical analysis

The data were analyzed using SPSS 13.0 for Windows. The comparisons between TD and non-TD groups with respect to socio-demographic and clinical characteristics were performed using independent samples t-test, Mann-Whitney -test, and χ²-test, as appropriate. Multiple logistic regression analysis was used to adjust for relevant demographic and clinical covariates and to determine the independent contributors to TD. The level of significance was set at 0.05 (two-tailed).

Results

Altogether, 31 psychiatric facilities were involved in 2001, 25 in 2004, and 50 in 2009. A total of 6,761 patients participated in the study between 2001 and 2009; 2,399, 2,136, and 2,226 patients in 2001, 2004, and 2009, respectively. Of the participants, 339 (5.0%) were rated as showing signs of TD; 37 (2.4%) patients were diagnosed with TD in China, 46 (14.9%) in Hong Kong, 4 (2.2%) in India, 112 (6.5%) in Japan, 41 (3.6%) in Korea, 14 (2.9%) in Singapore, 81 (6.4%) in Taiwan, 4 (4.0%) in Malaysia, and 0 in Thailand. Table 1 shows the socio-demographic and clinical characteristics of the study sample. Multiple logistic regression analysis revealed that the following factors were independently associated with TD: older age, male gender, more severe negative and extrapyramidal symptoms, and fewer anticholinergic drugs.

Discussion

According to the clinical judgment of experienced Asian psychiatrists, the point prevalence of TD in the pooled sample of 5.0% was in the lower range of the 3 – 62% worldwide figures [1]. To some extent this finding confirms the low frequency of TD in Asian schizophrenia patients that has been reported previously [2, 3, 4, 5, 16]. A high prevalence of TD in schizophrenia has been reported in only two Asian studies: in Singapore (39.3%, [19]) and in China (33.7%, [20]). The high frequency in these two studies is perhaps due to the older age of their sample, which had a mean of 52.8 years, and
The use of a standardized assessment instrument for TD in both surveys. Our finding of 5% was still lower than the figures that have been reported for Western patients (9.0%, [17]; 9.7%, [16]) using a similar assessment method. However, the difference between the antipsychotic drug profiles across studies precludes a direct comparison between our results and those reported in the literature. Of the participating countries and regions, Hong Kong reported the highest prevalence of TD (14.9%), followed by Japan (6.5%), Taiwan (6.4%), Malaysia (4.0%), Korea (3.6%), Singapore (2.9%), China (2.4%), and India (2.2%), while no TD was reported in Thailand. The diversity in the rates of TD found in REAP surveys may be real but could also point to insufficient awareness of TD in Asian psychiatrists. The low frequency of TD in Asian patients [2, 3, 4, 5, 16] could also reflect genetically determined ethnic differences in the metabolism of psychotropic drugs. This is evidenced by the ethnic variation in cytochrome P450 (CYP) [21, 22] and dopamine D3 receptor gene polymorphism [4, 23]. The simple “present” versus “absent” assessment of TD in this study might have underestimated its frequency. If more stringent criteria [24] had been used, it is probable that the frequency of TD would have been even lower. The difference in frequency of TD between the 2001 and 2004 surveys is unlikely due to non-random sampling in REAP studies.

In spite of the low point prevalence of TD in most study sites and the lack of standardized assessment, the results could provide valuable information about the association between TD and demographic and clinical variables. Advanced age was associated with more frequent TD in this study, as has been widely reported previously [4, 20, 25]. The reduced number...
and plasticity of dopamine neurons in the brain and the higher likelihood of neurological impairment with aging have been proposed to explain this association [26, 27].

There was a higher risk for TD in men in this study even after controlling for covariates. The relationship between gender and the frequency of TD remains ambiguous as both female [28, 29] and male [20] preponderance have been reported, in addition to no gender difference [9, 30]. The association between age, gender, and TD is complex. A review paper [1] concluded that the frequency of TD up to the age of 50 was not affected by gender, but the risk rose in women over that age.

With few exceptions [4], most studies found that more severe negative symptoms of schizophrenia were associated with a higher risk of TD [20, 26, 31, 32, 33]. This association may be an artifact owing to co-existing Parkinsonism, or an epiphenomenon of old age [27, 33]. After controlling for covariates, including age and co-existing Parkinsonism, this association remained significant in our study.

It has been thought that Parkinsonism might be an early phase or a risk factor for TD [8, 34]. Similar to previous studies [35, 36], there was a strong independent relationship between extrapyramidal symptoms and TD in our sample. Corroborating of the finding Leung et al. [4], there was an inverse association between anticholinergic drugs and TD. Discontinuation of anticholinergics is recommended once TD has developed, based on earlier reports that these drugs could worsen TD [37, 38]. Because TD is, by definition, a side effect that occurs after prolonged antipsychotic treatment [39, 40], the lower risk of TD at first admission was expected.

This study did not substantiate the significant association between TD and low [2, 19] or high doses of antipsychotics [41], confirming the findings of a previous study [4]. It may well be that antipsychotic doses were reduced when TD emerged. It has been well documented that the frequency of TD is lower in patients on SGA than FGA [17, 42]. This study failed to verify the positive relationship between TD and the current use of SGAs, although it was not possible to examine the relationship properly because a detailed drug history of the patients was not collected.

The strength of this study was its large sample size, long timespan, and the large number of mental health centers representing a range of clinical settings in Asia. There were several limitations that restrict the generalizability of the results. First, the survey used a simple clinical judgment (present/absent), which can only provide a rough estimate of the real prevalence of TD in schizophrenia [43]. Second, the inclusion of inpatients alone might have led to an underestimation of the frequency of TD. Third, the cross-sectional nature of this study made it impossible to distinguish between risk and prognostic factors for TD [26].

In conclusion, this survey found a low point prevalence of TD in several Asian countries with considerable inter-ethnic differences. The survey also confirmed the association between age, male gender, negative symptoms, extrapyramidal symptoms, anticholinergic medications, and TD in Asian schizophrenia patients.

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