The factor structure of extrapyramidal symptoms evaluated using the DIEPSS in patients with schizophrenia: results from the 2016 REAP AP-4 study

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Abstract

Drug-induced extrapyramidal syndrome (EPS) remains a major problem in clinical psychiatry. This study aimed to examine the factor structure of drug-induced extrapyramidal symptoms observed in patients with schizophrenia and assessed using the Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS). The participants were 1,478 patients with a diagnosis of schizophrenia whose EPS was assessed using the DIEPSS in India, Indonesia, Japan, Malaysia, and Taiwan in the 2016 REAP AP-4 study. The records of the participants were randomly divided into two subgroups: the first for exploratory factor analysis of the eight DIEPSS items and the second for confirmatory factor analysis.

The factor analysis identified three factors: F1 (sialorrhea, akathisia, dystonia, and dyskinesia), F2 (gait and bradykinesia), and F3 (muscle rigidity and tremor). The present results suggest that the eight individual items of the DIEPSS could be composed of three different mechanisms: central dopaminergic mechanisms with the pathophysiology other than acute parkinsonism (F1), acute parkinsonism observed during action (F2), and acute parkinsonism observed at rest (F3).

Introduction

Drug-induced extrapyramidal syndrome (EPS) remains a major problem in clinical psychiatry, especially in the treatment of schizophrenia. The appearance of drug-induced EPS has been reported to cause significant reductions in the activities of daily living, subjective distress, and impaired quality of life. It can contribute to stigma and may often result in nonadherence to antipsychotics. To improve adherence, the early detection and management of EPS is of great significance.

The Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) was developed in 1994 to evaluate the severity of antipsychotic-induced EPS on one scale. Examining the factor structure of various manifestations of drug-induced EPS is important in elucidating their individual symptomology. In previous reports examining the Korean and Japanese versions using the statistical method of principal component analysis, a similar factor structure has been shown [1]. Principal component analysis is a method for creating new synthetic variables from highly correlated observed variables, while factor analysis is a method of extracting the common factors affecting the observed variables. Principal component analysis postulates that no associations exist among the individual factor components. Therefore, factor analysis is frequently used instead of principal component analysis in clarifying the factor structure of scales whose individual items are not proven to be completely independent.

The Research on Asian Psychotropic Prescription Pattern (REAP) study began in 2001 in Asian regions to investigate the prescription patterns of patients with schizophrenia and mood disorders. Evaluation of the DIEPSS has been included in the REAP-AP4 study since 2016.

In the present study, the factor structure of the DIEPSS was examined using the REAP-AP4 data to explore the symptomatic characteristics of drug-induced EPS.

Results

Characteristics of the participants

Participants in the present study were 1,479 patients with schizophrenia (838 men and 641 women) who participated in the REAP-AP4 study and were evaluated for antipsychotic-induced EPS using the DIEPSS.
Their mean age was 40.2 (SD: 12.7) years.

The participant distribution by country was 456 from India, 261 from Indonesia, 56 from Japan, 305 from Malaysia, and 400 from Taiwan. The psychotropic prescription patterns of patients with schizophrenia are as follows: The number of types of antipsychotic agents the patients had been receiving were: 1 type, n = 957; 2 types, n = 456; and 3 types, n = 60. Six patients did not receive any antipsychotic agents. Of the 1479 total subjects, 25% (n = 375) had been receiving first generation antipsychotics, 81% (n = 1208) had been receiving second generation antipsychotics, and 38% (n = 559) had antiparkinsonian agents. Duration from the onset until now is: less than 3 months, n = 48; 3–6 months, n = 40; 6 month – 1 year, n = 47; 1 year – 5 years, n = 273; 5–10 years, n = 261, 10–20 years n = 444, 20 years or more, n = 363; no information n = 6. DUP is: less than 3 months, n = 543; 3 months – 1 year, n = 497; 1 year – 5 years, n = 287; 5 years or more, n = 76; no information n = 78.

Factor analysis

For the EFA, half of the participants (n = 739) were analyzed. The KMO value and the χ^2 value by Bartlett's test of sphericity were 0.867 and 2563.819 ($F = 28$, $p < 0.0001$), respectively. These values indicated reasonable values for the factor analysis. Mean, Standard Error (SE), and

the results of the EFA are shown in Table 1. Since no items with communality less than 0.2 were confirmed, all eight individual items were analyzed.

Table 1
Exploratory Factor Analysis (EFA) of the DIEPSS (n = 739)

	Mean (SD)	Communality	One-factor model	Two-factor model		Three-factor model			Four-factor model			
			F1	F1	F2	F1	F2	F3	F1	F2	F3	F4
1. Gait	0.35 (0.72)	0.566	**0.753**	0.058	**0.809**	0.064	**0.799**	0.022	**0.779**	0.036	0.029	0.036
2. Bradykinesia	0.43 (0.77)	0.535	**0.731**	-0.058	**0.926**	-0.049	**0.88**	0.054	**0.922**	-0.038	00.049	-0.053
3. Sialorrhea	0.31 (0.70)	0.334	**0.578**	**0.439**	0.176	**0.419**	0.173	0.037	-0.004	− .006	0.014	**0.687**
4. Muscle rigidity	0.40 (0.75)	0.520	**0.721**	**0.536**	0.237	0.016	0.026	**0.898**	0.039	.055	00.877	-0.045
5. Tremor	0.54 (0.84)	0.368	**0.607**	**0.389**	0.252	0.123	0.18	**0.395**	0.118	-0.013	0.415	0.191
6. Akathisia	0.27 (0.63)	0.434	**0.659**	**0.721**	-0.011	**0.634**	-0.017	0.115	-0.064	**0.394**	0.111	0.332
7. Dystonia	0.21 (0.55)	0.446	**0.668**	**0.886**	-0.147	**0.77**	-0.157	0.156	-0.084	**0.888**	0.122	-0.121
8. Dyskinesia	0.21 (0.55)	0.505	**0.71**	**0.603**	0.174	**0.77**	0.184	-0.163	0.233	**0.629**	-0.161	0.115
Factor loading (%)			52.97	52.97	11.12	52.97	11.12	9.05	52.97	11.12	9.05	8.14
Eigenvalue			4.237	4.237	0.890	4.237	0.890	0.724	4.237	0.890	0.724	0.651

DIEPSS: Drug-Induced Extrapyramidal Symptoms Scale

SD: standard deviation

For the CFA, another half of the participants (n = 739) were analyzed. From the result of the EFA, a one-factor model (F1: 1–8), a two-factor model (F1: 3–8 and F2: 1, 2), and a three-factor model (F1: 3, 6–8; F2: 1, 2; and F3: 4, 5) were examined. The goodness of fit was calculated for each of the models identified by the EFA shown in Table 2. The critical values of the χ^2 distribution at the significance level of $p < 0.001$ corresponding to *df* values of 1 and 2 were 10.83 and 13.82, respectively. The goodness of fit was not improved by increasing the number of factors because these critical values were all higher than the $\Delta\chi^2/df$ values corresponding to the individual factor models. The three-factor structure model had the best fit, as shown in Fig. 1.

Table 2
Confirmatory Factor Analysis (CFA) of the DIEPSS

Model	Items	χ^2	*df*	χ^2/df	$\Delta\chi^2/df$	CFI	GFI	AGFI	RMSEA	AIC
One-factor model	F1: 1–8	381.95	20	19.10		0.873	0.876	0.777	0.157	413.95
Two-factor model	F1: 3–8 F2: 1, 2	187.14	19	9.85	194.81	0.941	0.938	0.882	0.110	221.14
Three-factor model	F1: 3, 6–8 F2: 1, 2 F3: 4, 5	89.90	17	5.29	48.62	0.974	0.971	0.938	0.076	127.90

CFI: comparative fit index

GFI: goodness of fit index

AGFI: adjusted goodness of fit index

RMSEA: root mean square error of approximation

AIC: Akaike's information criterion

Discussion

In the present factor analysis of the DIEPSS, three factors were detected: F1 (akathisia, dystonia, dyskinesia, and sialorrhea), F2 (gait and bradykinesia), and F3 (muscle rigidity and tremor). The present results suggest that the eight individual DIEPSS items could be composed of three different mechanisms: central dopaminergic mechanisms with the pathophysiology other than acute parkinsonism (F1), acute parkinsonism observed during action (F2), and acute parkinsonism observed at rest (F3).

In the first factor, four symptoms of akathisia, dystonia, dyskinesia, and sialorrhea were detected. The pathophysiology of these symptoms is heterogeneous and various etiologies are included.

Sialorrhea was originally regarded as a parkinsonian symptom resulting from the decreased motility of the esophagus due to bradykinesia of the laryngeal muscle in the era of first-generation antipsychotics [2]. For example, chlorpromazine increases sialorrhea despite having an anticholinergic effect [3 4]. In contrast, sialorrhea occurs in approximately 54% of patients with schizophrenia receiving clozapine, who are known to develop less EPS [3]. For this reason, the pathophysiology of sialorrhea has been considered to include additional pathophysiology other than the dopamine D2 blockade. Clozapine also has an anticholinergic effect that diminishes salivary secretion [5]. The high frequency of sialorrhea observed in patients receiving clozapine is considered to be due to the pharmacological effects of the combination of the α2 receptor blockade [6] and the muscarinic M4 receptor agonist activity [7], in addition to bradykinesia of the laryngeal muscle that occurs as a result of the dopamine D2 blockade [8].

Various mechanisms have been proposed for the pathophysiology of akathisia other than the dopamine D2 blockade explained as the mechanism of parkinsonian symptoms. Unlike other antipsychotic-induced EPS, which appears associated with the dopamine D2 blockade of nigrostriatal traits, the dopamine D2 blockade action of the mesolimbic and midbrain cortical systems has also been postulated to be involved in its pathophysiology. Decreased GABA function has also been considered to be involved in the pathophysiology of akathisia since benzodiazepines are effective against it [9]. In addition, enhanced noradrenergic function is also postulated to be involved in the pathophysiology of akathisia due to the effectiveness of β blockers for relieving its symptoms.

Dyskinesia often develops following the discontinuation of antipsychotic agents in patients with schizophrenia after long-term use. In contrast to the dopamine D2 receptor blockade postulated in the pathophysiological mechanism of EPS observed in the acute therapeutic phase, the hypersensitivity of the postsynaptic dopamine D2 receptor has been implicated in the pathophysiological mechanism of dyskinesia, a late-onset delayed side effect. In addition to the hypersensitivity of the postsynaptic dopamine D2 receptor, other neurochemical mechanisms, such as the renewal of the noradrenergic system in the brain and the GABA dysfunction theory (Gunne et al., 1984, Anderson et al., 1989), are also assumed to be involved.

Antipsychotic-induced dystonia often develops in the early acute phase following the administration of antipsychotic agents. Presynaptic excessive dopamine synthesis and release have been proposed for its pathophysiology, unlike the dopamine D2 blockade as postulated in antipsychotic-induced parkinsonism. The clinical manifestation of dystonia develops in various patients with neurological diseases caused by the basal ganglia, and its pathophysiology is often not clearly explained, although noradrenergic systems, cholinergic systems, and GABAnergic systems may involve other than the dopaminergic systems. In addition, patients with schizophrenia who have never received antipsychotic agents are known to show dystonic postures. The pathophysiology of these dystonic manifestations is considered to include other mechanisms that are not associated with the dopamine D2 receptor blockade.

The representative three major symptoms of idiopathic Parkinson's disease are tremor, muscle rigidity, and behavioral hypokinetic symptoms including gait and bradykinesia [10]. In the present results, the three items were not classified as the same factor but divided into two factors: the two symptoms of muscle rigidity and tremor were separated from the behavioral hypokinetic symptoms of gait and bradykinesia.

The principal pathophysiology of the four symptoms subclassified in the second and third factors are all involved in the dopamine D2 blockade [11]. In patients with schizophrenia, it is often difficult to differentiate the negative symptoms of schizophrenia from the parkinsonian gait and bradykinesia detected in the first factors in the usual clinical setting [12,13], unlike the symptoms of tremor and muscle rigidity. The results could imply the separation of F2 and F3. The typical parkinsonian symptoms are considered to be divided into two factors depending on whether the heterogeneous pathophysiology underlying the negative symptoms contains or not.

As shown in the present study, subclassifying eight items of the DIEPSS using factor analysis is important in identifying the differentiation of mechanisms underlying the eight individual symptoms. The factor structure may change depending on whether patients are taking acute or chronic pharmacological treatments and whether or not they are receiving clozapine, first-generation antipsychotic agents, or second-generation antipsychotic agents. Further research with participants of various schizophrenic populations is needed to identify the potential differentiation of the mechanisms underlying the eight individual items in the DIEPSS.

Methods

Ethical considerations

This study was initiated after the approval of the ethical committees of National Institute of Mental (Japan), of Nagoya University (Japan), and of all other attending facilities listed in authors affiliations.
All study procedures were conducted in accordance with the Declaration of Helsinki.

Written informed consent for participation was obtained from all participants.

Participants

The participants were 1,478 patients with a diagnosis of schizophrenia who were evaluated for EPS using the DIEPSS in the 2016 REAP AP-4 study. These patients were seen in mental health services in India, Indonesia, Japan, Malaysia, and Taiwan. The criteria used to select patients for this study were: (1) diagnosis of a schizophrenic disorder according to the criteria of the DSM-Ⅳ, DSM5, or ICD-10, and (2) treatment using antipsychotic medications at the facilities included in the study.

Procedure

The participants were evaluated for EPS using the DIEPSS, and the following medical information was extracted from their records: age, gender, body mass index, duration from the onset until now, duration of untreated period, and psychotropic prescription.

Evaluation of the DIEPSS

The DIEPSS is a rating instrument to evaluate drug-induced EPS in psychiatric patients receiving antipsychotic agents. It consists of eight individual items (gait, bradykinesia, sialorrhea, muscle rigidity, tremor, akathisia, dystonia, and dyskinesia) and one global item. The DIEPSS uses a 5-point Likert scale: 0 = none, normal; 1 = minimal, questionable; 2=mild; 3 = moderate; 4=severe [14].

Statistical analyses

Factor analysis was conducted after an assessment of specimen validity using the Kaiser-Meyer-Olkin (KMO)[15] test and Bartlett's test of sphericity [16] to determine the sampling adequacy of the data. A KMO value greater than 0.6 is considered appropriate for conducting the factor analysis [17]. The distribution of the individual DIEPSS items was examined using the skewness and likelihood, and each item was logarithmically analyzed.

The participants were randomly divided into two sample sets.
The first sample set was used for exploratory factor analysis (EFA), and the second sample set was used for confirmatory factor analysis (CFA).

EFA was conducted for the items with communalities greater than 0.2 [18]. The number of factors was determined using the scree plot [18]. Maximum likelihood estimation and Promax rotation were adopted because a correlation between factors may exist. The DIEPSS items with a factor coefficient level greater than 0.3 were defined in the same factor.

The best-fit model of CFA was determined based on the models obtained from EFA.
To assess model fit, the following goodness of fit tests were performed: chi-square (χ^2)/degrees of freedom (*df*), comparative fit index (CFI; [19], root mean square error of approximation (RMSEA; [20], goodness of fit index (GFI; [21], adjusted goodness of fit index (AGFI; [21], and Akaike's information criterion (AIC; [22]. The CFI, GFI, and AGFI values are considered good when they are higher than 0.97, acceptable when they are between 0.95 and 0.97, and required for the adoption of the model when they are 0.95 or lower [19,21]. An RMSEA value is good when it is lower than 0.05, acceptable when it is between 0.05 and 0.08, and required for the adoption of the model when it is higher than 0.08 [20]. Lower χ^2/df and AIC values indicate better fit [22]. Whether the goodness of fit was sufficiently improved by increasing the number of factors was evaluated based on the $\Delta\chi^2$ value, using the table of χ^2 distribution.

The data were analyzed using IBM SPSS and Amos version 26.0 (IBM Japan, Ltd., Tokyo, Japan).

Declarations

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Taipei City Government prepared a necessary fund for web system construction, data compilation and analysis.

Author contributions

Norman Sartorius, Mian-Yoon Chong, and Chay-Hoon Tan conceived and designed the study. Shu-Yu Yang, Lian-Yu Chen, and Shih-Ku Lin organized and managed the data. Chika Kubota conducted the statistical analysis. Chika Kubota and Toshiya Inada wrote the first draft of the manuscript. All authors participated in the data collection, interpreted the results and revised the manuscript, and approved the final version of the manuscript.

Competing interests

The authors have no competing interests directly relevant to the content of this study.

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Figures

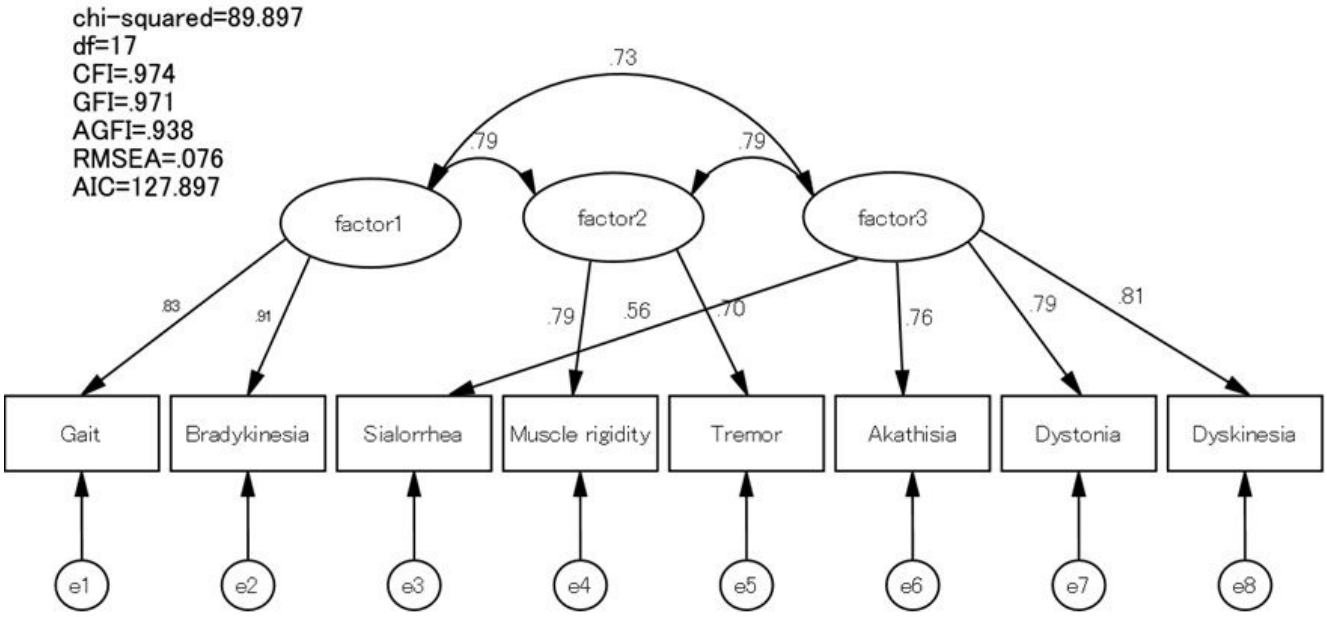

Figure 1

Best-fit model of the DIEPSS