

## Establishing a Comprehensive Questionnaire for Detecting Drug-induced Extrapyrimal Symptoms

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**Objective:** Drug-induced extrapyramidal symptoms (DIEPS) often substantially compromise quality of life (QOL) of patients receiving drugs with central antidopaminergic activities. A lack of comprehensive screening method based upon patients' subjective symptoms for detecting DIEPS appears to have prevented pharmacists from delivering satisfactory pharmaceutical care for these patients. Thus, we have attempted to develop a comprehensive questionnaire for screening patients having higher risks of developing DIEPS.

**Methods:** One hundred fourteen outpatients taking gastroprokinetic drugs (itopride, cisapride, trimebutine, domperidone and metoclopramide) at least 2 weeks participated in the study. One patient with familial Parkinson disease served as a positive reference. They undertook a questionnaire consisting of 9 comprehensive questions written in non-technical words that were aimed to detect typical symptoms of Parkinsonism including akathisia and dyskinesia. Each symptom was scored in a semiquantitative scale [i.e., from 1 (not at all) to 5 (very much)] by the patients.

**Results:** Of the 108 subjects who successfully completed the questionnaires, 43 gave scores 2 or greater indicating the presence of DIEPS. However, no statistically significant correlations were observed between the scores of any possible pairs of the questionnaire items. Five subjects had a mean questionnaire score of equal to or greater than 1.6, and the patient with familiar Parkinsonism had the highest mean score of 1.9. **Conclusion:** The questionnaire presented herein detected 4 patients with suspected DIEPS. Further studies should be warranted to assess whether it would be useful for pharmacists as a screening tool for DIEPS in patients having higher risks of DIEPS.

**Key words**—drug-induced extrapyramidal symptoms; questionnaire; adverse drug reactions; pharmaceutical care

### INTRODUCTION

Adverse drug reactions (ADRs) are associated with impaired quality of life (QOL) of patients despite that responsible drugs elicit adequate therapeutic efficacy.<sup>1)</sup> Early detection of ADRs in patients with chronic illness is particularly important for accomplishing a long-term pharmacotherapy with satisfactory QOL. Among the ADRs encountered in pharmaceutical care of patients who are on a chronic administration of antipsychotic drugs, gastroprokinetic drugs (e.g., metoclopramide) or antidepressants, drug-induced extrapyramidal symptoms (DIEPS) are most often associated with impaired QOL of the patients.<sup>2)</sup>

Many gastroprokinetic drugs (domperidone,<sup>3)</sup> metoclopramide,<sup>4)</sup> clebopride malate<sup>5)</sup> and others)

possess central antidopaminergic properties. They have been often implicated to be responsible to DIEPS in many anecdotal reports. While cisapride<sup>6)</sup> and itopride hydrochloride,<sup>7)</sup> are weak and peripheral dopamine D<sub>2</sub> receptors blocking properties, they may also be associated with the development of DIEPS. The prevalence of gastroprokinetics-associated DIEPS would be lower than that of antipsychotics-associated one. However, because numbers of patients receiving gastroprokinetic drugs are far greater than those receiving antipsychotics, gastroprokinetics-associated DIEPS should not be underscored.

While several methods have been developed for detecting DIEPS in patients taking antidopaminergic drugs [e.g., the Extrapyrimal Symptom Rating Scale (ES-RS),<sup>8)</sup> the St. Hans Rating Scale for Extrapyrimal Syndromes (St. Hans EPS),<sup>9)</sup> and the Drug-Induced Extrapyrimal Symptoms Scale (DIEPSS)<sup>10)</sup>], they are in general rather complicated

and difficult to implement in clinical practice particularly for pharmacists. Because substantial knowledge and skills are required to utilize these methods, the previous methods have been used rarely in the practice of pharmaceutical care by pharmacists. For instance, the ES-RS<sup>8</sup> consists of 3 subscales for Parkinsonism (8 items and clinical global impression), dystonia (2 items), and dyskinesia (7 items and clinical global impression). Each item is to be rated on 7- or 9-point scales. The St. Hans EPS consists of 4 subscales for hyperkinesia (8 regional body areas and summative evaluation), Parkinsonism (8 items and summative evaluation), akathisia, and dystonia. In addition, severity of each symptom is to be rated on a 7-point scale.<sup>9</sup> The DIEPSS developed in Japan consists of 4 subscales for Parkinsonism (5 items), akathisia, dystonia, and dyskinesia in combination with a global evaluation. Each item of assessment is to be rated on a 5-point scale.<sup>11</sup> In this context, we decided to develop a more comprehensive screening questionnaire system based upon patients' subjective symptoms in order to facilitate pharmacists' contribution to therapeutic monitoring of patients having higher risks of DIEPS. Here, we present such a questionnaire and discuss its usefulness based upon the results obtained from our first attempt to use the questionnaire in ambulatory patients.

## MATERIALS AND METHODS

One hundred fourteen ambulatory patients who were given gastroprokinetic drugs (i.e., itopride hydrochloride, cisapride, trimebutine maleate, domperidone and metoclopramide) for at least more than 2 weeks were recruited from those visiting at Nippon Medical School Tama-Nagayama Hospital in November 1998. A 77 year-old female patient who was diagnosed as having familial Parkinson's disease was also recruited from ambulatory patients and she served as a positive reference for assessing the validity of the questionnaire. When she underwent the questionnaire, she had refrained from taking her antiparkinson drugs for 4 weeks for a scheduled ophthalmological operation. All patients were explained the purpose of the study fully and informed consent was obtained from each of them. The research protocol had been approved by the institutional review board (IRB) of the hospital before the study began. Demographic data of the patients (e.g., age and sex) and other relevant medical information (e.g., underlying dis-

ease, concurrently prescribed gastroprokinetic drugs) were retrieved from their medical records and interview to patients.

The newly developed questionnaire for detecting DIEPS consisted of questions aimed to detect 9 representative symptoms of Parkinsonism including sialorrhea, gait disturbance, hesitation for start walking (freezing), bradykinesia, muscle rigidity, tremors, loss of vital facial expression (i.e., masked face), akathisia and dyskinesia. Questions of the questionnaires were written by non-technical words and expressions. Patients' self-assessment for each item of the questionnaire (i.e., the presence or absence of the symptoms and the their severity, if present) was semiquantitatively scored by using a 5-point scale. For instance, the lowest level (i.e., point 1) represents the absence of the condition and the highest level (i.e., point 5) represents the presence of the condition at the greatest degree. When a score of 2 or greater was given to a questionnaire item from a patient, we searched for clinical conditions or complications that might have strongly influenced the patient's assessment. If such a clinical factor was identified, we considered that the score of the questionnaire concerned was inapplicable. Those medical conditions included low back pain, sciatic neuralgia, poorly fitted dentures, and others that would substantially disturb or interfere with motor function of extremities or masticating function. Nonetheless, we included the scores of other questionnaires from the patient in the analysis.

**Statistical Analyses** Correlations between the score of different questionnaire items were assessed by Spearman's rank correlation test. Spearman's rank correlation test was also performed to determine whether total scores of the questionnaire would be correlated with any of the patients' characteristics (i.e., gender, age and the duration of administration for the gastroprokinetic drugs). All statistical analyses were performed using SPSS version 10.0 for Windows (SPSS Inc., Chicago, IL). All statistical tests were two-tailed and a *p* value of <0.05 was considered statistically significant.

## RESULTS

Clinical characteristics of 108 patients who completed the questionnaire are shown in Table 1. They are relatively old (the mean age: 61 years) and suffered mainly from gastrointestinal diseases (e.g.,

peptic ulcer diseases and constipation). Cisapride was administered approximately 60% of the patients. The mean duration of administration of gastroprokinetic drugs was 3.0 years. None of them was told to have DIEPS by physicians when the questionnaire was addressed. The patient diagnosed as having familiar

Parkinsonism (i.e., the positive reference) received cisapride and trimebutine for 8 years prior to the study.

Appendix shows the questionnaire items designed for detecting DIEPS. In 36 out of the 79 patients who scored 2 or greater for at least one of the questionnaire items, their answers to certain questionnaires were strongly influenced by their medical complications rather than DIEPS. The medical conditions detected in these patients were low back pain ( $n=21$ ), injury/bruise/distortion of the lower extremities ( $n=10$ ), poorly fitted dentures ( $n=4$ ), reflux esophagitis ( $n=4$ ), bronchial asthma ( $n=2$ ), diabetic neuropathy ( $n=2$ ), sciatic neuralgia ( $n=2$ ), postoperative status of colostomy ( $n=1$ ), postoperative status of shoulder joint ( $n=1$ ), shoulder-hand syndrome ( $n=1$ ), fracture ( $n=1$ ) and facial paralysis ( $n=1$ ). Because these complications disturbed motor functions of extremities, walking and mastication, thereby making it impossible to detect DIEPS by some, but not all, of the questionnaire items. Figure 1 shows the results of questionnaire after excluding the not applicable answers. While most of the patients (i.e., 84 to 97% for the respective items) gave the score of 1 (i.e., absence of DIEPS) for most of the questionnaire items, 43 patients scored 2 or greater for at least 1 item. The patient having familiar Parkinsonism

Table 1. Clinical Characteristics of Patients Participating to the Present Study

Number of subjects	108 (56 males and 52 females)
Age (yr)	61 ± 11*
Concurrent illness (%)	Gastrointestinal disease: 60 Cardiovascular disease: 22 Cerebrovascular disease: 8 Endocrinological disease: 6 Respiratory disease: 3 Neurological disease: 1
Gastroprokinetic drugs prescribed (%)	Cisapride: 59.3 Itopride hydrochloride: 17.6 Trimebutine maleate: 13.9 Metoclopramide: 3.7 Domperidone: 2.8 Others: 2.7
Duration of drug administration (yr)	3.0 ± 3.6 (range: 0.005—20)

Data are means ± SD.

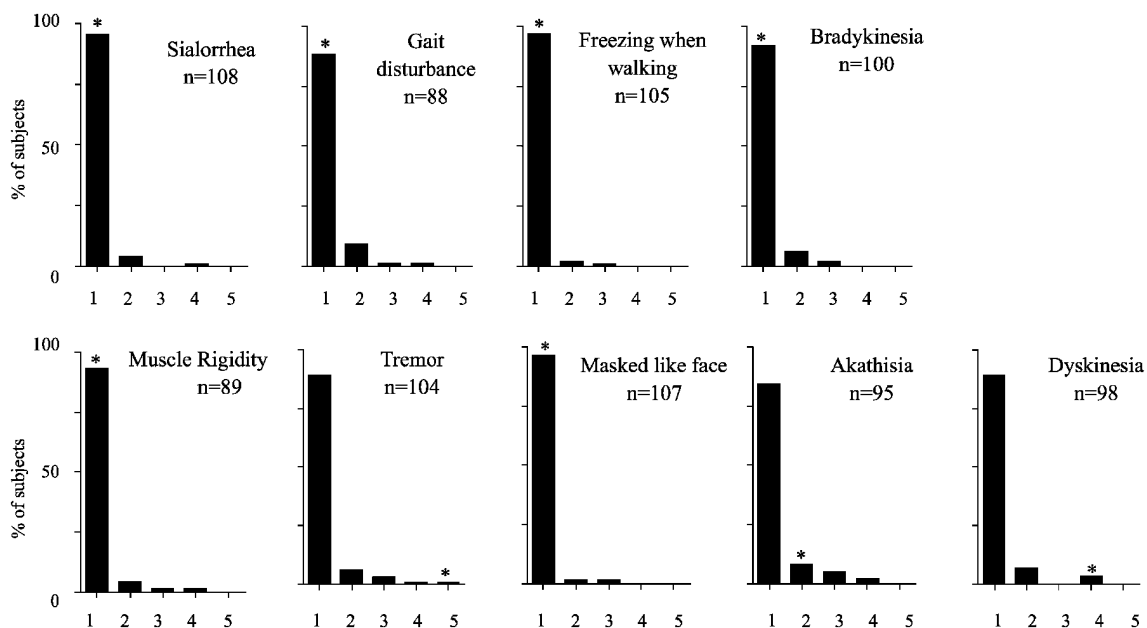


Fig. 1. Histograms for Percentages of Patients who Gave Different Scores for the Respective Questionnaire Items Intended to Detect 9 Different Clinical Symptoms Associated with Parkinsonism Including Akathisia and Dyskinesia that may be Attributable to DIEPS. The greater scores correspond to severer symptoms. The patient diagnosed as having familiar Parkinson's disease is indicated by asterisk (\*).

gave scores of equal to or greater than 2 for questionnaire items intended to detect akathisia, dyskinesia and tremor (i.e., 2, 4 and 5 point, respectively).

No significant correlation was observed between the scores of any pairs of the questionnaire items. Because no significant differences were found in the distribution of scores between questionnaire items using the Kruskal-Wallis test, scores obtained from each questionnaire item was summed up and divided by number of applicable item for each patient as follows:

The mean score

$$= \frac{\text{Total score of that obtained from each applicable questionnaire item}}{\text{Number of applicable questionnaire items}}$$

Figure 2 shows the histograms for the mean scores obtained from the patients. Five patients (4 males, 1 female) gave the scores of equal to or greater than 1.6. The mean age of them was 72 years (range; 60 to 83 years), and the mean duration of the administration of gastroprokinetic drugs was 2.9 years (range; 1 to 8 years). The patient with familial Parkinson's disease gave the highest mean score of 1.9. No significant correlation was observed between the mean scores for the questionnaire and sex, age or the duration of the administration of gastroprokinetic drugs.

## DISCUSSION

DIEPS has been shown to be one of the important

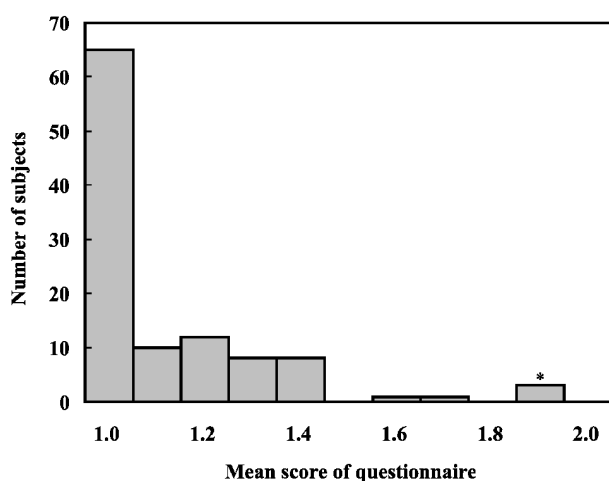


Fig. 2. Histograms of the Mean Questionnaire Scores Obtained from the Patients Participated in the Present Study. The greater scores correspond to severer symptoms. The patient diagnosed as having familial Parkinson's disease is indicated by asterisk (\*).

ADRs associated with the deterioration of patients' QOL and compliance of pharmacotherapy.<sup>12)</sup> In the present study we assessed whether our comprehensive questionnaire could detect clinical symptoms assumed associated with DIEPS in patients taking various dopamine receptor blockers. We were able to detect 43 out of 108 patients who might have been at risk of DIEPS. Among these patients, 5 had the mean questionnaire scores of equal to or greater than 1.6, indicating that their clinical symptoms were likely attributable to DIEPS. In addition, the patient having familiar Parkinsonism gave the highest mean questionnaire score of 1.9 among the participants. She gave scores of 2, 4 and 5 for the questionnaire items for akathisia, dyskinesia and tremor. In this context, we are tempted to speculate that our comprehensive questionnaire for screening DIEPS may warrant further studies to confirm its usefulness in greater populations.

One of the aims of the present study was to develop a comprehensive questionnaire that can be used easily by health care professionals who are not familiar with elaborated neurological examinations (e.g., pharmacists). Thus, questionnaire items were written non-technical words and expressions. Our questionnaire was formulated to assess the manifestations of DIEPS based upon the changes in the patients' activities during their daily living. Each item of the questionnaire was made with reference to those used in the Unified Parkinson's Disease Rating Scale.<sup>13)</sup>

Our questionnaire was successfully completed by most of the patients participated in the study. However, some of the questionnaire items were not applicable to patients with certain medical complications. For instance, a score of 2 or greater for the questionnaire 2 that was obtained from a patient with low back pain or a fracture of a lower extremity should not simply be attributable to DIEPS of concomitant medications. Nonetheless, because the participants of the present study were rather old (the mean age of 61 years), many of them were complicated with other medical conditions that would disturb accurate assessment of some, but not all, of the questionnaire items. Such an inherent difficulty should be encountered by any questionnaire approaches for detecting DIEPS in elderly patients.

Because patients with Parkinsonism exhibit a wide variety of clinical symptoms, we formulated the questionnaire so that it covers 9 representative symptoms

of the disease. However, we did not include a questionnaire item for dystonia. It usually develops within 3 to 5 days after the initiation of antidopaminergic drug administration.<sup>14)</sup> Because our patients were on a long-term antidopaminergic therapy, we consider that our patients would have a very remote possibility to developing dystonia during the present study. In addition, there was no significant correlation between the scores obtained from any pairs of the questionnaire items. This suggests that a certain combination or subset of the questionnaire items would not allow detecting DIEPS more sensitively than a whole battery of the questionnaire items. In this context, we decided to summarize the result of the questionnaire obtained from each patient as the mean score. Results showed that 5 patients displayed the mean scores of equal to or greater than 1.6 (Figure 2) and the patient with familial Parkinson's disease displayed the highest score of 1.9. These data may support the validity of our approach.

One of the drawbacks of the present study was a lack of comparison between the results obtained from our novel questionnaire system and those obtained from previous methods (e.g., St. Hans EPS, DIEPSS) in the same patients. Thus, further studies should be required to validate our questionnaire system with reference to the concurrent ones. In addition, it would be interesting to study if the present questionnaire may be applicable to patients receiving antipsychotic drugs having a greater dopaminergic blocking activity. Furthermore, we consider that applicability of the current scaling system to different patient populations should be assessed before further studies with a greater number of patients are to be conducted.

In conclusion, we have developed the comprehensive questionnaire for detecting DIEPS. The questionnaire was formulated so that health care professionals who are not neurology specialists can use it. The questionnaire was completed by most of the patients receiving drugs with dopaminergic blocking activity commonly prescribed in ambulatory clinics and it allowed detecting 4 out of 108 patients who may have DIEPS. We consider that the results warrant further studies to confirm whether our questionnaire would be a useful tool for pharmacists for monitoring ADRs.

### APPENDIX: A Newly Developed Questionnaire for Detecting DIEPS

Please circle the number that best indicates your present condition in each of the following questions.

(1) Do you feel that the amount of saliva has increased recently?

1    2    3    4    5  
 ───────────  
 not at all                      very much

(2) Do you feel that you walk slower than before or do you stumble easily? If you choose number equal to or greater than 2, please choose one reason that may accounts for your condition.

1    2    3    4    5  
 ───────────  
 not at all                      very much

- (Reason)
1. Injuries at present
  2. Sequela of the past injury
  3. Low back pain
  4. Rheumatoid arthritis
  5. Age
  6. No clear reason
  7. Other (            )

(3) Do you feel difficulty in crossing road on the green light?

1    2    3    4    5  
 ───────────  
 not at all                      very often

(4) Do you feel difficulty in fastening buttons on clothes or in putting on socks?

1    2    3    4    5  
 ───────────  
 not at all                      very much

(5) Do you feel difficulty in bending your elbows or knees during activity of daily living?

1    2    3    4    5  
 ───────────  
 not at all                      very much

(6) Do you notice that your hands sometimes tremble or do you have difficulty in writing?

1    2    3    4    5  
 ───────────

not at all                      very much

(7) Do you sometimes feel that your facial expression becomes stiff or have your family or friends told so to you?

1    2    3    4    5  
└───┬───┬───┬───┘  
not at all                      very often

(8) Do you sometimes feel that you cannot make your legs quit or unmoved while sitting on chair?

1    2    3    4    5  
└───┬───┬───┬───┘  
not at all                      very much

(9) Do you sometimes feel that you cannot speak or swallow food well?

1    2    3    4    5  
└───┬───┬───┬───┘  
not at all                      very often

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