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Liverpool University Neuroleptic Side-Effect Rating Scale (LUNSERS) as a subjective measure of drug-induced parkinsonism and akathisia

Hee-Yeon Jung[1,2], Jong-Hoon Kim[3], Yong-Min Ahn[1,4,5], Seong-Chan Kim[1,4], Samuel S. Hwang[4] and Yong-Sik Kim[1,4,5]*

[1]*Department of Psychiatry, Seoul National University College of Medicine, Seoul, Korea*
[2]*Boramae Hospital, Seoul, Korea*
[3]*Department of Psychiatry, Gil Medical Center, Gachon Medical School, Incheon, Korea*
[4]*Department of Psychiatry, Seoul National University Hospital, Seoul, Korea*
[5]*Institute of Human Behavioral Medicine, Seoul National University College of Medicine, Seoul, Korea*

The Liverpool University Neuroleptic Side-Effect Rating Scale (LUNSERS) was examined for its usefulness as a subjective measure of drug-induced parkinsonism and akathisia. Eighty-three subjects were assessed using the LUNSERS, the Simpson–Angus Scale (SAS) and the Barnes Akathisia Rating Scale (BARS), before and after a 6-week treatment with olanzapine. Significant correlations were found between the changes in scores of parkinsonism items of LUNSERS and SAS. The changes in scores of akathisia item (restlessness), extrapyramidal side effects (EPS) subscale and psychic side-effects subscale of LUNSERS were significantly correlated with those of the BARS. 'Shakiness', one item of the EPS subscale of LUNSERS, correctly classified between parkinsonism and non-parkinsonism groups with 81.0% accuracy. A combination of four items included in EPS and psychic side-effect subscales of LUNSERS identified akathisia and non-akathisia groups with 76.2% accuracy. These results suggest that the EPS and psychic side-effect subscales of LUNSERS may be useful in screening for drug-induced parkinsonism and akathisia. Copyright © 2004 John Wiley & Sons, Ltd.

KEY WORDS — Liverpool University Neuroleptic Side-Effect Rating Scale; parkinsonism; akathisia; antipsychotic agents

INTRODUCTION

It has become increasingly recognized that subjective experiences of adverse effects of antipsychotic drugs are significantly associated with a number of important clinical outcomes, such as compliance, treatment outcome and quality of life (Awad and Voruganti, 2000; Naber *et al.*, 2001). The Liverpool University Neuroleptic Side-Effect Rating Scale (LUNSERS) has been developed as a comprehensive self-rating instrument for assessing and quantifying the subjective adverse events during antipsychotic treatment (Day *et al.*, 1995). Most elements of the LUNSERS have been derived from the corresponding items of the Udvalg for Kliniske Undersogelser (UKU) side-effect rating scale (Lingjaerde *et al.*, 1987). The LUNSERS has proven to be useful in assessing subjective tolerability in previous studies (Morrison *et al.*, 2000a, 2000b; Voruganti *et al.*, 2000) and its psychometric properties were also reported by Lambert *et al.* (2003). Although it has shown a high level of concurrent validity with the UKU rating scale, the validity of the LUNSERS as a subjective measure of drug-induced parkinsonism and akathisia has not yet been investigated in comparison with the most common observer-rated movement scales such as the Simpson–Angus Scale (SAS) (Simpson and Angus,

* Correspondence to: Professor Yong-Sik Kim, Department of Psychiatry, Seoul National University College of Medicine, 28 Yongon-Dong, Chongno-Gu, Seoul, 110-744, South Korea. Tel: +82-2-760-2204. Fax: +82-2-744-7241. E-mail: kys@snu.ac.kr

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1970) and the Barnes Akathisia Rating Scale (BARS) (Barnes, 1989). This study investigated whether the LUNSERS is useful as a subjective measure of drug-induced parkinsonism and akathisia.

METHODS

The subjects consisted of 83 patients (46 men; 37 women) who were participating in an open study on switching from previous antipsychotics to olanzapine (Ahn *et al.*, 2002, 2003). All subjects met the ICD-10 diagnostic criteria for schizophrenia or schizoaffective disorder. The subjects had a mean age of 34.1 ± 8.4 years and a mean duration of illness of 8.4 ± 7.7 years. All subjects were receiving antipsychotic drugs with a mean dosage of 320.8 ± 395.6 mg/day of chlorpromazine equivalents. Most of the subjects (53 of 83) were already taking atypical antipsychotics and concurrent medications at the time of the study entry including benzodiazepines (56), anticholinergics (54), beta-adrenergic blockers (18), mood stabilizers (12), antidepressants (12) and buspirone (1). The open label olanzapine treatment period was 6 weeks. Gradual tapering of concomitant medications was encouraged during the first 2 weeks of olanzapine treatment. The mean olanzapine dose at the end of week 6 was 12.8 ± 6.0 mg/day. At the endpoint, 20 subjects were receiving benzodiazepines, ten anticholinergics and one a beta-adrenergic blocker.

All subjects completed the Korean version of LUNSERS (Jung *et al.*, 2002). It consists of 51 items that are divided into seven different subscales (including EPS, anticholinergic, autonomic, psychic, allergic, hormonal and miscellaneous side-effects) and ten 'red herring' items (runny nose, chilblains, hair loss, urine darker than usual, weak fingernails, mouth ulcers, greasy skin, flushing of face, neck muscle aching and painful joints). The EPS subscale consists of seven individual items and the psychic side-effect subscale consists of ten individual items (Table 1).

Table 1. The individual items of the EPS and the psychic side-effect subscales of LUNSERS

	Individual items
EPS subscale	muscle spasm
	muscle stiffness
	slowing of movements
	part of the body moving of their own accord
	shakiness
	restlessness
	drooling mouth
Psychic side-effect subscale	difficulty staying awake during the day
	increased dreaming
	difficulty in concentrating
	tension
	tiredness
	difficulty in remembering things
	lack of emotions
	difficulty getting to sleep
	depression
	sleeping too much

Objective assessments of drug-induced parkinsonism and akathisia were carried out using the SAS and BARS by sufficiently trained clinicians. The SAS was developed to measure drug-induced parkinsonism, providing standardized objective assessment of rigidity, tremor, bradykinesia and salivation. It consists of ten items such as gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, head dropping, glabellar tap, tremor and salivation. Each item is rated on a five-point scale (0–4). All items are assessed using clinical observation and neurological examination. According to the SAS, drug-induced parkinsonism was diagnosed if the total SAS score was 4 or greater (Simpson and Angus, 1970).

The BARS was devised specifically to measure drug-induced akathisia by the examiner. It comprises items for rating the objective motor manifestation (shuffling, tramping, crossing/uncrossing of legs, rocking from foot to foot, or walking on the spot when standing), the subjective awareness of inner restlessness (awareness of an inability to keep the legs still, a desire to move the legs, discomfort in the lower limbs or complaints of inner restlessness aggravated specifically by being required to stand still) and the associated distress. Specific questions about the subjective awareness of restlessness are asked and the presence and severity of the symptoms of akathisia are evaluated by the examiner after considering the responses to the questions. Each item is rated on a four-point scale (0–3). In addition, there is a global item for overall severity, rating on a six-point (0–5) scale. Definitions and instructions for examinations are clear and severity points are well anchored and relevant (Barnes, 1989; Owens, 1999). According to the BARS, akathisia was diagnosed if the score on the global assessment item of the BARS was 2 or greater (Barnes, 1989).

The severity of schizophrenic symptoms was assessed using the Korean version of the Positive and Negative Syndrome Scale (PANSS) (Yi *et al.*, 2001). Subjects were assessed at the time of study entry (baseline) and at the end of the weeks 1, 2, 4 and 6 (endpoint) after olanzapine administration.

Pearson's correlation analyses were conducted to examine whether the changes of LUNSERS scores correlated with those of SAS and BARS scores during the 6 weeks of olanzapine treatment. Changes in scores were defined as the difference between baseline and endpoint scores (Peralta and Cuesta, 1999). For excluding confounding factors (i.e. concomitant medications) which may significantly influence the LUNSERS ratings, we examined the correlations of the change scores. Discriminant function analyses were performed to determine the optimum LUNSERS items in distinguishing patients with or without each movement disorder using endpoint results. The items of LUNSERS subscales found to be significantly correlated with SAS and BARS were used as the independent variables of the discriminant function analyses. The dependent variables were the groups with or without each drug-induced movement disorder. A critical value of $p < 0.05$ was used in statistical evaluation. All statistical analyses were performed using SPSS 10.0 for windows (SPSS, Chicago, IL).

RESULTS

Table 2 shows the correlations between changes in the scores of SAS, BARS and the corresponding items and subscales of LUNSERS. There were significant correlations between the changes in the SAS score and the corresponding parkinsonism items (muscle stiffness, slowing of movements, shakiness and drooling mouth) score of LUNSERS. There were also significant correlations between the changes in the SAS and in the EPS subscale of LUNSERS. The changes in the scores of the subjective awareness of restlessness, the distress and the global severity of BARS were significantly correlated with the change for the corresponding akathisia item (restlessness), the EPS subscale and the psychic side-effect subscale of LUNSERS.

The change in the score of EPS subscale or the parkinsonism items of LUNSERS was not significantly correlated with the change in the positive or negative symptom scores of PANSS. Modest but significant correlations were found between the changes in the SAS score and the PANSS negative symptom score ($r = 0.25$, $p < 0.05$).

In classifying the patients according to the presence of drug-induced parkinsonism using discriminant function analysis, 81.0% of all cases were correctly classified (canonical correlation = 0.38; $\chi^2 = 12.7$; $p < 0.001$). The single item 'shakiness' produced a satisfactory degree of separation of the two groups (Wilks' lambda = 0.86; $F = 13.8$; $p < 0.001$). With regard to akathisia, discriminant function analysis revealed that a combination of four items of LUNSERS, i.e. 'difficulty getting to sleep' (Wilks' lambda = 0.88; $F = 11.7$; $p = 0.001$), 'restlessness' (Wilks' lambda = 0.88; $F = 10.8$; $p = 0.001$), 'tension' (Wilks' lambda = 0.94; $F = 5.6$; $p = 0.021$), and 'difficulty in concentrating' (Wilks' lambda = 0.94; $F = 5.5$; $p = 0.021$) made correct classification with 76.2% accuracy (canonical correlation = 0.44; $\chi^2 = 17.2$; $p = 0.004$).

DISCUSSION

In this study, the EPS and psychic side-effect subscales of LUNSERS were significantly correlated with the most commonly used observer-rated scales for drug-induced parkinsonism (SAS) and akathisia (BARS). These results suggest the utility and capacity

Table 2. Correlations between changes in the scores of drug-induced parkinsonism (SAS) and akathisia (BARS) and of the corresponding LUNSERS items and subscales ($n = 83$)

	SAS total score	BARS objective motor manifestation score	BARS subjective awareness of restlessness score	BARS distress related to restlessness score	BARS global severity score
LUNSERS PAR	0.31[b]	−0.03	0.24[a]	0.29[b]	0.21
LUNSERS AKA	0.03	−0.01	0.27[a]	0.30[b]	0.31[b]
LUNSERS EPS	0.28[a]	−0.14	0.28[a]	0.35[b]	0.27[a]
LUNSERS PSY	0.14	0.04	0.26[a]	0.30[b]	0.24[a]

PAR, total sum score of parkinsonism items, such as 'muscle stiffness', 'slowing of movements', 'shakiness' and 'drooling mouth' items.
AKA, score of akathisia item ('restlessness').
EPS, total sum score of extrapyramidal side-effect subscale, such as 'muscle spasm', 'muscle stiffness', 'slowing of movements', 'part of the body moving of their own accord', 'shakiness', 'restlessness' and 'drooling mouth' items.
PSY, total sum score of psychic side-effect subscale, such as 'difficulty staying awake during the day', 'increased dreaming', 'difficulty in concentrating', 'tension', 'tiredness', 'difficulty in remembering things', 'lack of emotions', 'depression', 'sleeping too much' and 'difficulty getting to sleep' items.
[a] $p < 0.05$.
[b] $p < 0.01$.

of the LUNSERS to assess effectively drug-induced parkinsonism and akathisia. The parkinsonism items and EPS subscale of LUNSERS yield nearly identical correlations because they only differ with respect to two items. Nonetheless, since all correlations were modest, the following limitations should be considered. First, most of the subjects (53 of 83) were already taking atypical antipsychotics at the baseline, and all subjects were treated with olanzapine during the study period, which has a favourable EPS profile, thereby possibly decreasing the level of correlations. Second, patients may have had difficulty discerning and reporting certain adverse effects (Day *et al.*, 1998). An alternative explanation is that there can be a difference of severity between the subjective symptoms and objective signs of EPS (Owens, 1999). Therefore, the clinicians and patients may differ in their evaluation of adverse effects and the associated distress.

The changes in the subjective awareness of restlessness and the global severity of the BARS were significantly correlated with the change in the corresponding akathisia item (restlessness) of LUNSERS. In discriminant function analysis, four items of LUNSERS, including restlessness, were found to be optimum in identifying akathisia patients. These are compatible with the report that the single item 'restlessness' was shown to correlate significantly with akathisia using the UKU rating scale (Lambert *et al.*, 2003). The change in the psychic side-effect subscale of LUNSERS was significantly correlated with changes in the subjective awareness of restlessness and the global severity of BARS as well. These are also highly consistent with previous reports that the patients with akathisia suffered from subjective emotional discomfort, such as dysphoria and tension, and cognitive impairment, including impairment of attention (Gerlach and Larsen, 1999; Kim *et al.*, 2002). In addition, these results suggest that the LUNSERS psychic side-effects subscale is useful in evaluating the subtle subjective manifestations of akathisia that are difficult to measure (Barnes, 1989; Kim *et al.*, 2002; Kim and Byun, 2003). In drug-induced parkinsonism, according to the discriminant function analysis, the single LUNSERS item 'shakiness' appears to discriminate adequately between the presence and absence of parkinsonism. In a previous study, 'shakiness' showed only a low to moderate relationship to 'tremor' of the UKU rating scale (Lambert *et al.*, 2003). It is possible that this item includes non-parkinsonian tremor, but the self-report 'shakiness' of LUNSERS seems to be valuable for screening the subjective experience of parkinsonian symptoms.

It is noteworthy that the change in the EPS subscale score of LUNSERS was not significantly correlated with the change in the negative symptom score of PANSS, while there was a significant correlation between the changes in the SAS score and the PANSS negative symptom score. These findings are in agreement with a previous report that the change in SAS score was significantly correlated with the change in negative symptom score during the acute phase of antipsychotic treatment (Peralta and Cuesta, 1999). These results imply that the EPS subscale of LUNSERS may have a discriminant validity for differentiating EPS from negative symptoms,

In conclusion, the present study suggests that the EPS and psychic side-effects subscales of LUNSERS may be useful in screening of the drug-induced parkinsonism and akathisia as a convenient and cost-effective subjective measure.

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