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ORIGINAL PAPER

Reliability and Validity of the Short Version of Udvalg for Kliniske Undersogelser in Antipsychotic Treatment

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Abstract The aim of this study was to develop a reliable and valid short version of the Udvalg for Kliniske Undersogelser (UKU) to efficiently evaluate the side effects of antipsychotics in patients with schizophrenia. This multi-site study included 10 hospitals, which included 331 inpatients and outpatients diagnosed with schizophrenia. UKU, Clinical Global Impression-Severity (CGI-S), Personal and Social Performance (PSP) and dosage of paliperidone were collected. The predictive validity of the UKU-short version, as well as that of the CGI-S, PSP and paliperidone dosages, was analyzed using structural equation modeling (SEM), latent growth models (LGM), and confirmatory factor analysis to test its content and construct validity. The UKU-short included nine-items of sedation, reduced sleep, rigidity, tremor, akathisia, headache, reduced salivation, constipation and orthostatic dizziness, and has good construct and content validity over time. Confirmatory factor analysis showed good construct validity, with the psychic, neurological and autonomic side effect dimensions having correlations between 0.60 and 0.71. The predictive validity of the short-version UKU for psychiatric symptoms (CGI-S), quality of life (PSP) and dosage showed that the effects of drug dosage were negligible, and only neurological side effects were associated with psychiatric symptoms and quality of life. The UKU-short showed good content, construct and predictive validity. It is a more time-efficient instrument than the original UKU. This study only included patients treated with paliperidone, larger scale studies is needed to validate the UKU-short in detection of side effects in routine clinical practice to prevent non-adherence in patients with schizophrenia.

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Introduction

Although the effectiveness of pharmacotherapy in improving psychiatric symptoms has been well established, patients with schizophrenia comprise a population with a high rate of non-adherence, with reports showing that less than 25% of patients with schizophrenia are fully compliant with antipsychotic therapy [1]. This low level of adherence contributes to the high rates of relapse and readmission [2]. Research has shown that factors which contribute to poor adherence include poor insight and lack of illness awareness, distress associated with specific side effects or a general fear of side effects, inadequate efficacy with persistent symptoms, and believing medications are no longer needed [3]. Therefore, one of the major causes of non-adherence in schizophrenia is the presence of side effects [4, 5], including anticholinergic, extrapyramidal, endocrine, cardiovascular and hematological side effects [6]. In addition, patients given antipsychotic drugs, compared to placebos, had the side effects of weight gain and movement disorders, and experienced sedation [7]. Therefore, it is important for clinicians to accurately evaluate the side effect of medications in their routine practice to prevent non-adherence.

Atypical antipsychotics have the advantage of a superior side effect profile, including a reduction of both the positive and negative symptoms of schizophrenia, and have a lower risk of extrapyramidal symptoms [8, 9]. However, a separate set of side effects have been found for atypical antipsychotics – these include weight gain, dizziness, sleep disturbance and appetite disturbance [10]. In addition, mild hypotension is a common cardiovascular side effect of atypical antipsychotic overdose [11, 12]. A study also found that olanzapine has infrequently caused seizures [13]. With the differences in side effects between typical and atypical antipsychotics, an instrument that can accurately evaluate the side effects of atypical antipsychotics is needed.

The Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale [14] is the most commonly used clinical measurement of a broad range of side effects. It is a comprehensive rating scale that includes 48 individual side effects that can be grouped into the four main dimensions of psychic, neurological, autonomic and other side effects. Even though the UKU has high reported reliability and validity, this semi-structured interview requires experienced researchers and considerable time, approximately 30 to 60 min, to complete. With the constraints in psychiatric services, it is difficult to use the UKU in routine clinical practice.

As mentioned earlier, comprehensive and systematic scales are vitally needed in clinical practice because of the various adverse reactions of patients to multiple psychotropic drugs and the interactions between the disease itself and the drug. To shorten the time needed when using the UKU, this study aimed to reduce the number of items in the UKU and evaluate the potential of the shortened version for use in clinical and research settings. Since atypical antipsychotic agents have reduced extrapyramidal side effects [9], only items with high patient-doctor reliability (p less than 0.01) as measured using the professionally rated UKU and the patient self-report Liverpool University neuroleptic side effect rating scale (LUNSERS) were selected [15]. In addition, the four symptoms of somnolence, insomnia, dry mouth and dizziness, which have been found in co-administration of quetiapine with

haloperidol, risperidone or thioridazine [16], were added. Sexual dysfunction [17–19] and metabolic syndrome have also been found to be debilitating adverse effects for patients. However, more specific instruments, such as the Sexual Drive Inventory [20, 21], have been developed to evaluate the dimension of sexual dysfunction affected by the drug. Thus, the sexual dysfunction items were removed from this short version of the UKU. The sexual items in the original UKU focused more on the physical adverse effects, such as galactorrhea, amenorrhea, erectile dysfunction, ejaculatory dysfunction, and only included two items measuring sexual desire (increased or decreased sexual desire). However, a case study showed that a women with schizophrenia experienced side effects of sexual dysfunction, amenorrhea and galactorrhea, but still had sexual desire and was not satisfied with her sexual life [22]. Therefore, although the side effect caused sexual dysfunction, it does not imply decrease in sexual desire, nor sexual satisfaction. Therefore, Sexual Drive Inventory, a specific inventory measuring sexual desire, which measures three dimensions of sexual desire with a partner, sexual desire without a partner, and general sexual desire [20, 21] is more suitable. However, there are eastern and western cultural differences with regards to the topic of sex. A study investigated the sexual activity of adolescents in three major Chinese cities (including Taipei, Taiwan) found the prevalence of sexually experienced adolescents in these Chinese cities was much lower (8%) compared to that of in the US (48%) [23]. Sex is still considered a private matter which is rarely discussed publically. When encountering patients with an onset age at adolescents, it may cause embarrassment discussing the issue of sex with their physicians. The Sexual Drive Inventory has been proven to be culturally fit for Taiwanese, therefore maybe a more suitable method of approaching the issue of sexual dysfunction for Chinese patients, and should be used when necessary, but not asked to every patient to cause unnecessary discomfort. After this elimination process, nine items remained in the final UKU-short version (details presented in the "Material and Methods" section).

Aims of the Study

A reliable and time-saving measurement is necessary to allow more frequent assessment of adverse effects and enable a better understanding of the patients' reaction to medication, thereby avoiding premature non-adherence. Therefore, this study aimed to develop the short version of the UKU to efficiently evaluate the side effects of antipsychotics and establish the reliability and validity of the instrument for use with patients with schizophrenia, being a preliminary study, the relationship between the UKU-short, drug dosage, psychiatric symptom and quality of life changes was investigated in paliperidone usage.

Material and Methods

Participants

This multi-site research included 10 hospitals throughout Taiwan, and a total of 353 inpatients and outpatients diagnosed with schizophrenia were recruited. Of these 353 patients, 331 (93.8%) agreed to participate in the study, including 230 inpatients and 101 outpatients. Informed consent was obtained from all participants after detailed explanation of the study. In addition, the study was approved by the institutional review board of a teaching hospital in Taiwan.

Materials

Demographic information, including gender, age, education, dosage of medication, age at onset, duration of illness, and relapse time, was gathered. UKU scores were collected at baseline and at 4, 8, and 12 weeks, and Clinical Global Impression-Severity (CGI-S) scores and dosage of paliperidone data were recorded at baseline and at the 2, 4, 8 and 12 weeks' follow-up. Personal and Social Performance (PSP) scores were collected at baseline and at 4 and 12 weeks. Height, weight, BMI, waist and hip measurements were also recorded for detection of metabolic symptoms. In addition, palieridone has been found to have minimal weight gain and metabolic disturbances [24].

The nine items in the UKU-short were selected from those having high patient-doctor reliability (p less than 0.01) [15], with the addition of the four symptoms of somnolence, insomnia, dry mouth and dizziness, which were found to occur in co-administration of antipsychotics [16], and the deletion of the sexual dysfunction item. The selection process resulted in the two items of sedation and reduced sleep in the psychic side effect dimension, the four items of rigidity, tremor, akathisia and headache in the neurological side effects dimension, and the three items of reduced salivation, constipation and orthostatic dizziness in the autonomic side effects dimension. The procedure for using the short version is the same as that for the original UKU [14], except each item is defined by means of a 2-point-scale (0–1). In general, 0 means "not or doubtfully present", and 1 indicates that a symptom is present to a mild or severe degree.

The CGI-S scale was used to measure the state of the patient's illness at the time of the measurement [25], and the PSP scale was used to measure the patient's personal and social functioning in the four domains of socially useful activities (including work and study), personal and social relationships, self-care and disturbing and aggressive behaviors over time and during different phases of the illness [26].

Statistical Analysis

Descriptive analysis was performed using the SPSS 17.0 for Windows software package (Chicago, IL). The construct validity of the UKU-short version was analyzed using structural equation modeling (SEM). In addition, confirmatory factor analysis with the linear structure model was used to test content and construct validity. The predictive validity of the UKU-short version, as well as that of the CGI-S, PSP and paliperidone dosages, was analyzed using SEM and latent growth models (LGM). SEM and LGM were analyzed using the AMOS software package (SPSS). Chi-square fit was used to investigate the overall fit of the SEM and LGM model; a non-significant chi-square result would indicate that the model adequately described the observed data, with p values greater than 0.05, a root mean square error of approximation (RMSEA) less than 0.08, and an adjusted goodness-of-fit (AGFI) greater than 0.9.

Results

Descriptive analysis results showed 213 (64.4%) of the 353 participants were male, and the average age of the participants was 41.17 (11.23) years (Table 1). The UKU, PSP, CGI-S and paliperidone dosage results are shown in Table 2.

Table 1 Demographic distribution of patients with schizophrenia ($N = 331$)

Variables	N (%)
Male	213 (64.4)
Employed	21 (6.3)
Level of education	
Illiterate	3 (0.9)
Elementary school	49 (14.8)
High school	227 (68.6)
College/University	48 (14.5)
Graduate school	4 (1.2)
Illicit drug use	22 (6.6)
Cigarette use	192 (58)
Alcohol use	129 (39)
Variable	Mean (SD)
Age (range: 19 ~ 66)	41.17 (11.23)
Age of onset	25.33 (7.88)
Duration of illness (years)	15.38 (10.25)

The content and construct validity by confirmatory factor analysis using SEM for the UKU-short version side effect rating scale over time, measured at 0, 4, 8, and 12 weeks, is shown in Fig. 1. The model resulted in a p value of 0.543 (greater than 0.5), AGFI of 0.962 (greater than 0.9), and RMSEA less than 0.001 (less than 0.08), thus showing a good fit. The psychic side effect dimension was positively significantly correlated with the neurological and autonomic side effect dimensions ($r = 0.60$, $p < 0.001$; $r = 0.71$, $p < 0.001$). In addition, the neurological side effect dimension was positively significantly correlated with the autonomic side effect dimension ($r = 0.63$, $p < 0.001$). These results showed good content and construct validity among the dimensions of the short version of the UKU.

Table 2 The results of the Udvalg for Kliniske Undersogelser (UKU), Personal and Social Performance (PSP), Clinical Global Impression-Severity (CGI-S) and paliperidone dosages

Variables (range)	Mean (SD)
UKU	
Baseline (0 ~ 22)	8.74 (4.46)
4 weeks (0 ~ 31)	7.68 (4.46)
8 weeks (0 ~ 19)	7.38 (4.38)
12 weeks (0 ~ 22)	7.33 (4.34)
CGI-S	
Baseline (4 ~ 7)	5.05 (0.82)
2 weeks (2 ~ 7)	4.62 (0.90)
4 weeks (1 ~ 7)	4.28 (0.96)
8 weeks (1 ~ 7)	3.98 (1.10)
12 weeks (1 ~ 6)	3.69 (0.98)
PSP	
Baseline (6 ~ 79)	42.63 (14.86)
4 weeks (7 ~ 95)	51.08 (14.06)
12 weeks (5 ~ 95)	56.66 (14.62)
Paliperidone dosage	
Baseline (3 ~ 12)	5.87 (1.40)
2 weeks (3 ~ 12)	6.55 (2.06)
4 weeks (2 ~ 15)	7.17 (2.45)
8 weeks (3 ~ 18)	7.41 (2.53)
12 weeks (1 ~ 18)	7.43 (2.69)

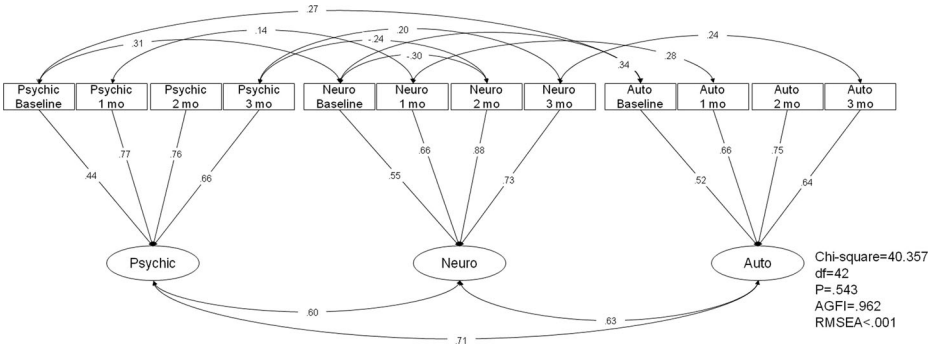

Fig. 1 Content and construct validity by confirmatory factor analysis using the structural equation modeling for the Udvalg for Kliniske Undersogelser (UKU)-short version side effect rating scale over time (0, 4, 8, and 12 weeks). Psychic: Psychic side effect; Neuro: Neurological side effect; Auto: Autonomic side effect; AGFI: adjusted goodness-of-fit indices; RMSA: root mean square error of approximation.

The predictive validity of the short version of the UKU in the LGM among psychiatric symptoms (CGI-S), quality of life (PSP), dosage and side effects is shown in Fig. 2. The model resulted in an adequate fit, with an AGFI of 0.885 and RMSEA of 0.045. The results showed the neurological side effect dimension of the UKU was positively associated with the slope of the psychiatric symptoms (CGI-S) (ß = 0.44, $p < 0.001$), and negatively associated with the slope of the quality of life (PSP) (ß = 0.44, $p < 0.001$). Furthermore, the intercept of the CGI-S was negatively associated with the intercept of PSP (ß = −0.80, $p < 0.001$) and positively associated with the intercept of drug dosage (ß = 0.35, $p = 0.001$).

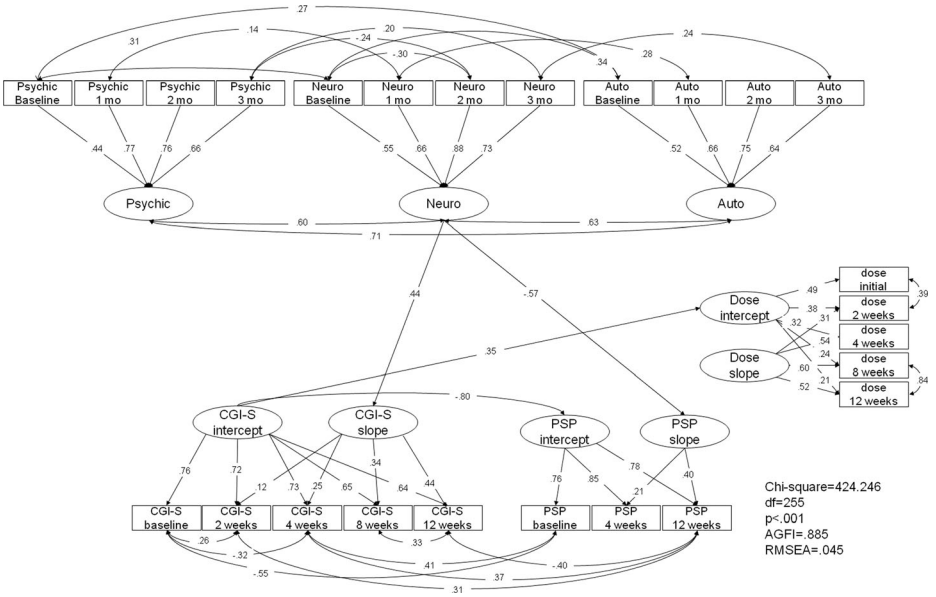

Fig. 2 Predictive validity of the short-version of the Udvalg for Kliniske Undersogelser (UKU) in latent growth model among psychiatric symptoms (Clinical Global Impression-Severity [CGI-S]), quality of life (Personal and Social Performance [PSP]), dosage and side effects. Psychic: Psychic side effect; Neuro: Neurological side effect; Auto: Autonomic side effect; AGFI: adjusted goodness-of-fit indices; RMSA: root mean square error of approximation.

Discussion

Our results showed the nine-item UKU-short has good construct and content validity overtime, measured at baseline and at 1, 2, and 3 months' follow-up. Confirmatory factor analysis (Fig. 1) showed good construct validity, with the psychic, neurological and autonomic side effect dimensions having correlations between 0.60 and 0.71. The predictive validity of the short-version of the UKU among psychiatric symptoms (CGI-S), quality of life (PSP) and dosage (Fig. 2) showed that the effects of drug (paliperidone) dosage were negligible, and only neurological side effects were associated with psychiatric symptoms and quality of life. The rating of psychic and autonomic side effects, especially, should be independent of the clinical symptoms. Showing good content, construct and predictive validity, the nine-item UKU-short is a more time-efficient instrument than the original UKU, and therefore can be used for detection of side effects in routine clinical practice to prevent non-adherence in patients with schizophrenia.

The confirmatory factor analysis (Fig. 1) showed good construct validity, with the three dimensions of psychic, neurological and autonomic side effects having correlations between 0.60 and 0.71. Anastasi and Urbina [27] proposed that to show good construct validity, the dimensions in each scale should correlate highly with the other dimensions; however, they should not correlate too significantly. A high correlation greater than 0.30 shows synchronization and convergent validity between the dimensions, but a correlation higher than 0.80 could imply low discriminant validity. Therefore, the ideal correlation among the dimensions of a questionnaire would be between 0.30 and 0.80. The UKU-short shows correlations between 0.60 and 0.71 among the 3 dimensions, thus showing good convergent and discriminant validity among the dimensions.

Besides construct and content validity, the side effects of paliperidone decreased after 2 months, especially the neurological side effects (Fig. 1). Furthermore, only neurologic side effects were associated with the slope of psychiatric symptoms and quality of life (Fig. 2). In other words, the rating of psychic and autonomic side effects should be independent of the clinical symptoms. Additionally, the neurologic side effect dimension is can be used to detect severity and presence of symptom change. The influence of extrapyramidal adverse effects on quality of life has been documented previously, including that akathisia symptoms help predict subjective quality of life [28], and that drug-induced extrapyramidal symptoms are positively correlated with the dose of the antipsychotic [29]. In addition, Fujimaki et al. [29] found a positive correlation between extrapyramidal side effects, quality of life and negative symptoms. This is consistent with our results, in that the initial condition of the psychiatric symptom is associated with the initial condition of the PSP and paliperidone dosage.

Structural equation LGM was used in investigating the predictive validity of the UKU-short among psychiatric symptoms, quality of life, and drug dosage. With the LGM, the distinction between initial condition and level of change can be made, which allows us to detect the process of change and control variables which may contribute to this change. As a consequence, the hypothesis of change regarding the initial level can be tested [30]. In this structural equation LGM (Fig. 2), we found that the effect of paliperidone drug dosage on side effects was negligible. Furthermore, the slope of the CGI-S and PSP were not influenced by the dosage of paliperidone. Paliperidone dosage change (slope) was only influenced by the initial dosage, and was indirectly associated with the initial condition of the psychiatric symptoms. Fujimaki et al. also found a correlation between positive symptoms and dose of antipsychotics, implying that low

doses of antipsychotics reflect positive symptoms, and lower doses imply more stabilized patients with less symptoms [29].

Moreover, structural equation LGM also showed that the initial condition of the psychiatric symptoms was associated with the initial condition of quality of life and paliperidone dosage, but not with the change over time (slope) in quality of life and dosage. Previous studies have also found that psychotic symptoms affect quality of life more in the early phase of schizophrenia than in those with chronic disease [31], and severe psychopathological symptoms have an adverse impact on various domains of quality of life in first-episode schizophrenia [32].

In conclusion, this preliminary study showed the 9-item UKU-short had good construct, content and predictive validity with psychiatric symptoms, quality of life and paliperidone dosage. Therefore it is a time-efficient instrument for the detection of atypical antipsychotic side effects in patients with schizophrenia. Since it is more time-efficient, the UKU-short can be used in routine clinical practice, allowing more frequent assessment of adverse effects and enabling a better understanding of the patients' reaction to medication, so as to prevent premature non-adherence. This is important, for side effects are one of the major causes of non-adherence in treating schizophrenia [4, 5]. Furthermore, using the structural LGM, our study found that only neurological side effects were associated with symptom and quality of life change over time. In other words, when examining the change in clinical symptoms, the rating of psychic and autonomic side effects may be eliminated. However, the limitation of this study is that only paliperidone was used. Paliperidone was chosen for a previous in vitro study showed, compared to typical APD (haloperidol) and other two APDs (olanzapine and risperidone), paliperidone showed better neuroprotective effect especially in combating hydrogen peroxide [33]. A broader and more vigorous validation, including using a spectrum of populations, as well as among a broader range of medications is needed to generalize the use of the UKU-short in clinical and research settings.

Compliance with Ethical Standards

Disclosure of Potential Conflicts of Interest All authors have no conflict of interest to declare.

Research involving Human Participants and/or Animals The study was approved by the institutional review board of a teaching hospital in Taiwan, and is in accordance in accordance with the ethical standards in the 1964 Declaration of Helsinki and its later amendments.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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