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JAPAN SERIES

MENTAL HEALTH CARE IN JAPAN

Mental health, including widespread depression, a high suicide rate and institutionalisation, is a major problem in Japan. At the same time, the mental health care system in Japan has historically been more restrictive than elsewhere in the world. This book looks at the challenges of mental health care in Japan, including problems such as the institutionalisation of long-term patients in mental hospitals. The book discusses the latest legislation to deal with mental health care, and explores the various ideas and practices concerning rehabilitation into the workforce, the community and service user groups that empower the mentally ill. It goes on to look at the social stigma attached to the mentally ill in Japan and Britain, which touches upon the issue of counselling those with post traumatic stress after the recent earthquake.

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JAPANESE STUDIES

www.routledge.com
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ISBN 978-0-415-69068-3
9 780415 690683
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Open Journal of Psychiatry, 2012, 2, 340-346 OJPsych
doi:10.4236/ojpsych.2012.224048 Published Online November 2012 (http://www.SciRP.org/journal/ojpsych/)

International variation in antipsychotic prescribing for schizophrenia: Pooled results from the research on East Asia psychotropic prescription (reap) studies

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Received 1 October 2012; revised 1 November 2012; accepted 10 November 2012

ABSTRACT

Objective: To identify updated trends in antipsychotic prescribing patterns in patients with schizophrenia in East Asia. Methods: Using the data from the 2001, 2004, and 2008 Research on East Asia Psychotropic Prescription (REAP) studies, we compared the proportions of acute inpatients (stay <6 months), new long-stay patients (6 months to 3 years), and old long-stay patients (≥3 years), the rates of excessive dosing (more than chlorpromazine 1,000 mg equivalent) and polypharmacy (the coprescription of more than 1 antipsychotic). Findings: While the proportion of long-term inpatients increased over time in Chinese mainland and Taiwan, it decreased in Japan, Singapore and Hong Kong. The proportion of acute inpatients receiving more than one drug was highest in Singapore, followed by Japan, Korea and Chinese Mainland. Two-drug combination therapy was especially high in Singapore. Korea had the highest rate of excessive dosing followed by Japan and Hong Kong. While the rates of both polypharmacy and excessive dosing decreased significantly over time in Japan, polypharmacy increased significantly in Chinese Mainland and Taiwan and excessive dosing increased significantly in Korea and Hong Kong. Conclusion: Our results suggest that the change in antipsychotic prescribing patterns, including excessive dosing and polypharmacy, varied among the participating East Asian countries/areas.

Keywords: Antipsychotic; East Asia; Polypharmacy; Schizophrenia

1. INTRODUCTION

Antipsychotic polypharmacy, the prescribing of more than one antipsychotic drug concurrently, is a common prescription pattern in clinical practice [1]. Although the prevalence of anitipsychotic polypharmacy varies, the results from most studies ranged between 10% and 30% [2]. Polypharmacy may result exceed the total dose of antipsychotics [3], and may cause increases in admissions to hospital [4] and mortality [5].

Polypharmacy was frequently observed in patients with severe conditions [4,6]. Long-stay patients are likely to be severe and treatment-resistant; therefore, they are at risk of polypharmacy. Recent studies showed that the length of stay of patients receiving antipsychotic polypharmacy was longer than that of patients receiving monotherapy [7,8]. The prescription of high-dose antipsychotics is also of concern because of the lack of evidence to support its effectiveness and because of its association with greater adverse effects [9]. The probability of the prescription of high-dose antipsychotics is increased by polypharmacy [1].

Compared with the West, hospital care for patients with schizophrenia is still prevalent in many East Asian countries/areas. The treatment pattern of inpatients, however, is changing in East Asia [10]. Of newly admitted patients, most are discharged earlier, but some stay longer due to treatment-resistant and severe diseases [11]. Those who are newly admitted and stay longer in hospitals are referred to as "new long-stay" patients in addition to "old long-stay" patients who are older and resistant to discharge.

The objective of this study was to identify updated trends in the prescription patterns of antipsychotics in patients with schizophrenia in East Asia. We compared the proportions of acute, new long-stay, and old long-stay inpatients and the rates of excessive dosing and polypharmacy in 2001, 2004 and 2008 using the data from the Research on East Asia Psychotropic Prescrip- tion (REAP) studies.

*Corresponding author.

2. METHODS

2.1. Study Design

The Research on East Asia Psychotropic Prescription (REAP) studies were designed as hospital-based cross-sectional surveys to examine the prescription patterns of psychotropic drugs (antipsychotics, mood stabilizers and antidepressants) among inpatients in East Asia. The details of the REAP studies have been described elsewhere [12-15]. The studies were conducted in 2001, 2004 and 2008 in six Asian countries/areas (Chinese mainland, Hong Kong, Japan, Korea, Singapore and Taiwan) using a standardized protocol and data collection procedure.

The REAP studies were approved by the Institutional Review Boards of all the participating centers in each country. The Institutional Review Board of the National Center of Neurology and Psychiatry, Japan, also approved the analysis of data for this study.

2.2. Participants

The participants were patients with schizophrenia who were consecutively admitted to each site. We identified inpatients using the diagnostic criteria for schizophrenia according to the International Classification of Disease, 10th edition (ICD-10) [16] or the 4th version of the Diagnostic and Statistical Manual of Mental Disorders (*DSM*-IV) [17]. The REAP study coordinators collected data from the medical charts of inpatients at each site, transcribed them into a uniform data entry sheet, and forwarded the sheet to the national coordinating centers of each country. Each national coordinating center compiled data from the participating centers and sent them on to the overall coordinator in Kobe, Japan, for compilation and analysis. Patients with clinically significant medical conditions or active psychotic symptoms related to comorbid substance use disorders were excluded.

2.3. Patient Groups by Length of Stay

We divided the patients into three groups based on length of stay: acute (stay <6 months), new long-stay (6 months to 3 years), and old long-stay inpatients (≥3 years). New long-stay patients were defined as those who occupied psychiatric beds for a prolonged period among individuals receiving services oriented towards community living [11].

2.4. Variables

The primary psychiatrist completed uniform questionnaires about the participating patient at each site. Alternatively the questionnaire was completed by a member of the research team with the agreement of the primary psychiatrist [15]. The questionnaire included sociodemographic information and clinical characteristics including psychopathology and all psychotropic drugs prescribed. Depot antipsychotics given within 30 days of admission were also documented. Daily doses of antipsychotics, including depot preparations, were converted to approximate daily mean chlorpromazine mg equivalents (CPZeq) using standard guidelines [18-21].

2.5. Indicators of Antipsychotic Prescription

In this analysis, we assessed the excessive dosing of antipsychotics and antipsychotic polypharmacy during inpatient care. In terms of excessive dosing, we divided the prescribing patterns of the total daily doses of antipsychotic medications into two categories: 1) those patients receiving ≤1000 CPZeq mg per day (appropriate dosing group) and 2) those receiving >1000 CPZeq mg (excessive dosing group). The second indicator, antipsychotic polypharmacy, was defined as the concurrent use of more than one antipsychotic drug.

2.6. Analysis

Data were analyzed using SPSS 13.0 for Windows. We performed t-tests, Mann-Whitney U tests and chi-square tests. The one-sample Kolmogorov-Smirnov test was used to assess the normality of distribution of continuous variables. The level of significance was set at 0.05 (two-tailed).

3. RESULTS

3.1. Participants

The 2001, 2004, and 2008 studies included 2399, 2136, and 1906 participants with schizophrenia admitted to psychiatric hospitals at the study sites, respectively.

3.2. Changes in Patient Groups

In 2008, the proportion of patients in acute care was 57.7% in Chinese mainland, 68.9% in Hong Kong, 33.0% in Japan, 63.9% in Korea, 100% in Singapore, and 43.2% in Taiwan (**Table 1**), and was significantly higher in Hong Kong, Japan and Singapore and lower in Chinese mainland than in 2001.

3.3. Prescription of Antipsychotics for Acute patients

The trend in the prescription of antipsychotics in acute patients is shown in **Table 2**. Excessive dosing was seen in 18.8% of cases in Korea, 15.3% in Japan and 13.7% in Hong Kong in 2008. In Korea, the rate of excessive dosing in 2008 was significantly higher than that in 2004 (7.0%). The rates in 2004 in Japan and Hong Kong were significantly lower than those in 2001.

The rate of polypharmacy in 2008 was 74.0% in Sin-

Table 1. Changes in patient groups.

	2001		2004		2008			Multiple comparison		
Patients by region	n	%	n	%	n	%	p	a	b	c
Chinese mainland										
Acute	421	69.9	388	78.5	209	57.7	0.00*	0.00*	0.00*	0.00*
New long stay	110	18.3	70	14.2	99	27.3				
Old long stay	71	11.8	36	7.3	54	14.9				
Hong Kong										
Acute	51	49.5	41	41.8	51	68.9	0.00*	0.35	0.02*	0.00*
New long stay	38	36.9	46	46.9	21	28.4				
Old long stay	14	13.6	11	11.2	2	2.7				
Japan										
Acute	94	15.2	172	30.1	150	33.0	0.00*	0.00*	0.00*	0.61
New long stay	119	19.3	111	19.4	85	18.7				
Old long stay	405	65.5	289	50.5	220	48.4				
Korea										
Acute	254	58.4	228	57.4	69	63.9	0.08	-	-	-
New long stay	124	28.5	102	25.7	32	29.6				
Old long stay	57	13.1	67	16.9	7	6.5				
Singapore										
Acute	149	51.2	90	100.0	96	100.0	0.00*	0.00*	0.00*	1.00
New long stay	71	24.4	0	0.0	0	0.0				
Old long stay	71	24.4	0	0.0	0	0.0				
Taiwan										
Acute	182	59.1	262	60.4	212	43.2	0.00*	0.91	0.00*	0.00*
New long stay	73	23.7	102	23.5	172	35.0				
Old long stay	53	17.2	70	16.1	107	21.8				

p, p values derived by chi-squared test or Fisher's exact test; a, p values derived by multiple comparisons for proportional differences between 2001 and 2004; b, p values derived by multiple comparisons for proportional differences between 2001 and 2008; c, p values derived by multiple comparisons for proportional differences between 2004 and 2008. *$p < 0.05$.

gapore, 51.3% in Japan, 40.6% in Korea, 36.8% in Chinese mainland, 29.4% in Hong Kong and 25.0% in Taiwan in 2008. In Japan, the rate in 2008 was significantly lower than that in 2001 (73.4%). In contrast, the rate in 2008 was significantly higher than that in 2001 (25.2%) in Chinese mainland, that in 2004 in Chinese mainland (22.7%) and that in Taiwan (14.1%). The most frequent patterns of polypharmacy in Singapore in 2008 were risperidone and zuclopenthixol decanoate (n = 8), followed by risperidone and flupentixol decanoate (n = 7), and trifluoperazine and fluphenazine decanoate (n = 5).

The proportion of inpatients receiving three or more antipsychotics in 2008 was 23.3% in Japan, 12.5% in Singapore, 5.9% in Hong Kong, 4.3% in Chinese mainland, 2.9% in Korea and 0.9% in Taiwan.

3.4. Prescription of Antipsychotics for New Long-Stay Patients

As shown in **Table 3**, excessive dosing was seen in 34.4% of cases in Korea, 17.6% in Japan and 17.2% in Chinese mainland in 2008. In Chinese mainland, the rate of excessive dosing in 2008 was significantly higher than those in 2001 (0.9%) and 2004 (2.9%).

The rate of polypharmacy in 2008 was 65.9% in Japan, 50.5% in Chinese mainland, 46.9 in Korea, 33.3% in Hong Kong and 26.2% in Taiwan. The rate in 2008 in Chinese mainland was significantly higher than that

Table 2. Excessive dosing and polypharmacy in acute patients by region.

	2001			2004			2008					Multiple comparison		
Region	n	%	N	n	%	N	n	%	N	ES	p	2001 vs 2004	2001 vs 2008	2004 vs 2008
							Polypharmacy							
Chinese mainland	106	25.2	421	88	22.7	388	77	36.8	209	0.25	0.00*	0.45	0.01*	0.00*
Hong Kong	19	37.3	51	6	14.6	41	15	29.4	51	0.17	0.05	-	-	-
Japan	69	73.4	94	106	61.6	172	77	51.3	150	0.46	0.00*	0.14	0.00*	0.14
Korea	86	33.9	254	67	29.4	228	28	40.6	69	0.14	0.20	-	-	-
Singapore	102	68.5	149	69	76.7	90	71	74.0	96	0.12	0.35	-	-	-
Taiwan	36	19.8	182	37	14.1	262	53	25.0	212	0.13	0.01*	0.29	0.29	0.01*
							Excessive dosing							
Chinese mainland	27	6.4	421	26	6.7	388	17	8.1	209	0.07	0.71	-	-	-
Hong Kong	11	21.6	51	1	2.4	41	7	13.7	51	0.21	0.02*	0.03*	0.44	0.14
Japan	25	26.6	94	22	12.8	172	23	15.3	150	0.28	0.01*	0.02*	0.09	0.62
Korea	33	13.0	254	16	7.0	228	13	18.8	69	0.16	0.01*	0.09	0.30	0.02*
Singapore	18	12.1	149	11	12.2	90	7	7.3	96	0.16	0.43	-	-	-
Taiwan	8	4.4	182	16	6.1	262	21	9.9	212	0.22	0.08	-	-	-

n, number of patients receiving two or more antipsychotics (polypharmacy) or greater than 1,000 CPZeq mg antipsychotics (excessive dosing); ES, Cohen's effect size index for differences in proportions between 2001 and 2008; p, p values derived by chi-squared test or Fisher's exact test for proportional differences among three years. *$p < 0.05$.

Table 3. Excessive dosing and polypharmacy in care for new long stay patients by region.

	2001			2004			2008					Multiple comparison		
Region	n	%	N	n	%	N	n	%	N	ES	p	2001 vs 2004	2001 vs 2008	2004 vs 2008
							Polypharmacy							
Chinese mainland	32	29.1	110	26	37.1	70	50	50.5	99	0.44	0.01*	0.34	0.01*	0.24
Hong Kong	12	31.6	38	15	32.6	46	7	33.3	21	0.04	0.99	-	-	-
Japan	92	77.3	119	72	64.9	111	56	65.9	85	0.26	0.08	-	-	-
Korea	47	37.9	124	52	51.0	102	15	46.9	32	0.18	0.14	-	-	-
Singapore	52	73.2	71	0	-	0	0	-	0	-	-	-	-	-
Taiwan	20	27.4	73	15	14.7	102	45	26.2	172	0.03	0.06	-	-	-
							Excessive dosing							
Chinese mainland	1	0.9	110	2	2.9	70	17	17.2	99	0.66	0.00*	0.56	0.00*	0.01*
Hong Kong	5	13.2	38	1	2.2	46	3	14.3	21	0.03	0.07	-	-	-
Japan	28	23.5	119	19	17.1	111	15	17.6	85	0.15	0.41	-	-	-
Korea	29	23.4	124	31	30.4	102	11	34.4	32	0.24	0.33	-	-	-
Singapore	13	18.3	71	0	-	0	0	-	0	-	-	-	-	-
Taiwan	5	6.8	73	5	4.9	102	10	5.8	172	0.04	0.91	-	-	-

n, number of patients receiving two or more antipsychotics (polypharmacy) or greater than 1,000 CPZeq mg antipsychotics (excessive dosing); ES, Cohen's effect size index for differences in proportions between 2001 and 2008; p, p values derived by chi-squared test or Fisher's exact test for proportional differences among three years. *$p < 0.05$.

in 2001 (29.1%).

3.5. Prescription of Antipsychotics for Old Long-Stay Patients

In the prescription of antipsychotics for old long-stay patients in 2008, excessive dosing was seen in 18.6% of cases in Japan and 14.3% in Korea (**Table 4**). In Japan, the rates in 2008 (14.3%) and 2004 (23.5%) were significantly lower than that in 2001 (35.3%).

The rate of polypharmacy in 2008 was 63.6% in Japan and 33.6% in Taiwan. The rate in Japan in 2008 was significantly lower than those in 2001 (81.5%) and 2004 (73.7%). In Taiwan, the rate in 2008 was significantly higher than that in 2004 (10.0%).

4. DISCUSSION

The trends in the number of inpatients and in excessive dosing and polypharmacy varied across East Asia. While the proportion of long-term inpatients increased over time in Chinese mainland and Taiwan, it decreased in Japan, Singapore and Hong Kong. In Singapore and Hong Kong, inpatient care is now focused on acute care. Japan and Korea, where the numbers of beds per capita and long-stay inpatients are high, seem to be in a process of deinstitutionalization. In contrast, inpatient-care facilities are still lacking and the number of beds is increasing in Chinese mainland [22], thus, long-stay inpatients linger.

Japan has been often criticized for the use of polypharmacy [13-14,23]. There are multiple factor involved in the use of polypharmacy, such as physician distrust of the practice guidelines, requests to increase the number of nursing staff members, and patient characteristics [24]. The change in reimbursement which encourages the use of less than three antipsychotics over the use of more than three antipsychotics and third-party evaluation might have facilitated the changes in antipsychotic prescription patterns. Japan had the highest rate of the prescription of three or more drugs, but the percentage of patients treated with polypharmacy in acute care has been decreasing over time.

The rate at which acute care inpatients were prescribed two or more drugs was highest in Singapore, followed by Japan, Korea and Chinese mainland; however, the prescripion pattern in Singapore is different from those in the other countries/areas. A high rate of polypharmacy in Singapore has been demonstrated by previous studies [12,13]. However, the prescription of two drugs only was most prevalent, and most of these prescriptions are co-prescription with depot. Chinese mainland, Korea, and Taiwan show opposite trends of increased polypharmacy.

Although polypharmacy has long been discouraged due to issues of limited efficacy, long-term safety, mortality and higher cost [2], an increase in antipsychotic prescriptions has been prevalent [25-26]. According to a meta-analysis of randomized controlled trials comparing single-drug and multiple-drug regimens in schizophrenia, polypharmacy was demonstrated to be superior in terms of efficacy and the discontinuation of medicine [2], which suggests that polypharmacy may not necessarily always be contraindicated. However, it remains controversial [2,9].

Table 4. Excessive dosing and polypharmacy in care for old long stay patients by region.

	2001			2004			2008					Multiple comparison		
Region	n	%	N	n	%	N	N	%	N	ES	p	2001 vs 2004	2001 vs 2008	2004 vs 2008
Polypharmacy														
Chinese mainland	15	21.1	71	6	16.7	36	10	18.5	54	0.07	0.90	-	-	-
Hong Kong	7	50.0	14	3	27.3	11	1	50.0	2	0.00	0.60	-	-	-
Japan	330	81.5	405	213	73.7	289	140	63.6	220	0.41	0.00*	0.04*	0.00*	0.04*
Korea	23	40.4	57	36	53.7	67	2	28.6	7	0.25	0.21	-	-	-
Singapore	55	77.5	71	0	-	0	0	-	0	-	-	-	-	-
Taiwan	13	24.5	53	7	10.0	70	36	33.6	107	0.20	0.00*	0.11	0.32	0.00*
Excessive dosing														
Chinese mainland	4	5.6	71	1	2.8	36	4	7.4	54	0.07	0.69	-	-	-
Hong Kong	2	14.3	14	0	0.0	11	0	0.0	2	0.78	0.56	-	-	-
Japan	143	35.3	405	68	23.5	289	41	18.6	220	0.38	0.00*	0.00*	0.00*	0.22
Korea	19	33.3	57	24	35.8	67	1	14.3	7	0.46	0.62	-	-	-
Singapore	20	28.2	71	0	-	0	0	-	0	-	-	-	-	-
Taiwan	8	15.1	53	10	14.3	70	7	6.5	107	0.28	0.14	-	-	-

n, number of patients receiving two or more antipsychotics (polypharmacy) or greater than 1,000 CPZeq mg antipsychotics (excessive dosing); ES, Cohen's effect size index for differences in proportions between 2001 and 2008; p, p values derived by chi-squared test or Fisher's exact test for proportional differences among three years. *$p < 0.05$.

Regarding excessive dosing, Korea had the highest rate of patients who received excessive dosing, followed by Japan and Hong Kong, while this rate was relatively low in Singapore. Interestingly, while the rates of excessive dosing were declining significantly in Japan, the rate of excessive dosing was increasing in Korea. This study demonstrated the characteristic prescribing trends in Chinese mainland and Korea. Previous studies reported that the antipsychotic dosage prescribed in Chinese mainland was lower than that prescribed in Japan [23]. However, the results of the present study demonstrated that the dosage was increasing among long-stay inpatients in Chinese mainland. China is currently undertaking a policy of expanding mental hospitals and psychiatric departments in general hospitals [22], which is leading to an increase in the number of patients who become resistant to treatment, resulting in higher rates of excessive dosing. Higher antipsychotic doses may be needed in cases with more severe illness [27], but the efficacy of higher doses (sometimes with polypharmacy) should be employed only as a strategy for dealing with treatment-resistant schizophrenia [28,29].

A further question to be considered is whether the prescription styles used in the treatment of long-stay inpatients influence the prescription practice for acute care patients. Implementing changes in care styles, such as improving polypharmacy and excessive dosing, takes a long time; for example, Japan needed at least 20 years to improve the prescription patterns and nearly 50 years to achieve deinstitutionalization in psychiatric inpatient care because of the predominance of private hospitals.

There are several limitations to this study. First, due to its cross-sectional research design, this study does not investigate the efficacy of different prescription regimens. Second, we examined the antipsychotic prescription patterns at a single or several sites within each country. Although we could examine the chronological changes that occurred in each country, it is difficult to determine across-country differences because the population samples used are non-representative.

Despite these limitations, this cross-sectional study provides insights into the antipsychotic prescription patterns for inpatients with schizophrenia in East Asian countries. The West and the East have pursued different paths in the field of mental health care. Western countries started to reduce the number of psychiatric beds in the middle of the 20th century and shifted from traditional hospital care to community care [30,31]. In contrast, institutionalized care has remained a mainstream practice in many Asian countries [10]. Although a recent global trend involves a shift in care from hospitals to communities, the role of inpatient care is different among individual East Asian countries, and the development of community services is at different stages in each of these countries. At any stage, the recommendations for the prescription of antipsychotics should be followed in practice.

5. ACKNOWLEDGEMENTS

This study was supported by Grants-in-Aid for Research on Regulatory Science of Pharmaceuticals and Medical Devices (Ministry of Health, Labour and Welfare, H22-IYAKU-IPPAN-013). This study was presented in part at the International College of Neuropsychopharmacology Thematic Meeting at Salzburg, April, 2011.

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Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

A comparison between augmentation with olanzapine and increased risperidone dose in acute schizophrenia patients showing early non-response to risperidone

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ARTICLE INFO

Article history:
Received 26 September 2011
Received in revised form 5 January 2012
Accepted 7 January 2012

Keywords:
Add-on
Combination
Polypharmacy
Antipsychotic
Emergency
Clinical trial

ABSTRACT

We examined whether augmentation with olanzapine would be superior to increased risperidone dose among acute schizophrenia patients showing early non-response to risperidone. We performed a rater-blinded, randomized controlled trial at psychiatric emergency sites. Eligible patients were newly admitted patients with acute schizophrenia. Early response was defined as Clinical Global Impressions-Improvement Scale score ≤3 following 2 weeks of treatment. Early non-responders were allocated to receive either augmentation with olanzapine (RIS + OLZ group) or increased risperidone dose (RIS + RIS group). The 78 patients who completed 2 weeks of treatment were divided into 52 early responders to risperidone and 26 early non-responders to risperidone (RIS + OLZ group, $n=13$; RIS + RIS group, $n=13$). No difference in the achievement of ≥50% improvement in Positive and Negative Syndrome Scale total score was observed between RIS + OLZ and RIS + RIS groups. Although time to treatment discontinuation for any cause was significantly shorter in the RIS + RIS group (6.8 weeks [95% confidence interval, 5.2–8.4]) than in early responders to risperidone (8.6 weeks [7.9–9.3]; $P=0.018$), there was no significant difference between the RIS + OLZ group (7.9 weeks [6.3–9.5]) and early responders to risperidone. Secondary outcomes justify the inclusion of augmentation arms in additional, larger studies comparing strategies for early non-responders.

1. Introduction

As a strategy for antipsychotic treatment of schizophrenia, monotherapy is clearly optimal when both effective and tolerated. When a patient fails to respond to an adequate dose of an antipsychotic, the alternatives include switching, administering a higher dose (above the licensed dose), polypharmacy, or clozapine. Clozapine is the only option with established efficacy. However, clozapine is less manageable than other antipsychotics, because the frequency of clozapine-induced agranulocytosis is relatively high. Other options therefore need to be comprehensively evaluated.

A substantial proportion of schizophrenia patients receive more than one antipsychotic (Edlinger et al., 2005; Correll, 2008). The problem currently is that the degree of polypharmacy being practiced seems far in excess of the supporting data (Kane and Leucht, 2008). In a systematic review of 19 randomized studies, the pooled odds ratio suggested a small effect favoring combination treatment, and positive effects appear to have been associated with studies using clozapine combinations (Correll et al., 2009). However, clozapine is not tolerated by some patients. Studies combining non-clozapine second-generation antipsychotics with each other and with the first-generation antipsychotics utilized most in clinical practice are thus required (Correll et al., 2009). Kotler et al. (2004) indicated no significant differences in changes to positive or negative symptomatology between patients receiving a combined regimen of olanzapine with sulpiride augmentation and patients receiving olanzapine monotherapy among chronic schizophrenia patients unresponsive to olanzapine. Kane et al. (2009) reported that addition of aripiprazole to either risperidone or quetiapine in 323 patients showed no efficacy over placebo added to either risperidone or quetiapine. In contrast, Essock et al. (2011) reported that patients assigned to a switch to monotherapy displayed shorter times to all-cause treatment discontinuation than those assigned to remain on polypharmacy. These studies were indicators of what could happen with antipsychotic combinations in chronic-phase patients. In acute-phase patients, however, randomized controlled trials of second-generation antipsychotic combinations have not yet been reported.

In emergency and acute-phase wards, not all patients respond to antipsychotic monotherapy, and we are often faced with difficulties in managing psychotic and aggressive patients. As early non-response to a standard dose of risperidone (≤6 mg) can predict subsequent response (Kinon et al., 2010; Hatta et al., 2011), taking measures to improve outcomes among early non-responders to risperidone is reasonable. We therefore prospectively examined whether augmentation with olanzapine would be superior to increasing the risperidone dose in acute schizophrenia patients showing early non-response to risperidone. The present study was performed with emergency-based, newly admitted patients without support from pharmaceutical companies, reflecting real-world practice.

2. Methods

2.1. Setting and participants

Of the 63 psychiatric emergency wards authorized by the Japanese government, 18 (29%) participated in the present study. These wards were located all over Japan, and were responsible for local emergency cases. Most admissions to these hospitals represented behavioral emergencies and approximately 60% were brought in by the police. All were involuntary admissions as an immediate danger to themselves or others, according to the 1995 Law Concerning Mental Health and Welfare for the Mentally Disabled. Details of the clinical setting are described elsewhere (Hatta et al., 1998). According to government policies, psychiatric emergency services have been expanded in both metropolitan and local areas over the last 16 years. The quality of sites and patients in the present study was therefore homogenous. This activity was conducted by the Japan Acute-phase Schizophrenia Trial (JAST) study group (Hatta et al., 2009, 2011).

During the study period, between July 1 and October 31, 2010, a total of 786 patients were admitted and assessed for eligibility. Eligible patients were 18–64 years old, newly admitted as emergency cases, and meeting the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) for schizophrenia, schizophreniform disorder, or schizoaffective disorder. Patients with obvious complications such as liver dysfunction, renal dysfunction, heart failure, respiratory failure, or diabetes mellitus were excluded, as were patients who were pregnant or who wanted to become pregnant.

2.2. Study design

All study protocols were approved by the institutional review board at each site, and written informed consent was obtained from patients or their legally authorized representatives. Patients who refused oral medication were initially treated with injections. After resolution of agitation, the investigators informed patients orally and in writing about the trial, and invited them to participate.

Patients were treated with flexible-dose oral risperidone for 2 weeks, then divided according to the Clinical Global Impressions-Improvement Scale (CGI-I) (Guy, 1976) into early responders (CGI-I score ≤3) and early non-responders (CGI-I score ≥4). Early responders to risperidone continued with risperidone therapy, whereas early non-responders to risperidone were randomized using the sealed envelope method in a rater-blind manner to either continue on risperidone at an increased dose (RIS + RIS) or to receive risperidone with addition of olanzapine (RIS + OLZ) for the next 8 weeks. For randomization, we referred to a random number table, with sequentially numbered, opaque, sealed envelopes used to conceal the allocation sequence.

The initial dose of risperidone was 3 mg/day. Doses were subsequently increased or decreased at the discretion of the treating psychiatrist. During the first 2 weeks, the maximum dose of risperidone was 6 mg/day. During the next 8 weeks, the dose of risperidone was allowed to reach 12 mg/day for the RIS + RIS group, while the maximum doses of risperidone and olanzapine were 6 mg/day and 20 mg/day, respectively, for the RIS + OLZ group, considering dose equivalency (Kane et al., 2003). Use of benzodiazepines was allowed and documented. Use of valproate as a mood stabilizer was also allowed and documented. However, use of other mood stabilizers and antidepressants was not permitted. Use of anticholinergic drugs was also not allowed unless acute extrapyramidal side effects appeared.

2.3. Procedures

Before starting the trial, site-coordinators were trained to assess outcomes as raters. All site-coordinators were experienced psychiatrists. A training video was used to train raters in assessment of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1991). The primary outcome measure was ≥50% improvement in PANSS total score by 10 weeks.

Efficacy outcomes consisted of PANSS, CGI-I (1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; and 7, very much worse), and the Global Assessment of Functioning (GAF) (Jones et al., 1995). Safety and tolerability outcomes were determined based on vital signs, weight, laboratory data, electrocardiography (ECG), and the Drug-induced Extrapyramidal Symptom Scale (DIEPSS), which includes parkinsonism, akathisia, dystonia, and dyskinesia (Inada, 1996). Data including PANSS, CGI, GAF, vital signs, weight, laboratory data, ECG, and DIEPSS were collected on admission and every 2 weeks thereafter. Data were also collected at the time of discontinuation of the allocated treatment. Sexual side effects were recorded when reported by patients, and sedation was recorded when described by patients as an aversive subjective experience or when observed. Raters did not work on the wards involved in the study, were not involved with treatment, and were blinded to the drug assignments of early non-responders to risperidone. The tested drug was discontinued when the treating psychiatrist judged the efficacy of the drug to be insufficient, when the treating psychiatrist judged side-effects of the drug to be intolerable, or when the patient reported non-adherence. Before a judgment of insufficient efficacy could be made, the drug dosage was increased to the maximum. Another outcome measure was treatment discontinuation for any cause.

2.4. Statistical analysis

Differences between categorical variables in patient demographics and clinical characteristics were calculated using Fisher's exact test. Differences between sequential variables were calculated using the unpaired t test (with Welch correction if applicable). If data were not sampled from Gaussian distributions, a non-parametric test (Mann–Whitney test) was used. Mean improvement in the PANSS total score was calculated as 100 × (baseline score − week × score)/(baseline score − 30) (Leucht et al., 2009). Kaplan–Meier curves were used to estimate the probability of treatment discontinuation at 10 weeks. Statistical analyses were performed using SPSS version 17.0 J software (SPSS, Tokyo, Japan). All statistical tests were two-tailed. Values of $P<0.05$ were regarded as statistically significant.

In our previous randomized clinical study, 9% of early non-responders to risperidone staying on risperidone subsequently achieved ≥50% response (Hatta et al., 2011). No previous data are available regarding the rate of response to adding olanzapine among early non-responders to risperidone. Suzuki et al. (2008) reported that 17 patients with treatment-refractory schizophrenia who failed to respond to sequential monotherapy with olanzapine, quetiapine and risperidone were subsequently treated using combination therapy with olanzapine plus risperidone for ≥8 weeks. Of these, seven responded according to the primary endpoint, four showed sufficient improvement to be discharged from hospital, and six patients showed no response. That open-label study thus found that 11 of 17 patients (65%) with treatment-refractory schizophrenia were full or partial responders to combination therapy comprising olanzapine plus risperidone. Accordingly, we assumed that subsequent response among early non-responders to risperidone by increasing the dose (RIS + RIS group) would be 9%, and that subsequent response among early non-responders to risperidone by addition of olanzapine to risperidone (RIS + OLZ group) would be 60%. The statistical power was set as power $=1-\beta=80\%$, and sensitivity as $\alpha=5\%$ to enable detection of differences in the effects of the augmentation strategy. Power analysis consequently set the required number of patients at 13 patients per group.

This study is registered in the UMIN Clinical Trials Registry (number: UMIN000003531; http://www.umin.ac.jp/ctr).

3. Results

The trial profile is shown in Fig. 1. Eighty-eight patients were enrolled and started on risperidone treatment. The rate of study participation among eligible patients was 23% (88/389). Two patients

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doi:10.1016/j.psychres.2012.01.006

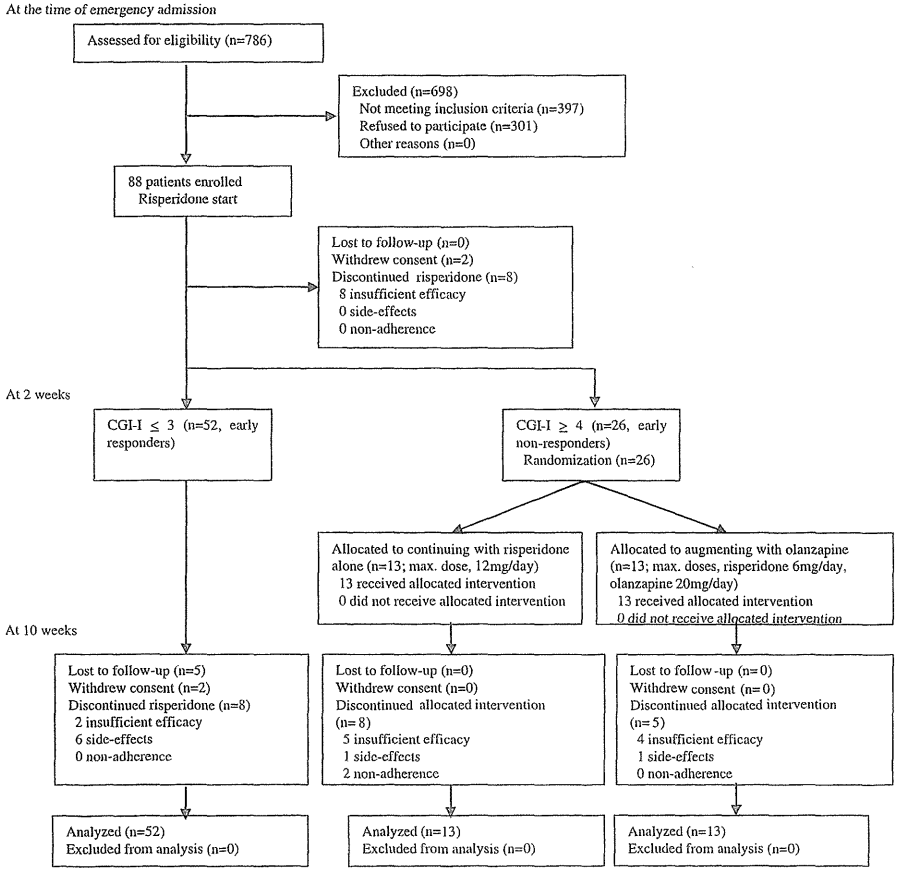

Fig. 1. Trial profile.

withdrew consent, and eight patients discontinued risperidone treatment due to a lack of efficacy before the end of the first 2 weeks. Data from these patients were not included in the final analysis. A total of 78 patients thus completed 2 weeks of treatment. Mean age was 39.5 years (standard deviation (S.D.), 11.9 years), and 49% (38/78) were men. Sixty of the 78 patients were enrolled at the time of emergency admission. The remaining 18 patients were enrolled within 3 days after admission, during which time only haloperidol injections were given. The median interval before enrolment was 0 day. Diagnoses were as follows: schizophrenia/schizophreniform disorder, 94% (73/78); and schizoaffective disorder, 6% (5/78). Six patients (7%) showed comorbidities of substance dependence, involving alcohol in all cases. Antipsychotic-naïve patients comprised 40% (35/78), while haloperidol injection had been received prior to enrolment in 20% (18/78). Mean CGI-S score was 5.6 (S.D., 0.8), and mean PANSS total score was 106.2 (S.D., 24.3). Mean PANSS subscale scores were as follows: positive scale, 29.5 (S.D., 7.3); negative scale, 23.9 (S.D., 9.1); general psychopathology scale, 52.8 (S.D., 13.0); and PANSS-excitement component (PANSS-EC), 18.0 (S.D., 6.1). Mean GAF score was 20.6 (S.D., 7.9). Mean body mass index was 22.5 (S.D., 3.9).

The 78 patients were first divided into early responders to risperidone ($n=52$, 67%), and early non-responders to risperidone ($n=26$, 33%), according to the CGI-I score at 2 weeks, as mentioned in the Study design section. Baseline characteristics of early responders to risperidone and early non-responders are listed in Table 1. No significant differences in each item were found between groups, although the proportion of antipsychotic-naïve patients tended to be higher among early responders to risperidone than among early non-responders.

Mean CGI-I scores at 2 weeks in early responders and early non-responders to risperidone were 2.3 (S.D., 0.6) and 4.5 (S.D., 0.7), respectively. Mean improvements in PANSS total score between baseline and at 2 weeks in early responders and early non-responders to risperidone were 52.2% (S.D., 18.7) and −11.7% (S.D., 26.9), respectively.

Table 1
Baseline characteristics of early responders to risperidone and early non-responders.

	Early responders to risperidone ($n=52$)	Early non-respondersto risperidone ($n=26$)	P
Age (years)	39.6 (12.0)	39.4 (12.0)	0.94
Men	25/52 (48%)	13/26 (50%)	0.81
Asian	52/52 (100%)	26/26 (100%)	
Diagnosis			
Schizophrenia/ schizophreniform	49/52 (94%)	24/26 (92%)	1.00
Schizoaffective	3/52 (6%)	2/26 (8%)	
Substance dependence	3/52 (6%)	3/26 (12%)	0.39
Antipsychotic-naïve	27/52 (52%)	8/26 (31%)	0.09
Haloperidol injection received before enrolment	14/52 (27%)	4/26 (15%)	0.39
CGI-S	5.5 (0.9)	5.8 (0.8)	0.26
PANSS			
Total	106.2 (24.2)	106.1 (24.9)	0.98
Positive scale	29.7 (6.8)	29.1 (8.3)	0.76
Negative scale	23.1 (9.1)	25.2 (9.0)	0.35
General psychopathology scale	53.5 (13.1)	51.8 (12.9)	0.61
PANSS-EC	17.6 (6.5)	18.6 (7.3)	0.58
GAF	20.0 (8.3)	21.6 (7.2)	0.41
BMI (kg/m^2)	22.5 (3.5)	22.3 (4.5)	0.84
Overweight (BMI ≥25)	13/52 (25%)	6/26 (23%)	1.00
Hyperglycemia	0/52 (0%)	0/26 (0%)	
Hypercholesterolemia	7/52 (13%)	4/26 (15%)	1.00
Hypertriglyceridemia	3/52 (6%)	5/26 (19%)	0.11
Median dose of risperidone at 2 weeks (mg/day)	5.5	6.0	0.17

Data represent mean (S.D.) or n/N (%), unless otherwise indicated. Diagnosis was made at discharge according to DSM-IV-TR. All substance dependence was alcohol dependence. 'Haloperidol injection received before enrolment': the maximal duration until enrolment was 3 days. CGI-S, Clinical Global Impression Severity rating scale; PANSS, Positive and Negative Syndrome Scale; PANSS-EC, excitement (item number P4), hostility (P7), tension (G4), uncooperativeness (G8), poor impulse control (G14); GAF, Global Assessment of Functioning; BMI, body mass index. Hyperglycemia: ≥200 mg/dL or fasting glucose ≥126 mg/dL. Hypercholesterolemia: cholesterol concentration ≥220 mg/dL. Hypertriglyceridemia: triglyceride level ≥150 mg/dL. Differences in age, CGI-S, PANSS, GAF, and BMI were calculated using the unpaired t-test. Differences in sex, diagnosis, and frequencies of substance dependence, haloperidol injection received before enrolment, and hypertriglyceridemia were calculated using Fisher's exact test.

Table 2
Baseline characteristics of early non-responders to risperidone.

	RIS + RIS ($n=13$)	RIS + OLZ ($n=13$)	P
Age (years)	41.9 (10.6)	36.8 (13.1)	0.29
Men	9/13 (69%)	4/13 (31%)	0.12
Asian	13/13 (100%)	13/13 (100%)	
Diagnosis			
Schizophrenia/schizophreniform	13/13 (100%)	11/13 (85%)	0.48
Schizoaffective	0/13 (0%)	2/13 (15%)	
Substance dependence	2/13 (15%)	1/13 (8%)	1.00
Antipsychotic-naïve	4/13 (31%)	4/13 (31%)	
Haloperidol injection received before enrolment	3/13 (23%)	1/13 (8%)	0.59
CGI-S	6.0 (0.7)	5.5 (0.9)	0.15
PANSS			
Total	109.7 (26.8)	102.5 (23.4)	0.48
Positive scale	29.7 (9.5)	28.5 (7.2)	0.73
Negative scale	26.6 (9.8)	23.8 (8.3)	0.44
General psychopathology scale	53.4 (15.7)	50.2 (9.6)	0.53
PANSS-EC	19.4 (7.9)	17.8 (6.8)	0.58
GAF	21.9 (6.9)	21.4 (7.7)	0.86
BMI (kg/m^2)	22.4 (5.5)	22.2 (3.6)	0.92
Overweight (BMI ≥25)	3/13 (23%)	3/13 (23%)	
Hyperglycemia	0/13 (0%)	0/13 (0%)	
Hypercholesterolemia	2/13 (15%)	2/13 (15%)	
Hypertriglyceridemia	1/13 (8%)	4/13 (31%)	0.32

RIS + RIS, Allocated to continuing with risperidone alone (max. dose, 12 mg/day); RIS + OLZ, Allocated to augmenting with olanzapine (max. doses, risperidone 6 mg/day, olanzapine 20 mg/day).
Data represent mean (S.D.) or n/N (%). Diagnosis was made at discharge according to DSM-IV-TR. All substance dependence was alcohol dependence. 'Haloperidol injection received before enrolment': the maximal duration until enrolment was 3 days. CGI-S, Clinical Global Impression Severity rating scale; PANSS, Positive and Negative Syndrome Scale; PANSS-EC, excitement (item number P4), hostility (P7), tension (G4), uncooperativeness (G8), poor impulse control (G14); GAF, Global Assessment of Functioning; BMI, body mass index. Hyperglycemia: ≥200 mg/dL or fasting glucose ≥126 mg/dL. Hypercholesterolemia: cholesterol concentration ≥220 mg/dL. Hypertriglyceridemia: triglyceride level ≥150 mg/dL. Differences in age, CGI-S, PANSS, GAF, and BMI were calculated using the unpaired t-test. Differences in sex, diagnosis, and frequencies of substance dependence, haloperidol injection received before enrolment, and hypertriglyceridemia were calculated using Fisher's exact test.

Among early non-responders to risperidone, 13 patients were allocated to continue receiving risperidone alone (RIS + RIS group), and the remaining 13 patients were allocated to receive risperidone augmented with olanzapine (RIS + OLZ group). Baseline characteristics of patients were much the same between the RIS + RIS and RIS + OLZ groups (Table 2). In the RIS + RIS group, previous antipsychotics taken by patients who were not on their first episode were as follows: risperidone, two patients; aripiprazole, two patients; haloperidol, two patients; fluphenazine, one patient; and unknown, two patients. Those taken by patients in the RIS + OLZ group were as follows: risperidone, two patients; aripiprazole, two patients; haloperidol, one patient; and unknown, four patients. Unfortunately, data on exact dosages were not available. No significant differences between groups were seen according to the kinds of previous antipsychotics taken.

Between 2 and 10 weeks, among the early responders to risperidone, five patients were lost to follow-up, and two patients withdrew consent. In addition, eight patients discontinued risperidone due to insufficient efficacy ($n=2$) and side-effects ($n=6$; extrapyramidal side effects, $n=4$; hyperprolactinemia, $n=2$). In the RIS + RIS group, eight patients discontinued the allocated intervention due to insufficient efficacy ($n=5$), extrapyramidal side effects ($n=1$), and non-adherence ($n=2$). In the RIS + OLZ group, five patients discontinued the allocated intervention due to insufficient efficacy ($n=4$) and side-effects ($n=1$, weight gain) (Fig. 1).

Scattergrams of changes in PANSS total score at 10 weeks from baseline are shown in Fig. 2. At 10 weeks, early responders to risperidone showed a significantly higher percentage of improvement in PANSS total score than the RIS + RIS group (66.3% [S.D., 23.9] vs. 26.6% [S.D., 31.7]; $t=4.89$, $P<0.0001$). Meanwhile, no significant difference was observed between the RIS + RIS and RIS + OLZ groups (26.6% [S.D., 31.7] vs. 35.7% [S.D., 26.4]; $t=0.80$, $P=0.43$). A

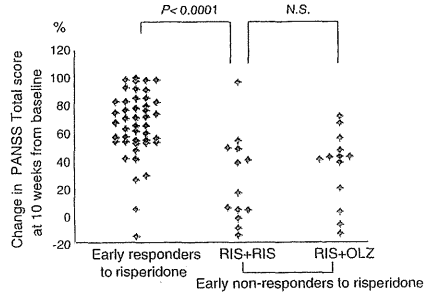

Fig. 2. Scatterplot of change in PANSS total score at 10 weeks from baseline. Early responders to risperidone showed significantly higher percentage of improvement in PANSS total score than the RIS + RIS group (66.3% [S.D., 23.9%] vs. 26.6% [S.D., 31.7%]; $t=4.89$, d.f. = 56, $P<0.0001$). No significant difference was observed between the RIS + RIS and RIS + OLZ groups (26.6% [S.D., 31.7%] vs. 35.7% [S.D., 26.4%]; $t=0.80$, d.f. = 24, $P=0.43$).

comparison of outcomes between the RIS + RIS and RIS + OLZ groups is shown in Table 3. Mean maximum dose of olanzapine in the RIS + OLZ group was 16.9 mg/day, equivalent to 5.1 mg/day of risperidone (Kane et al., 2003). The total dose of antipsychotics in the RIS + OLZ group was thus equivalent to 10.6 mg/day (5.5 + 5.1 mg) of risperidone, higher than that in the RIS + RIS group (8.5 mg/day). In the RIS + RIS group, adjunctive benzodiazepines were given to nine patients: lorazepam, three patients, 1 mg; nitrazepam, one patient, 10 mg; flunitrazepam, six patients, mean 1.8 mg (S.D., 0.4 mg). In the RIS + OLZ group, adjunctive benzodiazepines were given to 12 patients: lorazepam, nine patients, mean 1.5 mg (S.D., 0.9 mg); nitrazepam, four patients, mean 12.5 mg (S.D., 5.0 mg); flunitrazepam, one patient, 1 mg. In the RIS + RIS group, adjunctive valproate was given to four patients with the mean dose of 750 mg (S.D., 300 mg). In the RIS + OLZ group, adjunctive valproate was given to five patients, with a mean dose of 540 mg (S.D., 195 mg).

Achievement rates of ≥20%, ≥30%, ≥40%, and ≥50% improvement in PANSS total score in the RIS + OLZ group were 77%, 69%, 62% and 23%, respectively. Achievement rates of ≥20%, ≥30%, ≥40%, and ≥50% improvement in PANSS total score in the RIS + RIS group were 46%, 46%, 38% and 23%, respectively (Fig. 3). With respect to the primary outcome measure, no difference in the rate of achieving ≥50% improvement in PANSS total score was observed between groups (23% [n/N = 3/13] in each). There were no differences in the rate of achieving ≥20%, 30%, and 40% improvement in PANSS total score between the RIS + OLZ group and the RIS + RIS group (77% vs. 46%, $P = 0.23$, 69% vs. 46%, $P = 0.43$, 62% vs. 38%, $P = 0.43$). These are post hoc analyses, and no significant difference was found either with or without Bonferroni correction. Likewise, no significant differences in safety and tolerability outcomes were identified (Table 3). Among the six patients with akathisia in the RIS + RIS group, only two patients showed akathisia at the time of treatment discontinuation. Severity of akathisia in these two patients was just '1: minimal, questionable' (full score, 4), and the reasons for treatment discontinuation in both patients were insufficient efficacy. A trend-level difference in fasting glucose change from baseline was apparent between the RIS + RIS and RIS + OLZ groups.

Treatment discontinuation for any cause did not differ significantly between treatment groups ($P = 0.060$, Fig. 4). Comparisons by log-rank test showed that although time to treatment discontinuation was significantly shorter in the RIS + RIS group (6.8 weeks; 95%CI, 5.2–8.4 weeks) than in early responders to risperidone (8.6 weeks; 95%CI, 7.9–9.3; $P = 0.018$), it was not significantly shorter in the RIS + OLZ group (7.9 weeks; 95%CI, 6.3–9.5 weeks) than in early responders to risperidone (8.6 weeks; 95%CI, 7.9–9.3 weeks; $P = 0.37$).

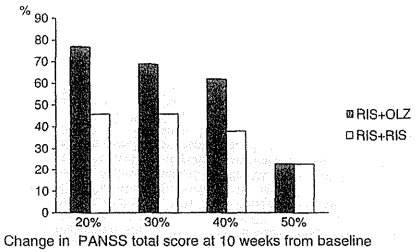

Fig. 3. Change in PANSS total score at 10 weeks from baseline among early non-responders to risperidone. Rates of achieving ≥20%, ≥30%, ≥40%, and ≥50% improvement in PANSS total score in the RIS + OLZ group were 77%, 69%, 62% and 23%, respectively. Rates of achieving ≥20%, ≥30%, ≥40%, and ≥50% improvement in PANSS total score in the RIS + RIS group were 46%, 46%, 38% and 23%, respectively.

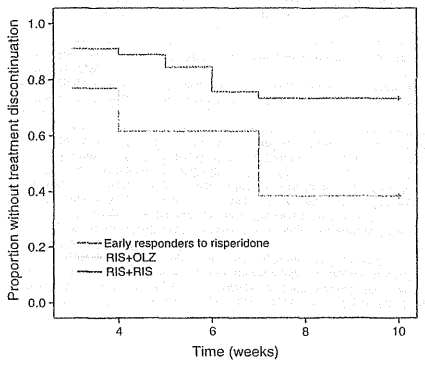

Fig. 4. Time to treatment discontinuation for any cause. Kaplan–Meier estimates of time to discontinuation were 8.6 weeks (95%CI, 7.9–9.3 weeks) for early responders to risperidone, 7.9 weeks (95%CI, 6.3–9.5 weeks) for the RIS + OLZ group, and 6.8 weeks (95%CI, 5.2–8.4 weeks) for the RIS + RIS group. Comparisons by log-rank test showed that time to treatment discontinuation was significantly shorter in the RIS + RIS group than in early responders to risperidone ($P = 0.018$), but was not significantly shorter in the RIS + OLZ group than in early responders to risperidone ($P = 0.37$).

Table 3
Comparison of outcomes between early non-responders to risperidone allocated to continuing with risperidone alone (RIS + RIS) and those allocated to augmenting with olanzapine (RIS + OLZ).

	RIS + RIS (n = 13)	RIS + OLZ (n = 13)	P
Dose of risperidone at 2 weeks (mg/day)	5.2 (0.9)	5.4 (1.2)	0.54
Max. dose of risperidone (mg/day)	8.5 (2.7)	5.5 (1.1)	
Max. dose of olanzapine (mg/day)	0	16.9 (6.0)	
Adjunctive benzodiazepines	9/13 (69%)	12/13 (92%)	0.32
Adjunctive valproate	4/13 (31%)	5/13 (38%)	1.00
Anticholinergic drug	6/13 (46%)	4/13 (31%)	0.69
PANSS (mean change from baseline)			
Total	−21.4 (22.8)	−25.9 (25.2)	0.63
Positive scale	−10.1 (9.0)	−10.1 (9.4)	1.00
Negative scale	−2.9 (6.1)	−4.2 (5.6)	0.60
General psychopathology scale	−8.4 (12.2)	−11.7 (11.7)	0.49
Percentage of improvement in PANSS total	26.6 (31.7)	35.7 (26.4)	0.43
≥50% improvement in PANSS total	3/13 (23%)	3/13 (23%)	
CGI-I	4.3 (1.9)	3.5 (1.3)	0.20
GAF	36.1 (12.6)	42.8 (19.4)	0.32
Any serious adverse event	0/13 (0%)	0/13 (0%)	
Extrapyramidal symptoms (DIEPSS)			
Any symptoms	9/13 (69%)	8/13 (62%)	1.00
Parkinsonism	6/13 (46%)	8/13 (62%)	0.70
Akathisia	6/13 (46%)	2/13 (15%)	0.20
Dystonia	1/13 (8%)	0/13 (0%)	1.00
Dyskinesia	0/13 (0%)	1/13 (8%)	1.00
Weight change from baseline (kg)	1.0 (2.8)	2.0 (3.2)	0.46
Fasting glucose change from baseline (mg/dL)	−2.0 (10.7)	7.8 (16.3)	0.081
Cholesterol change from baseline (mg/dL)	5.1 (37.3)	8.6 (38.6)	0.81
Triglycerides change from baseline (mg/dL)	24 (median)	27 (median)	0.80

Data represent mean (S.D.) or n/N (%), unless otherwise indicated. CGI-I, Clinical Global Impression Improvement rating scale; PANSS, Positive and Negative Syndrome Scale; GAF, Global Assessment of Functioning; DIEPSS, Drug-induced Extrapyramidal Symptom Scale.

4. Discussion

As the definitions of the outcomes adopted in a study represent a critical factor, the characteristics of the CGI classification to identify early non-response in this study require some discussion. Although we used CGI-I, another possibility may be to use a certain cutoff in the PANSS score to decide early non-response. However, such lengthy measures are not used in standard clinical practice. We have recently shown that early response/non-response to risperidone according to CGI-I at 2 weeks can predict subsequent clinical outcomes (Hatta et al., 2011). The negative likelihood ratio for the prediction of achieving ≥50% response at 4 weeks according to early response status to risperidone at 2 weeks was 0.057. This value was sufficiently small (<0.1), meaning that early non-response to risperidone at 2 weeks can predict <50% response at 4 weeks. The result was consistent with prospective findings by Kinon et al. (2010), in which the full 30-item PANSS had been used to assess early response and non-response. Furthermore, the present finding of a −11.7% mean improvement in PANSS total score between baseline and 2 weeks in early non-responders to risperidone is consistent with the linking of CGI-I to percentage PANSS reduction (Leucht et al., 2005). Using CGI-I (score ≥ 4 as a cutoff) to identify early non-response thus appears reliable.

In the present study, a predominance of early responders to early non-responders was observed, with 67% of patients identified as early responders to risperidone. This is consistent with the findings of our previous randomized clinical study on early prediction of antipsychotic response (Hatta et al., 2011), but inconsistent with the retrospective analysis and prospective studies by Kinon et al. (2008, 2010). The discrepancies can be explained by the following points. First, severity of symptoms differed between investigations. With respect to baseline PANSS, mean total scores were approximately 92 in the retrospective analysis (Kinon et al., 2008) and 99 in the prospective trial (Kinon et al., 2010), compared to 106.2 in the present investigation. Extremely high baseline PANSS scores were thus one characteristic of our study, as all patients required emergency admission. Agitation/excitement can be a particularly responsive domain during early treatment (Breier et al., 2002), and may be associated with the predominance of early responders to early non-responders in our emergency-based study. Another difference is that 40% of patients in the present study were drug-naïve, in contrast with the chronically ill patients investigated by Kinon et al. (2010). Since a substantial proportion of the patients in the present study were receiving treatment for the very first time, response times of such patients might have differed (Emsley et al., 2006). The tendency toward a higher rate of antipsychotic-naïve patients among early responders to risperidone compared to early non-responders (Table 1) may support this.

The objective of this study was to clarify whether augmentation with olanzapine would be superior to increased risperidone dose among acute schizophrenia patients showing early non-response to risperidone at 2 weeks in a real-world setting. The present finding that a ≥50% improvement in PANSS total score at 10 weeks among early non-responders allocated to augmentation with olanzapine (RIS + OLZ group) was achieved by 23% is new. In addition, the finding that a ≥50% improvement in PANSS total score at 10 weeks among early non-responders allocated to receive an increased risperidone dose (RIS + RIS group) was achieved by 23% is informative. Although we assumed that the subsequent response rate in the RIS + RIS group was 9%, and that the subsequent response rate in the RIS + OLZ group was 60% as described in the Statistical analysis section, we could not confirm our original hypothesis. This point requires further elaboration. A ≥50% improvement in PANSS total score was achieved by 23% in both groups. This rate was unexpectedly low for the RIS + OLZ group, and unexpectedly high for the RIS + RIS group. The assumption of 9% for the RIS + RIS group was based on our previous finding at 4 weeks, but the present study included a 10-week follow-up period. This prolonged follow-up period might have led to better outcomes than we had expected. Remarkably, rates of achieving a ≥40% improvement in PANSS total score in the RIS + OLZ and RIS + RIS groups were 62% and 38%, respectively (Fig. 3). If the primary outcome measure had been the achievement of ≥40% rather than ≥50%, yielding improvement in PANSS total score for a larger number of patients, a significant difference between groups might have been observed. Kinon et al. (2008) analyzed data from five randomized clinical trials in the treatment of chronically ill patients with schizophrenia, suggesting that the 40% cut-off may be a more appropriate criterion for subsequent improvement. Also, Kinon et al. (2010) reported that later response of ≥40% improvement in PANSS total score was associated with the greatest predictive accuracy. Stauffer et al. (2011) reported that at a threshold for later response of ≥50% improvement in PANSS total score, early non-response most strongly predicted later non-response in the treatment of patients with first-episode psychosis. Thus, what is the appropriate rate as a threshold for later response is still controversial.

Time to treatment discontinuation was significantly shorter in the RIS + RIS group than in early responders, but was not significantly shorter in the RIS + OLZ group than in early responders. In the case of increasing risperidone above a standard dose of 3–6 mg daily, many studies (in Caucasian populations) have shown this either has no benefit or may result in more extrapyramidal symptoms, less improvement in negative symtpoms, and longer hospital stays (Kopala et al., 1997; Emsley, 1999; Love et al., 1999; Lane et al., 2000; Volavka et al., 2002). However, only one treatment discontinuation due to side-effects was seen in the RIS + RIS group and in the RIS + OLZ group (Fig. 1). Among the six patients with akathisia in the RIS + RIS group (Table 3), only two patients showed akathisia at the time of treatment discontinuation. Furthermore, the severity of akathisia in these two patients was just '1: minimal, questionable' (full score, 4), and the reason for treatment discontinuation in both patients was insufficient efficacy. Flexible dose design and allowing use of anticholinergics and benzodiazepines as needed might have helped to prevent treatment discontinuations for side-effects. Toxicity from high-dose risperidone in the RIS + RIS group might not necessarily have been the primary cause for the disadvantage of the RIS + RIS group and the advantage of the RIS + OLZ group. In addition, the lack of significant difference in rates of discontinuation due to side-effects between groups suggests that the combination of risperidone and olanzapine is not necessarily risky.

Kinon et al. (2010) recently reported that switching risperidone to olanzapine at week 2 resulted in a small but significantly greater reduction in PANSS total score than continuing on risperidone among early non-responders. Tenacious monotherapy with risperidone without increasing the dose may thus be inferior to switching to olanzapine. However, the clinical significance of the switching strategy appears to be slight during acute-phase treatment, because the difference in mean PANSS total score between switching to olanzapine and staying on risperidone at 10 weeks was only 3 points. Unfortunately, the present study lacked a switching arm to another antipsychotic monotherapy. We therefore cannot claim that some benefit of augmentation therapy in the present study is superior to the small but significant effects of switching from risperidone to olanzapine reported by Kinon et al. (2010). Further studies comparing augmentation effects with switching effects seem justified.

To the best of our knowledge, this represents the first randomized clinical trial of olanzapine augmentation of risperidone in patients with acute-phase schizophrenia unresponsive to risperidone monotherapy. One strength of this study was that all participants were psychiatric emergency cases requiring admission, mirroring

real clinical practice. The absence of support from pharmaceutical companies was also a key characteristic of this study. One limitation was that the sample size was relatively small. Obtaining informed consent in emergency situations is often difficult. Accordingly, the rate of participation in the study among eligible patients was 23%. This rate is not particularly low for emergency situations (Hatta et al., 2008, 2009, 2011). Second, the study used a single-blind design. Both clinicians and patients may have had expectations about individual antipsychotics in terms of therapeutic potency for acute psychotic episodes, dosage requirements, side-effect profile, and likely need for as-needed medication. Such expectations could influence the dosage prescribed, decisions to prescribe as-needed medications, and decisions to discontinue the assigned drug. However, obtaining informed consent for a double-blind study of emergency situations may be extremely difficult, and the rate of participation in a double-blind study among eligible patients could well be much lower than that in a single-blind study. As excessively low participation rates cannot reflect real practice, this issue is of particular concern for research into emergency situations. Third, the time to all-cause discontinuation may be a more appropriate measure for double-blind trials in which both prescriber and patient expectations are controlled and both study conditions include newly started medications (Essock et al., 2011). In an open-label trial with blind raters, patients and prescribers in the switch condition may be more inclined to attribute alterations in feelings, symptoms, or side-effects to the change in medication compared to patients and prescribers in the stay condition, who may have experienced these same alterations as part of normal variations in illness and medication response. In the present study, neither randomized group represented a stay condition, using either augmentation or an increase in dose. As both groups were conditions with a change in medication, the comparisons may have been more appropriate than a comparison between stay and switch conditions, with respect to the time to all-cause discontinuation. Fourth, an interval of ≥1 week after increasing the doses of risperidone to 6 mg may be needed when determining early non-response. If such an interval is not applied, delayed effects could be seen after the decision to randomize, and thus affect the results. We should be wary of polypharmacy, as multiple agents are too often prescribed by clinicians when not warranted. However, when patients fail to respond to an adequate dose of antipsychotic, it is incumbent upon us to test other options. There was no *RIS + OLZ* advantage over *RIS + RIS* in the primary outcome of the present study. However, secondary outcomes justify the inclusion of augmentation arms in additional, much larger studies comparing strategies for early non-responders. More studies performed in real clinical practice with minimal bias are required to assist clinicians in making rational treatment decisions.

Acknowledgments

This work was supported by grants from the Ministry of Health, Welfare, and Labor of the Japanese Government (Intramural Research Grant for Neurological and Psychiatric Disorders of NCNP, 20B-8 and Comprehensive Research on Disability Health and Welfare, H23-008). The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation, writing of the report, and the decision to submit the paper for publication.

The authors thank Dr. Hiroshi Hamakawa, Dr. Haruo Watanabe, Dr. Aya Ogura, Dr. Ena Kawashima, Dr. Yumi Kobayashi, Dr. You Nakashima, Dr. Atsushi Onohara, Dr. Mari Ejiri, Dr. Shinichro Nakajima, Dr. Reiko Nakase, Dr. Kazuki Kuno, Dr. Naoki Hayashi, Dr. Yuriko Sudo, Dr. Tomoko Rai, Dr. Yutaka Hatada, Dr. Takashi Sunami, Dr. Kijiro Hashimoto, Dr. Tomoyuki Mizuno, Dr. Hiromo Kawada, Dr. Fusako Enokido, Dr. Fumichika Nishimura, Dr. Yuko Nagaji, Dr. Hirotaka Imayuki, Dr. Takashi Hirata, Dr. Tsukasa Takahashi, Dr. Hajime Sugiyama, Dr. Hirofumi Abe, Dr. Yutaka Shirai, Dr. Masaaki Sasaki, Dr. Makoto Asano, Dr. Hidekazu Mori, Dr. Tomohiko Mitsutsuka, Dr. Takayuki Yamada, Dr. Chie Hasegawa, Dr. Yuki Shiratori, Dr. Nagafumi Doi, Dr. Emi Yoshida, Dr. Naomi Kimura, Dr. Yusuke Suzuki, Dr. Tomohiro Sudo, Dr. Takeshi Tanaka, Dr. Tomoyuki Maehara, Dr. Aya Matsuoka, Dr. Zenji Mita, Dr. Mitsuru Takei, Dr. Takao Nishimura, Dr. Hidekazu Masaki, Dr. Akira Hori, Dr. Juichiro Naoe, and Dr. Asaho Hasegawa, for the collection of data, and Dr. Toshitaka Kawabata, Dr. Nozomu Asukai, and Dr. Teruhiko Higuchi, for helpful comments.

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Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

The possibility that requiring high-dose olanzapine cannot be explained by pharmacokinetics in the treatment of acute-phase schizophrenia

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ARTICLE INFO

Article history:
Received 17 July 2012
Received in revised form
18 March 2013
Accepted 8 July 2013

Keywords:
Serum concentration
Risperidone
Negative symptom
Emergency
Randomized clinical trial

ABSTRACT

We examined clinical characteristics including serum olanzapine concentrations for acute schizophrenia patients who required above conventional doses. We performed a rater-blinded, randomized clinical trial in 12 psychiatric emergency sites. Eligible patients were 18–64 years old and met diagnostic criteria for schizophrenia, acute schizophrenia-like psychotic disorder, or schizoaffective disorder. A total of 42 patients were randomly assigned by means of sealed envelopes to receive risperidone (3–12 mg/day; $n=20$) and olanzapine (10–40 mg/day; $n=22$), with follow-up at 8 weeks. The Negative score of the Positive and Negative Syndrome Scale was significantly higher in patients who required high doses than in patients who responded to conventional doses. Serum olanzapine concentrations at the time of oral 20 mg/day could be obtained from 5 out of 7 patients who subsequently required high-dose olanzapine. All values were more than 30 ng/mL after 11–16 h from dosing to sample collection, and the mean value was 47.876 (S.D. 21.546) ng/mL. Such concentrations are appropriate with respect to a therapeutic range of 20–50 ng/mL. The present study has shown evidence that the reason for requiring high-dose olanzapine cannot be explained by pharmacokinetics in the treatment of acute-phase schizophrenia.

1. Introduction

Olanzapine and risperidone are most frequently used among second generation antipsychotics for the acute treatment of psychosis in hospitalized patients (Choi et al., 2011), as the superiority of them has been reported in several randomized clinical trials (RCTs) (Kraus et al., 2005; McCue et al., 2006; Hatta et al., 2009). However, no difference in effectiveness between the two antipsychotics has been reported in the previous RCTs, in which both antipsychotics were given within the licensed doses, i.e. 20 mg/day for olanzapine and 12 mg/day for risperidone. Remarkably, the upper dose of olanzapine is equivalent to half of the upper dose of risperidone (Gardner et al., 2010). Therefore, a clinical question has been raised whether olanzapine would be superior to risperidone when olanzapine is allowed to be given above the licensed dose as needed.

In clinical practice, it has been reported that nearly 50% of olanzapine prescription were above 20 mg/day in the U.S. (Citrome et al., 2007) and that the median for olanzapine recommendation dose by U.S. experts was 30 mg/day (Gardner et al., 2010). The upper limit of olanzapine dose in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, in which olanzapine was the most effective in terms of the rates of discontinuation, was designed to be 30 mg/day (Lieberman et al., 2005).

In chronic schizophrenia inpatients that showed suboptimal response to treatment, there is a RCT that the use of high doses of olanzapine were allowed (Volavka et al., 2002). In the study, it has been reported that clozapine and olanzapine were superior to haloperidol, but that the superiority of risperidone over haloperidol was not obvious. In treatment-resistant schizophrenia patients, there were reports that olanzapine at higher than customary doses demonstrated similar efficacy to clozapine (Meltzer et al., 2003) or less effective than clozapine (Kumra et al., 2008). Meanwhile, such a RCT has not been conducted in acute-phase schizophrenia patients.

Another clinical question was who needs high-dose risperidone or olanzapine. Especially, olanzapine has little active metabolites (Callaghan et al., 1999), in contrast to risperidone. Furthermore, there is a high correlation between serum and cerebrospinal fluid olanzapine concentrations (Skogh et al., 2011). Therefore, serum olanzapine concentrations would reflect most activity of olanzapine. Accordingly, serum olanzapine concentrations for patients who require high doses are worth measuring to investigate pharmacokinetic characteristics of such patients. However, serum olanzapine concentrations at 20 mg/day for patients who do not respond to conventional doses have not been well investigated.

We therefore prospectively examined whether olanzapine within 40 mg/day would be superior to risperidone within 12 mg/day in acute schizophrenia patients. In addition, we examined clinical characteristics for patients who required above conventional doses. Especially, in order to investigate whether serum olanzapine concentrations for patients who did not respond to conventional doses would be inappropriately low, serum olanzapine concentrations were measured. The present study was performed with emergency-based, newly admitted patients without support from pharmaceutical companies, reflecting real-world practice.

2. Methods

2.1. Setting and participants

Of the 80 psychiatric emergency wards authorized by the Japanese government, 12 (15%) participated in the present study. These wards were located all over Japan, and were responsible for local emergency cases. Most admissions to these hospitals represented behavioral emergencies and approximately 60% were brought in by the police. All were involuntary admissions as an immediate danger to themselves or others, according to the 1995 Law Concerning Mental Health and Welfare for the Mentally Disabled. Details of the clinical setting are described elsewhere (Hatta et al., 1998). According to government policies, psychiatric emergency services have been expanded in both metropolitan and local areas over the last 17 years. The quality of sites and patients in the present study was therefore homogenous. This activity was conducted by the Japan Acute-phase Schizophrenia Trial (JAST) study group (Hatta et al., 2009, 2011, 2012).

During the study period, between June 1, 2011 and January 31, 2012, a total of 1746 patients were admitted and assessed for eligibility. Eligible patients were 18–64 years old, newly admitted as emergency cases, and meeting the criteria of the DSM-IV-TR for schizophrenia, schizophreniform disorder, or schizoaffective disorder. Patients with obvious complications such as liver dysfunction, renal dysfunction, heart failure, respiratory failure, or diabetes mellitus were excluded, as were patients who were pregnant or who wanted to become pregnant.

2.2. Study design

All study protocols were approved by the institutional review board at each site, and written informed consent was obtained from patients or their legally authorized representatives. Patients who refused oral medication were initially treated with injections. Times of injections before enrollment were not limited. After resolution of agitation, the investigators informed patients orally and in writing about the trial, and invited them to participate.

Patients were randomized using the sealed envelope method in a rater-blind manner to either risperidone or olanzapine for 8 weeks. For randomization, we referred to a random number table, with sequentially numbered, opaque, sealed envelopes used to conceal the allocation sequence.

The initial doses of risperidone and olanzapine were 3 mg/day and 10 mg/day, respectively. Doses were subsequently increased or decreased at the discretion of the treating psychiatrist. The maximum of licensed dose for olanzapine is 20 mg/day, which is equivalent to 6 mg/day for risperidone (Gardner et al., 2010). Therefore, the definition of higher dose in the present study was more than 20 mg/day for olanzapine and more than 6 mg/day for risperidone. The maximum doses of risperidone and olanzapine were 12 mg/day and 40 mg/day, respectively, considering dose equivalency (Gardner et al., 2010). Use of benzodiazepines was allowed and documented. Use of valproate as a mood stabilizer was also allowed and documented. However, use of other mood stabilizers and antidepressants was not permitted. Use of anticholinergic drugs was also not allowed unless acute extrapyramidal side effects appeared.

2.3. Procedures

Before starting the trial, site-coordinators were trained to assess outcomes as raters. All site-coordinators were experienced psychiatrists. A training video was used to train raters in assessment of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1991). The primary outcome measure was all-cause discontinuation by 8 weeks.

Efficacy outcomes consisted of PANSS, the Clinical Global Impressions-Improvement Scale (CGI-I: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; and 7, very much worse) (Guy, 1976), and the Global Assessment of Functioning (GAF) (Jones et al., 1995). Safety and tolerability outcomes were determined based on vital signs, weight, laboratory data, electrocardiography (ECG), and the Drug-induced Extrapyramidal Symptom Scale (DIEPSS), which includes parkinsonism, akathisia, dystonia, and dyskinesia (Inada, 1996). Data including PANSS, CGI, GAF, vital signs, weight, laboratory data, ECG, and DIEPSS were collected on admission and every 2 weeks thereafter. Data were also collected at the time of discontinuation of the allocated treatment. Sexual side effects were recorded when reported by patients, and sedation was recorded when described by patients as an aversive subjective experience or when observed. Raters did not work on the wards involved in the study, were not involved with treatment, and were blinded to the drug assignments. The tested drug was discontinued when the treating psychiatrist judged the efficacy of the drug to be insufficient, when the treating psychiatrist judged side-effects of the drug to be intolerable, or when the patient reported non-adherence. Before a judgment of insufficient efficacy could be made, the drug dosage was increased to the maximum. The definition of drug non-adherence in the study performed in emergency and acute wards, where drug administration was managed by nurses, was that a patient declines the continuation of assigned medication.

2.4. Determination of olanzapine in human serum

Fasting blood samples were collected in the morning at least 10 h after the last evening dose of olanzapine for analyses of olanzapine. Serum for concentration analysis was separated and stored frozen at −20 °C until analysis.

A liquid chromatography/tandem mass spectrometry method was used for analysis of olanzapine. Olanzapine and internal standard (IS: LY170222) were extracted from serum (100 μL) by liquid–liquid extraction using tert-butyl methyl ether. The processed sample (10 μL) was injected into high-performance liquid chromatograph/tandem mass spectrometer that was equipped with a C_{18} column, using 10 mmol/L ammonium acetate/acetonitrile and acetonitrile as the mobile phase under gradient conditions. Olanzapine and IS were detected using a multiple reaction monitoring mode with positive ion (olanapine: m/z 313→256; IS: m/z 327→270). Calibration for olanzapine was linear within the concentration range of 0.25–100 ng/mL.

2.5. Statistical analysis

Differences between categorical variables in patient demographics and clinical characteristics were calculated using Fisher's exact test. Differences between sequential variables were calculated using the unpaired t test (with Welch correction if applicable). If data were not sampled from Gaussian distributions, a non-parametric test (Mann–Whitney test) was used. Mean improvement in the PANSS total score was calculated as 100 × (baseline score − week × score)/(baseline score − 30) (Leucht et al., 2009). Kaplan–Meier curves were used to estimate the probability of treatment discontinuation at 8 weeks. Statistical analyses were performed using SPSS version 17.0J software (SPSS, Tokyo, Japan). All statistical tests were two-tailed. Values of $P<0.05$ were regarded as statistically significant.

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0165-1781/$ - see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.psychres.2013.07.005

In our previous randomized clinical study, 25% of patients allocated to risperidone, of which the maximum dose was allowed up to 12 mg/day, discontinued risperidone by 8 weeks, while 12% of patients allocated to olanzapine, of which the maximum dose was allowed up to 20 mg/day, discontinued olanzapine by 8 weeks (Hatta et al., 2009). In the present study, the maximum dose of olanzapine was allowed up to 40 mg/day. As no previous data are available regarding the discontinuation rate for patients allocated to olanzapine with such conditions, we assumed 10% decrease in discontinuation rate by 8 weeks from our clinical experiences. The statistical power was set as power=$1-\beta$=80%, and sensitivity as α=5% to enable detection of differences in the effects of the augmentation strategy. Power analysis consequently set the required number of patients at 34 patients per group.

This study is registered in the UMIN Clinical Trials Registry (number: UMIN000005526; http://www.umin.ac.jp/ctr).

3. Results

3.1. Comparison between patients allocated to risperidone and patients allocated to olanzapine

Fig. 1 shows the trial profile. Forty-two patients were randomly assigned to two treatment groups. Baseline characteristics of randomized patients were much the same between groups, and mean (±S.D.) maximum doses of risperidone and olanzapine were 6.9±2.7 mg/day and 23.0±10.2 mg/day, respectively, suggesting relative dose equivalency. However, the number of patients allocated to each treatment group did not reach the required number of patients set by power analysis. Therefore, it is not conclusive about the primary outcome measure although time to treatment discontinuation for any cause did not differ between treatment groups (47.0 days [95%CI 39.9–54.0] for risperidone vs. 47.0 days [40.0–54.0] for olanzapine, P=0.93).

With respect to safety and tolerability outcomes, the rate of extrapyramidal symptoms was significantly higher in patients taking risperidone than in patients taking olanzapine (P=0.0080), corresponding to the significant difference in the rate of adjunctive anticholinergic drug use between the groups (P=0.013). No significant differences between treatment groups were identified in mean change from baseline for fasting glucose, cholesterol, triglycerides, or weight. Over-sedation was observed in one patient taking olanzapine (max. dose, 30 mg/day). Sexual side effects were not observed.

No significant difference in the rate of patients who required high doses was seen between the risperidone group and the olanzapine group (40% [8/20] vs. 32% [7/22], P=0.75). The rates of patients who achieved a ≥50% improvement in PANSS total score by 8 weeks in patients requiring high-dose risperidone and in patients requiring high-dose olanzapine were 25% [2/8] and 0% [0/7], respectively. Meanwhile, the rates of patients who achieved moderate (≥30%) improvement in PANSS total score in patients requiring high-dose risperidone and in patients requiring high-dose olanzapine were 63% [5/8] and 57% [4/7], respectively.

3.2. Comparison between patients having required high doses and patients having responded to conventional doses

Fifteen patients required high doses. Of these patients, six patients were drug-naïve. Among the rest nine patients, only one patient that was allocated to risperidone met the definition of treatment-resistant schizophrenia at the time of study entry (Suzuki et al., 2011). The high-dose group was in a greater trend in the mean PANSS total score at baseline than the conventional-dose group (P=0.051, Table 1). In line with it, the high-dose group was in a greater trend in the rate of patients who received haloperidol injections at the time of admission than the conventional-dose group (P=0.085). Also, the high-dose group was in a greater trend in the times of haloperidol injections at the time of admission than the conventional-dose group (median 1 vs. 0, P=0.098). All subscale scores of PANSS were very high in both groups. Although there were no significant differences in scores of PANSS Positive scale and General psychopathology scale between groups, PANSS Negative scale score was significantly higher in the high-dose group than in the conventional-dose group (P=0.0077).

The mean PANSS total score at the time of starting high doses in the high-dose group was 104.5 (S.D. 21.5), which is as high as that at baseline in the conventional-dose group (105.2 [S.D. 24.8], Table 1).

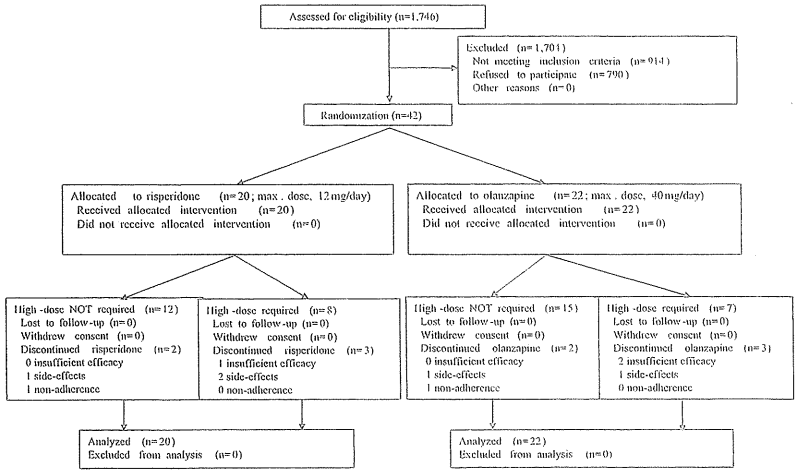

Fig. 1. Trial profile.

Table 1
Comparison of baseline characteristics between patients requiring high-dose and patients with conventional-dose.

	High-dose (n=15)	Conventional-dose (n=27)	P
Age	37.4 (12.8)	36.7 (9.0)	0.85
Men	7/15 (47%)	14/27 (52%)	1.00
Asian	15/15 (100%)	27/27 (100%)	
Substance dependence	2/15 (13%)	3/27 (11%)	1.00
Duration from onset (year)	9.9 (11.6)	8.1 (7.7)	0.56
Antipsychotic-naive	6/15 (40%)	17/27 (63%)	0.20
Haloperidol injection received before enrollment	8/15 (53%)	6/27 (22%)	0.085
CGI-S	5.9 (0.7)	5.8 (0.9)	0.56
PANSS			
Total	120.5 (21.0)	105.2 (24.8)	0.051
Positive scale	32.6 (6.1)	30.5 (6.5)	0.30
Negative scale	28.9 (9.2)	20.9 (8.7)	0.0077
General psychopathology scale	58.9 (11.1)	53.8 (14.1)	0.23
GAF	20.3 (8.3)	23.7 (8.0)	0.20
BMI (kg/m^2)	21.1 (4.0)	21.7 (3.4)	0.66
PANSS total score at the time of starting high-dose	104.5 (21.5)		

Data represent mean (S.D.) or n/N (%), unless otherwise indicated. All substance dependence except one patient with benzodiazepine dependence in the conventional-dose group was alcohol dependence. 'Haloperidol injection received before enrollment': the maximal duration until enrollment was 3 days. CGI-S, Clinical Global Impression Severity rating scale; PANSS, Positive and Negative Syndrome Scale; GAF, Global Assessment of Functioning; BMI, body mass index. Differences in age, duration from onset, CGI-S, PANSS, GAF, and BMI were calculated using the unpaired t-test. Differences in sex, and frequencies of substance dependence, antipsychotic-naïve, and haloperidol injection received before enrollment were calculated using the Fisher's exact test.

3.3. Serum olanzapine concentrations at the time of taking 20 mg/day in patients who subsequently required high-dose olanzapine

Serum olanzapine concentrations at the time of taking 20 mg/day could be obtained from five out of seven patients who subsequently required high-dose olanzapine. The rest two patients refused additional blood samples. The mean time from dosing to sample collection was 14.2 h (S.D. 2.5, range 11–16). Values are shown in Table 2, and the mean value was 47.876 ng/mL (S.D. 21.546). Although Case 2 was a smoker, the serum concentration was not low. The serum olanzapine concentration at the time of taking 20 mg/day in the patient who subsequently discontinued olanzapine due to over-sedation was extremely high (84.856 ng/mL).

4. Discussion

The number of patients allocated to each treatment group did not reach the required number of patients set by power analysis to examine whether olanzapine within 40 mg/day would be superior to risperidone within 12 mg/day in acute schizophrenia patients. Meanwhile, comparison between patients having required high doses and patients having responded to conventional doses revealed a difference in PANSS Negative scale score at baseline, i.e., the score in the former was significantly higher than that in the latter. It suggests that patients with severe negative symptoms do not respond to conventional-dose antipsychotics and require high doses in acute-phase schizophrenia. So far the association between negative symptoms and antipsychotic treatment-resistance has been pointed out (Kinon et al., 1993; Hatta et al., 2003). The association between negative symptoms and gray matter decrease has also been pointed out (Cahn et al., 2006). Severe negative symptoms stood on pharmacological and morphological abnormality, which makes treaters hard to emotionally communicate with such patients, might need additional doses of antipychotics for patients' behavior affected by severe positive and general psychopathology symptoms to be managed.

Although the rates of patients who achieved a ≥50% improvement in PANSS total score by 8 weeks in patients requiring high doses were low (25% for risperidone and 0% for olanzapine), more than half of such patients achieved moderate (≥30%) improvement in PANSS total score (63% for risperidone and 57% for olanzapine). Consequently, monotherapy could be continued in more than half of patients who did not respond to conventional doses. In addition, severe adverse events did not happen as the safety of high-dose olanzapine has been reported (Kinon et al., 2008; Mitchell et al., 2006). When monotherapy is valued more than polypharmacy, olanzapine dosing above the licensed range for non-responders to conventional doses may be acceptable as risperidone up to 12 mg/day is licensed.

Another question was whether patients who require high-dose olanzapine could be predicted by means of pharmacokinetics. In other words, this study examined whether serum olanzapine concentrations for patients who do not respond to conventional doses would be inappropriately low. Olanzapine has little active metabolites (Callaghan et al., 1999), and there is a high correlation between serum and cerebrospinal fluid olanzapine concentrations (Skogh et al., 2011). Therefore, serum olanzapine concentrations reflect most activity of olanzapine. Furthermore, a relationship between clinical outcomes and plasma concentrations has been strongly indicated, and a therapeutic range of 20–50 ng/mL has been found (Mauri et al., 2007). In the present results, serum olanzapine concentrations after 11–16 h from 20 mg/mL dosing to sample collection for patients who subsequently required high doses were above 30 ng/mL. As mean olanzapine plasma concentrations at 24 h after dosing were approximately 70% of those at 12 h after dosing, irrespective of ethnicity (Callaghan et al., 1999), trough plasma concentrations of the five cases that did not respond to 20 mg/day olanzapine must not have fallen below 20 ng/mL (Table 2). Thus, serum olanzapine concentrations for patients who subsequently required high doses were not low, suggesting that the reason for requiring high doses in such patients cannot be explained by pharmacokinetics. Roth (2008) mentioned the possibilities for the efficacy of high-dose olanzapine for treatment-resistant schizophrenia: pharmacodynamics, pharmacokinetics, and pharmacogenetics. So far, Kelly et al. (2006) reported that plasma levels of olanzapine given 50 mg/day were not associated with symptom response, and Citrome et al. (2009) reported no significant correlation between olanzapine concentration and either change in PANSS score or response to treatment. The present study has directly shown evidence that the reason for requiring high-dose olanzapine cannot be explained by pharmacokinetics. To our knowledge, this is the first finding of serum olanzapine concentrations at such timing for patients who did not respond to conventional doses and subsequently required high doses.

In contrast, some side effects might be partly explained by pharmacokinetics because the serum concentration of Case 5 during

Table 2
Characteristics and serum olanzapine concentrations at the time of oral 20 mg/day in patients who did not respond to conventional-dose olanzapine and subsequently required high doses.

	Case 1	Case 2	Case 3	Case 4	Case 5
Age (year)	58	42	28	50	53
Sex	Male	Male	Female	Female	Female
Smoking	Non	One pack of cigarettes/4 weeks	Non	Non	Non
Timing of sample collection after the increase in olanzapine to 20 mg/day (day)	1	11	1	8	1
Time from dosing to sample collection (hour)	16	12	16	11	16
Serum olanzapine concentration (ng/mL)	30.730	36.267	40.103	47.424	84.856
Estimated trough plasma concentrations (ng/mL)[a]	> 21.511	25.387	> 28.072	Slightly low value at 33.197	> 59.399
Discontinuation before 8 week period	No	No	Yes	No	Yes
The reason for discontinuation			NE		SE
The final improvement in PANSS (%)	42.4	31.0	32.3	31.4	24.6

NE, insufficient efficacy; SE, side effects; PANSS, Positive and Negative Syndrome Scale.

[a] Estimated trough plasma concentrations (ng/mL) were determined based on evidence that mean olanzapine plasma concentrations at 24 h after dosing were approximately 70% of those at 12 h after dosing, irrespective of ethnicity (Callaghan et al., 1999).

receiving 20 mg/day that subsequently discontinued olanzapine due to over-sedation was extremely high (84.856 ng/mL, Table 2). This suggests that the patient might have been a slow metabolizer, and that over-sedation might have been associated with the extremely high serum concentration. Similar finding has been observed about olanzapine concentrations and prolactin levels (Citrome et al., 2009).

One strength of this study was that all participants were psychiatric emergency cases requiring admission, mirroring real clinical practice. The absence of support from pharmaceutical companies was also characteristics of the study. One limitation was that sample size was small. Obtaining informed consent in emergency situations is often difficult. In the present study, especially, obtaining consent to use above licensed doses of olanzapine was extremely difficult. Accordingly, the rate of participation in the study among eligible patients was 5%. Second, the present finding may not be applicable to African American, because 89% of them are CYP3A43 genotype AA carriers, and 50% of AA carriers have predicted concentrations less than 20 ng/mL in the range of 15–20 mg/day (Bigos et al., 2011). Third, the study design was single-blinded. Both clinicians and patients may have had expectations about individual antipsychotics in terms of therapeutic potency in acute psychotic episodes, dosage requirements, side-effect profile, and likely need for p.r.n. medication. Such expectations could influence the dosage prescribed, decisions to prescribe p.r.n. medication, and decisions to discontinue the assigned drug. The present findings suggest that conventional doses are hard to take effects irrespective of levels of serum concentrations in Asian acute-phase schizophrenia patients whose negative symptoms clearly exist at the time of admission, and that more than half of such cases show moderate improvement resulted from subsequent treatment with high doses. More studies performed in real clinical practice with minimal bias are required to assist clinicians in making rational treatment decisions.

Acknowledgments

This work was supported by grants from the Ministry of Health, Welfare, and Labor of the Japanese Government (Comprehensive Research on Disability Health and Welfare, H23-008). The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, and the decision to submit the paper for publication.

The authors thank Dr. Haruo Watanabe and Dr. Kozo Fukao (Sawa Hospital), Dr. Kazuya Hata (Hokutokurinikku Hospital), Dr. Juichiro Naoe, Dr. Ayumi Iida and Dr. Nanase Kawabata (Asahikawa Keisenkai Hospital), Dr. Yuko Nagaji, Dr Hirotaka Imayuki and Dr. Takashi Hirata (Saitama Prefectural Psychiatric Hospital), Dr. Yuko Kozuka (Mie Prefectural Mental Medical Center), Dr. Kaori Imura, Dr. Toshinao Takahashi, Dr. Masanori Arihara, Dr. Masamichi Fukuda, Dr. Kenjiro Kiuchi and Ms Asami Orihara (Seijin Hospital), Dr. Yuya Tenjin (Narimasu Kousei Hospital), Dr. Yuriko Sudo (Tosa Hospital), Dr. Kiyoaki Takeshi, Dr. Mayuka Ike, Dr. Hiroyo Sato and Dr. Kazuhisa Ishigaki (Tokyo Musashino Hospital), Dr. Hiroko Taki (Hyogo Prefecture Kofu Hospital), Dr. Makiko Murakami (Shizuoka Psychiatric Medical Center), Dr. Kijiro Hashimoto, Dr. Yasuhiro Nishijima and Dr. Yasufumi Tomiyama (National Hospital Organization Hizen Psychiatric Center), Dr. Fusako Enokido (Fukui Prefectural Hospital), and Dr. Masaki Okumura (Tokyo Metropolitan Toshima General Hospital), for the collection of data, and Mr Akira Maihara (JCL Bioassay Corporation), Dr. Toshitaka Kawabata (Kyoto Prefectural Rakunan Hospital) and Dr. Nozomu Asukai (Tokyo Institute of Psychiatry), for the helpful comments. The authors also thank Eli Lilly and Company for providing LY170222 to analyze serum olanzapine concentrations.

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Regular Article

Secluded/restrained patients' perceptions of their treatment: Validity and reliability of a new questionnaire

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Aim: To develop a standardized self-reporting questionnaire to evaluate patients' perceptions of their overall treatment in specific relation to the use of seclusion and/or restraint (SR) measures as part of the treatment program.

Methods: A 17-item self-rating questionnaire was given to 56 patients with experience of SR-related treatment to develop a new scale, the Secluded/Restrained Patients' Perceptions of their Treatment (SR-PPT). Concurrent validity was examined against the Client Satisfaction Questionnaire-8 Japanese Version (CSQ-8J). In addition, Patient burden induced by answering the SR-PPT was evaluated.

Results: On factor analysis, two factors named as Cooperation with Staff (nine items) and Perceptions of SR (two items) were derived. Cronbach's coefficient alphas were 0.928 and 0.887, and correlation coefficients against the CSQ-8J were 0.838 and 0.609, respectively. Answering the SR-PPT was found to induce little burden on the patients.

Conclusion: Adequate internal consistency and concurrent validity of the final version of the SR-PPT, which consists of 11 items, indicate that it is acceptable as a measurement scale. Use of this questionnaire will add the patient's view to the assessment of overall treatment involving SR.

Key words: coercion, inpatients, patient participation, patient satisfaction, profession–patient relations.

IN PSYCHIATRIC INPATIENT care, seclusion and/or restraint (SR) is often used to secure the safety of a patient whose disruptive behaviors due to mental disorder pose a potential danger to the patient him/herself and to others in the immediate vicinity, such as patients and care staff.[1] The aims of SR are to ensure a secure environment and to provide medication and care smoothly until SR is no longer considered necessary. It is also reported, however, that patients who have experienced SR felt fear, helplessness and distress. This suggests that they do not consider such intervention beneficial, but rather a form of punishment under the control of care staff.[2–5]

Through various discussions aimed at SR minimization and elimination,[6,7] it has been clarified that the amount of SR in Japan is high compared to other countries. The minimization of SR is an urgent task in Japan.[8] Finland, another country that recognizes itself as a heavy user of SR among European countries, has conducted substantial investigations and has been taking measures for SR minimization.[9,10] From this common awareness, Japan and Finland launched a bilateral project called SAKURA in 2007 to investigate the quality of care involving SR. The project follows the structure, process and outcome proposed by Donabedian[11] and as one of the outcomes, focuses on the evaluation of the patient's own perceptions of his/her treatment.

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Received 18 February 2011; revised 27 March 2012; accepted 28 March 2012.

Recent studies have found that patient perception of coercive interventions and/or a weak alliance with care staff lead to poorer adherence to treatment,[12] and that an involuntary admission without understanding the justification for treatment results in a higher rate of readmission.[13] It has been shown that in community mental health care, where patients generally receive treatment at will, closer agreement between the patient's needs and the physician's justification of treatment is associated with a higher level of patient satisfaction and consequently better adherence to the treatment.[14] In addition, the patient's involvement in making treatment decisions improves his/her quality of life (QOL) and satisfaction level.[15,16] Such findings can possibly be extrapolated to patients who have experienced SR, because their perceptions of such treatment and its justification as well as their perceptions of therapeutic collaboration with the staff might influence their prognosis. It is, therefore, necessary for staff providing SR treatment to make efforts to build a therapeutic relationship with the patients, identify their therapeutic needs, and involve them in establishing their own treatment goals. Such tasks are accomplished not only through close communication with SR patients but also by various types of quality care provided to them, such as offering medication, supporting nutrition and hydration, assisting in personal hygiene, and observing the somatic condition. Thus, any evaluation of how these tasks are accomplished must examine the patients' own rigorously measured perceptions of both the SR itself and the overall treatment related to SR.

Among the existing questionnaires examining how SR is perceived, some focus on negative emotions such as fear, hopelessness and punishment, or about positive experiences such as a calming effect or feeling of safety. Other questionnaires directly ask about the efficacy of SR.[2–5,17] The surveys of involuntarily admitted patients' perceptions of their treatment include questions referring to the involuntary admission itself such as perceived coercion, being respected and feeling safe, and those asking about the relationship with care staff, perceived improvement and satisfaction.[18–21] Most of those surveys explain the results by item individually, but do not provide a discussion using a composite score of each item, to grasp the overall aspects of patient perceptions.

In contrast, several questionnaires addressing patient satisfaction and collaboration between the patient and care staff were designed as a measurement using the total score, but did not include items specific to SR.[22–25] Moreover, some of them involve many questions, which imposes an excessive burden on a patient just after an SR event.

Accordingly, a questionnaire that measures all of the aforementioned aspects of patient perceptions in only a few items, to reduce patient burden, does not exist.

The aim of this study was to develop a self-reporting questionnaire as a tool for measuring patient perception in order to evaluate the quality of overall treatment related to SR – a questionnaire applicable even to emotionally labile patients right after an SR event.

METHODS

Scale development

To determine the items that would constitute the new questionnaire (hereafter referred to as the 'Secluded/Restrained Patients' Perceptions of their Treatment', SR-PPT), the items used in previous surveys and existing questionnaires were examined. These included surveys on perception of SR[2–5,17] and involuntarily admitted patients' perceptions of their treatment,[18–21] questionnaires on patient satisfaction,[22,23] and the Working Alliance Inventory (WAI).[24,25] The items identified from the existing questionnaires for development of the SR-PPT were reviewed by a professional group consisting of two psychiatrists, three psychiatric nurses and one psychiatric occupational therapist. In total, 17 items were selected and categorized into the following five domains: 'working alliance for treatment' (seven items) and 'respect and autonomy' (four items), which are considered to be the domains most influenced by the coercive manner of SR; and second, 'how patients felt about their SR' (three items), and then 'satisfaction' (two items) and 'perceived improvement' (one item) as general impressions. With regard to the number of items, careful consideration was given to minimize the survey-related burden on patients who might be distressed during or immediately after SR.

The SR-PPT consists of several existing items in English and new items originally drafted by the main author (T.N.) in Japanese. Both English and Japanese versions of the SR-PPT were prepared. Permission was obtained from all authors of the existing questionnaires in order to use the exact wording of the items. The existing items in English were translated into Japanese by the same author (T.N.) and back-

translated into English by two independent native speakers. The back-translation was checked against the original English sentences by another native English-speaking psychiatric care worker. The original items in Japanese were translated into English by two independent native English speakers and then back-translated into Japanese. The back-translation was then checked by the same author (T.N.).

A 100-mm visual analogue scale (VAS) was chosen as the measurement scale, allowing responses ranging from 'strongly disagree' to 'strongly agree' (scored correspondingly from 0 to 100 mm). Respondents were requested to answer based on their perceptions at the time of filling in the questionnaire and not to recall retrospectively the feelings experienced during SR.

The study was conducted between May and August 2008.

Setting

Two emergency wards and one acute ward in two psychiatric hospitals (N Hospital and K Hospital) in Japan participated in the study. 'Emergency ward' and 'acute ward' are ward categories stipulated by the national reimbursement system in Japan. The emergency and acute wards are those with ≥40% of patients newly admitted and with ≥40% of the newly admitted patients discharged to their home within 3 months. Emergency wards must also accept a required minimum number of compulsory involuntary admissions under orders from the hospital's catchment area. Accordingly, the average registered nurse allocation for an emergency ward is 10 patients per nurse per day (vs 13 patients per nurse per day for an acute ward).

The characteristics of the participating wards (emergency ward in N hospital, emergency ward in K hospital and acute ward in K hospital) are, respectively, as follows: number of beds, 60, 26 and 44; mean hospital stay days, 56.7, 25.0 and 37.7 days (in 2007); mean seclusion days per 1000 patient-days 176, 487 and 154 (in February 2008); and mean restraint days per 1000 patient-days 24, 32 and 5 (in February 2008). All three wards were mainly responsible for patients with schizophrenia or schizophrenia-related disorders (F 20-F29 category of the ICD-10).

Participants

The inclusion criteria were: age 18–65 years, an SR episode during current hospitalization, and written informed consent from the patient and his/her family (mandatory in Japan). Patients were excluded if they were receiving i.v. infusion due to a somatic disease, if their psychiatrist in charge did not agree to cooperate with the researchers, or if their clinical condition prevented their participation as judged by their psychiatrist.

Eligible candidates were selected by checking the patient records. At the same time, baseline variables (sex, age, diagnosis, number of admissions), duration of current hospitalization, interval from last SR treatment event until the date of survey and total duration of all SR treatment events were obtained for each of the eligible candidates.

Assessment

Prior to filling out the SR-PPT, the investigator showed the patient how to fill in the VAS and the patient practiced answering the questionnaire using an example. The patient then filled in each VAS of the 17 items of the SR-PPT.

Following the SR-PPT, the patient filled in another newly developed VAS form, enquiring how much difficulty, fatigue and strain they felt when answering the SR-PPT.

To evaluate the criterion-related validity of the SR-PPT, the Japanese version of the Client Satisfaction Questionnaire-8 (CSQ-8J) was filled out on the same occasion. The CSQ-8J is a measurement tool to rate the patients' satisfaction of a care service and contains eight items, all 4-point Likert scales. The overall score ranges from 8 to 32, and higher score indicates higher satisfaction.[22] It has been widely used with patients as part of the outcome assessments for health and welfare services.

There exists evidence of a correlation between the subjective outcome evaluation (completed by the patient him/herself) and the objective outcome evaluation (symptom assessment by a rater).[13,26] To assess such a kind of correlation between additional external criteria and the SR-PPT, the following assessments were performed by the psychiatrist in charge on the same day as the SR-PPT: the Brief Psychiatric Rating Scale (BPRS; 18 items, score range 1–7),[27] the Global Assessment of Functioning (GAF)[28] and GAF improvement (change from the admission date).

Ethics

The study was approved by the Ethics Review Board of the National Center of Neurology and Psychiatry.

In accordance with the national ethics requirement to first obtain proxy consent for research participation of an involuntarily admitted patient with limited comprehension, consent from the patients' relatives was obtained. Before completing the survey, all eligible patients for whom the informed consent by proxy was obtained were given a comprehensive description of the study and informed that their participation or refusal would not affect their care. Patients were informed that the ward staff would not see their SR-PPT responses, that the completed questionnaire would be sealed in an envelope directly in front of them and that the data would be treated anonymously. Thereafter their own written consent was obtained.

Taking into consideration the fact that some of the patients were currently under treatment programs that included SR, the main author (T.N., a psychiatrist) carefully observed the patient's level of fatigue or irritability and discontinued the procedure when necessary. In addition, after completing all of the questionnaires, the ward head nurse monitored the patients for any deleterious symptoms that might have been induced by the study procedure.

Statistical analysis

For the 86 participant candidates who met the inclusion criteria, the differences in patient characteristics between those who completed the SR-PPT and those who did not were analyzed using Student's *t*-test for continuous variables of normal distribution (Shapiro–Wilk test, $P \geq 0.1\%$) and the Mann–Whitney *U*-test for variables of non-normal distribution (Shapiro–Wilk test, $P < 0.1\%$). The χ^2 test was applied for categorical variables. The reliability was estimated by identifying factors using factor analysis (main factor method) and by examining the internal consistency of the subscales using Cronbach's alpha coefficient. The concurrent validity was estimated using Pearson's correlation coefficient between the SR-PPT score and the CSQ-8J score. To estimate the correlation of SR-PPT score with the external criteria, Pearson's correlation coefficient (for GAF and BPRS) and the partial correlation coefficient (for GAF improvement) were used. The relationship between patient characteristics and patient burden induced by answering the SR-PPT was tested using Pearson's correlation coefficient for continuous variables of normal distribution, and Spearman's rank correlation coefficient for variables of non-normal distribution. For categorical variables, one-way ANOVA was applied. The significance level was set according to two-tailed test. All statistical analyses were performed using SPSS version 15.0 (SPSS, Chicago, IL, USA).

RESULTS

Of 182 patients hospitalized on the study wards on the date of the survey, 110 patients were aged 18–65 years and had experienced SR. Of these, nine patients had been discharged prior to the survey date, five patients were treated by physicians who refused to cooperate in the study and 10 patients were, according to their attending psychiatrists, unable to tolerate the study procedure. Of the remaining 86 patients, two patients did not volunteer their consent. The families of 27 more patients could not be contacted by the staff and proxy consent was thus not obtained. One patient was excluded by the main author (T.N.) due to the patient's excessive fatigue while answering the questionnaire. Finally, the SR-PPT was completed fully by a total of 56 patients.

Patient characteristics are listed in Table 1 including the mean GAF and BPRS scores. There were no

Table 1. Patient characteristics ($n = 56$) and GAF/BPRS scores

	n, mean ± SD, or median (IQR 25%–75%)	%
Sex		
Male	31	55
Age (years)	42.4 ± 13.0	
Diagnosis†		
F20–F29	39	69
F30–F39	11	20
F10–F19	4	7
Others	2	4
No. admissions	1.5 (1.0–4.0)	
Days between last seclusion/restraint event and investigation	10.0 (3.5–38.5)	
Days between admission and investigation	36.0 (16.0–64.0)	
Days of seclusion	12.0 (6.0–21.0)	
Days of restraint‡	5.0 (2.0–8.0)	
GAF at admission	27.9 ± 11.4	
GAF at investigation	49.8 ± 16.3	
BPRS at investigation	40.1 ± 15.3	

†International Classification of Disease Tenth revision (ICD-10); ‡20 patients experienced restraint.
BPRS, Brief Psychiatric Rating scale (18 items, score range 1–7); GAF, Global Assessment of Functioning.

significant differences in the patient characteristics between the 56 participants and the 30 excluded patients.

Factor analysis

Principal factor analysis on the 17 items selected as candidates was performed, because none of the 17 items exhibited ceiling or floor effects. The eigenvalue shifts were 9.80, 1.48, 1.1 and 0.85, assuming that the two-factor structure was valid. In addition, one item having low commonality of 0.224 following factor extraction was removed. At this point, a two-factor hypothesis emerged and factor analysis was performed using the principal factor method and varimax rotation. Next, the five items with a loading of ≥0.35 on both the primary and secondary factors were removed. The factor analysis was then repeated using the principal factor method and varimax rotation on the remaining 11 items. Table 2 lists the final factor pattern following varimax rotation. Incidentally, the ratio explaining the total variance of the 11 items for the two factors prior to rotation was 64.5%. In the nine primary factor items, those items that involved communication with staff toward mutual understanding of the treatment process and goals had a high loading and were therefore named 'Cooperation with Staff'. In the two secondary factors, those items involving perceptions of SR had a high loading and were thus named 'Perceptions of SR'.

Internal consistency of the SR-PPT

The subscale coefficient alpha was also calculated in order to evaluate internal consistency. Adequate alpha coefficients were obtained for Cooperation with Staff (0.928) and Perceptions of SR (0.887). The value for the 11 items of the SR-PPT was 0.916.

SR-PPT scores

The mean ± SD total score for all the final 11 items (ranging from 0 to 1100) was 658.7 ± 245.4, and the mean subscale scores for Cooperation with Staff (max. 900) and for Perceptions of SR (max. 200) were 559.3 ± 208.9 and 99.4 ± 65.9, respectively. Correlations between each subscale score and the total score were observed as shown (Table 3). No significant differences nor correlations between ST-PPT total scores and the patient characteristics (sex, age, diagnosis, number of admissions, days between last SR event or admission and investigation, and days of SR) existed.

Criterion-related validity

The mean ± SD CSQ-8J score was 21.7 ± 5.6. Significant correlations were observed between CSQ-8J score, SR-PPT scale score, SR-PPT Cooperation with Staff subscale score and SR-PPT Perceptions of SR subscale score (Table 3).

A significant negative correlation was found between SR-PPT total score and BPRS total score ($r = -0.417$, $P < 0.01$), and a significant positive correlation was seen between SR-PPT total score and both the GAF ($r = 0.472$, $P < 0.001$) and the GAF improvement ($r = 0.406$, $P < 0.01$) scores.

Table 2. Rotated factor matrix for 11 items of the SR-PPT

	Factor loading 1	2
Factor 1: Cooperation with staff		
Do you and the staff agree about the things you will need to do in treatment to help improve your situation?	0.838	0.204
Are you and the staff working towards mutually agreed upon goals?	0.832	0.323
Do you feel that the staff members understand your concerns?	0.825	0.251
Have you been respected on the ward as a person?	0.810	0.333
Is your opinion taken into account with regards to your treatment?	0.746	0.184
Are you being given enough time during your treatment or care?	0.737	0.216
Do you collaborate with the staff on setting goals for your treatment?	0.685	0.066
Can you voice your opinion?	0.667	0.130
Do you feel that staff members have ignored you in any way?	0.557	0.176
Factor 2: Perception of seclusion/restraint		
Was being restrained and/or secluded beneficial in treating your difficulties?	0.202	0.868
Was it necessary for you to be restrained and/or secluded?	0.228	0.860
Factor contribution	5.96	1.13
Contribution variance rate	54.2%	10.3%

SR-PPT, Secluded/Restrained Patients' Perception of their Treatment.

Table 3. SR-PPT subscale correlations with total score

	SR-PPT scale	SR-PPT Cooperation with Staff subscale	SR-PPT Perception of SR subscale
SR-PPT Cooperation with Staff subscale	0.971**		
SR-PPT Perception of SR subscale	0.648**	0.445*	
CSQ-8J	0.876**	0.838**	0.609**

*$P < 0.01$, **$P < 0.001$.
CSQ-8J, Client Satisfaction Questionnaire-8 Japanese version; SR-PPT, Secluded/Restrained Patients' Perception of their Treatment.

Burden of answering the SR-PPT

The mean ± SD scores for difficulty, fatigue and strain experienced by the patients when answering the SR-PPT were 23.5 ± 26.7, 24.8 ± 29.2 and 30.2 ± 30.0, respectively (max. 100). The rate of the lowest burden scores for patients (<20) with regard to difficulty, fatigue and strain was 41.9%, 40.7% and 34.9% and that of the highest burden scores for patients (>80) was 3.5%, 5.8% and 5.8%, respectively. No correlation was observed between length of the interval from the last SR event to day of the survey and the burden of answering the SR-PPT. The BPRS and (inversely) the GAF correlated with fatigue ($r = 0.377$, $P < 0.01$ and $r = -0.296$, $P < 0.05$) and strain ($r = 0.519$, $P < 0.001$ and $r = -0.272$, $P < 0.05$), respectively. No cases of worsening of symptoms due to participation in the survey were observed.

DISCUSSION

To our knowledge, the SR-PPT is the first measurement developed for assessments by patients of their overall treatment in specific relation to the use of SR measures as part of the treatment program. It assesses not only the patients' perceptions of experienced SR itself but aspects such as respect, autonomy, and working alliance, which are often hindered by coercive interventions. Of 17 candidate questions, 11 were found to be relevant and sufficient. These questions constituted two factors, namely, Cooperation with Staff (nine items) and Perceptions of SR (two items). Both had sufficient internal consistency and concurrent validity. Furthermore, the SR-PPT total score had a significant inverse correlation with BPRS score, and direct correlations with GAF and GAF improvement on the day of the survey used as external criteria. The rater's assessment using GAF (assess impairment in social functioning) and/or BPRS (assess anxiety, hostility, suspiciousness) reflected on some level the patient's negative perception of cooperation with staff. These results suggest the validity of the SR-PPT.

In cases when SR is applied to secure patients against imminent danger caused by their disruptive behavior due to mental disorder, the patient's own view of such intervention is often left behind, yet the objective and subjective views may also diverge.[4] Indeed, although the correlations between the SR-PPT and, in contrast, the observer-rated assessment scales (GAF and BPRS) in the present study were statistically significant, the correlation coefficient of <0.7 was weak. This indicates that it is not sufficient to rely solely on the objective instruments, and that the staff assessment alone seems most likely to fail to identify adequately the dimension of patient perceptions. Because the patient's own perceptions of treatment considerably affect his/her prognosis, as mentioned in previous studies,[12–16] it is crucial to make these perceptions overt and measurable. It is especially true for such elements of treatment as respect for patient dignity and empowerment in shared decision making – even if the overall treatment includes coercive measures. Against such need for a standardized self-rating subjective measure that is easy to complete immediately after or even during SR, the SR-PPT appears to be a feasible, as well as a valid and reliable tool.

The items derived from the five domains using factor analysis were assumed to have a two-factor structure. One of the domains, Perception of SR, loaded to the secondary factor, and the rest of the domains to the primary factor. Hansson *et al.* and McCabe *et al.* reported that subjectively important aspects of outcome interact via a common powerful mediator, namely, positive and negative feeling, and could be explained by a single factor.[29,30] This is in accordance with the present factor analysis results. The high correlation of the primary factor with the CSQ-8J ($r = 0.838$, $P < 0.001$) means that both questionnaires have a similar powerful mediator. In contrast to the CSQ-8J, however, the SR-PPT consists of items specific to treatment involving SR. Moreover, the SR-PPT also allows examination by individual item.

It is preferable that the SR-PPT be used immediately after an SR treatment event, because if other treatment programs following SR are underway, they can affect the patient's response and thus influence the results. Because only 14 participants in this survey had experienced an SR event within the previous 3 days, whether earlier use of the SR-PPT is possible or not warrants future investigation. In addition, the median number of SR treatment days for the 56 participants in this study was longer than reported in the USA and Europe,[10,31,32] and this raises the question of whether the SR-PPT is feasible for use in countries in which SR treatment events are routinely shorter. It is reported that in the USA, for instance, the mean duration of SR treatment events is a few hours.[32] The recommendation of the Core Strategies[7], however, suggests a debriefing be held between staff and the patient after an SR treatment event. Assuming that such debriefings are routinely performed even after short SR events, it seems feasible for patients to fill in the SR-PPT at that time.

Family informed consent, which is mandatory in Japan for research involving SR patients, was not available for 27 patients and they were therefore excluded. This exclusion criterion did not, however, bias the results, because it cannot be attributed to clinical or demographic patient characteristics.

The size and field of the present patient group were limited to ensure sufficient stability of loadings. Therefore further investigation with a larger sample is required including not only patients in the acute psychiatric setting but also those who are difficult to manage in chronic wards, and, furthermore, patients in other countries. A bilateral study using the SR-PPT, which is currently underway in both Finland and Japan, has a larger sample size and will enable a comparison of cross-national data.

ACKNOWLEDGMENTS

This study was funded by the Pfizer Health Research Foundation and was conducted as part of a research and development project on seclusion and restraint in psychiatric hospitals in Finland and Japan (the SAKURA project). The researchers would also like to thank the hospital staff who assisted with the survey. T.N. has received grants from the Pfizer Health Research Foundation. All other authors declare that they have no conflict of interest.

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Factors affecting assessment of severity of aggressive incidents: using the Staff Observation Aggression Scale – Revised (SOAS-R) in Japan

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Keywords: aggression, assessment, incident, mental health nursing, psychiatric inpatient, SOAS-R

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Accepted for publication: 9 October 2011

doi: 10.1111/j.1365-2850.2011.01838.x

Accessible summary

- Consumer gender and age, and nurse gender influenced the perception of overall severity of aggressive incidents, in addition to the aggression data provided by the Staff Observation Aggression Scale – Revised (SOAS-R) scores.
- The factors influencing assessments of aggression incident severity can be identified from the severity scores provided by concurrently conducting objective (i.e. SOAS-R) and overall (i.e. visual analogue scale) assessments.

Abstract

The aim of this study is to investigate factors associated with overall judgements of aggression severity as provided by ward nurses, using the Japanese-language version of the Staff Observation Aggression Scale – Revised (SOAS-R). Nurses who observed 326 aggressive incidents involving psychiatric inpatients at five mental health facilities in Japan provided their assessments of the incident severity both on the established rating scale, the SOAS-R, and on a visual analogue scale (VAS), a one-item scale to indicate overall aggression severity. To evaluate the factors influencing the VAS severity scores, a multiple regression analysis was performed, in which consumer, nurse and ward characteristics were added consecutively, along with SOAS-R severity scores as independent variables. SOAS-R scores explained 17.6% of the VAS severity scores. Independently from the SOAS-R scores, the gender and age of the aggressive consumers (adjusted $R^2 = 10.0\%$), as well as the gender of the nurses who reported the aggression (adjusted $R^2 = 4.1\%$), each explained VAS severity score to a significant degree. Apart from the SOAS-R scores, consumer and nurse characteristics appeared to influence the overall judgements of severity of aggressive incidents, which may be connected to decisions about the use of coercive measures, such as seclusion/restraint or forced medication.

Introduction

Aggressive incidents occur frequently during inpatient treatment in psychiatric settings (Nijman *et al.* 2005). Such incidents often threaten the safety of consumers and staff and may result in the use of coercive measures such as seclusion or restraint (Fisher 1994, Busch & Shore 2000). Seclusion and restraint are widely recognized as an intervention that has negative consequence for the consumers, such as a violation of their autonomy and respect, and a traumatic experience for them (Huckshorn 2004). Staff members who witness an aggressive incident must afterwards document and evaluate the event. However, they may experience emotions such as fear, anger or shame regarding the incident (Needham *et al.* 2005), which can undermine the objectivity of their evaluation. A lack of objectivity may result in underestimation of a potential danger with consequent risks or, conversely, an exaggeration of this danger, which may prompt unnecessary initiation or prolongation of seclusion or restraint. To avoid such mistakes and improve coercion practices, it is therefore important to understand what are the elements associated with the staff's assessment of aggression severity in incidents that have resulted in seclusion or restraint.

The Staff Observation Aggression Scale – Revised (SOAS-R) was developed in order to record the nature and severity of aggressive incidents in a time-efficient manner (Nijman *et al.* 1999). The SOAS-R consists of checklist items asking whether specific aspects of aggressive behaviour occurred, and staff members have to mark the items that apply to the aggression they experienced or witnessed objectively. Therefore, by using the SOAS-R, it is possible to quickly document various aspects of aggressive incidents as well as perform post-event situation analyses on the basis of this information. For these reasons, the SOAS-R is widely applied in psychiatric wards worldwide (Nijman *et al.* 1999, 2005).

Previous studies investigating the reliability of the Staff Observation Aggression Scale (SOAS) (Palmstierna & Wistedt 1987), on which the SOAS-R is based, have been conducted in various countries (Nijman *et al.* 2005), and have demonstrated a correlation coefficient of 0.61–0.87 for reliability between individuals performing the assessments. Validity has been confirmed for both the SOAS and SOAS-R. Although an evaluation of concurrent validity for the SOAS-R based on a severity rating using the visual analogue scale (VAS) produced correlation coefficient values ranging from 0.49 to 0.62 (Nijman *et al.* 2005), high values of greater than 0.7 were not obtained.

Thus, unlike SOAS-R scores, which are calculated on the basis of the checklist items, consisting of mostly specific and observable behaviours, the addition of a VAS severity assessment provides an additional option for staff members to provide their personal opinion on the overall severity of an aggressive incident they just experienced. It is possible that certain characteristics of the reporting staff members, as well as those of the aggressive consumers, are associated with these judgements of aggression severity. The perceived severity and dangerousness of the disruptive behaviour displayed by the consumer will influence the decisions to use restrictive measures, such as seclusion or restraint (Nijman *et al.* 1999).

The aim of this study is to consider what factors influence the overall judgement made by ward nurses of the severity of aggressive incidents. To this end, the associations between consumer, nurse and ward characteristics, in addition to SOAS-R scores, are considered in relation to the VAS assessments of overall aggression severity made by the nurses.

Materials and methods

Settings

This study was conducted over an 8-month period starting in November 2008 for six wards in four hospitals and for a 2-month period starting from November 2008 for nine wards in one hospital. According to the medical reimbursement system in Japan, four wards were classified as 'emergency wards' (E type), five wards as 'acute wards' (A type) and six wards as 'wards with a nurse ratio of 15 consumers to 1 nurse' (S type). The requirements for both an emergency and acute ward are that more than 40% of the inpatients are those newly admitted, and 40% of the newly admitted consumers are to be discharged to their home within 3 months after admission. The additional requirement for an emergency ward is the responsibility to accept more involuntary admissions than other types of ward, under the order of the prefectural governor of the catchment area, which is stricter than for admissions under proxy consent. Accordingly, the average nurse allocation on an emergency ward is 10 consumers per nurse per day, compared to 13 consumers on an acute ward.

The average number of beds was 53.0 [standard deviation (SD) = 10.8]. The most frequent diagnoses were F20-F29 (schizophrenia group) of the International Classification of Disease, 10th Edition (ICD-10). The prevailing age range of subjects were adults aged 20–65 years for 13 wards and geriatric consumers aged over 65 years at two wards. Average length of hospital stay for 2007 was less than 3 months for nine wards (all E and A type wards) and was over 10 years for the remaining six wards (all S type wards).

The mean of cumulative secluded days per 1000 patient days in the E type, A type and S type wards in November 2007 was 401 (SD = 245) days, 83 (SD = 80) days and 47 (SD = 52) days, respectively, and the mean of cumulative mechanical restrained days was 41 (SD = 53) days, 10 (SD = 11) days and 1 (SD = 2) day, respectively.

Instrument

The SOAS-R is used to assess the severity of aggressive incidents which are defined as 'any verbal, non-verbal or physical behavior that was threatening (to self, others or property), or any physical behavior that did harm (to self, others or property)' (Morrison 1990). The SOAS-R scores are comprised of a distribution of scores ranging from 0 to 9 according to the severity of the checked item (Nijman *et al.* 1999, 2005), with the score for the highest checklist item in the column being the column score. The first column 'Provocation' is comprised of items with scores ranging from 0 to 2. Similarly, the second column 'Means used by the patient' contains items for which the scores can range from 0 to 3, the third column labelled 'Target of aggression' can range from 0 to 4, the fourth column labelled 'Consequence for victim' can range from 0 to 9, and the fifth column labelled 'Measures to stop aggression' can range from 0 to 4 severity points. The sum of the five column scores forms the total SOAS-R score. The theoretical range of total SOAS-R scores is from 0 to 22 points, with higher scores indicating greater incident severity.

Development of SOAS-R Japanese version

Permission for the development of a Japanese version of the SOAS-R was obtained from the first author of the SOAS-R (H. N.). The English version of the SOAS-R was translated into Japanese by two independent psychiatrists (T. N. and N. S.) skilled in English and, based on each of these, the Japanese draft was prepared through discussion with two translators, another psychiatrist, two psychiatric nurses and a psychiatric occupational therapist all together. Two native English speakers then independently performed a back-translation of the Japanese draft from Japanese to English. The first author of the SOAS-R (H. N.) verified these two back-translations, and the selection of the final Japanese-language translation was made through discussion between the authors (H. N. and T. N.).

Regarding inter-rater reliability of the Japanese-language version of the SOAS-R, of 168 incident records completed on the wards for a period of 2 months starting in November 2008, independent SOAS-R assessments were made by two nurses for 33 incidents (19.6%) when they actually saw the incident happen. It was possible to perform a complete analysis with no missing items for 26 of the incidents (78.8%), for which a significant and high correlation coefficient between the total SOAS-R severity scores was found ($n = 26$, $r = 0.701$, $P < 0.001$), which indicates that the inter-rater reliability of the severity scores as assessed with the Japanese SOAS-R is fair-to-good.

To evaluate concurrent validity, VAS severity assessments were used, in which nurses can mark on a 100-mm line the perceived severity of the aggressive incident they witnessed, ranging from 'not severe at all' at the 0-mm end to 'extremely severe' at the 100-mm end. It was possible to evaluate 290 completed SOAS-R reports that had no missing VAS severity assessments or SOAS-R rating items out of 326 reports gathered during the survey period for the wards (89%). A modest, but significant correlation coefficient ($n = 290$, $r = 0.387$, $P < 0.001$) was found between the SOAS-R severity scores and the VAS severity judgements obtained this way.

Although these findings confirmed to a certain extent the reliability and validity of the Japanese SOAS-R for rating aggressive incidents occurring on Japanese psychiatric inpatient wards, it should be noted that earlier studies found somewhat higher correlations for the concurrent validity with the VAS ratings (Nijman *et al.* 2005).

Procedures

Nurses recorded and assessed the aggressive incidents by means of the Japanese SOAS-R and the VAS severity assessments (which had also been utilized for the development of the Japanese version of the SOAS-R). In addition, nurses recorded details about the consumers who engaged in aggressive behaviour (gender, age and diagnosis), as well as details about themselves (gender, age and years of psychiatric nursing experience) during the survey period.

The study protocol was approved following an ethical review by the National Center of Neurology and Psychiatry in Japan.

Statistical analysis

Descriptive statistics were used to explore the characteristics of aggressive consumers and the nurses who rated the aggressive incidents. Then, four regression analyses were performed with VAS severity score set as the dependent variable and consumer characteristics (gender, age, diagnosis) set as the independent variables in Model 1, adding nurse characteristics (gender, years of psychiatric experience) for Model 2, adding ward characteristics (ward type) for Model 3, and finally adding SOAS-R score for Model 4. SPSS ver15.0 for Windows (SPSS Inc., Chicago, IL, USA) was used to perform all statistical analyses.

Table 1
Multiple regression analysis of visual analogue scale severity scores as the dependent variable in association with consumer and nurse characteristics and Staff Observation Aggressive Scale – Revised (SOAS-R) severity scores as the independent variables

	Model 1	Model 2	Model 3	Model 4
	β	β	β	β
Consumer characteristics				
Female (ref = male)	−0.241***	−0.214**	−0.202**	−0.238***
Age	−0.169**	−0.094	−0.039	−0.135*
Diagnosis (ref = F2)				
F3	−0.173**	−0.190**	−0.181**	−0.156**
Other	−0.030	−0.010	0.007	0.005
Nurse characteristics				
Female (ref = male)		−0.193**	−0.170*	−0.176**
Years of experience as a psychiatric nurse		0.054	0.049	0.047
Ward type (ref = E ward)				
A ward			−0.149*	−0.086
S ward			−0.197*	−0.111
SOAS-R				
SOAS-R severity score				0.421***
R^2	0.114	0.162	0.187	0.361
adjR^2	0.100***	0.141***	0.160***	0.336***
ΔR^2		0.041	0.019	0.176

E ward, emergency ward; A ward, acute ward; S ward, ward type with staff ratio of 15 consumers to 1 staff.
***$P < 0.001$, **$P < 0.01$, *$P < 0.05$.

Results

Occurrence rate and severity of aggressive incidents

Three hundred and twenty-six incidents were recorded and assessed using the SOAS-R and the VAS, for a rate of 3.28 incidents per 1000 beds (1.23/bed/year). By ward type, the rate of occurrence was 3.24 (1.65/bed/year) for E type wards, 3.27 (0.96/bed/year) for A type wards and 3.35 (1.22/bed/year) for S type wards. Mean SOAS-R score was 10.7 (SD = 4.7) and mean VAS severity score was 52.8 (SD = 26.2).

Consumer and nurse characteristics

Of consumers who participated in aggressive incidents recorded with the SOAS-R, 64.7% were male, mean age was 50.1 (SD = 17.7, range 17–88) years, and the primary ICD-10 diagnoses were F20-F29 (schizophrenia group, 65.4%), F30-F39 (mood disorders, 13.4%), F10-F19 (disorders due to psychoactive substance use, 7.2%) and F00-F09 (organic, including symptomatic, mental disorders, 4.8%). Of nurses who provided SOAS-R ratings, 45.5% were male, the mean age was 34.0 years (SD = 8.7, range 21–60), and the mean psychiatric nursing experience was 9.3 years (SD = 7.8, range 0–36).

Contribution to VAS severity scores

The explanatory value of consumer characteristics for Model 1 was 10.0%. For the other models, the explanatory value was 4.1% for nurse characteristics, 1.9% for ward characteristics and 17.6% for SOAS-R score. In Model 4, VAS severity score was explained to a significant degree by consumer gender and age, and nurse gender, with male consumer and nurse gender and younger consumer age corresponding to higher VAS scores (Table 1). By diagnoses, the VAS severity score was significantly lower for the F30-F39 group than that for the F20-F29 group. No correlations exceeded 0.45 for correlation matrices between variables.

Discussion

The regression analyses revealed that SOAS-R scores explained 17.6% of the VAS severity scores, while consumer gender and age (adjusted $R^2 = 10.0\%$), and nurse gender (adjusted $R^2 = 4.1\%$) were significant explanatory factors for VAS severity score.

In this study, although a significant relationship was found between the SOAS-R and the VAS severity scores, the observed correlation coefficient of 0.387 was lower than that seen in previous studies (0.49–0.62) (Nijman *et al.* 2005). In other words, the correlation between the VAS severity assessments, which probably include more subjective elements, and the SOAS-R scores, which are primarily comprised of more objectively rated items, was modest. The results of regression analyses suggest that adding elements related to consumer or nurse characteristics to SOAS-R score increased the correlation with the overall judgement of severity of aggressive incidents. Even if the SOAS-R check items are the same, if the consumer is

a younger man, or if the rating nurse is a man, these overall judgements have a tendency to be more severe.

This finding may not be surprising in the light of common sense and face validity of the VAS. However, to the best of the authors' knowledge, the observed phenomenon has not been previously explored with an appropriate scientific methodology.

Aggressive incidents frequently lead to seclusion or restraint, and younger consumers are also found to be subjected to seclusion or restraint more frequently (Gudjonsson *et al.* 2004, Migon *et al.* 2008, Keski-Valkama *et al.* 2010). Likewise, some studies suggest that male consumers are more frequently subjected to seclusion (Gudjonsson *et al.* 2004), although others find no gender difference in this respect (Keski-Valkama *et al.* 2010). While one can imagine that young male consumers might be more likely to behave aggressively, it cannot be ruled out that such consumer characteristics also could lead to an overestimation of dangerousness and a higher subjective perception of severity. Of course, this may have to do with the potential consequences in case of further escalation. These consequences may be more severe in cases where the aggressor is a young man compared to an older woman.

However, a previous report revealed a larger number of violent female consumers than violent male consumers (Weizmann-Henelius & Suutala 2000), and results from other reports indicated that mental health professionals were particularly limited in their ability to assess the risk of future violence for female consumers (Skeem *et al.* 2005). Therefore, the risk of underestimation in regard to female aggressive incidents requires attention.

One could argue that male nurses might be psychologically and physically more prepared to face violence and thus should be less cautious of the potential risks of underestimation of aggression and hence of the risks of earlier discontinuation of seclusion/restraint. In some studies, nurses and physicians appeared to rely heavily on workforce, especially on male nurses, in aggressive situations in order to avoid seclusion or restraint (Kontio *et al.* 2010). Interestingly, our results showed quite the opposite, as male nurses in general tended to assign higher VAS severity scores than female nurses. Correlations with gender and perception of aggression, such as whether it was functional (communicative and protective for the consumer) or dysfunctional (offensive, destructive or intrusive aspect of feeling victimized), were explored in earlier studies using the Perception of Aggression Scale (Needham *et al.* 2004, Palmstierna & Barredal 2006). However, the results were inconsistent. In the present study, it may be difficult to speculate how gender alone played a role in judging the severity of aggressive behaviour.

As far as we know, this study is one of the first to investigate both consumer and nurse characteristics in association with the severity of aggressive behaviour as perceived by the rating staff member. The variables included in this study, however, were rather global and crude. This analysis method, when psychological factors are included as independent variables, will clarify to which extent those factors influence the assessment of the severity of aggressive behaviour.

According to a recent report by Bowers *et al.* (2011), the better functioning wards, in which the staff have positive attitudes to difficult consumers and feel lower burnout, and which were assessed to have good leadership and teamwork by ward staff, seemed to have significantly lower rates of containment. Therefore, staff perception of their own characteristics and their wards environments may be associated with a high psychological impact of aggressive incidents. We believe a follow-up study is worthwhile to investigate these aspects in more detail.

Acknowledgments

This study was conducted with the aid of the Pfizer Health Research Foundation. This study was also conducted as part of a research and development project on seclusion and restraint in psychiatric hospitals in Finland and in Japan (the SAKURA project). The researchers wish to express their gratitude for the cooperation of the staff members who participated in this study.

Declaration of interests

Toshie Noda has received grants from the Pfizer Health Research Foundation. All other authors declare that they have no conflict of interest.

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研究と報告

隔離室入室期間に投入される人的資源に関する研究

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精　神　医　学
第54巻　第8号 別刷
2012年8月15日　発行

医学書院

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隔離室入室期間に投入される人的資源に関する研究*

コストおよび行動制限最小化の視点から

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抄録　精神医学　54：801-809　2012

精神科急性期医療のあるべきケア体制を明らかにするため，精神科病棟における急性期多職種チームへの直接ケア時間に関するヒアリング調査を実施した。対象は以前に予備的研究を実施した3病院を含む合計11病院である。その結果，病院の立地条件により直接ケア投入量が異なった。非都市部の病院では，より多くの投入量がみられ，隔離室入室1日目の直接ケア時間と隔離日数に有意な負の相関を認めた。新たに調査した8病院中5病院は理想的なケア時間が達成できれば隔離日数を短縮化できると回答したが，全8病院で理想的なケア時間の投入は収支を悪化させた。最適なケア提供のためには合理的な診療報酬の設定が必要である。

Key words

Psychiatric emergency, Psychiatric acute care, Reimbursement, Seclusion, Human resource

はじめに

日本の精神科医療における隔離・身体拘束などの行動制限量は他の先進国に比べ長いといわれる[1)]。その理由について，最小化の議論とともにさまざまな要因が検討されているが，最も大きな要因は人的資源である。また，精神科疾患の平均在院日数が他の先進国より長いことも良く知られている。この要因には療養入院の多さが挙げられ，今後急性期医療に重点を置き，早期の地域移行を実現して，地域ケアサービスを充実させていく方向性が重視されている。新たな長期入院患者

2012年1月31日受稿，2012年5月17日受理

* A Quantitative Analysis of Human Resources for Patients in Seclusion in Acute Psychiatric Care：From the perspective of economic balance and the minimization of seclusion

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0488-1281/12/¥500/論文/JCOPY