OXFORD

International Journal of Neuropsychopharmacology, 2015, 1–8

doi:10.1093/ijnp/pyu016
Research Article

RESEARCH ARTICLE

Evaluation of the Individual Safe Correction of Antipsychotic Agent Polypharmacy in Japanese Patients with Chronic Schizophrenia: Validation of Safe Corrections for Antipsychotic Polypharmacy and the High-Dose Method

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Abstract

Background: Polypharmacy for schizophrenia treatment is not justified by the available clinical evidence. We evaluated a treatment reduction approach that reduces the dose and number of antipsychotic medications simultaneously prescribed to patients.
Methods: In a randomized open study of the Safe Correction of Antipsychotic Polypharmacy and High-Dose Prescriptions program funded by the Japanese Ministry of Health, Labour, and Welfare, we evaluated a drug reduction method consisting of a dose reduction intervention performed on 163 patients with schizophrenia for twelve or 24 weeks. One antipsychotic medication was removed each week from each patient's treatment regimen by reducing the dose by 0 to 50 chlorpromazine equivalents. Data on health-related indices of quality of life, clinical symptoms, and risk of side effects were analyzed using a two-way repeated-measures mixed linear model.
Results: Despite a 23% reduction in antipsychotic dose, no differences in outcomes were observed between the dose reduction and observation groups (effect size = 0.001 – 0.085, P = .24–.97), despite high statistical power (1-β = 0.48–0.97). The findings are limited by the nonuniformity of the participants' treatment history, duration, and dose reduction amount. Dose reduction protocol patients exhibited no difference in psychotic symptoms or adverse events compared with the observation group.
Conclusions: Importantly, the low dropout rate in our study (6.9% of participants withdrew because of patient factors and 23.8% for all secondary reasons) indicates that our "slowly" method is well tolerated. We hope that this approach will result in therapeutic improvements.

Received: March 11, 2014; Revised: August 6, 2014; Accepted: August 28, 2014

Keywords: psychopharmacology; clinical trial; schizophrenia; polypharmacy; antipsychotics

Introduction

Receptor occupancy at doses commonly used in the polypharmacy treatment of schizophrenia frequently surpasses the dose needed for effective therapy. Despite an increased risk of side effects (Farde et al., 1992), therapy with a combination of agents remains a part of the general practice (Barnes and Paton, 2011). In particular, polypharmacy is widely practiced in the treatment of schizophrenia in Japan. Between 26 and 34% of Japanese patients with schizophrenia are treated with a single agent, whereas between 32 and 42% of patients undergo therapy with more than 3 agents (Yoshio et al., 2012; Okumura et al., 2013). In a study comparing treatment practices in East Asian countries, the Japanese usage of more than 3 agents simultaneously was found to be high in comparison with treatment regimens commonly used in other countries in the region (Ito et al., 2012; Xiang, 2012). A review comparing monotherapy with treatment with a combination of multiple antipsychotic agents (Collell et al., 2009) evaluated 22 studies (n=1202) performed under a variety of clinical situations. The findings of the review indicate that combination therapy may be superior to monotherapy (confidence interval=0.63–0.90), although the results were very heterogeneous (evolution of heterogeneity, I^2=78.9%). To address this issue, the Ministry of Health, Labour, and Welfare proposed in 2009 "a study on understanding of the actual condition and correction of polypharmacy" and provided incentives to approximately one-half of psychiatric clinics and institutions for the use of 2 or less antipsychotic agents starting in 2010. Such a study would provide robust scientific data potentially supporting the general criticism of polypharmacy and justifying the government's incentives for the reduction in doses of antipsychotic agents.

A recent review discussed the issues associated with antipsychotic polypharmacy and proposed potential approaches for reducing the number of agents concurrently used in the treatment of schizophrenia (Fleischhacker and Uchida, 2014). A number of interventions were proposed that could be implemented to modify the physicians' prescribing habits regarding polypharmacy. Two clinical studies (Suzuki et al., 2004; Essock et al., 2011) presented the effects of dose reduction on patients who were previously treated by polypharmacy. An evaluation of the effectiveness of various interventions showed that approaches relying on education account for only a small effect in the reduction of polypharmacy. Overall, the results of clinical studies evaluating dose reduction implementations suggest that clinical symptoms do not change, whereas symptoms were reported to worsen in 20% of subjects and more subjects discontinued their treatment. Therefore, evidence supporting the safety and effectiveness of antipsychotic dose reduction is presently very limited, and not enough validated dose reduction approaches are currently available.

In our study, therefore, we aimed to provide evidence that would establish a novel, realistic approach to polypharmacy correction for use in Japanese psychiatric institutions. We conducted a realistic and fair correction of polypharmacy in Japanese psychiatric medical care environments comparing the consequences of reducing the various combined agents used. If no changes were observed in antipsychotic effectiveness between treatments with single and multiple agents, as suggested by a number of previous studies, it is feasible that the side effects and health-related quality-of-life (QOL) indices are not altered by a switch from multiple agents. We carefully considered biologic factors and psychological stress when modulating the speed of drug reduction, particularly in reducing agents that had been administered for a long time. The Study of the Safe Correction of Antipsychotic Polypharmacy and High-Dose Prescriptions (SCAP) was supported solely by scientific research funds from the Ministry of Health, Labour, and Welfare. We analyzed the safety and effectiveness of the correction of polypharmacy in Japan. Based on previous limited reports, we analyzed the protocol (SCAP method) in 2010 and conducted a randomized open study (Sukegawa et al., 2014) to develop a safe and effective correction method.

Methods

The SCAP trial is a study of antipsychotic agent dose reduction in patients with chronic schizophrenia who were previously treated with multiple antipsychotic agents in Japanese medical institutions. All procedures performed in this study were developed with input from epidemiologic statisticians and were reviewed by the Fujita Health University ethical review board and the ethical review boards of the participating institutions. The study is registered in the Japanese clinical research database, University Hospital Medical Information Network Clinical Trials Registry (https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000005391&language=E; UMIN-CTR; ID: UMIN000004511), and meets the standards of the International Committee of Medical Journal Editors (http://www.icmje.org/faq_clinical.html). In addition, the study was reported in the annual report of the Ministry of Health, Labor, and Welfare for the 3-year period from 2011 to 2013.

Design

The subjects were recruited from outpatient clinics or from among hospitalized patients diagnosed with schizophrenia using the structured clinical interview for DSM-IV-TR module B (First et al., 1997; American Psychiatric Association, 2000). Recruited subjects were administered 2 or more antipsychotic agents on a regular basis (continuously for 2 months or more) with a total chlorpromazine (CP) dose equivalent of 500 to 1500 mg/d. The subjects were selected according to the judgments of the participating institutions. To evaluate the patient population for any selection bias, we compared the initial drug administration regimen between the subjects and hospitalized patients with schizophrenia at the participating institutions. The subjects were given a thorough explanation of the study procedures based on an approved document and provided written consent. Subjects who met the inclusion/exclusion criteria and gave consent were assigned to the dose-reduction group or observation group using a simple randomization with a random number table prepared by the study group organization and an agency independent of the participating institutions. According to the SCAP protocol, the dosage of 1 antipsychotic agent was reduced every week for subjects in the dose reduction group. The choice of which agents' dose was reduced was

left to the discretion of the attending physician. High-potency antipsychotics are defined as agents for which a dose equivalent to 100 mg of CP is achieved with 10 mg or less, whereas agents for which the dose equivalent of CP exceeds 10 mg are considered low potency. Agents with low potency were reduced by 0 to 25 mg/wk of the Japanese version of their CP dose equivalents (Inagaki and Inada, 2008), whereas dosages of high-potency agents were reduced by 0 to 50 mg/wk of their CP dose equivalents. Each week, the attending physician determined whether to reduce the dose or temporarily revert to a higher dose based on the patient's condition. In addition to psychiatric symptoms and safety, health-related QOL indices were also evaluated. The reduction in antipsychotic dose was continued for 12 weeks. The dose reduction procedures were discontinued in subjects who met all of the following criteria: treated effectively with <2 agents, the total dose was reduced to <1000 mg of CP equivalent and to 80% or less of the initial dose, and 1 of 2 agents were reduced to <50 mg. The subjects were then followed-up with the same dose for 12 weeks. Subjects who did not meet the above criteria were given another 12-week dose reduction, followed by a 12-week follow-up with a constant final dose. Subjects in the observation group were followed up for 12 weeks without any change in treatment dose. All changes in drug administration based on the judgment of the attending physician were recorded.

The Manchester scale was used for the evaluation of age, the patient's history of hospitalization, and the severity of psychiatric symptoms (Manchanda et al., 1986; Takekawa et al., 1994). The drug-induced extrapyramidal symptoms scale was used for the assessment of extrapyramidal system side effects (Inada, 2009), and the UKU side effects rating scale was used to rate autonomic nervous system side effects (Lingjaerede, 1987). Additionally, general condition was evaluated using the Global Assessment of Function (American Psychiatric Association, 2000) and Clinical Global Impression of Symptom scales (Guy, 2000). The assessments of psychiatric symptoms and adverse effects were not blinded. The Manchester scale evaluated 8 basic symptoms, including positive, negative, and depressive symptoms. It was selected for use in this study based on its practicality, facilitating easy use in a daily clinical setting for the assessment of patients with chronic schizophrenia. To detect adverse effects on general health, we evaluated body height and weight, performed general biochemical blood tests, and carried out a typical 12-lead electrocardiography examination. Additionally, the EQ-5D (Tsuchiya et al., 2002) scale was used for the evaluation of health-related QOL using a self-recorded survey. The EQ-5D is commonly used for the evaluation of healthy life expectancy in a wide range of illnesses. Functional disturbances in 5 distinct items (movement, personal management, daily activity, pain/discomfort, and anxiety/depression) were evaluated in 3 stages, with 243 indexes allocated for each rating, ranging from 0 (dead) to 1 (best possible health status) and using the time trade-off approach. Visual analog scales were also administered at the same time to evaluate health indices using a 0- to 100-point scale. Since there is no verification of the Japanese version of visual analog scales evaluations, only the time trade-off approach scale, which has established reliability and validity in a Japanese clinical context, was used in the analysis (Tsuchiya, 2002). These evaluations were carried out every 12 weeks, with the Manchester scale and EQ-5D considered the primary standard evaluations. To perform a detailed observation, evaluations were carried out every 4 weeks in the first 12 weeks of the drug-reduction period.

Data Management and Statistical Analysis

Study progress data were collected and stored using an electronic data capture input to a secured cloud database. Analysts independent of the study group performed monitoring and management of the data input. Additionally, data were encoded in a way that prevented any possibility of identifying the individuals in the database.

The χ^2 and Mann-Whitney tests were used for statistical comparisons of the characteristics of both groups, the drug administration dose (expressed in CP dose equivalents), and the dropout rate in both groups. Taking into consideration the effect of time, we tested group interactions in a comparison of the evaluation scales in both groups using the "no-response binary set-up repeated measurement linear mixed model" by setting the groups and period as fixed effects. The time period was unevenly distributed among the cases (ie, 12 weeks in the observation group and either a 12- or 24-week program, depending on progress, in the dose reduction group). Additionally, a number of institutions provided incomplete clinical study data, resulting in complicating effects that needed to be considered. The period of 4 weeks was considered as 1 unit, and 0, 1, 2, 3, 6, and 9 time points were used corresponding to 0, 4, 8, 12, 24, and 36 weeks. In addition, each evaluation scale was independently analyzed. Statistical analyses were performed using the Japanese version of SPSS 21.0 (IBM, Tokyo, Japan). Calculation of the statistical power was carried out using G*power 3.1.5 (Dusseldorf University, Dusseldorf, Germany).

Sample sizes were estimated for the clinical study to allow an evaluation of the noninferiority of the drug reduction group compared with the observation group on the primary evaluation scale based on a binary set-up repeated measurement linear mixed model. Parameters were set according to the customary practice used for repeated-measures analysis of variance analysis (Mizumoto and Takeuchi, 2010) with an α error of 0.025 (to allow for the analysis of multiple scales), a statistical power of 0.8, a noninferiority margin of Cohen's D of 0.2 (the difference was predicted to be smaller than moderate), a correlation among repeated measures of 0.5, and the number of measurements was 6 times the calculated n, or n=142. Based on these parameters, the target number of cases for each group was 72.

Results

A total of 50 psychiatric medical institutions participated in the SCAP study (Acknowledgements) from November 2010 to March 2012. Each medical institution participating in the study was assessed by the Fujita Health University ethical review board and the ethical review board of the participating institution, with the evaluation reported in the annual report of Ministry of Health, Labor, and Welfare. A total of 6786 hospitalized patients with schizophrenia were undergoing treatment at the participating medical institutions (0–308 patients per institution, mean=138.5, SD=69.6). The patients participating in the study were receiving between 0 and 8 antipsychotic agents at the time of study commencement (mean=1.9, SD=1.1) with dosages ranging from 0 to 5309 CP equivalent mg/d (mean=774.5, SD=615.4). From November 2010 to March 2012, an additional 1 to 12 patients (mean=3.4, SD=2.7) were enrolled based on the judgments of the medical institutions. In total, 169 subjects were included in the clinical study.

As shown in Figure 1, among the 169 study participants, 6 subjects withdrew consent or did not meet the inclusion criteria. Among the remaining 163 subjects, 101 subjects were

assigned using a simple randomization to the dose reduction group, and 62 subjects were assigned to the observation group. The demographics of both groups are provided in Table 1. The randomized subjects were undergoing treatment with 2 to 5 antipsychotic agents (median, 2; interquartile range, 2–3) in accordance with the inclusion criteria at a dosage of 500 to 1499.9 CP equivalent mg/d (median, 1000; IQR, 800–1200). A comparison with the total patient population of the participating institutions showed a higher use of multiple agents ($Z=9.0, 8.9$, $p=.000, .000$, Mann-Whitney U test) among the study participants. The length of the intervention period in the dose reduction group was 24 or 36 weeks, depending on the effectiveness of the antipsychotic treatment. A total of 24 subjects (23.8%) dropped out of the SCAP group; 18 subjects dropped out before 12 weeks and 6 subjects dropped out prior to the study conclusion; 17 subjects (16.8%) were withdrawn because of protocol violations (excessive dose reduction due to a mistake by the treating physician) and 7 subjects (6.9%) because of patient factors (3 subjects withdrew because of a lack of efficacy, 2 because of physical disease; and 2 refused to continue participation in the study). In the observation group, 8 subjects (12.9%) dropped out prior to the study conclusion: 3 subjects because of protocol violations within the 12-week program (the dose was mistakenly reduced by the treating physician, as in the dose reduction group) and 5 subjects because of patient factors (3 subjects with worsening psychiatric symptoms and 2 subjects that voluntarily withdrew from the study). Among the subjects that experienced a worsening of psychiatric symptoms and physical complications, no serious health problems were observed, according to the Ministry of Health, Labor, and Welfare report. The results from the chi-squared tests did not show any difference in the total dropout rate between the groups ($\chi^2=2.87$, $p=.090$) or in the dropout rate, except from physician mistakes ($\chi^2=0.00$, $p=.976$). In total, 75 subjects in the dose reduction group and 54 subjects in the observation group concluded the study, but the data from all randomized subjects were analyzed.

The changes in the evaluation scales in both groups over time are shown in Table 2. Limitations in the interpretation of the study results are explained in the Discussion regarding the differences in the number of subjects at each time point and with each scale. No adverse effect of the intervention was observed in the blood biochemical analysis or electrocardiography results. Drug administration in the dose reduction group was as follows: 2 (IQR, 2–3) agents per patient with a 1012.3 (799.9–1212.3) CP equivalent mg/d dose at the initial time (n=101) to 2 (1–2) agents per patient, with a 762.5 (600–950) CP equivalent mg/d dose at 24 weeks (n=77), corresponding to a 24.8% median dose reduction. At the study onset, 59% of the subjects used 2 agents, 35% used 3 agents, 6% used 4 agents, and 1% of the subjects used 5 agents (n=101). At the 24-week time point, 38%, 48%, 12%, and 3% of the participants used 1, 2, 3, and 4 agents, respectively (n=77). Therefore, 29 subjects switched to using a single agent. The changes between agent types are shown in Table 3. A comparison of the evaluation scales between the 2 groups using a linear mixed model analysis is shown in Table 4. No interaction was found ($p\geq.05$) when considering all the scales administered. The effect size was <0.1, and the 95% confidence interval of the estimated difference was 0 in the evaluations of all the scales used. There were no significant differences between the 2 groups. Effect sizes in the EQ-5D, UKU, drug-induced extrapyramidal symptoms scale, and Global Assessment of Function were all >0.8, suggesting high statistical power in the analysis. These results support the noninferiority of the dose reduction group compared with the observation group.

Discussion

The practicality of reducing the antipsychotic agent dose in an individualized manner was verified in a randomized controlled trial evaluating 163 patients with schizophrenia enrolled from 50 Japanese psychiatric medical institutions. The aim of the trial was to propose and validate a safe, effective, and realistic method of correcting the high rate of polypharmacy in the

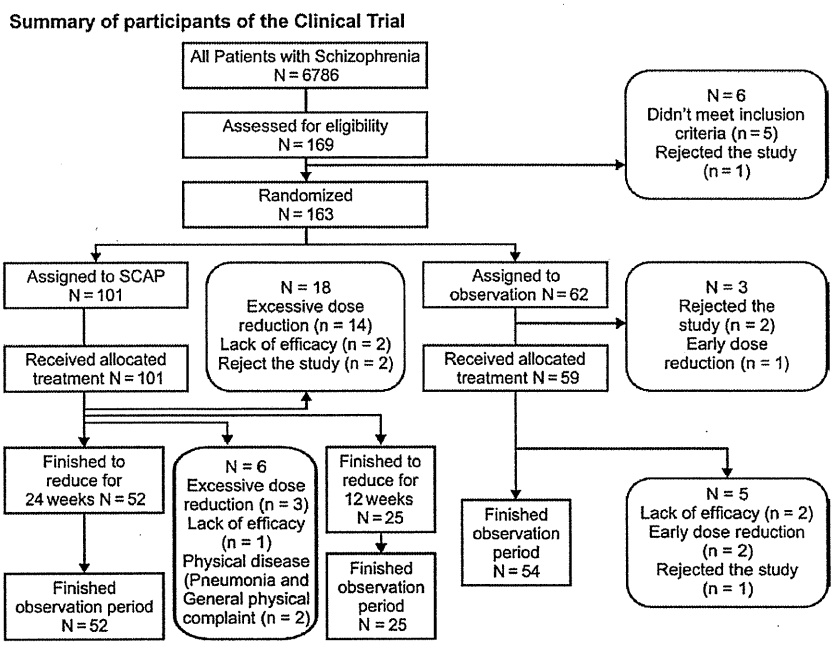

Figure 1. Summary of the participants in the clinical trial.

Table 1. Demographics of the Dose Reduction and Observation Groups

	Dose reduction group, %		Observation group,%		Statistics		P
N	101		62				
Male	58 (57.4)		38 (61.2)		χ^2	0.237	0.63
Diagnosis							
Paranoid type	49 (48.5)		30 (48.4)		χ^2	1.92	0.75
Disorganized type	25 (24.8)		11 (17.7)				
Catatonic type	3 (3.0)		2 (3.2)				
Residual type	13 (12.9)		12 (19.4)				
Undifferentiated type	11 (10.9)		7 (11.3)				
Hospitalized patients	81 (80.2)		49 (79.0)		χ^2	0.032	0.86
	med	IQR	med	IQR			
Age, y	60	51 to 64	59	50 to 64	U[a]	3055	0.80
Disease duration, y	32	19 to 40	31.5	3 to 19.3	U	2405	0.92
Total hospitalization duration, y	9.3	4.5 to 17	10.1	3 to 19.3	U	2481	0.88
Body weight, kg	62	52 to 68	60	52 to 70	U	2983	0.95
Number of administered antipsychotic agents	2	2 to 3	2	2 to 3	U	3088	0.96
Dose of administered antipsychotic agents, CP mg/mL	1012.3	800 to 1212	1000	800 to 1174.8	U	2876	0.44

Abbreviations: CP, chlorpromazine; IQR,. interquartile range

[a]The Mann-Whitney test was used because the data were not normally distributed.

Table 2. Temporal Changes in the Evaluation Scales of the Dose Reduction and Observation Groups

		Dose reduction group						observation group	
		Week						Week	
Scale		0	4	8	12	24	36	0	12
	n	101	94	85	83	77	52	62	54
Manchester scale[a]	Mean	12.7	12.3	11.7	12.1	11.7	12.1	13.2	12.5
	SD	5.2	5.5	5.6	5.6	6.0	6.1	5.6	5.7
EQ-5D TTO[b]	Mean	0.83	0.75	0.79	0.85	0.85	0.83*	0.79**	0.8
	SD	0.71	0.23	0.23	0.53	0.55	0.65	0.17	0.19
UKU[c]	Mean	3.5			2.7	2.6	2.3	3.6	3.2
	SD	2.7			2.6	2.2	2	3.3	3.5
DIEPSS[d]	Mean	5			4.3	3.9	3.8	5	4.2
	SD	4.4			4.4	3.9	4	4.1	4.2
CGI-S[e]	Mean	4.5			4.5	4.5	4.4	4.6	4.5
	SD	1.02			1.08	1.1	1.16	0.88	0.9
GAF[f]	Mean	45.8			46.6	47.7	48.1	47.7	49.8
	SD	17.6			17.6	18.5	17.2	16.3	17.9

Abbreviations: CGI-S, Clinical Global Impression of Symptom; DIEPSS, drug-induced extrapyramidal symptoms scale; GAF, Global Assessment of Function; TTO, time trade-off approach.

* n = 51, **n = 61; both because 1 subject rejected the evaluation.

[a]Manchester Scale: Psychiatric symptoms, 8–32 points (milder cases show lower values).

[b]EQ-5D TTO: 0.111–1.000 points (healthy participants show higher values)

[c]UKU-11: Autonomic nervous system side effects, 0–33 points (milder cases show lower values).

[d]DIEPSS: Motor system side effects, 0–36 points (milder cases show lower values)

[e]CGI-S: General impression of the clinician, 1–7 points (milder cases show lower values).

[f]GAF: Overall function evaluation, 0–100 points (higher functionality shows a higher value).

Japanese medical therapy of schizophrenia, which is considered unnecessarily high by international standards. The enrollment was focused on chronic patients and included patients that had a significantly higher use of multiple agents compared with the general patient populations of the participating institutions. Regardless of the 23% drug reduction, the clinical study results using the SCAP method of dose reduction demonstrated that clinical symptoms, risk of side effects, and health-related QOL were not significantly different in the dose reduction group compared with the observation group at 12 and 24 weeks following the beginning of the dose reduction regimen. These observations support the hypothesized noninferiority of the dose reduction group to the observational group and suggest that the findings were obtained with high statistical power. In the current study, the dose was reduced by 9.7 mg/wk, which is slower than the proposed dose reduction limit for a low-potency agent, that is, 25 mg/wk. Additionally, no significant worsening of symptoms was observed at the follow-up 3 months after the dose reduction, suggesting that the SCAP method is a safe and useful method that can be applied in a clinical setting.

In previously reported approaches, Essock et al. (2011) reduced the agents over 30 days, whereas Suzuki et al. (2004)

Table 3. Changes in the Number of Subjects Administered Antipsychotic Agents in the Dose Reduction Group

Agent	Before dose reduction	After dose reduction	Reduction rate, %
Risperidone	63	47	25
Olanzapine	34	25	26
Chlorpromazine	31	11	65
Levomepromazine	27	8	70
Zotepine	19	10	47
Haloperidol	19	13	32
Quetiapine	17	14	18
Aripiprazole	16	10	37
Blonanserin	9	6	33
Perospirone	8	5	37

Before dose reduction, n = 101; after dose reduction, n = 77. Only agents administered to more than 5 subjects are included.

Table 4. Analysis of the Evaluation Scales in the Dose Reduction Group and Observation Group Based on an LMM Analysis

Dependent variables	n	Type III test of fixed effect					Estimated difference (Bonferroni correction)		
		F intercept	F fixed factor	P value	Effect size	Power	Estimated mean[a]	95% CI	P value
Mann	163	864.2	0.25	0.62	0.017	0.65	−0.83	(−2.56–0.9)	0.35
EQ-5D	162	1002.7	0.0013	0.97	0.001	0.97	0.02	(−0.08–0.13)	0.68
UKU-11	163	194.5	1.41	0.24	0.085	0.84	−0.64	(−1.48–0.2)	0.14
DIEPSS	163	192.8	1.39	0.24	0.085	0.84	−0.55	(−1.85–0.75)	0.4
CGI-S	163	3381.4	0.56	0.45	0.013	0.48	−0.082	(−0.39–0.23)	0.6
GAF	163	1283.7	0.041	0.84	0.0057	0.84	−1.4	(−6.73–3.97)	0.61

Abbreviations: CGI-S, Clinical Global Impression of Symptom; DIEPSS, drug-induced extrapyramidal symptoms scale; GAF, Global Assessment of Function.
[a]Comparison of values between the dose reduction group and observation group.

replaced polypharmacy with another agent of equal power. The approach used by Essock et al. (2011) may have been excessively fast, preventing them from arriving at a single dosage. We focused on optimizing the speed of dose reduction and obtained a dropout rate that was lower than that in their study for a similar period (24% and 31%, respectively). Dopamine hypersensitivity has been reported as a possible consequence of the long-term use of antipsychotic agents (Samaha, 2013). An abrupt reduction in antipsychotic dose is believed to severely disturb the homeostasis of patients receiving polypharmacy. The SCAP method adopts a gradual dose reduction, which can minimize the disruption to the patient's neurophysiology, resulting in the demonstrated maintenance of effective treatment with no difference in adverse effects.

In the SCAP method, the choice of which agents to reduce is left to the discretion of the attending physician. Before the reduction in dose, 1 main agent is selected and the doses of the other agents are sequentially reduced. The agents selected for dose reduction in this study are presented in the Results, with the first generation of low-potency agents such as CP and levomepromazine generally chosen. In a Japanese clinical setting, in addition to the main agent, it is common to prescribe a small amount of CP (and combined agent) and levomepromazine for sedation. A dose reduction of the secondary agents in the SCAP method is achievable, because the selection of primary agent is generally clear.

On the other hand, the intervention methods varied in terms of differences in the dose reduction amounts and time period. Additionally, differences in the initial combinations and doses of antipsychotic agents at the onset of the study represent a limitation of the present study. To address this issue, a repeated measurement linear mixed model was used in the statistical analysis, taking into consideration the variability in the period between the subjects as well as missing values.

Medical therapy for schizophrenia is usually administered over a prolonged period of time. Several important aspects need to be considered when administering antipsychotic therapy, such as the effects of the antipsychotic agent on extrapyramidal motor function, autonomic visceral function, and the maintenance of the patient's QOL. In this study, because changes in treatments other than the antipsychotic agents such as anti-Parkinsonian therapy, sedatives prescribed for sleep regulation, and laxatives used to treat constipation were not restricted, the effects of the changes on the primary outcomes are not known. However, based on the clinical judgment of each participating institution and considering that the above agents were adjusted in accordance with the dose reduction of the antipsychotic agents, no worsening of motor function or autonomic nervous system function was observed. This finding suggests that a gradual reduction in doses of antipsychotic agents according to the SCAP method can avoid the harmful effects of rapid treatment discontinuation. Additionally, no major health problems were reported during the study period, providing additional support for the safety of the proposed dose reduction protocol. There were also no significant changes in health-related QOL. Because most subjects in this study were long-term hospitalized patients, daily living activities were limited to their experiences inside the medical institution. Additionally, because of social cognitive function deficits common in patients with psychiatric disorders, a concern remains regarding whether health-related QOL can be compared with the impact of other diseases. Finally, the fact that the psychiatric patients' health-related QOL was assessed using the EQ-5D self-reported survey

completed by the patients is considered to be a limitation (Atkinson et al., 1997).

There was no stratification of participants based on age or sex in this study. The subjects were assigned to either the dose reduction group or the control group by a simple randomization using a random sampling table. As an outcome of the randomization, 101 subjects completed the protocol in the dose reduction group compared with 62 subjects in the observation group. Simple randomization is thought to keep the quality of both groups even, but the chance exists that the number of participants in the groups will become uneven with a total enrollment of <100 subjects (Kang et al., 2008). The target number of subjects for both groups was a total of 144 subjects in this study. Despite the prediction that the group numbers would be even in the study planning stage, the end result was an imbalance of 5:3, suggesting a limitation in the results because there were more subjects than targeted in the dose reduction group but 10 fewer subjects than planned in the observation group. Although options for a change in plans and to conduct stratification were available, we opted for a simple randomization for the study period. Additionally, if Cohen's D was set at a moderate level of 0.25, the required number of subjects in each group would have been 38, which would conceivably show that dose reduction-related worsening was not higher than a moderate effect.

Conclusion

We conducted a verification of a realistic dose reduction method (the SCAP method) to minimize the risk of adverse effects caused by the abrupt discontinuation of long-term exposure to high doses of antipsychotic agents in schizophrenia treatment. The standard of care for the management of schizophrenia in Japan commonly involves the concurrent use of more than 3 antipsychotic agents, which is considered high by international standards. When interpreting the outcomes of this study, one should consider several limitations, including variability in the subjects' antipsychotic treatment history, the magnitude of dose reduction, heterogeneity in the agents selected for reduction, the possibility of rater bias, the lack of consideration of other agents (ie, anti-Parkinsonian drugs), the difference in the numbers between the 2 groups because of the simple randomization method used, and the time period during which the dose reduction was implemented as well as the use of self-reported evaluation scales in patients with cognitive dysfunction. Patients who underwent the SCAP dose reduction method were observed not to exhibit any significant difference in psychiatric symptoms or nonpsychiatric side effects compared with participants in the observation group. Additionally, our study observed a low dropout rate and high tolerability of the SCAP dose reduction protocol. The distribution of an appropriate and safe dose reduction method with a suitable remuneration incentive using the SCAP method is thought to have the potential to positively influence decision-making towards reduced polypharmacy in medical therapy (Goh et al., 2011). This method could become one of the steps towards the reasonable optimization of polypharmacy.

Acknowledgments

The authors thank all those who collaborated with us in this study, namely the SCAP study cooperation group, everyone at the Research Office, as well as the Japanese Ministry of Health, Labor, and Welfare. Editage, an editing agency, assisted in the preparation of this manuscript.

Statement of Interest

None

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Sukegawa et al. BMC Psychiatry 2014, 14:103
http://www.biomedcentral.com/1471-244X/14/103

BMC Psychiatry

STUDY PROTOCOL Open Access

Study protocol: safety correction of high dose antipsychotic polypharmacy in Japan

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Abstract

Background: In Japan, combination therapy with high doses of antipsychotic drugs is common, but as a consequence, many patients with schizophrenia report extrapyramidal and autonomic nervous system side effects. To resolve this, we proposed a method of safety correction of high dose antipsychotic polypharmacy (the SCAP method), in which the initial total dose of all antipsychotic drugs is calculated and converted to a chlorpromazine equivalent (expressed as milligrams of chlorpromazine, mg CP). The doses of low-potency antipsychotic drugs are then reduced by ≤ 25 mg CP/week, and the doses of high-potency antipsychotics are decreased at a rate of ≤50 mg CP/week. Although a randomized, case-controlled comparative study has demonstrated the safety of this method, the number of participants was relatively small and its results required further validation. In this study of the SCAP method, we aimed to substantially increase the number of participants.

Methods/design: The participants were in- or outpatients treated with two or more antipsychotics at doses of 500–1,500 mg CP/day. Consenting participants were randomized into control and dose reduction groups. In the control group, patients continued with their normal regimen for 3 months without a dose change before undergoing the SCAP protocol. The dose reduction group followed the SCAP strategy over 3–6 months with a subsequent 3-month follow-up period. Outcome measures were measured at baseline and then at 3-month intervals, and included clinical symptoms measured on the Manchester scale, the extent of extrapyramidal and autonomic side effects, and quality of life using the Euro QOL scale. We also measured blood drug concentrations and drug efficacy-associated biochemical parameters. The Brief Assessment of Cognition in Schizophrenia, Japanese version, was also undertaken in centers where it was available.

Discussion: The safety and efficacy of the SCAP method required further validation in a large randomized trial. The design of this study aimed to address some of the limitations of the previous case-controlled study, to build a more robust evidence base to assist clinicians in their efforts to reduce potentially harmful polypharmacy in this vulnerable group of patients.

Trial registration: UMIN Clinical Trials Registry 000004511.

Keywords: Schizophrenia, Antipsychotics, Polypharmacy, High dose

Background

Antipsychotics should be used as monotherapy, but in many countries patients may be prescribed two or more antipsychotic drugs as combination therapy [1]. The use of more than one antipsychotic drug is particularly prevalent in East Asia [2], and polypharmacy with high dose antipsychotics is relatively common in Japan [3].

As antipsychotic polypharmacy may cause adverse drug reactions [4], these drugs should be used as monotherapy at the minimum necessary dose whenever possible. After a warning on the inappropriate use of antipsychotics was issued in Japan, the situation improved to some extent [5]. Nonetheless, dose reduction may be challenging in patients receiving high dose antipsychotic polypharmacy. We have previously proposed a protocol for the gradual reduction of antipsychotic drug dose for patients on high doses of more than one agent [6].

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We examined the safety and efficacy of this method in a randomized, case-controlled comparative study (the Reduction and Simplification [RAS] study) [7]; however, the number of participants was small and the results required further validation. To support the reliability of this method, we conducted a randomized, case-controlled comparative study (the "Safety Correction of high dose Antipsychotic Polypharmacy [SCAP] study). This article describes the methods used.

The SCAP protocol

The chlorpromazine equivalent dose (mg) is expressed as "mg CP". To convert the doses of various antipsychotics to chlorpromazine equivalent doses, we used the calculation table prepared by Inagaki and colleagues, which is routinely adopted in Japan [8]. Antipsychotics of which the doses equivalent to 100 mg of chlorpromazine are 10 mg or less were regarded as high-potency drugs, and those of which the doses equivalent to 100 mg of chlorpromazine exceed 10 mg were regarded as low-potency drugs.

Tanabe [9] and Murasugi et al. [10] have published articles reporting both successful and unsuccessful strategies for reducing the doses of antipsychotics, including the extent of dose reduction reported as a chlorpromazine equivalent dose, and the dose reduction period. On the basis of these studies, we calculated the rate of dose reduction in those that succeeded in reducing the dose and those who failed. In participants who failed to reduce the dose, the rate of reduction was approximately 100 mg CP per week in patients initially taking 2,000 mg CP daily (Table 1). In those in whom the dose was reduced successfully, the rate of reduction was about 40 mg CP per week in patients in whom the starting dose was 1,400 mg CP. As such, the maximum acceptable reduction speed may be 50 mg CP or less per week. Low-potency antipsychotics' different affinity for dopaminergic D_2 receptors, acetylcholine receptors, histamine receptors and serotonin receptors compared with high-potency antipsychotics require doses 10–100 times higher than those of high-potency antipsychotics. When decreasing the doses of drugs with potent anticholinergic actions, anticholinergic withdrawal symptoms such as insomnia, anxiety and restlessness may occur. To take this into account, the rate of reduction of low-potency antipsychotics was established as being half that of high-potency antipsychotics, namely 25 mg or less per week. Furthermore, it was established that the total amount of drug that can be subtracted from the daily dose, that is the maximum acceptable amount of reduction, was twice the value of the maximum acceptable reduction rate. This amount was applied to each drug, and the actual dose of the drug (not a chlorpromazine equivalent dose) was calculated as shown in Tables 2 and 3 [11]. The SCAP study was conducted in accordance with the maximum acceptable amount of dose reduction and maximum acceptable reduction rate based on these tables.

The chlorpromazine equivalent dose was adopted as a means of calculating the rate of dose reduction for the following reasons. It is known that the potency of antipsychotics is proportional to their binding capacity to dopamine D_2 receptors. In patients who have taken very high dose antipsychotics over a long period, D_2 receptor expression may have been upregulated to compensate for D_2 antagonism. Recurrent psychiatric symptoms induced by decreasing the doses of antipsychotics are sometimes called "dopamine supersensitivity psychosis" [12]. Therefore, we adopted the chlorpromazine equivalent dose, which represents the potency of the antipsychotic, to allow us to evaluate the degree of reduction in anti-D_2activity caused by dose reduction.

The rate of reduction was expressed as an absolute value, not as a proportion of the total chlorpromazine equivalent dose of the antipsychotic. Intuitively, a method of decreasing the dose by a small proportion (for example 1%) of the total dose per week may be appropriate;

Table 1 Rates of reduction used in previous research

Tanabe's research [9]					
Group	Mean dose before reduction	Reduction speed	GAF	SOI	n
Successful	1,372 mg CP	40.4 mg CP/week	34.1	4.5	37
Unsuccessful	1,832 mg CP	95.4 mg CP/week	29.8	4.8	11
Murasugi's research [10]					
Group	Mean dose before reduction	Reduction speed	GAF	SOI	n
Successful	1,581 mg CP	43.0 mg CP/week	35.2	4.8	5
Unsuccessful	2,389 mg CP	97.4 mg CP/week	44.0	4.5	5
Combination of both studies					
Group	Mean dose before reduction	Reduction speed	GAF	SOI	n
Successful	1,397 mg CP	40.7 mg/week	33.5	4.5	42
Unsuccessful	2, 006 mgCP	96.0 mg/week	34.2	4.7	16

Abbreviations: *GAF* global assessment of functioning in DSM-4-TR; *SOI* severity of illness; n number of patients.

Table 2 Reduction protocol for high-potency drugs

Generic name	Product name	Maximum reduction rate†(mg/week)	Maximum reduction‡(mg)
Perphenazine	PZC, others	5	10
Perospirone	Lullan	4	8
Trifluoperazine	Trifluoperazine	2.5	5
Nemonapride	Emilace	2.25	4.5
Aripiprazole	Abilify	2	4
Blonanserin	Lonasen	2	4
Pimozide	OLAP	2	4
Olanzapine	Zyprexa	1.25	2.5
Bromperidol	Impromen	1	2
Haloperidol	Serenace, others	1	2
Fluphenazine	Flumezin	1	2
Timiperone	Tolopelone	0.65	1.3
Spiperone	Spiropitan	0.5	1
Risperidone	Risperdal, others	0.5	1

†Maximum reduction rate represents the maximum acceptable reduction per week.
‡Maximum reduction represents the maximum amount of reduction at a time. After maximum reduction, subsequent reduction is performed after a minimum 2-week observation period.
(Cited and partially modified from Sukegawa [11]).

Table 3 Reduction protocol for low-potency drugs

Generic name	Product name	Maximum reduction rate† (mg/week)	Maximum reduction‡ (mg)
Sulpiride	Dogmatyl, others	50	100
Sultopride	Barnetil	50	100
Pipamperone	Propitan	50	100
Chlorpromazine	Contomin, others	25	50
Levomepromazine	Levotomin, others	25	50
Carpipramine	Defecton	25	50
Oxypertine	Forit	20	40
Zotepine	Lodopin, others	16.5	33
Quetiapine	Seroquel	16.5	33
Clocapramine	Clofekton	10	20
Mosapramine	Cremin	8.25	16.5
Propericiazine	Neuleptil	5	10
Prochlorperazine	Novamin	3.75	7.5
Moperone	Luvatren	3.125	6.25

†Maximum reduction rate represents the maximum acceptable reduction per week.
‡Maximum reduction represents the maximum amount of reduction at a time. After maximum reduction, subsequent reduction is performed after a minimum 2-week observation period.
(Cited and partially modified from Sukegawa [11]).

however, when the total chlorpromazine equivalent dose of antipsychotics is high, D_2 receptors may become supersensitive to compensate for the D_2-mediated actions inhibited by the antipsychotics. Therefore, when decreasing the dose of an antipsychotic, dopamine supersensitivity psychosis may occur if the chlorpromazine equivalent dose of the antipsychotic administered at the start of dose reduction is high. When the dose is higher, the dose must be weaned at a reduced rate. To achieve this, the reduction speed should be considered as an absolute value, not as a proportion of the total dose.

Gradually reducing the dose of antipsychotics in this way may be a useful strategy for rationalizing high dose antipsychotic regimes. A pilot randomized study involving 39 patients at 10 institutions was completed in 2007 (the RAS study) [7]. The participants were patients with schizophrenia who had been hospitalized for 1 year or more, treated with three or more antipsychotics at a dose of 1,500 mg CP/day or higher, and were capable of understanding the explanatory document and giving informed consent. In the reduction and simplification group, the 6-month reduction and simplification protocol was completed before a 3-month follow-up period, targeting reduction by 500 mg CP per day or more and the number of antipsychotics to one or two. In the reduction and simplification group (which consisted of 19 patients taking a mean of 3.7antipsychotic drugs at a mean dose of 2,067 mg CP at the time of enrollment), the mean dose reduction was 674 mg CP, and the mean reduction in the number of drugs was 1.0. Eleven patients succeeded in reducing their dose by 500 mg CP or more. However, the number of drugs taken could be reduced to one or two in only five patients. Hallucinations or delusions recurred in four patients, which were successfully treated by dose escalation in all cases. Two patients dropped out because of transfer to another hospital or the aggravation of physical symptoms. Three patients violated the protocol, one of whom experienced recurrence of hallucinations and delusions. Overall, 11 (79%) of the 14 patients excluding those who deviated from the protocol or dropped out succeeded in reducing their dose by 500 mg or more. In the control group (which consisted of 20 patients taking a mean of 3.5antipsychotic drugs at a mean dose of 2,143 mg CP at the time of enrollment), three patients dropped out owing to the aggravation of physical symptoms, extrapyramidal adverse drug reactions, or hallucinations or delusions, and two violated the protocol. Hallucinations or delusions were reported by four of the 19 patients in the reduction and simplification group and one of the 20 patients in the control group, but this difference was not statistically significant. Comparison of the clinical characteristics of the reduction and simplification and control groups at the time of enrollment found no significant differences other than a higher proportion of women in the reduction and simplification group. After

6 and 9 months, the number of antipsychotics and chlorpromazine equivalent dose were significantly lower in the reduction and simplification group. No significant differences were noted in the evaluation or test items between the groups. When the group who achieved dose reductions of 500 mg or more (11 patients) was compared with the control group excluding those who violated the study protocol or dropped out (15 patients), the incidence of autonomic adverse drug reactions (particularly nausea and vomiting) had significantly reduced by the ninth month. A limitation of the RAS study was that there were only 39 participants. We undertook the SCAP study to confirm the usefulness of the SCAP method in a larger cohort of patients with schizophrenia.

Methods

This was an open-label, multicenter, randomized study conducted between November 2010 and March 2012. The recurrence and dropout rates during the study period, as well as changes in psychiatric symptoms, side effects of the extrapyramidal and autonomic nervous systems, and quality of life, were compared between the dose reduction and control groups. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. The study protocol was also examined and approved by the ethics review board of each center, and by the Ethics Review Board of Fujita Health University for applications from those centers without their own panel.

The participants were inpatients or outpatients, aged 20 years or older, diagnosed with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorder, 4th edition text version (DSM-IV-TR) [13], who were taking two or more antipsychotics at doses of 500–1500 mg CP/day. Written informed consent was obtained from all participants. Each participant was assigned to the dose reduction or control group according to a randomization protocol administered by Fujita Health University. A total of 163 patients were ultimately enrolled; 101 were assigned to the dose reduction group and 62 to the control group.

In the dose reduction group, the dose was decreased to 80% or less than the initial dose over 3–6 months according to the SCAP method. Participants were subsequently followed up for a further 3 months. Clinical symptoms were evaluated using the Manchester scale [14], the extent of extrapyramidal side effects using the Drug-induced Extrapyramidal Symptoms Scale (DIEPSS) [15], autonomic side effects using the Udvalg for Kliniske Undersogelser11-item scale (UKU-11) [16], and quality of life using the Euro QOL scale [17]. In addition, measurement of blood drug concentrations and drug efficacy-associated biochemical parameters were performed. The Brief Assessment of Cognition in Schizophrenia, Japanese version (BACS-J) [18] was also performed in centers where it was available.

According to the SCAP method, the doses of high-potency drugs were reduced at a rate of 50 mg CP per week or less, and those of low-potency drugs at a rate of 25 mg CP per week or less [6]. In the control group, the doses of antipsychotics were not changed for 3 months if clinically feasible, and then doses were reduced according to the same protocol.

Sample size calculation and statistical techniques

Sample size calculation was undertaken to allow detection of non-inferiority of the dose reduction group compared with the control group on the basis of the primary outcome measure based on a binary set-up repeated measurement linear mixed model using G*power3.1.5 (http://www.gpower.hhu.de/). For repeated measures analysis of variance (ANOVA) between factors, if the α error was assumed to be 0.025 (to analyze multiple scales), statistical power was 0.8, non-inferiority margin of Cohen's d was 0.2 (it was predicted that the difference was smaller than moderate), the correlation among repeated measures was 0.5 and the number of measurements was six, then the size of the cohort was determined as 142. On this basis, we aimed to enroll 72 participants to each group. Data were finalized on January 31, 2013. Missing values were supplemented using the mixed model repeated measures (MMRM) method and a *t*-test was performed to examine differences in the means of each outcome measure between the groups. All analyses were undertaken using the Japanese version of SPSS (version 21.0. IBM, Tokyo, Japan).

Discussion

The doses of antipsychotics were reduced in the RAS study and the SCAP study using the same method, but the two studies are different. The RAS study had been completed by December 2007, but the SCAP study did not commence until November 2010. The main limitation of the RAS study was its small sample size, but there were additional problems with the study design. The SCAP study aimed to enroll a larger number of participants to address these limitations.

For the convenience of our investigators, we stipulated the rate of dose reduction in the SCAP study. In the RAS study, participating psychiatrists had calculated the rate of dose reduction by themselves based on SCAP criteria.

Criteria for enrollment in the SCAP study were as follows: both inpatients and outpatients were considered acceptable, treatment with two or more antipsychotics at doses of 500–1,500 mg CP, and a follow-up period of 3 months in the control group. Practically, it can be difficult to obtain written informed consent from patients taking antipsychotics at a dose in excess of 1,500 mg CP. Furthermore, some patients refuse to participate, claiming that they did not wish to be assigned to the control group

and thus have to remain on an elevated dose for an extended period despite their agreement to participate in a study regarding dose reduction. We therefore established a shorter follow-up period for those in the control group, despite the fact that this might influence our findings. These elements of the SCAP study design differentiate it from the RAS study, in which only inpatients were enrolled, participants had been treated with more than three antipsychotics at doses in excess of 1,500 mg CP, and the follow-up period was 9 months in both the dose reduction and control groups.

The missing data in the control group are a consequence of our study protocol. The missing data were regarded as "Missing Completely At Random (MCAR)" or at least "Missing At Random (MAR)". Therefore, the MMRM was thought to be most suitable for supplementation of the missing data in this study [19].

Many psychiatrists in Japan understand that very high doses of antipsychotics should be avoided, but also that overly rapid dose reduction may result in withdrawal symptoms mediated by dopaminergic D_2, cholinergic or other receptors. These symptoms may be misdiagnosed as relapse and consequently dose reduction may be abandoned. If our findings suggest that the SCAP method is a useful means of reducing the dose of antipsychotic drugs and rationalizing antipsychotic polypharmacy, the strategy might help the prescription of antipsychotic drugs in Japan meet international standards.

Abbreviations

SCAP: Safety correction of high-dose antipsychotic polypharmacy; RAS study: Reduction and simplification study; mg CP: mg as a chlorpromazine equivalent dose; D_2 receptor: Dopamine 2 receptor; DSM-IV-TR: The diagnostic and statistical manual of mental disorders, 4th edition text version; DIEPSS: Drug-induced extrapyramidal symptoms scale; UKU-11: 11 items reporting autonomic side effects measured on the Udvalg for Kliniske Undersogelser scale; BACS-J: Brief Assessment of Cognition in Schizophrenia, Japanese version; MMRM: Mixed model repeated measures; ANOVA: Analysis of variance; MCAR: Missing completely at random; MAR: Missing at random.

Competing interests

Competing interests are as follows: TS has received grants from Otsuka. AI and TY have received grants from the Japan Pharmaceutical Manufacturers Association. TI has received lecture fees from Otsuka, Dainippon Sumitomo, GlaxoSmithKline, Eli Lilly, Janssen, Astellas and Mitsubishi Tanabe. NI has received lecture fees from Otsuka, Janssen, GlaxoSmithKline, Shionogi and Eli Lilly, grants from Otsuka and honoraria from Otsuka, Dainippon Sumitomo, GlaxoSmithKline, Mitsubishi Tanabe, Yoshitomi yakuhin and Eizai. None of the other authors have competing interests to declare.

Authors' contributions

All authors conceived the study and its design, and wrote the draft manuscript. All have read and approved the final manuscript.

Acknowledgments

We are grateful to the members of the national project team supported by a research grant for nervous and mental disorders from the Ministry of Health, Labour and Welfare, Japan (from 2001 to 2012). We are also grateful to the 56 centers that participated in the SCAP study. In the following 15 centers, the protocol was approved by each institution's own Ethics Review Board: Asahi Hospital, Atago Hospital, Fujita Health University School of Medicine, HigashiowariHospital, Kurayoshi Hospital, Kyowa Hospital, Ryukyu Hospital, Seijuji Hospital, Seiwa Hospital (Institute of Neuropsychiatry), Seiwa Hospital (Seiunkai), Shin-abuyama Hospital, Shizuoka Psychiatric Medical Center, Tottori Medical Center, Yamanashi Prefectural Kita Hospital and Watarigawa Hospital. In the following 41 centers, the protocol was approved by the Ethics Review Board of Fujita Health University: Amekudai Hospital, Dazaifu Hospital, Hayashi Hospital, Hiagari Hospital, Hino Hospital, Hiratsuka Hospital, Hokuriku Hospital, Hotei Hospital, Ichiyo Hospital, Ishibashi Hospital, Izumihara Hospital, Jikei-chuo Hospital, Jindai Hospital, Kariya Hospital, Katsushika Hospital, Kawada Hospital, Komine-eto Hospital, Kurono Hospital, Meisei Hospital, Minamigaoka Hospital, Morimoto Hospital, Musashino Chuo Hospital, Nagano Prefectural mental wellness center Komagane, Nishikawa Hospital, Numazu Central Hospital, Oitashimogori Hospital, Okehazama Hospital, Rainbow & Sea Hospital, Sagatasou, Saigata Hospital, Sanmaibashi Hospital, Sanyo Hospital, Shioiri Mental Clinic, Sumiyoshi Hospital, Takamatsu Hospital, Tokiwa Hospital, Tokyo-ome Hospital, Tosa Hospital, Tsukubahigashi Hospital, Yahatakousei Hospital and Wakakusa Hospital.

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Received: 5 February 2014 Accepted: 3 April 2014
Published: 7 April 2014

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doi:10.1186/1471-244X-14-103
Cite this article as: Sukegawa *et al.*: Study protocol: safety correction of high dose antipsychotic polypharmacy in Japan. *BMC Psychiatry* 2014 14:103.

doi:10.1111/pcn.12275

Psychiatry and Clinical Neurosciences

PCN Frontier Review

Psychotropic dose equivalence in Japan

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Psychotropic dose equivalence is an important concept when estimating the approximate psychotropic doses patients receive, and deciding on the approximate titration dose when switching from one psychotropic agent to another. It is also useful from a research viewpoint when defining and extracting specific subgroups of subjects. Unification of various agents into a single standard agent facilitates easier analytical comparisons. On the basis of differences in psychopharmacological prescription features, those of available psychotropic agents and their approved doses, and racial differences between Japan and other countries, psychotropic dose equivalency tables designed specifically for Japanese patients have been widely used in Japan since 1998. Here we introduce dose equivalency tables for: (i) antipsychotics; (ii) antiparkinsonian agents; (iii) antidepressants; and (iv) anxiolytics, sedatives and hypnotics available in Japan. Equivalent doses for the therapeutic effects of individual psychotropic compounds were determined principally on the basis of randomized controlled trials conducted in Japan and consensus among dose equivalency tables reported previously by psychopharmacological experts. As these tables are intended to merely suggest approximate standard values, physicians should use them with discretion.

Key words: antidepressant, antiparkinsonian drugs, antipsychotic, anxiolytic, dose equivalence, hypnotic.

PSYCHOTROPIC DOSE EQUIVALENCE is widely used for approximate dose estimation and prescription strategies in current clinical practice, and for selection of switching methods and subjects in research protocols in the field of psychiatry.[1] Psychiatric clinicians usually consider therapeutic equivalent doses when switching from one psychotropic to another. In clinical trials and psychopharmacological studies, switching from a current psychotropic prescription to a standard agent is often employed as a standard protocol.

In fact, the concept of psychotropic dose equivalence has been an important clinical psychopharmacological tool for estimating the approximate psychotropic doses that patients actually receive, and for deciding on the approximate titration dose when switching from one psychotropic agent to another. In psychopharmacological research, it is also important to define and extract specific subgroups of subjects, such as patients with treatment-resistant schizophrenia or treatment-resistant depressive disorders. Unification of various psychotropic agents into a single standard agent also facilitates easier analytical comparisons in psychopharmacological research, especially epidemiological research that considers a variety of psychiatric subjects, or intervention studies focusing on psychiatric patients receiving a range of psychotropic agents.

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Accepted 15 January 2015.

The traditionally high frequency of psychotropic polypharmacy in Japan can be considered to necessitate a constant need for psychotropic dose equivalency tables, not only for antipsychotics, but also for antidepressants, anxiolytics, sedatives and hypnotics, and such tables are now becoming an indispensable psychopharmacological tool for assessing the psychotropic doses patients actually receive. It is often necessary to estimate the approximate psychotropic doses that are equivalent to standard agents. Clinical psychiatrists in Japan must often be mindful of the approximate psychotropic doses for patients receiving various types of psychotropic agents simultaneously, including chlorpromazine-equivalent doses of antipsychotics, biperiden-equivalent doses of antiparkinsonian agents, imipramine-equivalent doses of antidepressants, diazepam-equivalent doses of anxiolytics, and nitrazepam-equivalent doses of hypnotics.

As to why psychotropic polypharmacy is frequently employed in Japan, a few reasons can be suggested. First, it has been pointed out that polypharmacy is related to the traditional therapeutic concept of oriental herbal medicine in which the best prescriptions usually include a mixture of many ingredients: the larger the number of ingredients, the more effective the drug action.[2] There is also anecdotal evidence that some Japanese physicians prescribe particular mixtures of drugs that have been handed down through generations in the form of proprietary medicines with secret components.

Second, it has been considered that the public medical insurance system in Japan has led to an increase in psychotropic polypharmacy. Under the existing system, the dose of each psychotropic agent that clinicians can prescribe is limited to within the maximal dose approved for routine clinical practice, whereas the number of psychotropic agents that clinicians can prescribe on a prescription sheet is not limited. Furthermore, the approved dose of each psychotropic agent under the current regulations in Japan is relatively low in comparison to the USA and European countries. For example, the approved maximal dose of sertraline in Japan for treatment of depressive disorders is 100 mg/day. Due to this regulation, psychiatric physicians are often unable to increase the dose of a psychotropic to the recommended dose suggested in Western therapeutic guidelines, and this often results in psychotropic polypharmacy. Therefore, concomitant use of a number of psychotropic agents exerting similar effects is quite routinely performed, especially for psychiatric patients who require high doses of psychotropics or who do not respond to psychotropics effectively. Recently, the public medical insurance system has been revised to improve this situation and to prevent psychotropic polypharmacy. According to the revised insurance payment system effective since 1 October 2014, the prescription fees paid from public insurance payers to medial institutions is reduced when a psychiatrist prescribes at least one of the following four types of polypharmacy on a single prescription sheet: (i) simultaneous use of three or more anxiolytics; (ii) simultaneous use of three or more hypnotics; (iii) simultaneous use of four or more antipsychotics; or (iv) simultaneous use of four or more antidepressants. However, as concomitant use of various, different kinds of psychotropic combinations (antipsychotics, antiparkinsonian drugs, antidepressants, anxiolytics and hypnotics) is possible, and the simultaneous use of a few agents exerting similar effects within the same group of psychotropic is also permitted, the importance of psychotropic dose equivalency tables has not changed at all.

To establish psychotropic dose equivalency tables that are useful in Japanese clinical practice, we initially collected as many worldwide publications as possible listing psychotropic dose equivalency tables. Wide variation is evident in these tables because most of them have been developed on the basis of clinical experience, and differ from each other, and also over time. These differences have been reported to be large enough to be clinically significant (often two- to threefold and sometimes more). We found it difficult to import these data automatically due to this large variation among the tables. An additional problem is the big difference in approved psychotropic agents among countries, and the lack of any equivalency data for compounds that have been developed exclusively in Japan. In addition, a third problem that must be considered is differences in the frequency of hepatic metabolizing enzymes among the races. For example, the proportion of poor metabolizers of cytochrome P450 2D6 (CYP2D6) has been estimated to be 7–10% among Caucasians but approximately 1% among Orientals,[3] whereas the corresponding proportions of poor cytochrome P450 2C19 (CYP2C19) metabolizers are approximately 4% and as many as 18–23%,[3] respectively. Psychiatric physicians must therefore have a grasp of such racial differences when switch-

ing from one psychotropic agent to another, according to the major metabolizing enzyme that will be present.

Along with a critical review of the variety of existing dose equivalency tables we collected, we also surveyed the published work on randomized controlled trials of psychotropic agents in comparison with active agents employed in Japan. We have reviewed virtually all of the Japanese published reports on clinical trials of psychotropic agents conducted in Japan, including antipsychotics, antidepressants, anxiolytics, sedatives and hypnotics. Interestingly, only a quarter to a third of all relevant Japanese randomized controlled trials were retrievable from the Cochrane group registers,[4] suggesting that the psychotropic dose equivalency tables developed in Western countries do not take Japanese data into consideration.

PSYCHOTROPIC DOSE EQUIVALENCY TABLES IN JAPAN

Considering the differences in psychopharmacological prescription features, the available psychotropic agents and their approved doses, and racial differences between Japan and other countries, psychotropic dose equivalency tables specifically for Japanese patients have been available since 1998, and have been used widely in psychiatric practice and psychopharmacological research in Japan. For psychotropic dose equivalency tables in Japan, equivalent doses for the therapeutic effects of individual psychotropic agents have been determined principally on the basis of: (i) the results of randomized controlled trials of comparative active agents conducted in Japan; and (ii) consensus regarding dose equivalency tables developed previously by psychopharmacological experts for psychotropic agents that were introduced in Japan in the initial phase of psychopharmacological treatment, and for which no double-blind comparative studies with active agents for Japanese subjects could be found or reported in the public domain. Since the equivalent doses introduced here are merely suggested approximate standard values for individual agents based on the above rules, physicians should use these tables with discretion, and in routine practice always prescribe the optimal psychotropics for patients while bearing careful clinical observations in mind.

Dose equivalence of antipsychotics

The dose equivalence of orally administered antipsychotics is shown in Table 1.[5–15] Of the psychotropic dose equivalency tables, those for antipsychotics are the most extensively studied and published in the literature. A large number of dose equivalency tables for oral antipsychotic agents have been developed worldwide. To develop a dose equivalency table of antipsychotics that are useful in Japanese practice, we first examined tables reported previously elsewhere since chlorpromazine was first introduced in the field of clinical psychiatry. In fact, various dose equivalency tables have been developed and introduced in various psychopharmacology texts, reviews, and guidelines, such as the Psychotropics Drug Directory (Salisbury) by Bazire, the Practice Guidelines of the American Psychiatric Association, the Maudsley Prescribing Guidelines (London) by Taylor *et al.*, the Pocket Handbook of Psychiatric Drug Treatment (Philadelphia) by Kaplan & Sadock, and the US Expert Consensus Guideline Series. We have cited some of these publications here among the references,[16–25] while the remaining sources we have referred to, but are not cited in the references, are listed elsewhere.[5–15]

Table 1 Dose equivalence of antipsychotics†

Aripiprazole	4	Perospirone	8
Blonanserin	4	Perphenazine	10
Bromperidol	2	Pimozide	4
Carpipramine‡	100	Pipamperone	200
Chlorpromazine	100	Prochlorperazine	15
Clocapramine	40	Propericiazine	20
Clotiapine‡	40	Quetiapine	66
Clozapine	50	Reserpine	0.15
Fluphenazine	2	Risperidone	1
Haloperidol	2	Spiperone	1
Levomepromazine	100	Sulpiride	200
Moperone	12.5	Sultopride	200
Mosapramine	33	Thioridazine‡	100
Nemonapride	4.5	Tiapride	100
Olanzapine	2.5	Timiperone	1.3
Oxypertine	80	Thiothixene‡	3.3
Paliperidone	1.5	Trifluoperazine‡	5
Perazine‡	100	Zotepine	66

†Adapted from the previous publications.[5–15] Reproduced with permission. ©Ataru Inagaki & Toshiya Inada. ‡No longer available in Japan.

Table 2 Dose equivalence of short-acting injectable antipsychotics

Based on oral chlorpromazine 100 mg (p.o.)		Based on the same oral agent (p.o.)			
Injectable antipsychotics	Equivalent dose of 100 mg chlorpromazine (p.o.) (mg)	Injectable antipsychotics (mg)		Equivalent dose of oral administration (mg)	
Chlorpromazine (p.o.)	100				
Haloperidol (i.m./i.v.)	1	Haloperidol (i.m./i.v.)	5	Haloperidol (p.o.)	10
Chlorpromazine (i.m.)	33	Chlorpromazine (i.m.)	50	Chlorpromazine (p.o.)	150
Levomepromazine (i.m.)	25	Levomepromazine (i.m.)	25	Levomepromazine (p.o.)	100
Sulpiride (i.m.)	50	Sulpiride (i.m.)	50	Sulpiride (p.o.)	200
Perphenazine (i.m.)	2	Perphenazine (i.m.)	2	Perphenazine (p.o.)	10
Prochlorperazine (i.m.)	2.14	Prochlorperazine (i.m.)	5	Prochlorperazine (p.o.)	35
Timiperone (i.m./i.v.)	0.19	Timiperone (i.m./i.v.)	4	Timiperone (p.o.)	28
Olanzapine (i.m.)	2.25	Olanzapine (i.m.)	9	Olanzapine (p.o.)	10

Adapted from the previous publication[28] and the booklet '2014 Year Edition of Drug Directory for Neuropsychiatric Diseases' (not for sale) designed by the Mitsubishi Tanabe Pharma Corporation (Osaka) and the Yoshitomiyakuhin Corporation (Osaka), published by the Seiwa Shoten Publishers Inc. (Tokyo) in 2014. Reproduced with permission. ©Ataru Inagaki & Toshiya Inada.
i.m., intramuscular injection; i.v., intravenous injection; p.o., oral administration (per os).

The development of antipsychotic agents by Japanese pharmaceutical companies has been quite active in comparison with other psychotropic agents. For example, the following original compounds were all developed by Japanese pharmaceutical companies: clocapramine (marketed since 1974), zotepine (marketed since 1982 in Japan), timiperone (marketed since 1984), mosapramine (marketed since 1991), nemonapride (marketed since 1991), perospirone (marketed since 2001), blonanserin (marketed since 2008), aripiprazole (marketed since 2006 in Japan), and lurasidone (not yet marketed in Japan). Although some of them, such as zotepine, aripiprazole, and lurasidone, are used in various countries other than Japan, other agents are marketed exclusively in Japan and therefore no equivalency data are available in most of the dose equivalency tables developed outside Japan. Chlorpromazine equivalent doses for these compounds have been determined based on clinical double-blind trials carried out in Japan.

As dose equivalency tables sometimes have a significant influence on decision-making by psychiatric physicians, they are often used when switching doses of psychotropic agents, and accordingly this may influence the sales of the pharmaceutical companies concerned. As examples, a couple of references discussing the psychotropic equivalent doses of quetiapine in Japan are provided.[26,27] Ziprasidone, asenapine and lurasidone are not included in this table because they are not yet available in Japan.

The dose equivalence of short-acting injectable antipsychotics is shown in Table 2,[28] while that of long-acting injectable antipsychotics is shown in Table 3.[13,29–31] As clinical double-blind studies of short-acting injectable antipsychotics have been quite scarce in Japan, their chlorpromazine-equivalent doses have been determined on the basis of: (i) previous publications, such as the Psychotropics Drug Directory (Salisbury) by Bazire and the Maudsley Prescribing Guidelines (London) by Taylor *et al.*, showing the equivalent oral doses for the intravenous or intramuscular administration route; and (ii) the bioavailability ratio calculated from the area under the blood concentration-time curve (AUC) ratio for the intravenous or intramuscular administration route when compared with oral administration. As for the chlorpromazine-equivalent doses of long-acting injectable antipsychotics, they have been determined principally on the basis of the results of randomized controlled trials comparing long-acting injectable antipsychotics with oral agents, in addition to (i) and (ii) for the intramuscular administration route mentioned above. Most of the AUC data have been collected from the 'Interview Form' published by the Japanese Society of Hospital Pharmacists.

Table 3 Dose equivalence of long-acting injectable antipsychotics†

Oral antipsychotics		Long-acting antipsychotics	
Chlorpromazine	100 mg/day		
Haloperidol	2 mg/day	HP-D	30 mg/4 weeks
Fluphenazine	2 mg/day	FE‡	7.5 mg/2 weeks
		FD	15 mg/4 weeks
Risperidone	1 mg/day	RLAI	10 mg/2 weeks
Paliperidone	1.5 mg/day	PAL-P	18.75 mg/4 weeks

†Adapted from the previous publications[13,29–31] and the booklet '2014 Year Edition of Drug Directory for Neuropsychiatric Diseases' (not for sale) designed by the Mitsubishi Tanabe Pharma Corporation (Osaka) and the Yoshitomiyakuhin Corporation (Osaka), published by the Seiwa Shoten Publishers Inc. (Tokyo) in 2014. Reproduced with permission. ©Ataru Inagaki & Toshiya Inada. ‡No longer available in Japan.
FD, fluphenazine decanoate; FE, fluphenazine enanthate; HP-D, haloperidol decanoate; PAL-P, paliperidone palmitate; RLAI, risperidone long-acting injection.

Dose equivalence of antiparkinsonian drugs

Table 4 shows the dose equivalence of antiparkinsonian drugs available in Japan.[32,33] Although benztropine has been designated as a standard agent in the previous published reports,[34–37] it is no longer available in Japan. Therefore, we selected biperiden as a standard agent because it has been widely used in Japan, instead of benztropine. Actual biperiden-equivalent doses have been determined based on clinical double-blind trials carried out in Japan,[32,33] with reference to the dose equivalency tables published previously.[34–37] The rationale for antiparkinsonian dose equivalency is based on clinical treatment efficacy, not for idiopathic parkinsonian symptoms, but for antipsychotic-induced extrapyramidal symptoms. Therefore, a subgroup of antiparkinsonian drugs that have agonistic effects on the dopaminergic system is not included in this table.

Table 4 Dose equivalence of antiparkinsonian drugs†

Amantadine	100
Benztropine‡	1
Biperiden	2
Diphenhydramine	30
Hydroxyzine	65
Mazaticol	8
Metixene‡	10
Piroheptine	4
Profenamine	100
Promethazine	50
Trihexyphenidyl	4

†Adapted from the previous publications.[32,33] Reproduced with permission. ©Ataru Inagaki & Toshiya Inada. ‡No longer available in Japan.

Dose equivalence of antidepressants

The dose equivalence of antidepressants available in Japan is shown in Table 5.[13,38–40] The dose equivalency is determined based on comparison of the therapeutic antidepressive effects demonstrated in clinical double-blind trials with the active agents in the treatment of depressive disorders carried out in Japan. For most of the compounds developed as antidepressants, the comparative double-blind clinical trials were carried out using imipramine or amitriptyline, or both. Imipramine-equivalent doses have been determined based on clinical double-blind trials carried out in Japan for recently developed antidepressants, such as selective serotonin reuptake inhibitors, serotonin noradrenaline reuptake inhibitors, and mirtazapine. We have also referred to a number of dose equivalency tables published previously.[41,42] Fluoxetine, venlafaxine and bupropion are not included in this table because they are not yet available in Japan.

Dose equivalence of anxiolytics, sedatives and hypnotics

Table 6 summarizes the dose equivalence of anxiolytics, sedatives and hypnotics available in Japan.[13,43–45]

Table 5 Dose equivalence of antidepressants†

Amitriptyline	150	Milnacipran	100
Amoxapine	150	Mirtazapine	30
Clomipramine	120	Nortriptyline	75
Desipramine‡	150	Paroxetine	40
Dosulepin	150	Paroxetine CR	50
Duloxetine	30	Safrazine‡	30
Escitalopram	20	Sertraline	100
Fluvoxamine	150	Setiptiline	6
Imipramine	150	Sulpiride	300
Lofepramine	150	Trazodone	300
Maprotiline	150	Trimipramine	150
Mianserin	60		

†Adapted from the previous publications[13,38–40] and the booklet '2014 Year Edition of Drug Directory for Neuropsychiatric Diseases' (not for sale) designed by the Mitsubishi Tanabe Pharma Corporation (Osaka) and the Yoshitomiyakuhin Corporation (Osaka), published by the Seiwa Shoten Publishers Inc. (Tokyo) in 2014. Reproduced with permission. ©Ataru Inagaki & Toshiya Inada. ‡No longer available in Japan.

The table includes barbiturates that act as central nervous system depressants, benzodiazepines and other non-benzodiazepine agents, such as zolpidem, eszopiclone, bromvalerylurea and tandospirone. Tandospirone is a non-benzodiazepine anxiolytic marketed in Japan and China that acts primarily at the serotonin-1A receptor. The equivalent dose of tandospirone is included in this table based on data from a direct double-blind comparative study with diazepam. Its chemical structure is closely related to buspirone, marketed in the USA (not marketed in Japan). Ramelteon is a new class of sleep agent that selectively binds to the melatonin MT1 and MT2 receptors and has been available in Japan since 2010. Suvorexant, a selective dual orexin receptor antagonist, is also another new class of sleep agent that has been available in Japan since 2014. However, ramelteon and suvorexant have yet to be included in the table because no comparative double-blind studies with other active hypnotics have been reported in Japan. The dose equivalency is determined based on comparison of the therapeutic effects observed in double-blind clinical trials compared with the active agents in the treatment of anxiety or insomnia in Japan. For most of the benzodiazepines developed as hypnotics for treatment of insomnia, nitrazepam is principally used as a standard active control compound, together with a placebo as an inactive control compound, whereas for most of those developed as anxiolytics for the treatment of 'neurosis or psychosomatic disease', diazepam is principally used as a standard active control compound, together with a placebo as an inactive control compound in clinical double-blind trials conducted in Japan during the 20th century.[46] Therefore, diazepam-equivalent doses for anxiolytic effects and nitrazepam-equivalent doses for the treatment of insomnia have been estimated based on comparative double-blind trials conducted in Japan. In addition to the data from clinical double-blind studies, a number of previous Japanese psychopharmacological reviews are also referred to, as no double-blind comparative clinical trials have been reported for the following agents: secobarbital, amobarbital, phenobarbital, barbital, triclofos, chloral hydrate, and oxazepam.

Table 6 Dose equivalence of anxiolytics, sedatives and hypnotics†

Alprazolam	0.8	Amobarbital	50
Bromazepam	2.5	Barbital	75
Chlordiazepoxide	10	Bromvalerylurea	500
Clobazam	10	Brotizolam	0.25
Clonazepam	0.25	Butoctamide‡	500
Clorazepate	7.5	Chloral hydrate	250
Clotiazepam	10	Estazolam	2
Cloxazolam	1.5	Eszopiclone	2.5
Diazepam	5	Flunitrazepam	1
Etizolam	1.5	Flurazepam	15
Fludiazepam	0.5	Haloxazolam	5
Flutazolam	15	Lormetazepam	1
Flutoprazepam	1.67	Nimetazepam	5
Loflazepate	1.67	Nitrazepam	5
Lorazepam	1.2	Passiflora extract	100
Medazepam	10	Pentobarbital	50
Mexazolam	1.67	Phenobarbital	15
Oxazepam‡	15	Quazepam	15
Oxazolam	20	Rilmazafone	2
Prazepam‡	12.5	Secobarbital	50
Tandospirone	25	Triazolam	0.25
Tofisopam	125	Zolpidem	10
		Zopiclone	7.5

†Adapted from the previous publications.[13,43–45] Reproduced with permission. ©Ataru Inagaki & Toshiya Inada. ‡No longer available in Japan.