TABLE 1. Demographic characteristics of the sample at baseline ($n = 46$)

	n	%
Female	33	71.7
Past treatment history	29	63.0
Family history (any mental illness)	18	39.1
Married	9	19.5
Employed	19	41.3
Student	16	34.8
APS	46	100.0
BIPS	9	19.6
GRD	21	45.7
	Mean	SD
Age, years	23.5	6.6
Duration of illness, weeks	26.0	24.0
Education, years	12.3	2.5
GAF current	54.0	12.9
SOPS		
Positive symptoms	18.9	4.8
Negative symptoms	18.3	5.8
Disorganized symptoms	8.3	3.7
General symptoms	13.1	4.2
Total	58.6	15.7
SFS		
Withdrawal	9.0	2.6
Interpersonal	7.1	3.1
Pro-social activities	13.6	9.7
Recreation	17.1	6.9
Independence–competence	23.3	6.3
Independence–performance	33.5	6.9
Employment	5.1	3.0
Total	107.9	26.5
SWNS		
Mental functioning	10.7	3.9
Self-control	11.6	3.6
Emotional regulation	11.3	3.8
Physical functioning	11.2	3.0
Social integration	10.7	3.9
Total	55.4	13.2
WHO-QOL26		
Physical domain	16.4	4.4
Psychological domain	12.9	4.3
Social relationship	8.0	2.7
Environmental domain	21.6	5.1
General	3.9	1.5
Total	62.8	14.7
SUMD, current disorder		
Item 1-3 (global insight) awareness	2.3	0.9
Item 4-10 (symptom items) awareness	1.5	0.5
Item 4-10 (symptom items) attribution	3.0	0.9

APS, Attenuated Positive Symptom Group; BIPS, Brief Intermittent Psychosis Group; GAF, Global Assessment of Functioning Scale; GRD, Genetic Risk and Deterioration Group; SD, standard deviation; SFS, Social Functioning Scale; SOPS, Scale of Prodromal Symptoms; SUMD, Scale to Assess Unawareness of Mental Disorder; SWNS, Subjective Well-being under Neuroleptics Short version; WHO-QOL26, WHO-Quality of Life 26.

outcome at the follow-up point (Table 5). Results suggest that less severe negative symptoms, more severe general symptoms, or lower subjective well-being at baseline could significantly predict poorer outcome after 1 year.

DISCUSSION

Our findings are of some clinical relevance when treating help-seeking individuals with the features of early psychosis. The current naturalistic study revealed that quite a few patients (48%) showed little improvement in both their positive/negative symptoms and subjective well-being after having received intervention for over 1 year, regardless of transition to full-blown psychosis. Additionally, nearly half of the entire sample (41%) dropped out of the study within 1 year for any reason. These results suggest that the current early interventions cannot truly meet the subjective needs of individuals at risk for psychosis.

One explanation for the unmet needs among the at-risk patients might be that the early interventions for psychosis in clinical settings tended to favour antipsychotic medication, as seen in the present study. We found that about 80% of the patients who were followed up had received antipsychotic medication at the follow-up point. Although such antipsychotic medication would be generally administered to reduce risks that are focused on the attenuated positive symptoms, the results indicated that poorer outcome could not be significantly predicted by severity of positive symptoms at baseline but less severe negative symptoms, more severe general symptoms, and lower subjective well-being at baseline. This suggests that other symptoms than positive symptoms might be a key to patients' subjective difficulties in their daily lives, possibly shedding new light on early intervention strategies for psychosis; for example, a targeted intervention for affective symptoms might be more effective with regard to the subjective response than interventions for positive symptoms.

In addition, to make matters worse, the off-label use of antipsychotics for psychosis prodrome has presented some ethical issues associated with unexpected adverse effects, social stigmatization and low self-esteem.[19] Given that poor adherence to the initial treatment may hinder an adequate intervention,[20] ethical issues regarding pharmacological intervention during the earliest stage of psychosis cannot be ignored. However, recent clinical research has revealed that not a few clinicians in the community have administered pharmacological interven-

TABLE 2. Comparisons at baseline between the followed-up patients and the withdrawn patients

	Followed-up (n = 27)		Withdrawn (n = 19)		Chi-square	P
	n	%	n	%		
Female	19	70.3	14	73.7	0.60	1.00
Past treatment history	21	77.8	8	42.1	0.01	0.90
Family history (any mental illness)	10	37.0	8	42.1	0.12	0.77
Married	7	25.9	2	10.5	2.20	0.33
Employed	11	40.7	8	42.1	0.01	1.00
Student	7	25.9	9	47.4	2.26	0.21
APS	27	100.0	19	100.0	–	–
BIPS	7	25.9	2	10.5	1.68	0.27
GRD	16	59.3	5	26.3	4.88	0.04*
	Mean	SD	Mean	SD	Z	P
Age, years	25.3	7.2	20.9	4.8	−2.16	0.03*
Duration of illness, weeks	30.7	24.5	19.2	21.9	−2.08	0.04*
Education, years	12.3	2.6	12.3	2.4	−0.23	0.82
GAF current	53.9	12.7	54.2	13.7	−0.06	0.96
SOPS						
Positive symptoms	19.6	3.4	18.0	6.3	−0.46	0.65
Negative symptoms	20.3	4.5	15.3	6.3	−2.69	<0.01**
Disorganized symptoms	8.7	3.1	7.7	4.4	−0.62	0.54
General symptoms	14.7	2.7	10.8	5.0	−2.66	<0.01**
Total	63.3	10.0	51.7	20.1	−1.93	0.05
SFS total	103.7	23.1	113.9	30.4	−1.18	0.24
SWNS total	52.0	10.3	60.3	15.6	−1.64	0.10
WHO-QOL26 total	58.4	11.5	69.5	16.7	−2.31	0.02*
SUMD, current disorder						
Item 1-3 (global insight) awareness	2.3	0.9	2.4	1.0	−0.45	0.65
Item 4-10 (symptom items) awareness	1.6	0.5	1.3	0.3	−2.04	0.04*
Item 4-10 (symptom items) attribution	3.0	0.9	3.1	1.0	−0.02	0.99

*P < 0.05; **P < 0.01.

APS, Attenuated Positive Symptom Group; BIPS, Brief Intermittent Psychosis Group; GAF, Global Assessment of Functioning Scale; GRD, Genetic Risk and Deterioration Group; SD, standard deviation; SFS, Social Functioning Scale; SOPS, Scale of Prodromal Symptoms; SUMD, Scale to Assess Unawareness of Mental Disorder; SWNS, Subjective Well-being under Neuroleptics Short version; WHO-QOL26, WHO-Quality of Life 26.

tions, including antipsychotics, to individuals who have attenuated psychotic symptoms but do not meet the criteria for psychosis. A naturalistic study from the Recognition and Prevention program showed that individuals presenting with more severe (but non-psychotic) attenuated positive symptoms were nearly all treated with antipsychotics, often in combination with other agents.[21] The data from the NAPLS demonstrated that 60% of the clinical high-risk sample had a lifetime history of receiving psychotropic medication prior to their entry in the research program.[22] Also, anonymous surveys in Japan and Singapore have indicated that most psychiatrists in the community would treat prepsychotic patients with active management, including antipsychotic medication.[23,24] Generally, most clinical psychiatrists in the community are likely to overestimate the use of pharmacological intervention, including antipsychotics, for individuals who have attenuated (but non-psychotic) psychotic symptoms. However, as a number of medication-free studies have found, antipsychotic medication does not seem to be an essential component of effective treatment for psychosis, even in patients with established illnesses.

The high dropout rate in the study (41%) may be partially due to this strategy for intervention that was focused on attenuated positive symptoms. The patients who withdrew within the 1-year follow-up period were younger and had shorter duration of illness, less severe negative symptoms/general symptoms, better awareness of symptoms, and higher subjective QOL at baseline than the patients who were followed up. Although the reasons for dropping out are needed to be explored, it is noteworthy that although the withdrawn patients had better clinical characteristics at baseline, there were no significant differences in positive symptom at baseline between the withdrawn patients and the followed patients. This result suggests that adher-

TABLE 3. Comparisons at baseline between the 'improved' group and the 'not improved' group

	Improved (n = 14)		Not improved (n = 13)		Chi-square	P
	n	%	n	%		
Female	10	71.4	9	69.2	0.16	0.62
Past treatment history	8	57.1	13	100.0	7.16	0.02*
Family history (any mental illness)	8	57.1	2	15.3	5.04	0.04*
Married	3	21.4	4	30.8	3.09	0.21
Employed	7	50.0	4	30.8	1.03	0.27
Student	3	21.4	4	30.8	0.31	0.45
APS	14	100.0	13	100.0	–	–
BIPS	3	21.4	4	30.8	0.31	0.45
GRD	11	78.6	5	38.5	4.49	0.05
Antipsychotic use	3	21.4	3	23.1	<0.01	0.99
	Mean	SD	Mean	SD	Z	P
Age, years	25.9	8.0	25.0	7.3	−0.21	0.84
Duration of illness, weeks	34.4	26.0	26.7	23.3	−0.95	0.34
Education, years	12.8	3.4	11.4	1.4	−0.90	0.37
GAF current	53.2	11.4	55.0	15.6	−0.03	0.98
SOPS						
Positive symptoms	19.9	3.1	19.0	3.7	−0.32	0.75
Negative symptoms	21.1	3.7	19.2	5.7	−1.12	0.26
Disorganized symptoms	9.0	2.9	8.0	3.8	−0.62	0.54
General symptoms	14.0	2.5	15.3	2.8	−1.27	0.21
Total	64.1	9.4	61.5	12.0	−0.56	0.58
SFS total	101.5	26.8	108.4	19.9	−0.21	0.84
SWNS total	50.3	11.2	55.3	11.2	−1.29	0.20
WHO-QOL26 total	2.11	0.4	2.45	0.42	−1.67	0.10
SUMD, current disorder						
Item 1-3 (global insight) awareness	2.5	0.9	2.1	0.8	−1.42	0.16
Item 4-10 (symptom items) awareness	1.5	0.5	1.6	0.5	−0.65	0.52
Item 4-10 (symptom items) attribution	2.9	1.1	3.1	0.8	−0.65	0.52

*P < 0.05

APS, Attenuated Positive Symptom Group; BIPS, Brief Intermittent Psychosis Group; GAF, Global Assessment of Functioning Scale; GRD, Genetic Risk and Deterioration Group; SD, standard deviation; SFS, Social Functioning Scale; SOPS, Scale of Prodromal Symptoms; SUMD, Scale to Assess Unawareness of Mental Disorder; SWNS, Subjective Well-being under Neuroleptics Short version; WHO-QOL26, WHO-Quality of Life 26.

TABLE 4. ANOVA for comparing clinical outcomes between the 'improved' group and the 'not improved' group

	Score difference (T2-T1; mean ± SD)		Non-adjusted		Adjusted†	
Variables	'Improved'	'Not improved'	F	P	F	P
SWNS total	17.5 ± 17.3	2.4 ± 17.3	4.896	0.037*	5.125	0.034*
SFS total	13.7 ± 21.7	4.6 ± 15.0	1.509	0.231	1.575	0.223
GAF	19.3 ± 11.6	12.7 ± 17.4	1.363	0.254	3.058	0.094
WHO-QOL total	3.7 ± 3.8	1.2 ± 3.9	2.855	0.104	1.024	0.323
SUMD global insight	−0.3 ± 1.0	0.2 ± 0.9	0.484	0.494	0.005	0.947
SUMD symptom awareness	0.9 ± 0.9	−0.1 ± 0.7	8.632	0.008**	8.435	0.009**
SUMD symptom attribution	0.5 ± 1.0	0.1 ± 0.3	0.645	0.432	0.647	0.432

*P < 0.05; **P < 0.01.

†Adjusted for age, DUI and baseline scores.

T1, baseline, T2, at the follow-up point.

ANOVA, analysis of variance; GAF, Global Assessment of Functioning Scale ; SD, standard deviation; SFS, Social Functioning Scale; SUMD, Scale to Assess Unawareness of Mental Disorder; SWNS, Subjective Well-being under Neuroleptics Short version; WHO-QOL, WHO-Quality of Life.

TABLE 5. Multiple linear regression analysis for exploring variables that can predict poor outcome at the follow-up point

Variables	B	SE	β	*t*	*P*
Negative symptoms at T1	−0.060	0.020	−0.525	−2.907	0.008
General symptoms at T1	0.174	0.039	0.915	4.454	<0.001
SWNS total score at T1	0.024	0.009	0.510	2.677	0.014

T1, baseline.
SWNS, Subjective Well-being under Neuroleptics Short version.

ence to treatment in individuals with clinical high risk of psychosis does not depend on the extent to which interventions are based on the target for reducing positive symptoms.

Other clinical variables may also have some impacts on treatment outcome. Patients in the 'not improved' group had past treatment histories and had fewer family members with mental health illness. There are two potential interpretations for this finding. First, it may be that those with family experience of psychiatric illness tended to have effective care or support during the earlier stage of illness. Although previous studies have failed to confirm that family history of psychiatric illness was positively associated with a shorter duration of untreated psychosis,[25–27] families with previous experience of mental health illness may facilitate earlier help seeking through the enhancement of knowledge about potential symptoms and their significance.[25] Second, patients in the 'not improved' group may be treatment resistant. These patients would continue to receive treatment because their symptoms had not been relieved, as we hypothesized, partly because the current early interventions were not effective for this type of patients. Another explanation for considerable rate of having past treatment history is the preponderance of women in the present study sample. Several studies showed that women in general are more likely to have a past history of any psychiatric disorder.[28,29] Given that gender differences may influence the course of illness,[29] our results would be skewed by the predominance of women in this sample.

Our data further suggest that negative symptoms do not appear to have an impact on both clinical outcomes and treatment adherence. Less severe negative symptoms at baseline were found to be associated with withdrawal from treatment and to predict significantly poorer outcomes, contrary to previous findings.[30,31] These findings are also contrary to our previous expectation that severe negative symptoms would be associated with withdrawal from treatment and poorer outcomes. Rather, it appears that general symptoms play a key role more than negative symptoms for both clinical outcomes and treatment adherence. Whereas less severe general symptoms at baseline were found to be associated with withdrawal from treatment, more severe general symptoms at baseline predict poorer clinical outcomes after 1 year. General symptoms include sleep disturbance, dysphoric mood, motor disturbance and impaired tolerance to normal stress.[13] These symptoms may be directly linked to difficulties in daily living, in other words, subjective difficulties. Therefore, fluctuation of general symptoms should be carefully evaluated as a measure of effectiveness in the treatment.

The present study had some methodological weaknesses. First, an evaluation of the extent of the patients' needs is needed to clarify the relationship between subjective difficulties and help-seeking behaviour. Subjective difficulties would be hard to be evaluated precisely by the objective ratings and thus further development of objective ratings on subjective wellness/difficulties should be needed. Second, a considerable attrition rate was also observed in the current study, as in most prospective studies, but the reason for the high rate of patients lost to attrition remains unclear. Third, the present sample was skewed by both this high attrition rate and high rates of previous treatment with relatively long duration of 'being well'. Finally, the small number of subjects in this study may certainly limit the generalizability of the findings. A larger sample with a longer period of observation is needed.

Despite these limitations, our findings have important clinical implications. A notable number of patients had a poor outcome with symptomatic deterioration, providing a rational for early intervention for psychosis. However, the current strategy for reducing the risk of psychosis, which is focused on the attenuated positive symptoms, should be reappraised. Further comprehensive longitudinal studies are needed to develop truly needs-based interventions for these at-risk patients.

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Long-term Efficacy and Tolerability of Perospirone for Young Help-seeking People at Clinical High Risk: a Preliminary Open Trial

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Objective: Interest in the "at-risk mental state" (ARMS) for psychosis has increased because early intervention is expected to delay or prevent the onset of schizophrenia. However, the optimum intervention strategy remains controversial, especially with regard to antipsychotics. Although administration of antipsychotic medications is often associated with adverse effects and raises ethical considerations, recent studies have shown that some novel antipsychotics are safer and more tolerable for young people than conventional antipsychotics. We investigated whether administration of perospirone, a combined serotonin (5-HT)/dopamine antagonist and 5-HT1A receptor agonist, could alleviate prodromal symptoms and be well tolerated by clinical high risk patients.
Methods: The participants were outpatients seeking help. The Structured Interview for Prodromal Symptoms was performed in patients identified as being at clinical high risk. The Scale of Prodromal Symptoms (SOPS) was also completed and changes of subjective experience were assessed with the Subjective Well-being under Neuroleptics, short version. The incidence of akathisia was recorded by using the Barnes Akathisia Scale. Subjects were monitored for 26 weeks after starting medication.
Results: SOPS scores improved significantly after 26 weeks of perospirone therapy, while BAS scores did not show deterioration. No serious adverse events occurred during the study.
Conclusion: This trial suggests that perospirone therapy provides a clinical benefit for clinical high risk subjects without causing serious adverse events. Although further placebo-controlled studies are needed for confirmation, perospirone might be one of optimum treatments for individuals at imminent risk of psychosis.

KEY WORDS: Perospirone; Prodrome; Psychotic disorders; Early intervention; Schizophrenia.

INTRODUCTION

Interest in the clinical high risk state or "at-risk mental state" (ARMS) for psychosis has been increasing because early intervention is expected to delay or prevent the onset of schizophrenia. Recently, treatment that alleviates prodromal symptoms as well as preventing the onset of schizophrenia has attracted attention. It was reported that 35% of individuals meeting criteria for a psychosis risk syndrome made the transition to psychosis during a 2.5 year period.[1] Even if they do not undergo the transition to psychosis, many patients seek help because they are suffering from symptoms of ARMS. Addington *et al.*[2] found that about 40% of clinical high risk subjects who did not progress to psychosis continued to suffer from attenuated positive symptoms for 2 years, with their social and role functioning being significantly worse relative to those of non-psychiatric control subjects. Although these reports suggest that long-term therapy should be provided to clinical high risk patients seeking help, the optimum intervention strategy remains controversial, especially with regard to use of antipsychotics.

Recent controlled studies using antipsychotics have demonstrated a decrease of the conversion rate,[3,4] but most researchers and clinicians still hesitate to prescribe drugs for ARMS due to ethical considerations such as the risk of false-positive identification of ARMS and the adverse reactions related to pharmacotherapy. In fact, antipsychotics are often associated with adverse effects that are undesirable for young people, such as pronounced weight gain and sexual dysfunction.[3,5] While this clinical dilemma has been emphasized, antipsychotics tend to be prescribed for ARMS in the real-world setting. Cadenhead *et al.*[6] reported that psychotropic medications were

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prescribed for 60.1% of patients at clinical high risk over their lifetime. Moreover, among those who had taken psychotropic medications, 23.7% had received an antipsychotic agent. In Japan, research based on the vignette has shown the possibility that many of the clinical high risk sample who were diagnosed as schizophrenia might be received an antipsychotic.[7] Similar research conducted in Singapore showed that most psychiatrists who diagnosed patients as being at clinical high risk chose to treat them with atypical antipsychotics.[8] Accordingly, antipsychotics are being prescribed for ARMS, and we should think about the efficacy and safety of pharmacotherapy.

A few recent studies on the psychosis prodrome have shown that some novel antipsychotics are safer and more tolerable for young subjects.[9,10] Perospirone is a combined serotonin (5-HT2)/dopamine antagonist and 5-HT1A receptor partial agonist that was developed in Japan, and it has been shown to be as effective as other antipsychotic agents for symptoms of schizophrenia.[11,12] The 5-HT1A receptor partial agonist activity of perospirone[13] could have an antianxiety effect and reduce adverse reactions such as extrapyramidal symptoms and weight gain.[14] In addition, activation of 5-HT1A receptors ameliorates a deficiency of dopaminergic neurotransmission in the frontocortical region in schizophrenic patients, which could improve the negative symptoms and cognitive deficits of schizophrenia.[15] Such pharmacological properties of perospirone may make it both effective and safer for clinical high risk patients.

Accordingly, this study was performed to investigate whether administration of perospirone for the treatment of psychotic prodrome was effective and tolerable in a help-seeking clinical high risk sample.

METHODS

Participants

This study was performed at the Toho University Omori Medical Center in Tokyo. All participants were help-seeking outpatients. They were eligible for enrollment if they were aged 15-39 years and fitted the Criteria of Prodromal Syndromes.[16] Patients were excluded from the study if they had (1) a previous diagnosis of any psychotic disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition;[17] (2) symptoms fully accounted for by an Axis 1 disorder or sequelae of drug/alcohol use; (3) abuse of alcohol or drugs; or (4) antipsychotic medication use. Adult participants gave written informed consent and minors gave written informed assent with consent from their parents. Data were collected between May 2009 and December 2010. This study was approved by the Ethical Research Committee of Toho University Omori Medical Center.

Procedures

During the week before beginning study medication, participants underwent eligibility assessment and examinations. After starting the medication, participants were monitored for 26 weeks.

Dosing was done according to a flexible schedule. Participants continued to take any antidepressants, mood stabilizers, or benzodiazepines that had been prescribed before the study (without changing the dose). Individual and family psychosocial interventions with supportive and psychoeducational components were available for each participant.

Measures

Clinical variables

The Structured Interview for Prodromal Symptoms (SIPS)[16] was performed in patients who were identified as having ARMS. We used the Japanese version of SIPS, which we previously demonstrated to have excellent interrater reliability.[18] Psychiatric measures included the Scale of Prodromal Symptoms (SOPS) and the Global Assessment of Functioning (GAF). The SOPS covers 4 categories of symptoms, which are positive, negative, disorganized, and general symptoms. Akathisia was assessed by using the Barnes Akathisia Scale (BAS).[19] Transition to psychosis was defined by using the Presence of Psychotic Symptoms criteria.[16] The SOPS was assessed at baseline, as well as after 2, 4, 6, 8, 13 and 26 weeks of treatment. The other measures and laboratory tests were investigated at baseline and after 4, 8, 13, and 26 weeks.

Assessment of subjective experience

Changes of subjective experience were assessed by using the Subjective Well-being under Neuroleptics, short version (SWNS).[20] The SWNS is a 20-item and 6-point Likert-type self-rating scale. Naber *et al.*[20] reported a 5-factor solution of the scale, which interpreted as emotional regulation, self-control, mental functioning, social integration, and physical functioning. We used the Japanese version of SWNS, which has demonstrated good reliability and validity.[21]

Statistical Analysis

All analyses were done on an intent-to-treat basis. If patients withdrew from the study, data were handled by the last observation carried forward (LOCF) method. Treatment effects were assessed with the paired *t*-test. We used one way repeated-measures analysis of variance (ANOVA) to test differences among the changes of scores, and Bonferroni's correction was employed on a post hoc basis. A probability of less than 0.05 ($p<0.05$) was considered statistically significant for ANOVA and the *post hoc* tests. Calculation of descriptive statistics, ANOVA, and Bonferroni's test were performed with SPSS Statistics software (ver. 17.0; SPSS Inc., Chicago, IL, USA).

RESULTS

Eleven treatment-seeking prodromal patients (63.6% female, with a mean±standard deviation [SD] age of 26.7±6.5 years) were enrolled in this study (intent-to-treat sample). Their demographic and clinical characteristics are presented in Table 1. Eight (72.7%) of the 11 patients had attenuated positive symptoms, 2 (18.2%) patients had

Table 1. Demographic and clinical characteristics of subjects

Characteristic	Data
Total number	11
Age (year)	26.7±6.5
Gender (female)	7 (63.6)
First-degree family history	1 (9.1)
Dropout	3 (27.3)
Type	
COPS-A (brief intermittent psychotic syndrome)	2 (18.2)
COPS-B (attenuated positive symptom syndrome)	8 (72.7)
COPS-C (genetic risk and deterioration syndrome)	0 (0)
COPS-B+COPS-C	1 (9.1)

Values are presented as number only, mean±standard deviation, or n (%).
COPS, Criteria of Psychosis-risk Syndromes

Table 2. Summary of clinical features

Case no.	Age (year)	Gender	Main clinical presentation
1	21	M	Suspiciousness, transient auditory hallucinations and hypobulia
2	39	F	Anxiety, feeling that she had incurred enmity of others
3	15	F	Suspiciousness, complained of hostility of classmates, and peculiar somatic complaints
4	27	F	Transient auditory hallucinations, vague sense of her thoughts being laughed at by others
5	25	F	Brief intermittent auditory hallucinations, insomnia, and perplexity
6	28	M	Susurrus aurium, transient auditory hallucinations, felt that others were talking about him
7	27	F	Peculiar somatic complaints, vague sense of her thoughts being known by others, and compulsive checking
8	27	M	Transient auditory hallucinations, emotional turmoil, and difficulty in expressing his thinking
9	25	M	Fear of others' eyes, peculiar somatic complaints, transient auditory hallucinations, and illusions
10	36	F	Interpersonal oversensitivity, feeling of being watched, and anxiety
11	24	F	Transient auditory hallucinations, vague anxiety, and emotional turmoil

M, male; F, female.

Table 3. Mean changes of SOPS, SWNS, GAF, and BAS scores from baseline to 26 weeks (LOCF analysis)

	Mean (SD)		Percent change	*p* value
	Baseline	26 weeks		
SOPS				
Total score	41.7 (6.5)	22.3 (18.7)	−20.1	<0.05
Positive symptoms	15.0 (2.1)	6.2 (7.4)	−9.2	<0.05
Negative symptoms	13.2 (3.1)	8.9 (6.1)	−4.6	NS
Disorganized symptoms	3.6 (2.2)	2.2 (1.9)	−0.9	NS
General symptoms	9.9 (3.1)	5.0 (5.1)	−4.9	NS
SWNS				
Total score	54.5 (11.1)	67.2 (12.1)	11.2	NS
Physical functioning	11.6 (2.4)	12.9 (3.8)	1.1	NS
Social integration	10.0 (2.6)	12.5 (2.7)	2.3	NS
Mental functioning	10.9 (3.3)	13.8 (3.2)	2.4	NS
Self-control	11.4 (3.2)	14.5 (4.0)	2.8	NS
Emotional regulation	10.5 (2.7)	13.5 (1.9)	2.6	NS
GAF scale	54.5 (14.9)	68.0 (11.6)	11.8	NS
BAS total score	0.2 (0.6)	1.6 (2.9)	-	-

SOPS, Scale of Prodromal Symptoms; SWNS, Subjective Well-being under Neuroleptics, short version; GAF, Global Assessment of Functioning; BAS, Barnes Akathisia Scale; LOCF, last observation carried forward; SD, standard deviation; NS, not significant.

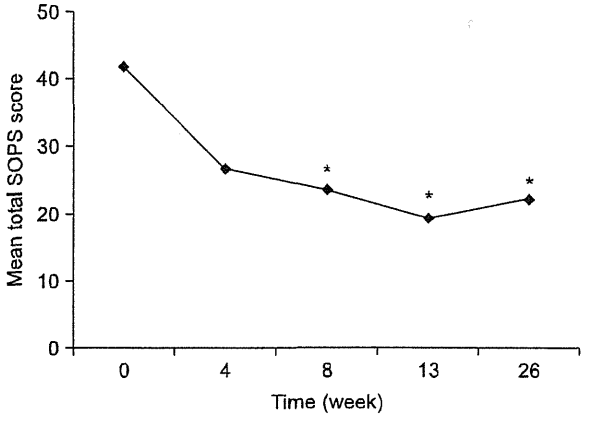

Fig. 1. Mean changes of total Scale of Prodromal Symptoms (SOPS) score from baseline in the patients. *$p<0.05$.

brief intermittent positive symptoms, and 1 (9.1%) patient had attenuated positive symptoms combined with genetic risk and deterioration according to the SIPS. Table 2 provides a summary of the clinical features of the 11 subjects.

After 26 weeks of follow-up, 8 subjects (72.7%) remained in the trial. None of them converted to psychosis. LOCF analysis revealed significant improvement of the SOPS total score and positive symptoms score compared with baseline (Table 3). The change of the SOPS total score from baseline was statistically significant ($p<0.05$) (Fig. 1). On the other hand, the SWNS total score (mean ±SD: 67.2±12.1; p=0.26) and the GAF scale (mean±SD: 68.0±11.6; p=0.57) did not show a significant change after 26 weeks (Table 3).

The mean±SD (chlorpromazine equivalent dose) daily dose of perospirone at baseline was 4.0±0.0 (50.0) mg, while the final mean±SD (chlorpromazine equivalent dose) daily was 10.2±6.0 (127.3) mg. The mean BAS total score returned to baseline by the final evaluation (Table 3). No serious adverse events including hyperglycemia or diabetes mellitus occurred during the study.

DISCUSSION

Perospirone was developed in Japan and has been marketed in this country for the treatment of schizophrenia since 2001. However, perospirone is not well-known outside Japan and could not be investigated in the international clinical practice guidelines established in 2005.[22] The present study showed the efficacy and tolerability of perospirone for patients at clinical high risk. Not all clinical high risk patients will convert to full-blown psychosis, so ethical problems are raised by prepsychotic intervention, especially with regard to prescribing antipsychotics that have various adverse effects. However, help-seeking individuals who meet the clinical high risk criteria are already suffering from their psychotic symptoms, even if they do not have full-blown psychosis. In addition, attenuated positive symptoms vary in severity, which raises the question as to whether a common approach can be applied to the severer symptoms of patients at imminent risk for psychosis. Antipsychotic agents can be expected to improve the more severe attenuated positive symptoms. In the present study, perospirone improved the symptoms of clinical high risk patients without causing severe adverse effects. Our findings suggested that perospirone therapy may be of clinical benefit for individuals with ARMS and could be one of optimum treatments for those at imminent risk of psychosis.

Pharmacologically, perospirone is a combined serotonin (5-HT)/dopamine antagonist and 5-HT1A receptor agonist, so it may not only improve positive symptoms but also be effective against anxiety, negative symptoms, and cognitive deficits. Perospirone is less potent than other atypical antipsychotics like risperidone, and causes fewer adverse effects such as sedation or akathisia. Moreover, perospirone has a lower propensity to elicit metabolic side effects.[14] These pharmacological properties of perospirone might have been important for achieving such a favorable outcome in our mostly young and previously untreated clinical high risk patients.

The SWNS scores and the GAF scale tended to improve after 26 weeks, but did not change significantly from baseline. It was thought that these results might have been influenced by the higher functioning of individuals with ARMS at baseline. The mean dose of perospirone was below the dose range used to treat schizophrenia, and this could also have been associated with the clinical features of ARMS.

This study had some limitations. First, it was not blinded and was uncontrolled. Another limitation is the small number of subjects. Further research on perospirone is needed to provide confirmation that it can produce a clinical benefit in prodromal subjects.

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Early psychosis in Asia: Insights from Japan

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ABSTRACT

The largest task for psychiatry in Japan today is the deinstitutionalization of patients with psychiatric disorders. In Japan, all citizens are covered by a national health plan, and about 70% of the total cost is covered by the national health insurance scheme. At present, however, there is still no category for early intervention in the national health reimbursement schedule. Recent research has shown that the mean duration of untreated psychosis (DUP) at seven university hospitals in Japan was 17.6 months. We present data using case vignettes suggesting that pharmacotherapy might be overused in prodromal cases. The concept of an At-Risk Mental State (ARMS)/prodromal state might not yet be widely recognized among Japanese psychiatrists. We outline early intervention initiatives in Japan; The Japanese Society for Prevention and Early Intervention in Psychiatry (JSEIP), and a representative early intervention facility for young people is the "Il Bosco" in Tokyo. There are several leading centers for early intervention research and practice in Japan. Most of them are driven by university departments of psychiatry with respect to both research and clinical activities. The development of services for early intervention is expected to reduce stigmatization, prevent suicide among young persons, and promote general knowledge about mental health. There are several common or similar issues among Asian countries, including service systems, community attitudes to psychiatric illness including stigma, and dependence on pharmacotherapy.

1. Introduction

1.1. Historical background of psychiatric services in Japan

In Japan today, "mental disorder" is usually taken to mean "depression" or "adjustment disorder." The stigma against consulting a psychiatrist or mental health service has decreased for subjects with depression. Depression is a very common disorder among working populations. Recently, the number of outpatient clinics for psychiatry has increased rapidly, especially in urban areas. On the other hand, the department in charge of the Ministry of Health, Welfare, and Labour has sent a warning note to clinicians regarding the inappropriate prescription of antipsychotic drugs, including inappropriate doses or treatment durations, and the polypharmacy of benzodiazepines. Japan has long had the tradition of administering traditional herbs in an add-on manner. Combination of many different types of herb was historically regarded an art (Takei et al., 2002). Patients who have attempted suicide by taking overdoses of prescribed medicine are frequently admitted to emergency and critical care medical centers in Japan. Many of them are females who had previously consulted a psychiatric clinic and had been diagnosed with stress-related poor personality disorders (Ozaki et al., 2007).

However, the real world of psychiatric services in Japan is more serious, with psychiatric wards containing more than 300,000 beds per 120 million population and around 32,000 suicides occurring every year. The number of mental hospitals in Japan increased during the rapid economic growth after World War II, when a comprehensive renewal of the nation's infrastructure was undertaken. Since then, even more mental hospitals have been built and, driven by the lack of social acceptance, more and more psychiatric patients have been institutionalized and forced into social isolation. Thus, the largest task for psychiatry in Japan today is deinstitutionalization of these patients (Mizuno and Murakami, 2002).

In Japan, all citizens are covered by a national health plan and have access to a wide range of medical resources, including medication, for which they pay only 10–30% of the actual cost, while the remaining cost is covered by the national health insurance scheme. At present, however, there is still no category for early intervention in the national health reimbursement schedule. Also, there is a paucity of efforts toward facilitating community level service delivery in psychiatry. Perhaps this slow and incomplete transition toward community-based psychiatry has prevented Japan from becoming an 'inclusive society' and

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remains a reason for the stigmatization of patients with schizophrenia.

Despite these conditions, following a trend toward early intervention and the raising of several issues regarding mental health services, the Japanese Ministry of Health, Welfare, and Labour (MHWL) has finally started research into early intervention by providing a Health Labour Sciences Research Grant (principal investigator: Masafumi Mizuno). According to the results obtained so far, the mean duration of untreated psychosis (DUP) was 17.6 months at seven university hospitals, where people could seek assistance without suffering much stigmatization. The DUP would probably be longer if data from specialist psychiatric hospitals were included, especially those in rural areas where the stigma associated with mental illness is stronger. Unexpectedly, about 10% of patients with their first episode of schizophrenia on the first day of consulting a psychiatrist had already attempted suicide using a potentially lethal method. This suggests that quite a large number of suicides are caused by untreated psychosis in Japan. It is regrettable that the DUP is relatively long, even though Japan is an advanced country with abundant medical resources with a public health insurance system for all citizens. Recently, the MHWL created a web site for young adolescents to inform them about the importance of early intervention for mental illness (http://www.mhlw.go.jp/kokoro/youth/).

Our previous study from Japan (Yamazawa et al., 2008) showed that none of the subjects were referred to the psychiatric services by the so-called "general practitioners" (GPs). The GP system does not exist in Japan, and certification as a specialist in primary care is not available. Family practitioners with offices in the community provide primary care for patients as "GPs", but they are not specialists in primary care. Instead, they have been trained in other specialties, such as internal medicine, pediatrics, or surgery. However, in Japan, about half of the patients who experienced an initial episode of mental disorder had consulted a GP or internist at a general hospital before consulting a psychiatrist (Koizumi et al., 2007). Unfortunately, GPs in Japan do not perform screening for the early detection of mental illness. The provision and modification of psychiatric services for easy access and a system for the early recognition and detection of mental illness are needed in Japan, rather than increasing the number of psychiatry clinics. The above results highlight the importance of further education for GPs about mental disorders to provide early and appropriate care for patients and to change prevailing attitudes regarding schizophrenia.

1.2. Recognition and decisions regarding the treatment of early psychosis by Japanese psychiatrists

Existing clinical guidelines (International Early Psychosis Association Writing Group, 2005) do not recommend antipsychotic use outside clinical trials unless rapid deterioration or stigmatizing behavior occurs in conjunction with attenuated psychotic symptoms. However, a proportion of patients receiving antipsychotic medication are not suffering from these conditions. The data from North American Prodrome Longitudinal Study (NAPLS) indicated that nearly 25% of prodromal individuals had been prescribed an antipsychotic, despite having never been psychotic according to the operationalized criteria (Cannon et al., 2008).

The concept of early intervention for psychosis has not been extensively acknowledged among professional psychiatrists in Japan. Partly, this might be related to controversies associated with the early intervention approaches like false positive assessments; early treatment, particularly antipsychotic medication during the prodromal phase, has been an area of increased interest and ethical debate over the last decades. Several studies have reported that antipsychotics improved the outcome of the prodromal phase, however, it has been postulated that antipsychotics could be hazardous to the health of young people.

2. Methods

To clarify the approach toward clinical diagnosis of early psychosis as well as to ascertain the strategies for the treatment of patients in the prodromal phase of psychosis, we sent a questionnaire by mail to 659 Japanese psychiatrists in Tokyo (Tsujino et al., 2010). The investigative period was from November to December 2007. The questionnaire consisted of four vignettes and questions regarding the diagnoses, interventions, and medications associated with each vignette. The vignettes included three cases of psychosis prodrome and one full-threshold schizophrenia case. We designed the vignettes so as to conceal the diagnosis. We created the vignettes based on the Criteria of Prodromal Syndrome (COPS) (McGlashan et al., 2001), which were used in the Structured Interview for Prodromal Symptoms and Scale of Prodromal Symptoms (SIPS/SOPS) (Miller et al., 1999). COPS-A referred to Brief intermittent psychotic syndrome; COPS-B: Attenuated positive symptom syndrome; and COPS-C: Genetic risk and deterioration syndrome.

3. Results

A total of 160 replies from psychiatrists in Tokyo Metropolitan City were received; the majority of respondents were practicing clinical psychiatry for 10–19 years. The questionnaire contained the following questions: (a) Which diagnosis would you make for these cases? (b) Using which approach should the people in each vignette be treated? (c) If you selected "pharmacotherapy" in question 2, which type of medication would you select? (d) If you selected "antipsychotic" in question 3, which type of antipsychotic would you select? and (e) Which dose would you prescribe as the initial dose for risperidone?

The majority of the diagnoses were 'schizophrenia' for the COPS-A, COPS-B and schizophrenia vignettes. For COPS-C, the respondents made a diagnosis of 'neurotic disorders' more frequently than a diagnosis of 'schizophrenia'. A few responders gave 'psychotic prodrome' or 'suspected schizophrenia' as their answer (Table 1).

Most responders answered 'pharmacotherapy' for all the vignettes. The frequencies of 'family psychoeducation' and 'observation' differed between the 'psychotic prodrome' and 'schizophrenia' responses. 'Family psychoeducation' was more frequently selected for 'schizophrenia' than for 'psychotic prodrome', while 'observation' was selected more frequently for 'psychotic prodrome' than for 'schizophrenia' (Table 2).

'Antipsychotic' was the most favored pharmacotherapy for all the vignettes, but the frequency of its use for COPS-C was lower than for the other groups. Anxiolytics and antidepressants were more favored in the COPS-C group than in the other groups (Table 3).

Risperidone was the most favored antipsychotic in all the vignettes, but it was less favored for the 'psychotic prodrome' responses than for the 'schizophrenia' responses. On the other hand, aripiprazole and perospirone were more favored for the 'psychotic prodrome' response. Perospirone is a serotonin-dopamine antagonist that is only prescribed in Japan; the potency of perospirone is lower than that of risperidone (Table 4).

A lower dose of risperidone was used for the 'psychotic prodrome' responses than for the 'schizophrenia' responses (Table 5).

Table 1
Diagnosis from case vignettes.

	COPS-A (%)	COPS-B (%)	COPS-C (%)	Full-blown schizophrenia (%)
Schizophrenia	97 (61)	110 (69)	51 (32)	147 (92)
Schizophrenia suspected	14 (9)	18 (11)	13 (8)	5 (3)
Prodrome	14 (9)	20 (13)	21 (13)	1 (1)
Mood disorders	1 (1)	15 (9)	4 (3)	2 (1)
Neurotic disorders	12 (8)	21 (13)	63 (39)	0 (0)
Others	33 (21)	27 (17)	40 (25)	8 (5)
Unknown	4 (3)	1 (1)	2 (1)	0 (0)
No reply	5 (3)	4 (3)	3 (2)	3 (2)

COPS-A: Criteria of Prodromal Syndrome-Brief intermittent psychotic syndrome; COPS-B: Criteria of Prodromal Syndrome-Attenuated positive symptom syndrome; COPS-C: Criteria of Prodromal Syndrome-Genetic risk and deterioration syndrome.

Table 2
Selected treatments for each vignette.

	COPS-A (%)	COPS-B (%)	COPS-C (%)	Full-blown schizophrenia (%)
Pharmacotherapy	124 (78)	151 (94)	125 (78)	158 (99)
Supportive psychotherapy	80 (50)	104 (65)	119 (74)	84 (53)
Family psychoeducation	32 (20)	30 (19)	19 (12)	62 (39)
CBT	5 (3)	10 (6)	17 (11)	7 (4)
Observation	57 (36)	40 (25)	65 (41)	14 (9)
Others	4 (3)	6 (4)	3 (2)	6 (4)
No reply	1 (1)	2 (1)	1 (1)	2 (1)
Not necessary	3 (2)	1 (1)	4 (3)	0 (0)

COPS-A: Criteria of Prodromal Syndrome-Brief intermittent psychotic syndrome; COPS-B: Criteria of Prodromal Syndrome-Attenuated positive symptom syndrome; COPS-C: Criteria of Prodromal Syndrome-Genetic risk and deterioration syndrome.

Table 3
Selected drugs as pharmacotherapy.

	COPS-A (%)	COPS-B (%)	COPS-C (%)	Full-blown schizophrenia (%)
Antipsychotics	118 (95)	123 (81)	66 (53)	156 (99)
Antidepressant	0 (0)	3 (2)	21 (17)	0 (0)
Mood stabilizer	1 (1)	4 (3)	0 (0)	0 (0)
Anxiolitics	2 (2)	11 (7)	33 (26)	0 (0)
Others	1 (1)	3 (2)	1 (1)	0 (0)

COPS-A: Criteria of Prodromal Syndrome-Brief intermittent psychotic syndrome; COPS-B: Criteria of Prodromal Syndrome-Attenuated positive symptom syndrome; COPS-C: Criteria of Prodromal Syndrome-Genetic risk and deterioration syndrome.

Table 4
First line drug in antipsychotics.

	COPS-A (%)	COPS-B (%)	COPS-C (%)	Full-blown schizophrenia (%)
Risperidone	62 (52)	63 (48)	24 (35)	104 (66)
Olanzapine	10 (8)	20 (15)	5 (7)	19 (12)
Aripiprazole	21 (18)	14 (11)	10 (15)	11 (7)
Perospirone	11 (9)	8 (6)	8 (12)	1 (1)
Quetiapine	2 (2)	6 (5)	4 (6)	3 (2)
Sulpiride	0 (0)	6 (5)	8 (12)	0 (0)
Others	3 (3)	4 (3)	3 (4)	7 (4)
Polypharmacy	11 (9)	9 (7)	6 (9)	13 (8)

COPS-A: Criteria of Prodromal Syndrome-Brief intermittent psychotic syndrome; COPS-B: Criteria of Prodromal Syndrome-Attenuated positive symptom syndrome; COPS-C: Criteria of Prodromal Syndrome-Genetic risk and deterioration syndrome.

Table 5
First dosage of risperidone.

	COPS-A (%)	COPS-B (%)	COPS-C (%)	Full-blown schizophrenia (%)
<1 mg	15 (24)	6 (10)	9 (38)	4 (4)
1–2 mg	28 (45)	35 (56)	9 (38)	30 (29)
2–3 mg	16 (26)	20 (32)	5 (21)	40 (38)
3–4 mg	1 (2)	2 (3)	1 (4)	22 (21)
4 mg≦	2 (3)	0 (0)	0 (0)	8 (8)

COPS-A: Criteria of Prodromal Syndrome-Brief intermittent psychotic syndrome; COPS-B: Criteria of Prodromal Syndrome-Attenuated positive symptom syndrome; COPS-C: Criteria of Prodromal Syndrome-Genetic risk and deterioration syndrome.

Many of the psychiatrists who diagnosed the vignettes as 'suspected schizophrenia' or 'psychotic prodrome' selected 'pharmacotherapy' as their approach and 'antipsychotic' as the medication.

4. Discussion

The present results suggest that pharmacotherapy might be overused in prodromal cases, since the psychiatrists tended to prescribe neuroleptics for positive symptoms before the diagnostic criteria for schizophrenia had been fulfilled. Thus, the criteria for full-blown psychosis needs to be reexamined, the risk of transition from an at-risk mental state (ARMS) to psychosis needs to be assessed, and guidelines for pharmacological intervention for the treatment of prodromal symptoms need to be established in Japan.

Our results suggested that prodromal individuals who have experienced only brief intermittent or attenuated positive symptoms might potentially be overdiagnosed as having 'schizophrenia'. In other words, the concept of an ARMS/prodromal state has not yet been widely recognized among Japanese psychiatrists. On the other hand, it is possible that Japanese psychiatrists might be simultaneously prescribing the medication for each individual in the prodromal phase or with full-threshold schizophrenia. Even where the psychiatrists had diagnosed the patients as being prodromal, antipsychotics were being prescribed for these patients.

4.1. Japanese Society for Prevention and Early Intervention in Psychiatry (JSEIP) (http://www.jseip.jp)

The JSEIP is an organization for people involved in the study and treatment of psychiatric disorders in Japan. It provides a forum for members to promote practice and research into the prevention of psychiatric disorders based on medical ethics, to arrange conferences and professional meetings regarding the prevention of psychiatric disorders, to facilitate research (including multicenter trials), and to enhance other efforts to achieve its goals. The JSEIP was inaugurated in March 1996 in Okinawa, just after the first symposium on the primary prevention of schizophrenia was held at the 16th meeting of the Japanese Society of Social Psychiatry. In 2007, the 10th annual academic conference was held in Yokohama; this conference emphasized multicenter research on early psychosis in Japan. The JSEIP had more than 300 members in 2010.

The 15th annual meeting was held in December 3–4, 2011, in Tokyo. Drs. David Shiers, Louis Arsenault, Jo Smith, and Paul French have been invited as guest lecturers. Not only topics on early intervention for psychosis, but also general topics on prevention and mental health promotion were covered.

4.2. Il Bosco (http://www.lab.toho-u.ac.jp/med/omori/mentalhealth/)

A representative early intervention facility for young people is the "Il Bosco", where the authors of the present report and their colleagues work. This facility was founded in May 2007 at the Toho University Omori Medical Center in Tokyo. The DUP of the hospital catchment area is longer (mean: 30 months) than for other areas of Tokyo. The unit is run according to an optimal treatment project (OTP) (Falloon et al., 2004) that employs a multi-disciplinary team and utilizes the cognitive remediation-oriented method advocated by Falloon et al. (2004). The service model includes early detection and intervention, repeated assessment, and psychoeducation. Treatment strategies consist of optimal pharmacotherapy based on atypical neuroleptics, cognitive function training, cognitive behavioral therapy, and job coaching as part of the final treatment program. The cognitive function training is aimed at stimulating divergent thinking, mainly using computers. The cognitive training program mainly targets divergent thinking deficits, since interventions for divergent thinking have been previously found to improve negative symptoms and social functioning significantly in patients with schizophrenia (Nemoto et al., 2009). Cognitive intervention to improve divergent thinking deficits during the early stage of psychosis may maximize the chance for functional recovery, and such interventions may minimize the risk of future progression in a subset of people with ARMS, since divergent thinking is critical for generating solutions to various social problems and for navigating the complexities of social interactions.

The clients are restricted to ARMS patients or first-episode schizophrenia patients between the ages of 15 and 30 years. Four years have passed since the opening of "Il Bosco", and so far 112 patients (62 women and 50 men with a mean age of 20.4 ± 3.5 years) have been registered. About 80% of the patients have improved through participation in a rehabilitation program that focuses on social cognition, and this has enabled them to return to their former workplace or school. The attendance rate is better than for standard day care, which has no age limit. We are currently developing some new programs for cognitive rehabilitation and remediation as well as a psychoeducation web site for individuals with early psychosis.

4.3. Other leading centers for early intervention in Japan

Other than the above, there are several leading centers for early intervention research and practice in Japan. Most of them are driven by university departments of psychiatry with respect to both research and clinical activities. The common aims of these services are as follows: (i) to provide young people suspected of being at risk for psychosis with opportunities for assessment by specialists and the chance to receive specific intervention; (ii) to reduce the delay in accessing evidence-based treatment for persons who have already developed psychosis, especially a first episode of schizophrenia; and (iii) to develop innovative and optimized approaches for diagnosing and treating people at risk of psychosis.

4.4. Research and education for specialists

Research from Japan has also focused on both the biological and psychosocial aspects of early psychosis. Various studies have demonstrated the anatomical basis of the schizophrenia spectrum in the brain by multivariate voxel-based morphometry (Kawasaki et al., 2007), the effect of DUP on brain morphology in ultra high-risk subjects (Takahashi et al., 2007, 2008a,b) as well as the applicability of structural brain imaging to the objective diagnosis of schizophrenia (Suzuki et al., 2005; Takahashi et al., 2009a,b, 2010a,b). The influence of DUP on brain function has also been investigated (Yamazawa, 2004; Mizuno et al., 2009; Nishii et al., 2010). The development of screening methods for ARMS (Kobayashi et al., 2008), the assessment of ARMS (Miyakoshi, 2009a,b), and psychopathological studies on psychosis-like experiences have been reported (Nishida et al., 2010; Oshima et al., 2010; Kinoshita et al., 2011; Kobayashi et al., 2011), contributing to early intervention and support for adolescents in Japan. Both comprehensive and pharmacological approaches (Kobayashi et al., 2009) to treatment have been investigated. Moreover, several important English monographs about early intervention in psychiatry have been translated into Japanese by leading researchers in this field (French and Morrison, 2004; Jackson and McGorry, 2009; McGlashan et al., 2010; McGorry and Jackson, 1999).

5. Conclusion

The development of services for early intervention is expected to provide a breakthrough in the treatment of psychosis in Japan,

including a reduction in stigmatization, the prevention of suicide among young persons, and the promotion of general knowledge about mental health. It seems that there are several issues pertinent to early intervention for psychosis Asian countries – for example the format of service systems, community attitudes to psychiatric illness (including stigma), and the dependence on pharmacotherapy. An integrated approach including pharmacotherapy and psychosocial approaches might be appropriate for early intervention for psychosis in the community.

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Conflict of interest

None.

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Clinical Practice at a Multi-dimensional Treatment Centre for Individuals with Early Psychosis in Japan

日本一所为早期思觉失调患者而设的多维治疗中心的临床实践

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Abstract

Early intervention for psychosis in Japan has lagged behind that in western countries, but has rapidly begun to attract attention in recent years. As part of a worldwide trend, a multi-dimensional treatment centre for early psychosis consisting of a Youth Clinic, which specialises in young individuals with an at-risk mental state for psychosis, and Il Bosco, a special day-care service for individuals with early psychosis, was initiated at the Toho University Omori Medical Center in Japan in 2007. The treatment centre aims to provide early intervention to prevent the development of full-blown psychosis in patients with an at-risk mental state and intensive rehabilitation to enable first-episode schizophrenia patients to return to the community. We presently provide the same programmes for both groups at Il Bosco. However, different approaches may need to be considered for patients with an at-risk mental state and for those with first-episode schizophrenia. More phase-specific and need-specific services will be indispensable for early psychiatric interventions in the future.

Key words: *Cognitive therapy; Early intervention (education); Japan; Schizophrenia*

摘要

虽然日本的思觉失调早期干预服务落后于西方国家，但近年开始备受注意。思觉失调早期干预已成全球趋势，有见及此，日本东邦大学大森病院于2007年成立针对思觉失调的多维治疗中心，包括为思觉失调潜伏期年青人提供服务的「青年诊所」，和以早期思觉失调患者为对象的日间精神复康中心「Il Bosco」，旨在为潜伏期患者提供早期干预以抑制典型思觉失调病发，以及为首发精神分裂症患者提供密集式复康服务，使他们能尽快重投社会。虽然Il Bosco正实施上述两种治疗计划，不过也须考虑这两类患者的需要而采用合适的治疗方案。阶段性和患者为本服务是思觉失调早期干预计划发展必不可少的部份。

关键词：*认知治疗、早期干预（教育）、日本、精神分裂症*

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Early Psychiatric Intervention in Japan

Early intervention for psychosis in Japan has lagged behind that in western countries because of the continued existence of hospital-based psychiatry which requires large numbers of psychiatric beds and long-term hospital stays,[1] as well as barriers resulting in delayed patient contact with psychiatric services. However, early intervention has rapidly begun to attract attention in recent years.[2] Despite the difficult

circumstances, reports indicated that earlier detection may enable better outcomes in addition to shortening the duration of untreated psychosis (DUP) in Japan.[3,4] The energetic activities of the Japanese Society for Prevention and Early Intervention in Psychiatry (Website: http://www.jseip.jp) have also promoted early psychiatric interventions. The latest multicentre retrospective study in Japan revealed that the mean and median DUP were 20.3 and 6.0 months, respectively.[5]

When thinking about the dissemination of early intervention for mental disorders in Japan, we must consider the culture and attitudes towards mental disorders among the Japanese people. In the light of our own clinical experience, individuals with mental health problems and their families are often reluctant to seek help for various reasons, including ignorance about the features and treatability of mental disorders, beliefs that the problem should be solved by themselves, confining the problem to close relations without consulting professionals, and stigma connected with psychiatry, although Japanese people generally accept the need for medical treatment for physical problems. These obstacles may explain the long DUP and the social stigma towards mental disorders in Japan. However, the nuclearisation of families may also be affecting this delay in seeking treatment. Nishii et al[5] reported that patients living alone in Japan had significantly longer DUP than those living with their families. These considerations should be further investigated.

Some treatment services specialising in the early stage of psychosis have recently been established in Japan, including the Tokyo Youth Club administered by the Minato Net 21 (a non-profit organisation in Tokyo), Tohoku University Hospital (Sendai at-risk mental state [ARMS] and first episode service), the University of Toyama Hospital (consultation and support service in Toyama), the University of Tokyo Hospital, Osaka University Hospital, Kochi Medical School Hospital, and the Tokyo Metropolitan Matsuzawa Hospital (Wakaba). The background and present situation of early psychiatric intervention in Japan have been detailed elsewhere.[6,7]

Practices at the Toho University Omori Medical Center

The Toho University Omori Medical Center is located in Ota, a city with a population of about 700,000 located in the southern area of the Tokyo Metropolitan region. Our department is named the 'Mental Health Center' to avoid the stigma of psychiatry and mental disorders. About 150 outpatients visit the department each day. Having 2 psychiatric wards — a closed ward with 18 beds and an open ward with 18 beds, the Center serves psychiatric patients with physical problems as well as regular psychiatric patients. Therefore, our department shoulders the responsibility of being a core institution for mental health care in the area. The strengths of our department are early intervention for young people and cognitive rehabilitation, which are practised at the Youth Clinic and at Il Bosco, a special day-care service. We aim at establishing a multi-dimensional treatment centre for early psychosis that encompasses symptom reduction, cognitive function, social functioning, quality of life, psycho-education, and family intervention.[8]

Youth Clinic

As part of the worldwide trend toward early psychiatric intervention, a Youth Clinic specialising in the treatment of young individuals with an ARMS was established in our department in 2007. The PRIME Screen-Revised test (PS-R)[9] is administered to all first-time patients younger than 40 years to screen for ARMS as part of the routine preliminary examinations. The PS-R is a self-reported screening test that consists of 11 items regarding attenuated psychotic symptoms and only requires 5 minutes to complete. Patients with positive PS-R results or who are suspected of having ARMS after an examination are introduced to the Youth Clinic, where they are interviewed for diagnostic purposes using the Structured Interview for Prodromal Syndromes / Scale of Prodromal Symptoms, Japanese version.[10] They are also supposed to undergo neuroimaging and cognitive testing for detailed examination. When a patient is found to meet the criteria for ARMS, treatment such as stress management, coping strategies for psychotic symptoms, and problem-solving skills is started. Medication with low-dose antidepressant, minor tranquilizer, or major tranquilizer might also be considered.

Il Bosco

Day-care Service for Patients with Early Psychosis

To develop early intervention in Japan and put it into practice, the conventional day-care service intended mainly for patients with chronic schizophrenia was terminated. In May 2007, a new day-care service, which specialises in the care and support of individuals with ARMS or first-episode psychosis aged 30 years or younger, was established. The service unit, named Il Bosco, aims at providing early intervention to prevent the development of full-blown psychosis in ARMS patients, as well as intensive rehabilitation to enable first-episode schizophrenia patients to return to the community.[7] The staff members consist of a variety of professionals, including psychiatrists, nurses, occupational therapists, clinical psychologists, social workers, and pharmacologists. The registration period is limited to 1 year for concentrated care in principle, and can be extended up to 2 years depending on the patient's condition. Adequate medication is offered at the Youth Clinic, and intensive psychosocial treatment is provided at Il Bosco. The contents of the daily programmes are specifically considered with the intention of promoting the brain plasticity of young patients and providing an environment and atmosphere where patients can feel relieved without stigma.

Approaches and Programmes

A comprehensive support system suitable for targeted generations is indispensable to the success of psychiatric rehabilitation, and multiple and integrated approaches are administered based on the Optimal Treatment Project[11] at Il Bosco, in collaboration with the Youth Clinic (Fig). We offer programmes for learning and training in interpersonal relationships using worksheet and role-playing activities, practices for daily living skills such as cooking, study time for patients to keep up with their friends at school, patient-managed meetings to promote responsibilities and roles within a group, family intervention and psycho-education, as well as group therapy. We sometimes address the stigma of mental illness in the education programme.

The creation of patient goals and plans to accomplish these goals carefully and quickly is vital during the introduction period, because delays can lead to a widening distance from the community and seem to create an inferiority complex or despair, especially among adolescents. Goals can also foster hope regarding an individual's prognosis and can motivate them to join programmes. Speed is requested in every situation at Il Bosco. Young patients need to start to make a return to the community early, because they usually wish to keep their previous role in the community. Therefore, the contents of each programme must be subdivided, and frequent interviews are necessary to respond to their needs individually. We sometimes offer special programmes to only a few patients who require such programmes. Our aim is for patients to be stable not only in the day-care service unit, but also in the community.

Supporting and paying attention to patients who are building interpersonal relationships within the service is also important because young patients often quickly approach other patients in the same generation using cell phones and emails; such relationships can fail because of poor and immature interpersonal relationship skills, although some patients are obstinately hesitant to communicate with others. Efforts to handle this problem may also contribute to the low dropout rate (11.9%) at Il Bosco.

Many patients (60.0%) have achieved their goals within 1 year since the establishment of Il Bosco; such goals include returning to school, transferring to a correspondence course school, starting to go to preparatory school, and beginning an occupation. Although many patients visit to ask for a consultation or to report on their present condition even after they have completed their course, some patients may be caught in a dilemma and may wish to forget their days at the centre. We are presently considering how to continue supporting these patients after they completed the Il Bosco programme.

Cognitive Rehabilitation

At Il Bosco, cognitive remediation, which directly targets brain function in addition to a psychosocial approach, is adopted. Both of these approaches are regarded as wheels in the promotion of early psychiatric intervention. Institutions that adopt such an approach to individuals with early psychosis are still uncommon throughout the world. Cognitive remediation has been in the spotlight as a novel approach to promoting remission and recovery

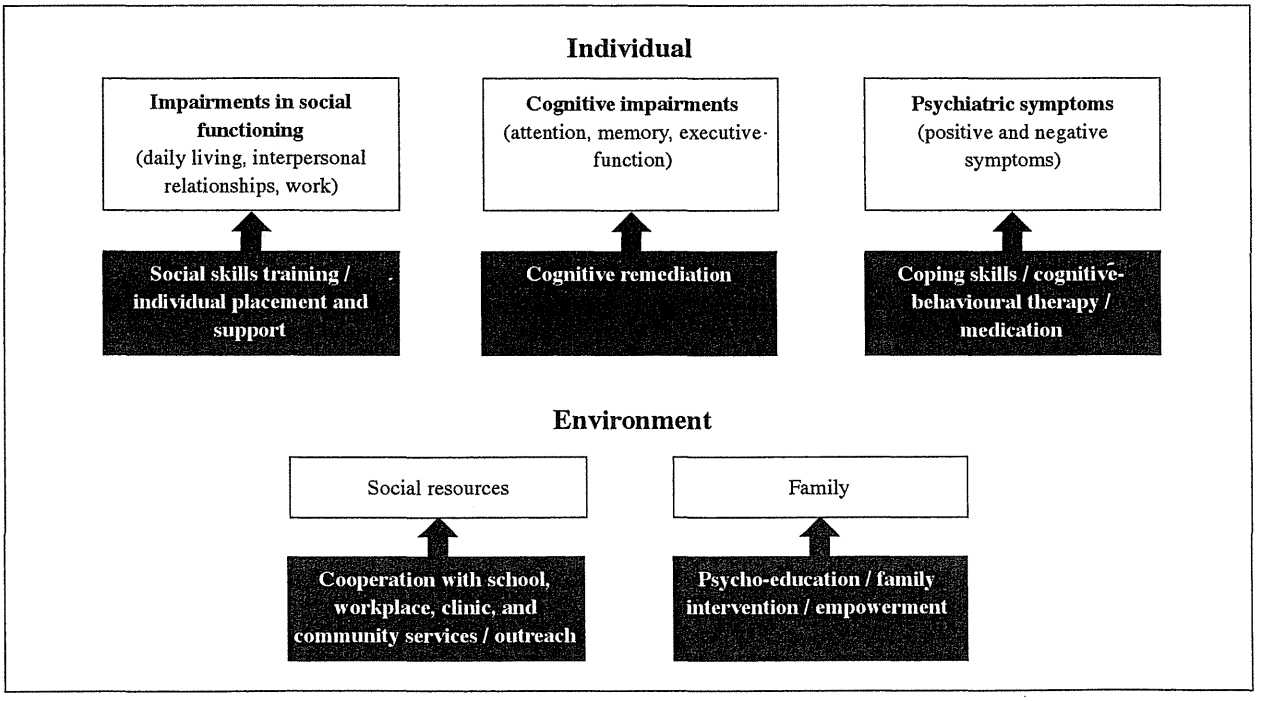

Figure. Multi-dimensional treatments provided at the Toho University Omori Medical Center.

under existing conditions in which medication is not effective for alleviating impairments in social functioning in schizophrenic patients,[12] although more empirical research is necessary to confirm the efficacy of cognitive remediation in the early course of schizophrenia.[13] Our cognitive remediation programme mainly targets divergent thinking deficits, because it is found that cognitive training for divergent thinking leads to significant improvements in negative symptoms and social functioning of patients.[14] Also, broad cognitive rehabilitation programmes are carried out and a suitable approach for young patients, such as outdoor cognitive remediation and combining cognitive remediation with physical exercise, is devised.[15]

Collaboration with Community Resources

We are actively engaged in activities to enlighten the community and to disseminate information on the prevention of mental disorders and to reduce the stigma associated with mental disorders. We distribute booklets and leaflets on early psychosis described in an easy and open-minded style to people in the field of education as well as to patients and their families, since collaborating with them is important for achieving early intervention. We also have many opportunities to collaborate with nursing teachers. Young people tend to stay away from medical services because of uneasiness. Therefore, a self-check sheet is offered to allow individuals to contemplate their mental condition. In addition to providing a means of introducing individuals who need help to appropriate psychiatric services, accurate psychiatric information is also available on the Il Bosco website (http://www.lab.toho-u.ac.jp/med/omori/mentalhealth/). Importantly, we focus not only on psychiatric symptoms, but also on patients' difficulties in daily living when starting the interventions.

Future Prospects

At present, we provide the same programmes both for individuals with first-episode schizophrenia and for those with ARMS at Il Bosco. However, ARMS patients usually maintain better cognition and social functioning than those with first-episode psychosis, and most of them are younger and are students in high school or college. Different approaches may be needed for patients with ARMS and for those with first-episode schizophrenia. More phase-specific and need-specific services will be indispensable for early psychiatric intervention in the future.

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Early Psychosis Declaration for Asia by the Asian Network of Early Psychosis

亚洲早期思觉失调网络发表的《亚洲早期思觉失调声明》

Asian Network of Early Psychosis*

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Abstract

In line with the Early Psychosis Declaration issued by the World Health Organization and the International Early Psychosis Association, as well as the International Clinical Practice Guidelines for early psychosis by the latter in 2005, increasing interest in early intervention programmes is evident throughout Asia. Experience sharing and close collaboration that take into account the unique Asian context are needed to facilitate development of early psychosis services, education, and research in the region. The Asian Network of Early Psychosis has defined a set of Asian-specific principles to guide best practice in mental health care delivery for psychotic disorders in Asia. These principles are outlined in this paper.

Key words: *Asia; Culture; Early intervention; Psychotic disorders*

摘要

随着2005年世界卫生组织和国际早期思觉失调协会颁布的《早期思觉失调声明》，以及后者颁布的《国际早期思觉失调临床方针》，思觉失调早期干预在亚洲越受关注。为了促进符合亚洲人口的早期思觉失调服务的发展、教育和研究，各地的经验交流和紧密合作是必要的。亚洲早期思觉失调网络（Asian Network of Early Psychosis）近期制定一套针对亚洲人口的思觉失调护理准则，为这地区精神病人口的精神健康护理提供最佳指引。本文将概述这些准则。

关键词：*亚洲、文化、早期干预、思觉失调*

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Introduction

Since the introduction of the concept of 'early intervention for psychotic disorders' in the 1990s, many early intervention programmes for psychosis have taken root in western countries. In Asia, the early intervention programmes were first introduced in Hong Kong and Singapore in 2001. Since then, several other similar programmes have been set up across Asia. Increasing interest in early intervention programmes is now evident in the region, and experience sharing and close collaboration are called for to facilitate development of early intervention for psychosis services, education, and research in Asia.

The Asian Network of Early Psychosis (ANEP) is an informal network of clinicians and researchers working in early intervention for psychosis in Asia. Addressing the specific culture and values in the Asian setting, the ANEP provides a platform to facilitate development of early intervention services in Asia through close exchanges and experience sharing across member sites. The ANEP also aims to promote research in the course, outcomes, and early intervention service delivery of first-episode psychosis in Asia, and encourage use of standardised instruments and assessment procedures for more comparable results. To date, the ANEP has contributors from cities in China, India, Indonesia, Japan, Korea, Malaysia, Singapore, and Taiwan. Through regional meetings and symposia, collaborative research, links with other regional and international networks, as well as an online discussion forum (https://sites.google.com/site/asianearlypsychosis), the ANEP encourages groups and researchers in the region to work together for the better care of psychosis in Asia.

In line with the Early Psychosis Declaration issued by the World Health Organization[1] and the International Early Psychosis Association, as well as the International Clinical Practice Guidelines for early psychosis by the latter institution,[2] and taking into consideration the unique Asian context, we have defined a set of common principles with input from regional consultants of the ANEP to guide best practice in mental health care delivery in the field of psychotic disorders in the region. The principles outlined below were first discussed at the International Conference on Early Psychosis in Asia Pacific 2012, held in Hong Kong