（倫理面への配慮）

調査実施にあたってはヘルシンキ宣言を遵守し、「臨床研究倫理指針（平成16年厚生労働省告示第459号）」「疫学研究に関する倫理指針（平成19年文部科学省・厚生労働省告示第1号）」に従った。担当医師は研究の概要、参加者に与えられる利益と不利益、随時撤回性、個人情報保護、費用について文書により対象者に説明し、検査データを研究に用いることについて自由意思による同意を文書で取得した。対象者が未成年の場合、本人および保護者の同意を得た。なお本研究は、金沢医科大学の臨床・疫学研究等に関する倫理委員会の承認を受けている。

C．研究結果

平成25年4月から平成26年3月までの「こころのリスク外来」の利用者は8例であった。うちARMSの判定基準を満たした者が3例、FESの統合失調症患者はなく、それ以外が5例であった。「こころの健康検査入院」の利用者は18名であった。また流暢性検査施行中の光トポグラフィ検査により、統合失調症患者の認知機能を評価した予備的検討を所属の大学院生（新田佑輔）が金医大誌に発表した。

E．結論

石川県におけるFES患者とARMS患者を対象にした臨床サービスを一般市民に周知させるために、メディア等の利用を試みたところ、一定の成果が得られ、今後も継続した広報活動が必要である。また、これらの対象者と頻繁に接触する機会を持つスクールカウンセラーや養護教諭など、学校関係者との連携・交流が対象者の発見に有用であった。

F．健康危険情報

総括研究報告書に記載

G．研究発表

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H．知的財産権の出願・登録状況
1. 特許取得
　なし
2. 実用新案登録
　なし
3.その他
　なし

研究協力者
　橋本 玲子（金沢医科大学医学部精神神経科学）
　小野 早知子（金沢医科大学病院医療技術部）
　嶋田 貴充（金沢医科大学医学部精神神経科学）
　木原 弘晶（金沢医科大学医学部精神神経科学）

Ⅲ.　研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

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古橋功一、岩田仲生	Ⅲ. 統合失調症の臨床　統合失調症の薬物療法「各病期における治療目標と薬物療法」	日本臨牀	第71巻・第4号	635-640	2013
新田佑輔	統合失調症患者における Design fluency test による前頭葉の賦活：NIRS 研究.	金医大誌	38	1-8	2013

Ⅳ.　研究成果の刊行物・別刷

Early Intervention IN PSYCHIATRY
First Impact Factor released in June 2010 and now listed in MEDLINE!
International Early Psychosis Association

Early Intervention in Psychiatry 2013; ••: ••–••
doi:10.1111/eip.12032

Original Article

Poor outcome associated with symptomatic deterioration among help-seeking individuals at risk for psychosis: a naturalistic follow-up study

Keiko Morita,[1] Hiroyuki Kobayashi,[2] Kiyoaki Takeshi,[1] Naohisa Tsujino,[1] Takahiro Nemoto[1] and Masafumi Mizuno[1]

Abstract

Aims: It remains debatable whether early intervention for psychosis is capable of meeting the needs of at-risk subjects. The aims of this study were to describe the actual impact of interventions on subjective difficulties and to explore the factors that may be associated with a poor outcome.

Methods: Participants were help-seeking outpatients at a university hospital who met the Criteria of Prodromal Syndromes. Changes in the symptoms, subjective experience and current insight were assessed using the Scales of Prodromal Symptoms, the Subjective Well-being under Neuroleptics, and the Scale to Assess Unawareness of Mental Disorder, respectively. Global functioning, social functioning and subjective quality of life were evaluated using the Global Assessment of Functioning Scale, the Social Functioning Scale, and the WHO-Quality of Life 26, respectively. These measures were assessed both at baseline and after 1 year.

Results: Forty-six patients agreed to participate. Of the 27 patients who completed the reassessment at the follow-up point, 13 patients (48%) showed little improvement in their positive/negative symptoms, subjective well-being or awareness of their symptoms. Additionally, less severe negative symptoms, more severe general symptoms and lower subjective well-being at baseline significantly predicted a deterioration of positive/negative symptoms after 1 year.

Conclusion: Our findings suggest that the current strategy for reducing psychosis risk based on positive symptoms should be reappraised.

Key words: at-risk mental states, early intervention, prodrome, psychosis, quality of life.

[1]Department of Neuropsychiatry, School of Medicine, Toho University, Tokyo, Japan; and [2]Department of Psychiatry, University of Cambridge, Cambridge, UK

Corresponding author: Dr. Hiroyuki Kobayashi, Department of Psychiatry, University of Cambridge, Box 189, Level 4, Addenbrooke's Hospital Hills Road, Cambridge CB2 2QQ, UK. Email: hiro.yuki.kob@gmail.com

Received 15 May 2012; accepted 30 September 2012

INTRODUCTION

In the last 15 years, a number of studies have supported the view that the earlier detection and care of psychosis can lead to a better outcome.[1,2] However, most of these studies were conducted in research settings; thus, the actual *effectiveness* of early intervention for psychosis remains unclear.[3] One of the issues that such studies have raised is that the diagnostic criteria or primary outcomes focus mainly on the attenuated positive psychotic symptoms.

Attenuated psychotic symptoms or psychotic-like experiences have been commonly found in the general population, and these symptoms or experiences may not necessarily be associated with distress or help-seeking behaviour.[4–6] In a previous study comparing help-seeking patients with the general population, the authors reported that psychosis-like experiences do not significantly contribute to help-seeking behaviour.[7] Attenuated positive symptoms may not always confer subjective difficulties or sufferings; therefore, the current interventions to reduce risk which are focused on the attenuated positive symptoms may not be truly capable of meeting the needs of individuals meeting at-risk criteria.

To date, longitudinal studies on the outcomes of individuals at risk for psychosis have underlined the considerably high rates of remission[8] and the low rates of transition to psychosis.[9,10] Given that the criteria for remission and transition are based on the attenuated psychotic symptoms, however, it would be doubtful whether or not these outcomes reflect the actual changes in subjective difficulties of individuals at risk for psychosis. Indeed, a large longitudinal study, the North American Prodrome Longitudinal Study (NAPLS), revealed that most individuals who met the at-risk criteria but did not convert to psychosis continued to suffer from lower levels of functioning or disabilities.[11] Additionally, an approach focused predominantly on the low rate of transition to psychotic disorder can obscure individual treatment effects. Subgroups of participants may respond to individual treatments particularly well or particularly poorly as a result of the participants' characteristics or baseline symptom patterns. A recent report on a randomized controlled trial examining the effect of various therapies on young people with a high risk for psychosis concluded that the interventions were equally effective or ineffective.[12] Thus, the *effectiveness* of interventions for early psychosis should be clarified in clinical settings, regardless of the transition to full-blown psychosis.

We hypothesized that the current strategy, which is focused on the attenuated positive symptoms, cannot sufficiently ameliorate the subjective difficulties of individuals at risk for psychosis, such as their subjective quality of life (QOL), role/social functioning, interpersonal relationships and subjective well-being. We also assumed that some patients would continue to receive treatment because their symptoms had not been relieved.

The aims of this study were: (i) to describe the actual 1-year outcome of individuals with a high risk of psychosis based on comprehensive assessments including subjective QOL, role/social functioning, interpersonal relationships, insight into illness and subjective well-being; and (ii) to clarify the characteristics of patients who continue to receive treatment for over 1 year so as to explore the factors that may lead to a poor outcome, even without a transition to psychosis.

METHODS

Participants

This study was performed at a university hospital (Toho University) located in a suburb of Tokyo. The participants were eligible for enrolment in the study if they were between the ages of 16 and 40 years and met the Criteria of Prodromal Syndromes (COPS).[13] Patients were excluded from the study if they had: (i) any lifetime DSM IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) diagnosis of any psychotic disorder; (ii) symptoms fully accounted for by an Axis 1 disorder or sequelae arising from drug/alcohol use; or (iii) abuse of alcohol or drugs. All the participants were help-seeking outpatients. Each adult participant provided his or her written informed consent and each minor provided written informed assent in addition to consent from a parent or guardian. Data were collected between June 2007 and October 2009.

Measures

The Structured Interview for Prodromal Syndromes (SIPS)[13] was performed for patients identified as having an 'at-risk mental state', including the Scale of Prodromal Symptoms (SOPS). The SOPS items consist of four symptoms: positive symptoms, negative symptoms, disorganized symptoms, and general symptoms, although the COPS focuses upon merely positive symptoms. We used the SIPS/SOPS Japanese version, which we previously reported to have an excellent interrater reliability.[14] The developers of this SIPS/SOPS Japanese version (H. Kobayashi and M. Mizuno) trained the staff to score these tests with accuracy, and the interviews (including the SIPS and the other assessments) were conducted by experienced psychiatrists (K. Morita, K. Takeshi and N. Tsujino).

Changes in subjective experience were assessed using the Subjective Well-being under Neuroleptics Short version (SWNS).[15] The SWNS is a 20-item test that uses a 6-point Likert-type self-rating scale. Naber *et al.* found a five-factor solution for the scale, which was interpreted as emotional regulation, self-control, mental functioning, social integration and physical functioning. We used the SWNS Japanese version, which has been shown to have a good reliability and validity.[16]

Current insight was measured using the Scale to Assess Unawareness of Mental Disorder (SUMD).[17] The SUMD rates awareness of 20 items was based on a 5-point Likert scale. To assess current insight, we used the 3 global insight items (awareness of mental disorder, awareness of achieved medication effects, and awareness of social consequences of medications) and the 17 subscales (awareness of symptoms).

Global functioning, social functioning and subjective QOL were evaluated using the Global Assessment of Functioning Scale, the Social Functioning Scale, and the WHO-Quality of Life 26, respectively.

These measures were assessed both at baseline and after 1 year. The Institutional Review Board at Toho University approved the study protocol and the procedure for obtaining informed consent.

Interventions

During the follow-up period, all the patients received usual supportive therapy and/or psychotropic medication, with the main aim of reducing the severity of psychotic symptoms. Psychotropic medication included the use of antipsychotics for positive symptoms, anxiolytics for anxiety symptoms, and antidepressants for comorbid depressive symptoms, if necessary. The administration of antipsychotics was generally judged according to the International Clinical Practice Guidelines for Early Psychosis.[18] The nature of the psychological intervention was left to the discretion of the psychiatrist in charge; cognitive therapy, psychoeducation, or family therapy, if used, were thus provided in diverse forms.

Clinical outcome

To determine the factors that may lead to a poor outcome, even without a transition to psychosis, the sample was subsequently split into two groups according to the degree to which either positive or negative symptoms had developed. At the follow-up point, patients with improvements from the baseline in both the SOPS positive and negative symptom scores without transitioning to psychosis were defined as 'improved', and patients with no improvements from the baseline in the SOPS positive or negative symptoms or who fulfilled the criteria for psychosis were defined as 'not improved'. The transition to psychosis was operationally defined using the Presence of Psychotic Symptoms criteria.[13]

Statistical analyses

All the statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) version 18.0 for Windows (SPSS Inc., Chicago, IL, USA). The baseline variables were compared between the patients who were lost because of attrition and the patients who were followed up after 1 year with the help of Mann–Whitney *U*-tests for continuous variables and with chi-square tests for categorical variables. Also, clinical variables at baseline were compared between the 'improved' group and the 'not improved' group using the Mann–Whitney *U*-tests for continuous variables and the chi-square tests for categorical variables. In addition, we compared clinical outcomes between the 'improved' group and the 'not improved' group using the analysis of variance, adjusting for age, duration of illness and baseline scores. To explore variables that can predict poor outcomes, multiple linear regression analysis was conducted. For each comparison, a value of $P < 0.05$ was considered statistically significant without any consideration for multiple comparisons.

RESULTS

At baseline, 46 treatment-seeking patients who had been clinically diagnosed as having clinical high risk of psychosis agreed to participate in the study and to be assessed. The demographic characteristics of the sample at baseline are presented in Table 1.

At the 1-year follow-up point, 27 participants (59%) completed the reassessment. Table 2 shows the sample characteristics of these 27 patients and the patients who withdrew from the study, indicating that the withdrawn patients were younger and had a shorter duration of illness, less negative/general symptoms and a higher QOL.

During the follow-up period, three patients, or 12% of the followed sample, converted to psychosis: two were diagnosed as having schizophrenia and one was diagnosed as having a schizoaffective disorder. According to the criteria mentioned above, 14 patients were defined as 'improved' (in both the SOPS positive and negative symptoms), but 13 patients, including the 3 psychotic cases, were defined as 'not improved' (in either the SOPS positive or negative symptoms). Detailed comparisons of these two groups are shown in Table 3, suggesting that although few differences in the clinical variables were found between the two groups at baseline, all the patients in the 'not improved' group had past treatment histories and had fewer family members with mental health illness.

Table 4 shows that 'not improved 'group demonstrated a decline of the SWNS total score and the SUMD sub-score (awareness of symptoms) over time, even after adjusting for age, duration of illness and baseline scores. Twenty-one (78% of the followed) patients had received antipsychotic medication at the follow-up point (aripiprazole: $n = 13$; quetiapine: $n = 5$; perospirone: $n = 2$; risperidone: $n = 1$), whereas only six patients (22%) were administered antipsychotic treatment at baseline (quetiapine: $n = 2$; risperidone: $n = 2$; aripiprazole: $n = 1$; perospirone: $n = 1$) (Table 3).

Multiple linear regression analysis was used to explore variables at baseline that can predict poorer

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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Original Article
http://dx.doi.org/10.9758/cpn.2013.11.3.132
Clinical Psychopharmacology and Neuroscience 2013;11(3):132-136
pISSN 1738-1088 / eISSN 2093-4327

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

Naohisa Tsujino[1], Takahiro Nemoto[1], Keiko Morita[1], Naoyuki Katagiri[1], Shinya Ito[2], Masafumi Mizuno[1]
Departments of [1]Neuropsychiatry and [2]Social Medicine, Toho University School of Medicine, Tokyo, Japan

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

Received: January 23, 2013 / **Revised:** May 11, 2013
Accepted: May 13, 2013
Address for correspondence: Naohisa Tsujino, MD, PhD
Department of Psychiatry, Toho University School of Medicine,
6-11-1, Omori-Nishi, Ota-ku, Tokyo 143-8541, Japan
Tel: +81-3-3762-4151, Fax: +81-3-5471-5774
E-mail: ntsujino@med.toho-u.ac.jp

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]