Impact of duration of untreated psychosis on remission in first-episode schizophrenia in Thailand: a cohort study

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Received: 11/06/2020 – **Accepted:** 22/08/2020

DOI: 10.15761/0101-60830000000296

ABSTRACT

Background: To scale up the services for first-episode schizophrenia in Thailand, it is essential to understand to what extent health care-seeking is delayed, and how much the delay affects the treatment outcome.
Objectives: To investigate the duration of untreated psychosis (DUP) and its impact on remission in first-episode schizophrenia across the country.
Methods: 276 outpatients with a first-episode schizophrenia were followed for 6 months and assessed whether they fulfilled the criteria for remission at the follow-up. The proportion of those achieving remission was compared by the DUP. The impact of DUP on remission was estimated in multivariate analyses.
Results: At the follow-up, 83% (71/86) of patients who had met the criteria for symptomatic remission at the baseline achieved enduring remission, whereas 63% (119/190) of patients who had not met the criteria for symptomatic remission at baseline met it at the follow-up. The shorter the DUP, the higher the proportion of those who achieved symptomatic or enduring remission at the follow-up. The impact of DUP on symptomatic remission appeared to be significant after controlling for other factors influencing remission.
Conclusion: Since the DUP would influence remission of patients with schizophrenia, early detection and intervention services should be provided in Thailand.

Takizawa P / Arch Clin Psychiatry. 2021;48(2):141-146

Keywords: Duration of untreated psychosis, first-episode schizophrenia, remission, cohort, Thailand

Introduction

Schizophrenia is a complicated disorder that requires prompt treatment at the first signs of a psychotic episode [1] as there is a rapid progression of the neurodegenerative process in the brain in the first year of untreated illness [2,3]. Delay in effective treatment, therefore, increases the risk of structural and functional brain changes [4] which might cause treatment resistance [2], resulting in poor treatment outcomes, such as less remission, less recovery, and more relapse [5,6]. To improve long-term prognosis, early treatment in the first onset of schizophrenia is called for [2].

In Thailand, the prevalence of schizophrenia is 8.8 per 1000, as compared to the point prevalence of 4.6 per 1000 and the period prevalence of 3.3 per 1000 globally [7,8]. Given this higher prevalence, the Ministry of Public Health has increased the number of mental health care personnel in both general and psychiatric hospitals [9]. Today, Thai people have access to essential mental health services in the hospitals at low costs because of the country's universal health coverage [10]. Nevertheless, there is reportedly a delay in health care-seeking among mentally ill patients [9]. Unlike in the Western countries, no early intervention services are provided for first-episode schizophrenia in Thailand [9,11].

To scale up the services for first-episode schizophrenia, it is essential to understand to what extent health care-seeking is delayed among the patients, and how much the delay affects the treatment outcome. In the present study, we therefore investigated the duration of untreated psychosis (DUP) among first-episode schizophrenic patients and examined the impact of their DUP on remission of schizophrenia. We recruited these patients from general and psychiatric hospitals and followed them for six months.

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Methods

Participants

Participants of this study were patients aged between 18 and 55 who were diagnosed with first-episode schizophrenia based on the International Classification of Diseases, Tenth Revision (ICD-10) criteria (F20.0-F20.9) in the past 12 months, and who were taking adequate doses of antipsychotic based on chlorpromazine equivalents [12]. The exclusion criteria included people with a history of psychotic condition associated with mental retardation or organic diseases, patients who discontinued treatment for more than 6 months, and those with severe medical conditions that hindered participation in the study. Eligible patients were recruited from one psychiatric hospital, six general hospitals, one community hospital, and one university hospital in Southern, Middle, and Northeastern parts of Thailand from June 2017 to February 2019. Ethical approval was obtained from each hospital and the University of Tsukuba.

Of the 319 eligible patients, 302 agreed to participate in the study. At the baseline (i.e., time of recruitment), 94 had achieved symptomatic remission (as explained later). At the 6-month follow-up, 8 patients refused to participate and 18 were lost to the follow-up. Consequently, a total of 276 patients (86 of 94 patients who had achieved symptomatic remission at the baseline, and 190 of 208 patients who had not) were subjected to the analyses.

Data collection

Hospital staff such as psychological nurses, psychologists, or psychiatrists conducted face-to-face interviews with the participants and their guardians based on semi-structured questionnaires after obtaining their informed consent. Interviews took place at designated rooms in each hospital. In case that the participants were unable to recall required information, their guardians were requested to provide the information if possible and appropriate. The participants were invited to the follow-up interview about six months after the baseline interview, to be attended during their regular visits to the hospitals or by phone.

Measures

Remission in schizophrenia is an outcome variable. We used remission criteria proposed by the Remission in Schizophrenia Working Group (RSWG) [13]. The achievement of remission is determined on the basis of schizophrenic symptoms and time. The symptoms are assessed using the Positive and Negative Syndrome Scale (PANSS). The scale consists of 30 items including 7 items on positive symptoms, 7 on negative symptoms, and 16 on general psychopathology. These items are scored from 1 (complete absence of symptoms) to 7 (extreme severity of symptoms), hence the total score ranges from 30 to 210. A Thai version of the scale is available and its inter-rater reliability is reportedly 0.89, 0.72, and 0.88 for positive symptoms, negative symptoms, and general psychopathology, respectively [14].

To meet the remission criteria, each of eight items (delusions, conceptual disorganization, hallucinatory behavior, blunted affect, social withdrawal, lack of spontaneity, mannerisms/posturing, and unusual thought content) needs to be scored 3 or below. This condition needs to last for at least six months. Patients who have met the remission criteria are considered to have achieved "symptomatic remission", and if this lasts for six months, they are considered to have achieved "enduring remission" [15]. Among the participants who had achieved symptomatic remission at the baseline and those who had not, the outcome variables were enduring remission and symptomatic remission, respectively.

The DUP is a predictor variable. The DUP was defined as the period in weeks from the first manifestation of positive psychotic symptoms to the first contact with a mental health service due to psychosis [16]. To identify the first manifestation of the symptoms, the participants or their guardians were asked for the approximate number of weeks before they recognized hallucinations, delusions, or clear disorganized speech or thinking in the participants [17]. In case that the first manifestation of the symptoms was not contiguous, and there were two or more episodes of the symptoms with a quiescence period in the past, we referred to the first manifestation of active symptoms to calculate the DUP. The DUP was categorized into less than 1 month, 1 to 3 months, and over 3 months. In statistical analyses, the DUP was treated as both continuous and categorical variables to facilitate the interpretation of the results.

The covariates were the participants' baseline characteristics including age, sex, marital status, education, employment, living arrangements, the distance to the hospital from their house, history of substance use, family history of mental disorders, history of hospital admission due to active psychosis, duration of antipsychotic drug treatment at the baseline, and severity of schizophrenic symptoms at the baseline. The severity of schizophrenic symptoms was assessed using a Thai version of PANSS. We determined the participants' history of hospital admission and the duration of antipsychotic drug treatment from their medical records.

Statistical Analyses

First, we compared the participants' characteristics between those who achieved enduring remission and those who did not (i.e., relapse) at the follow-up among those who had achieved symptomatic remission at the baseline. The comparison was also made between those who achieved symptomatic remission and those who did not at the follow-up among those who had not achieved symptomatic remission at the baseline. For this comparison, we used the effect size of Hedge's g and Cramer's V for continuous and categorical variables, respectively [16], instead of p value. We considered an effect size of 0.2 or above to be practically significant [18].

Then, we estimated the impact of DUP on enduring remission and symptomatic remission at the follow-up in a logistic regression model among those who had achieved symptomatic remission at the baseline and those who had not, respectively. The DUP was entered as a continuous variable in one model, and as a categorical variable in another. The both models controlled for potential confounders including age [19], sex[19], the history of substance use[18], family history of mental disorders [21], the duration of antipsychotic drug treatment at the baseline [5] and the baseline severity of schizophrenic symptoms [22], and provided adjusted odds ratio (OR) and 95% confidence interval (CI).

Results

The participants' mean age was 32.7 years (standard deviation [SD] 10.2). Out of 276 participants, 66% were males, 62% were single, 61% attained education up to junior high-school, 48 % were employed, 95% were living with family or friends, 66 % lived within 5 km from the hospitals, 68% had history of substance use, 24% had a family history of mental disorders, and 29% had history of hospital admission due to active psychosis. The median duration of antipsychotic drug treatment and untreated psychosis at the baseline was 6 weeks (interquartile range [IQR] 1-20) and 4 weeks (IQR 2-9), respectively. Regarding the severity of schizophrenic symptoms at the baseline, the mean total PANSS score was 74.3 (SD 34.3).

Among 86 who had achieved symptomatic remission at the baseline, 71 (83%) achieved enduring remission at the follow-up, and they had a longer duration of antipsychotic treatment drug use at the baseline and a lower PANSS score at the baseline than their counterparts (Table 1). Among 190 who had not achieved symptomatic remission at the baseline, 119 (63%) achieved symptomatic remission at the follow-up, and they had a longer duration of antipsychotic treatment drug use at the baseline, a lower PANSS score at the baseline, and a shorter DUP than their counterparts (Table 2). There were no significant differences in other characteristics between the two among both groups.

Tables 3 and 4 show the impact of the DUP on remission among the two groups. The proportion of the patients achieving remission is larger as the DUP is shorter in both groups, but the dose-response relationship between the DUP and remission is clearer for symptomatic remission. In the multivariate analyses controlling for the duration of antipsychotic treatment drug use at the baseline, the PANSS score at the baseline, and other variables that might influence remission, the DUP appeared to be a significant predictor for symptomatic remission.

Discussion

We found that a shorter duration of untreated psychosis (DUP) was associated with a higher chance of remission among first-episode patients with schizophrenia which is the widely known finding that was confirmed in Thailand for the first time. This finding is consistent with the conclusion from previous studies in the Western countries [5,23], supporting the view that DUP is an independent and potentially modifiable factor affecting prognosis of schizophrenia and response to treatment [5]. Shortening the DUP is necessary not only to increase a chance of remission but also to reduce the likelihood of relapse [24].

Table 1. Comparison of patients' baseline characteristics between those who achieved enduring remission (n=71) and those who relapsed (n=15) at the follow-up.

Variables	Relapsed		Enduring remission[a]		Effect size*
	n	(%)	n	(%)	
Sex					
Male	10	(67)	53	(75)	
Female	5	(33)	18	(25)	0.06
Age					
< 30 years	7	(47)	22	(31)	
30-40 years	3	(20)	32	(45)	0.19
>40 years	5	(33)	17	(24)	
Marital status					
Single	10	(67)	45	(63)	
Married	4	(27)	20	(28)	0.03
Widowed/Divorced/Separated	1	(6)	6	(9)	
Education					
Senior high school educational level or above	7	(47)	36	(51)	0.03
Junior high school educational level or below	8	(53)	35	(49)	
Employment status					
Employed	6	(40)	41	(58)	0.13
Unemployed	9	(60)	30	(42)	
Living arrangements					
Live with family or friends	14	(93)	68	(96)	0.04
Live alone	1	(7)	3	(4)	
Distances to hospitals, (km)					
≤ 5 km	9	(60)	45	(63)	
6 to 10 km	3	(20)	9	(13)	0.08
> 10 km	3	(20)	17	(24)	
Substance use history	8	(53)	53	(75)	0.18
Family history of mental disorders	3	(20)	19	(27)	0.06
History of mental illness treatment					
Hospital admission due to active psychosis	5	(33)	17	(24)	0.08
Duration of antipsychotic drug treatment, median weeks (IQR)	9	(4-12)	11	(4-48)	0.60
Total PANSS score, mean score (SD)	49.7	(15.2)	40.6	(11.7)	0.74
DUP, median weeks (IQR)	8	(4-12)	4	(2-8)	0.12

IQR: interquartile range; PANSS: Positive and Negative Syndrome Scale; SD: standard deviation.
[a]Enduring remission: full symptom remission for at least 6 months according to RSWG criteria [15].
*Effect size of ≥ 0.2 is considered practically significant.

Table 2. Comparison of patients' baseline characteristics between those who achieved symptomatic remission (n=119) and those who did not (n=71) at the follow-up.

Variables	Non-remission	Symptomatic remission[a]	Effect size*
	n (%)	n (%)	
Sex			
Male	42 (59)	77 (65)	
Female	29 (41)	42 (35)	0.06
Age			
< 30 years	35 (49)	53 (45)	
30-40 years	15 (21)	43 (36)	0.17
>40 years	21 (30)	23 (19)	
Marital status			
Single	45 (63)	72 (61)	
Married	14 (20)	31 (26)	0.08
Widowed/Divorced/Separated	12 (17)	16 (13)	
Education			
Senior high school educational level or above	25 (35)	79 (66)	0.02
Junior high school educational level or below	46 (65)	40 (34)	
Employment status			
Employed	37 (52)	48 (40)	0.11
Unemployed	34 (48)	71 (60)	
Living arrangements			
Live with family or friends	66 (93)	113 (95)	0.04
Live alone	5 (7)	6 (5)	
Distances to hospitals, (km)			
≤ 5 km	43 (61)	86 (72)	
6 to 10 km	17 (24)	18 (15)	0.13
> 10 km	11 (15)	15 (13)	
Substance use history	41 (58)	86 (72)	0.15
Family history of mental disorders History of mental illness treatment	14 (20)	30 (25)	0.06
Hospital admission due to active psychosis	20 (28)	37 (31)	0.03
Duration of antipsychotic drug treatment, median weeks (IQR)	4 (1-8)	7 (1-24)	0.35
Total PANSS score, mean score (SD)	93.1 (37.2)	86.4 (26.3)	0.22
DUP, median weeks (IQR)	8 (4-16)	3 (1-8)	0.54

IQR: interquartile range; PANSS: Positive and Negative Syndrome Scale; SD: standard deviation.
aSymptomatic remission: fulfillment of symptom remission criteria only according to RSWG criteria [15].
*Effect size of ≥ 0.2 is considered practically significant.

Table 3. Proportion of enduring remission by the duration of untreated psychosis (DUP), and the impact of DUP on enduring remission among the patients who had achieved symptomatic remission at the baseline.

	Enduring remission[a]	Adjusted odds ratio (95% confidence interval)[b]
Model 1		
DUP (weeks)		0.98 (0.93 to 1.04)
Model 2		
DUP		
> 3 months	7/10 (70%)	Ref
1 to 3 months	35/46 (76%)	1.17 (0.19 to 7.34)
<1 month	29/30 (97%)	25.00 (1.43 to 433.81)

aEnduring remission: full symptom remission for at least 6 months according to RSWG criteria [15].
bAdjusted for age, sex, baseline severity of schizophrenic symptoms, history of substance use, family history of mental disorders and duration of antipsychotic treatment drug use at baseline.

Table 4. Proportion of symptomatic remission by the duration of untreated psychosis (DUP), and the impact of DUP on symptomatic remission among the patients who had not achieved symptomatic remission at the baseline.

	Symptomatic remission[a]	Adjusted odds ratio (95% confidence interval)[b]
Model 1		
DUP (weeks)		0.94 (0.91 to 0.97)
Model 2		
DUP		
> 3 months	10/30 (33%)	Ref
1 to 3 months	45/87 (52%)	3.01 (1.16 to 7.81)
<1 month	64/73 (88%)	23.70 (7.60 to 71.02)

[a]Symptomatic remission: fulfillment of symptom remission criteria only according to RSWG criteria [15].
[b]Adjusted for age, sex, baseline severity of schizophrenic symptoms, history of substance use, family history of mental disorders and duration of antipsychotic treatment drug use at baseline.

The DUP in our study participants appeared to be shorter than that reported in a previous systematic review (median DUP of 4 weeks vs. 12 weeks; [25]). There are several possible explanations for this difference. First, the definition of DUP varies across the studies. While we calculated the DUP from the onset of positive psychotic symptoms (hallucination, delusions, or clear disorganized speech or thinking), some of the previous studies made the calculation from the onset of prodrome symptoms (such as mood lability, and sleep disturbance) or negative symptoms (such as poverty of speech and thought, apathy, and anhedonia). Our strict definition might have resulted in a shorter DUP. Second, the shorter DUP in Thailand might be due to the achievement of universal health coverage that lessens financial barriers to health care services [26]. In fact, universal health coverage has led to an increase in hospital admissions and outpatient visits in Thailand [27]. Finally, a shorter DUP in our study participants might be due to the fact that more than half of them are living within 5 km from the hospital and had a good physical access to it. Reportedly, the distance to the hospital and associated transportation costs still influence health care-seeking among Thai people despite the achievement of universal health coverage [28,29].

Today, the World Health Organization and the International Early Psychosis Association recommend that the treatment of first-episode psychosis should be initiated within 3 months from the onset, though our findings indicate that the earlier the treatment started, the better the outcome would be [30]. Thai Ministry of Public Health should develop strategies for reducing DUP through, for example, enhanced psychosis screening and timely referral from primary care to specialist care, both of which are not in place [30,31].

We acknowledge several limitations of the study. First, the study participants were restricted to outpatients with first-episode schizophrenia. Hence, our findings might not be generalizable to the inpatients with severer symptoms and lower remission rates, and potentially with much longer DUP. Second, we are unsure whether those who achieved enduring remission at the follow-up had actually continued to keep symptomatic remission during the follow-up period of six months, as their remission status was assessed at the baseline and follow-up only. Therefore, there could be some patients that relapsed during the follow-up period and were misclassified as those who achieved enduring remission. Our findings, however, should not be distorted because this potential misclassification would have occurred irrespective of the length of DUP. Finally, our estimated effect of the DUP on remission was of reduced precision with wider confidence intervals due to a small number of the study participants, especially those who had achieved symptomatic remission at the baseline.

In conclusion, the duration of untreated psychosis would influence remission of patients with schizophrenia. This finding supports the need of early detection and intervention services for first-episode schizophrenia in Thailand.

Conflict of interests

The authors declare that there is no conflict of interest.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Universe Foundation [grant number 16-02-153, 2016].

Acknowledgments

We thank Ms. Pimchanok Hakham, Drs. Warith Mongkolnaowarat, Patraporn Kinorn, Chanon Sirikul, Piyanut Wanna and Wiwat Sarapat for their assistance with collecting data.

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