Original Article

Patient Characteristics and Treatment Discontinuation in a Taiwanese Cohort of the Intercontinental Schizophrenia Outpatient Health Outcomes (IC-SOHO) Study

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Objective: This report was to present the demographic and clinical outcomes of the Taiwanese cohort of the Intercontinental Schizophrenia Outpatient Health Outcomes (IC-SOHO) study for the readership of Taiwanese psychiatrists. **Methods:** The IC-SOHO was a three-year, naturalistic, prospective, observational study which was designed to compare outcomes of outpatients with schizophrenia who had initiated or changed antipsychotic medications. They were divided into olanzapine and other non-olanzapine antipsychotic groups. Evaluations included clinical severity, social functioning, health-related quality of life, and medication tolerability. Time to treatment discontinuation was analyzed using the Kaplan-Meier method. **Results:** A total of 300 patients was enrolled in this Taiwanese cohort, and 81.6% (245 patients) of them received initial antipsychotic monotherapy. Despite the absence of randomization in this study, no significant differences were found between the treatment cohorts in the socio-demographic and clinical characteristics at baseline of those two groups. The mean doses of treatments were increased in those two groups over the 36-month period and the uses of non-antipsychotic concomitant medications remained high throughout the study. Patients who remained at the end of the study showed a clinical response to treatment indicated by reductions in CGI-S scores in all domains, but these changes were not significantly different between those two groups. The estimated time to medication discontinuation for 50% of patients was 36.3 (95% CI 31.2, 38.4) months for those in the olanzapine group and 18.0 (95% CI 11.3, 30.1) months for patients receiving other monotherapy; the hazard ratio was 0.65 (95% CI 0.43, 0.99). But their weight gain was significantly greater for the olanzapine group over the first 12 months of treatment. **Conclusion:** The results of this naturalistic, observational study offer an important description of the clinical characteristics and outcomes associated with the long-term use of antipsychotic treatment of schizophrenia in a cohort of Taiwanese patients.

Key words: schizophrenia, observational study, time to discontinuation, olanzapine

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Introduction

The use of antipsychotic therapy has become widely recognized as essential in the long-term clinical management of patients with schizophrenia [1, 2]. Evidence from recent epidemiological studies highlights the importance of adherence to antipsychotic medication in preventing relapse and re-hospitalization [3, 4]; and medical adherence is a determinant factor of therapeutic outcomes in these patients [2, 5].

The use of the first-generation antipsychotic (FGA) or typical drugs has progressively declined over the past decade due to their associated neurological side effects such as extrapyramidal symptoms including tardive dyskinesia [6], and the poor efficacy in negative and depressive symptoms. The use of the second-generation antipsychotic drug (SGA) or atypical drugs is now more frequently recommended for their effectiveness in treating positive, negative, depressive, and cognitive symptoms of schizophrenia and in improving both social functioning and quality of life [7-9].

The efficacy and safety of using SGAs in schizophrenia have been established in randomized, controlled trials [10], but these trials have been focused on short-term measures of clinical status. Therefore, long-term, open-label, non-randomized observational studies addressing treatment outcomes in routine clinical practice would contribute to the current body of research.

The Intercontinental Schizophrenia Outpatients Health Outcomes (IC-SOHO) study was conducted across 27 countries, involving more than 700 psychiatrists and 7,500 patients. The study was designed to evaluate the treatment outcomes in a large and diverse cohort of patients with schizophrenia being treated in outpatient settings. Results of the IC-SOHO study (n =7,658) have been previously reported [11], and the data of its Asian sample (n=898) including patients from Taiwan, South Korea, and Malaysia has also been published [12]. The objective of this article was to report the demographic and clinical characteristics and outcomes of the Taiwanese patient cohort (n=300), specifically for the readership of Taiwanese psychiatrists.

Methods

Study design

The IC-SOHO study was a three-year, prospective, naturalistic, observational study comparing outcomes of schizophrenic patients initially treated with olanzapine and those initially treated with other antipsychotic medications [11, 12]. The study was designed to assess clinical, functional, and quality of life outcomes of outpatients treated in routine clinical practice [11, 12]. Patients were recruited into the study between November 1, 2000 and December 31, 2001. Although institutional review board approval for observational studies was not mandatory in Taiwan when the study was conducted, the study protocol was sent to the authorities of the study sites for notification at the request of the investigators. Each patient needed to sign written informed consent before being enrolled.

The enrolled patients were at least 18 years of age, and had a diagnosis of schizophrenia (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [DSM-IV] or International Classification of Diseases, 9th Revision [ICD-9] criteria*). They were presented as outpatients for their routine care, and had been initiated or changed antipsychotic medications. Participating psychiatrists made treatment decisions independent of the study before evaluating patient eligibility. As the study objective was to

compare treatment with olanzapine as a monotherapy or in combination with other agents with other antipsychotic medications, we systematically enrolled eligible patients to provide two patient cohorts of about equal size: (A) patients who had initiated or changed to olanzapine therapy, and (B) patients who had initiated or changed to a non-olanzapine antipsychotic drug. The recruitment period was intentionally long without requiring each psychiatrist to enroll a minimum number of patients. To preserve the authenticity of the clinical setting, all investigators kept all autonomous aspects of patient care (such as the type and dose of prescribed antipsychotic medication, the reason for treatment initiation or change, and the use of concomitant medications). Treatments were open-label and included any available antipsychotic drugs for the treatment of schizophrenia.

Study assessments

As described elsewhere [11, 12], patients were evaluated at baseline, 3 months, 6 months, and every 6 months thereafter for 36 months during routine outpatient visits. To minimize the influence on routine clinical practice, investigators were allowed to collect data up to 1 month before or after the target month. If a routine visit did not occur within the allowed time frame, the assessment was left blank. Patients who were not seen within one assessment interval, were not excluded from subsequent data collection.

Data collected included those typically collected in routine clinical practice. They were patients' demographics, duration of diagnosis, antipsychotic and concomitant medication use as well as alcohol and substance abuse. Outcome measures included an assessment of clinical status, social functioning, and health-related quality of life. Investigators measured clinical status with the Clinical Global Impressions-Severity (CGI-S) rating scale [13], which evaluates overall, positive, negative, cognitive, and depressive symptoms. The investigators also assessed social functioning with single-item questions that queried relationship, housing, employment status and availability to work, and involvement in social interaction. Besides, the investigators also assessed the health-related quality of life (QOL) with the EuroQol 5 Dimensions (EQ-5D) [14], which is a standardized instrument and widely used self-report questionnaire measuring patients' responses to questions about mobility, self-care, usual activities, pain/discomfort and anxiety/depression. An overall index measuring QOL, is derived from the responses to the five dimensions of EQ-5D. Health status was rated by patients with visual analogue scale.

Patients were considered to have responded to treatment if they had an overall baseline CGI-S score larger than or equal to 4, which subsequently decreased by 2 or more points, or an overall baseline CGI-S score of 3, which subsequently decreased by 1 or more points. Therefore, patients with CGI-S scores of 1, 2, or missing at baseline were excluded from the evaluation of response. Treatment discontinuation was defined to include discontinuation, interruption, replacement, or addition of a new antipsychotic medication to that initiated at baseline. Patients who were lost to follow-up or had missing drug information, were also considered a discontinuation. The possible reason for certain patient to discontinue his/her treatment was decided by the investigators at each site according to their clinical observation and experience. The time to all-cause treatment discontinuation was defined as the time from baseline to the last visit at which the patient was known to be taking the medication. The investigators recorded the reasons for treatment change or discontinuation and categorized them as lack of efficacy, in-

tolerability, lack of compliance, or patient request. The investigators also collected tolerability data with adverse event questionnaires including those for extrapyramidal symptoms, tardive dyskinesia, sexual function, and weight measures.

Statistical analysis

We did statistical analyses with Statistical Analysis System® Package Version 8.2 for Windows™ (SAS Institute, Cary, North Carolina, USA). We included patients who were initiating or changing treatment to olanzapine as a monotherapy or in combination, in the olanzapine group. All other patients consisting of those with missing data, were included in the other group. Patients were included in the analysis for as long as this treatment was maintained.

We summarized continuous variables with mean (unadjusted), standard deviation (SD), median, mode and range (minimum and maximum value), as well as categorical variables with the number and percentage of patients in each category for each treatment group. Variability of estimates was calculated using 95% confidence intervals (CI) based on normal and binomial distribution. No imputation of missing data was conducted. We excluded patients with missing data from relevant analyses, resulting in differences in patient numbers for some variables and time points.

For medication changes that occurred between visits, the time of medication discontinuation used was the mean time between visits. Patients with missing dates were not included in the calculations and the time to antipsychotic discontinuation was only calculated for patients receiving monotherapy. The time to all-cause treatment discontinuation was described using the Kaplan-Meier method.

Results

Figure 1 shows the disposition of all study patients (n=300), indicating that most (81.6%) were prescribed with monotherapy, and 51.8% (n=127) of them received olanzapine montherapy. The sum of 17.3 % (n=52) of all study patients received combination therapy. Table 1 presents the baseline demographic and clinical characteristics of the 300 study patients, including 154 (51%) received olanzapine (monotherapy or in combination therapy) and 146 (49%) received other antipsychotics.

Table 2 lists the medication doses of antipsychotics and the use of concomitant medications at baseline and at 36-months. Those who received other antipsychotics at baseline but later received olanzapine at 36 months follow-up had higher, though not statistically different, dose of olanzapine than those who were prescribed olanzapine at baseline (13.75 mg vs. 13.0 mg).

After 36-months of antipsychotic treatment, an improvement in clinical status was recorded for all patients receiving antipsychotic treatment as indicated by reductions in overall CGI-S scores and in the four symptoms associated with schizophrenia, the positive, negative, depressive, and cognitive. Table 3 presents the clinical status as measured by the Clinical Global Impression-Severity Rating Scale at baseline and at 36-months. No significant differences were evident between the groups on any of the domain scores at 36-months and baseline to 36-month changes by t-test.

Figure 2 shows the Kaplan-Meier Time (months) to antipsychotic discontinuation for the olanzapine and other monotherapy groups.

Figure 3 depicts patients' weight gain in both groups over the 36 -month period.

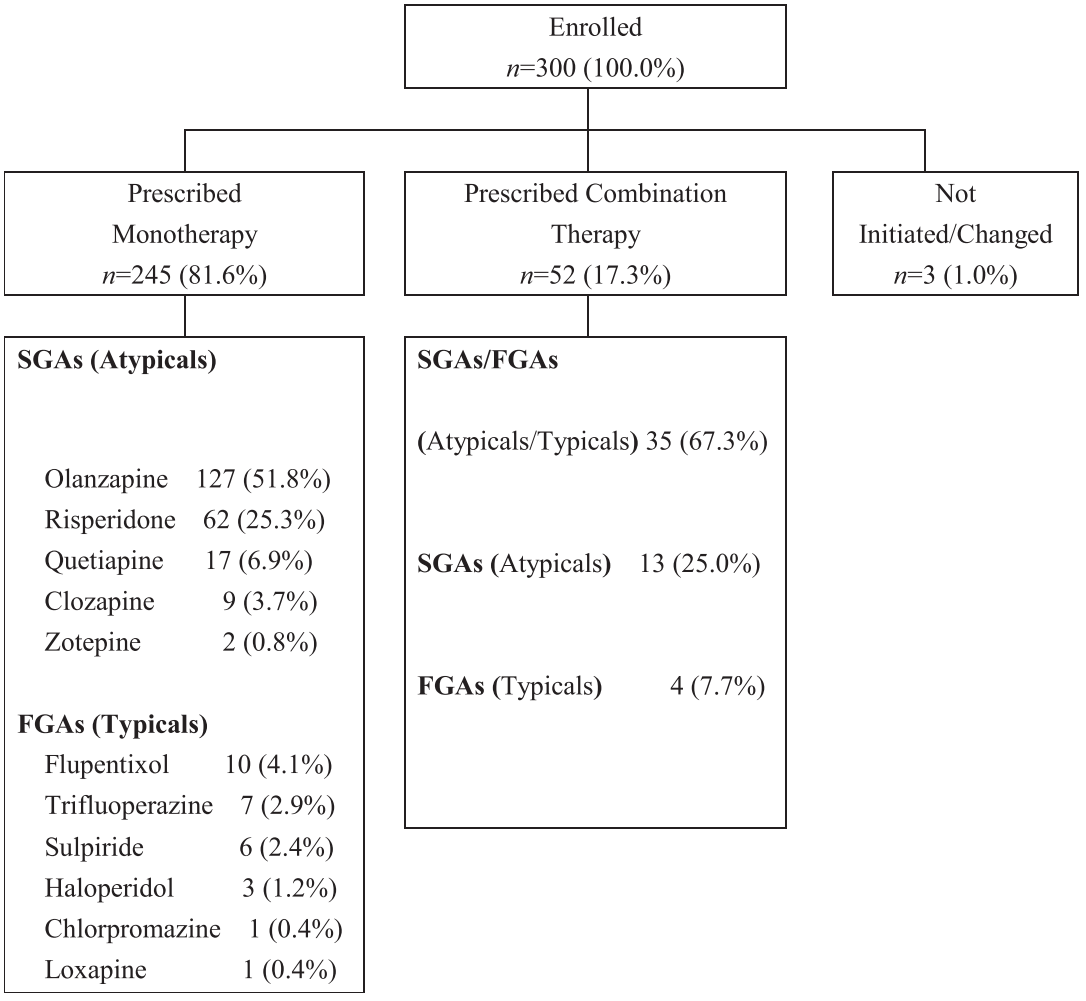

Figure 1. Disposition of study patients. FGAs=first generation antipsychotic drugs, SGAs= second generation antipsychotic drugs

Discussion

As stated previously, the IC-SOHO was designed to expand the existing knowledge of the treatment of schizophrenia in clinical practice. Results of this prospective, longitudinal, observational study offer information about the clinical outcomes of Taiwanese patients with schizophrenia and provide insight into their management in clinical practice.

Strengths of the study design include that the investigators were not restricted to choose any type and dose of antipsychotic treatment and to prescribe any concomitant medications prescribed. The clinical care of the patient remained at the discretion of the treating psychiatrists and any changes or additions to medications throughout the treatment period were permitted.

A total of 81.6% (245 of 300 patients) of patients in this Taiwanese cohort (Figure 1) was found to receive antipsychotic monotherapy. In a

Table 1. Baseline characteristics of patients (*n*=300) recruited in the IC-SOHO study in Taiwan

Characteristic	*n*	Olanzapine	*n*	Others	*n*	Total
Mean age, years (SD)	153	35.6 (11.7)	145	37.0 (11.5)	298	36.3 (11.6)
Gender, female, n (%)	154	76 (49.4)	146	81 (55.5)	300	157 (52.3)
Mean duration of diagnosis, years (SD)	147	8.2 (8.0)	140	8.8 (8.5)	287	8.5 (8.2)
First time use of antipsychotic, n (%)	153	10 (6.5)	145	3 (2.1)	298	13 (4.4)
Clinical status, mean CGI-S score (SD)	154		146		300	
Overall symptoms		4.2 (0.8)		4.2 (0.8)		4.2 (0.8)
Positive symptoms		4.1 (1.0)		4.0 (1.1)		4.1 (1.1)
Negative symptoms		3.5 (1.2)		3.6 (1.2)		3.5 (1.2)
Depressive symptoms		2.9 (1.0)		3.0 (1.0)		3.0 (1.0)
Cognitive symptoms		3.4 (1.0)		3.4 (1.0)		3.4 (1.0)
Functional status, n (%)						
Married/Partner	152	115 (75.7)	145	119 (82.1)	297	234 (78.8)
Housing status	154		146		300	
Independent residence		107 (69.5)		99 (67.8)		206 (68.7)
Dependent residence		45 (29.2)		47 (32.2)		92 (30.7)
Hospitalized patients		2 (1.3)		--		2 (0.7)
Work status	154		146		300	
Employed and paid		32 (20.8)		33 (22.6)		65 (21.7)
Employed and unpaid		5 (3.2)		--		5 (1.7)
Unemployed but available to work		45 (29.2)		34 (23.3)		79 (26.3)
Unemployed but unavailable to work		65 (42.2)		69 (47.3)		134 (44.7)
Retired		3 (1.9)		2 (1.4)		5 (1.7)
Other		4 (2.6)		8 (5.5)		12 (4.0)
Involved in social activity	154	52 (33.8)	145	38 (26.2)	299	90 (30.1)
Substance abuse or dependency	154	1 (0.6)	146	1 (0.7)	300	2 (0.7)
Alcohol abuse or dependency	154	5 (3.2)	146	3 (2.1)	300	8 (2.7)
Quality of life, EQ-5D score (SD)	154	0.6 (0.4)	146	0.7 (0.4)		-
Health Status, VAS score (SD)	154	60 (24)	146	56 (24)		-
Mean body weight, kg (SD)	154	65.5 (14.9)	146	66.9 (15.5)	300	66.2 (15.2)
Mean body mass index, kg/m² (SD)	154	24.4 (4.5)	146	25.3 (5.2)	300	24.8 (4.9)

CGI-S=Clinical Global Impressions-Severity, IC-SOHO=Intercontinental Schizophrenia Outpatient Health Outcomes, *n*=number of patients, SD=standard deviation

Table 2. Medication doses of antipsychotic drugs and use of concomitant medications at baseline and at 36 months

	Olanzapine	Others	Total
Olanzapine dose (mg/day) at baseline	*n* = 154	*n* = 0	*n* = 154
Mean (SD)	7.55 (3.50)		7.55 (3.50)
Median, range	5.00, 2.5-25.0		5.00, 2.5-25.0
Olanzapine dose (mg/day) at 36 months	*n* = 20	*n* = 6	*n* = 26
Mean (SD)	13.00 (4.70)	13.75 (9.71)	13.17 (5.98)
Median, range	10.00, 5.0-25.0	12.50, 2.5-25.0	10.00, 2.5-25.0
Concomitant medications at baseline, n (%)	*n* = 154	*n* = 146	*n* = 300
Patients prescribed concomitant medication	133 (86.4)	133 (91.1)	266 (88.7)
Patients prescribed anxiolytics/hypnotics	117 (76.0)	102 (69.9)	219 (73.0)
Patients prescribed anticholinergics	53 (34.4)	49 (33.6)	102 (34.0)
Patients prescribed antidepressants	35 (22.7)	41 (28.1)	76 (25.3)
Patients prescribed mood stabilizers	30 (19.5)	23 (15.8)	53 (17.7)
Concomitant medications at 36 months, n (%)	*n* = 52	*n* = 45	*n* = 97
Patients prescribed concomitant medication	46 (88.5)	42 (93.3)	88 (90.7)
Patients prescribed anxiolytics/hypnotics	37 (71.2)	34 (75.6)	71 (73.2)
Patients prescribed anticholinergics	24 (46.2)	22 (48.9)	46 (47.4)
Patients prescribed antidepressants	11 (21.2)	11 (24.4)	22 (22.7)
Patients prescribed mood stabilizers	10 (19.2)	11 (24.4)	21 (21.6)

n=number of patients, SD=standard deviation

study specifically investigating combined antipsychotic therapy in psychiatric outpatients at a general hospital in the central region of Taiwan, Huang et al. [15] reported that 88% of patients (838 out of 957 patients) receive antipsychotic monotherapy. In another cross-national antipsychotic-prescribing study which included Japan, Singapore, Korea, China, Taiwan, and Hong Kong, Sim et al. [16] reported that 77.8% of Taiwanese patients receive antipsychotic monotherapy, and that the rate of antipsychotic monotherapy prescribed in Taiwan is much higher than that prescribed in Japan (21.4%) or in Singapore (29.7%) [16]. In addition to the local prescribing tradition and cultural factors [16], we suggest that the influence of regulation from the third party payer (i.e. Bureau of National Health Insurance [BNHI]) may be one of the causes and can not be ruled out in this cross-national difference. A need exists for future research specifically investigating the use of antipsychotic mono/polypharmacy.

The dose of medications was increased across the cohort over the duration of the study (Table 2). This finding suggests that initial doses of olanzapine might not be effective. But patients receiving olanzapine therapy had a higher frequency of maintenance over those treated with other antipsychotic monotherapy. But treatment maintenance may have been biased by that participating psychiatrists. They might tend to include patients

Table 3. Clinical status as measured by the Clinical Global Impression-Severity Rating Scale at baseline and at 36 months

CGI-S domain	Baseline	36 Months	Change from baseline
Overall			
Olanzapine, mean (SD)	4.21 (0.76)	2.75 (0.71)	-1.46 (0.83)
Other, mean (SD)	4.22 (0.83)	2.87 (0.81)	-1.31 (0.97)
Positive			
Olanzapine, mean (SD)	4.12 (1.02)	2.65 (0.93)	-1.52 (1.09)
Other, mean, (SD)	4.03 (1.10)	2.78 (1.04)	-1.22 (1.06)
Negative			
Olanzapine, mean (SD)	3.48 (1.15)	2.54 (0.83)	-1.00 (1.07)
Other, mean (SD)	3.60 (1.17)	2.73 (0.91)	-1.13 (1.12)
Depressive			
Olanzapine, mean (SD)	2.92 (1.03)	2.12 (0.78)	-0.69 (1.08)
Other, mean (SD)	2.99 (1.01)	2.33 (0.93)	-0.69 (1.33)
Cognitive			
Olanzapine, mean (SD)	3.42 (1.03)	2.62 (0.77)	-0.87 (0.79)
Other, mean (SD)	3.40 (1.02)	2.62 (0.75)	-1.00 (0.85)

CGI-S=Clinical Global Impressions-Severity; SD=standard deviation
Not significantly different in changes of all items from baseline to 36 months

who were compliant although this potential selection bias should not have affected comparisons between two groups.

Adjunctive medication is commonly prescribed to patients with schizophrenia in an effort to manage the schizophrenia-related symptoms or the side effects experienced while receiving antipsychotic therapy. Many patients (88.7%) in this study received concomitant medications at baseline (Table 2). Anxiolytics/hypnotics were the most commonly prescribed concomitant drugs in this study cohort, with 73.0% of patients taking them at baseline and 73.2% at 36-months (Table 2). The rate of prescription did not differ significantly between the olanzapine and other monotherapy group for anxiolytics/hypnotics (71.2% vs. 75.6%) and antidepressant (21.2% vs. 24.4%) (Table 2). These results differ from those previously reported in the total IC-SOHO cohort [11] which reported that when compared to the olanzapine monotherapy group, the odds of receiving anxiolytics/hypnotics were significantly (p<0.001) greater for patients who maintained their baseline prescription of risperidone monotherapy and the odds of concomitant antidepressant prescription were 2.3 times greater for the quetiapine treatment group (p<0.001). Based on data of the Taiwan BNHI, Su et al. reported that the overall rate of outpatient prescription for anxiolytics/hypnotics by all medical subspecialty physicians is 43.6% [17]. Whether the comparison of concomitant medicine use in both groups would be different if

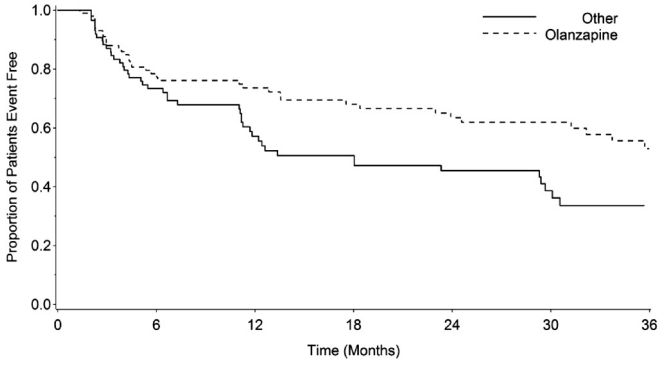

Figure 2. Kaplan-Meier Time (Months) to antipsychotic discontinuation: olanzapine versus other monotherapy (*n* = 245). The estimated time to medication discontinuation for 50% of patients was 36.3 (95% CI 31.2, 38.4) months for those in the olanzapine group and 18.0 (95% CI 11.3, 30.1) months for patients receiving other monotherapy; the hazard ratio was 0.65 (95% CI 0.43, 0.99). Of the patients assessed at 36-months, 91.2% (*n* = 176) had modified their medication due to a lack of, or incomplete effectiveness, 53.5% (*n* = 69) had modified their medication due to intolerability, and 28.2% (*n* = 33) had requested a change over the 36-month period. No significance was found between two groups for any period of time.

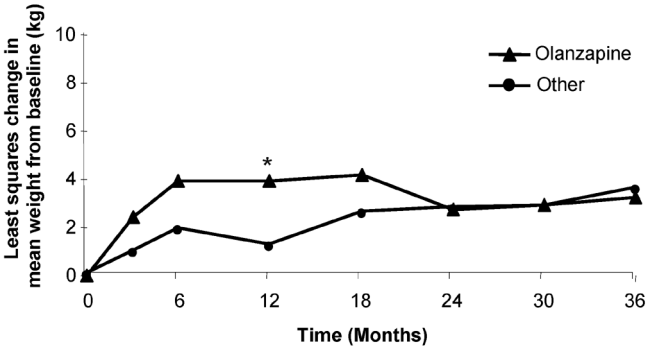

Figure 3. Least-squares change in mean weight (kg) over the 36-month observational period. By the end of the study, patients who remained in the olanzapine group (*n*=52) had gained an average of 3.28 (9.95) kg and 25 (48.1%) patients had a weight increase of greater than 7% from baseline. The average weight gain in patients who remained taking other antipsychotic treatment (*n*=45) was 3.56 (7.30) kg and 18 (40.0%) had a weight increase of greater than 7% from baseline. *Significant difference of body weight gain and percentage of patients with 7% or more weight gain at the 12-month period (*p*=0.0129), olanzapine group vs. other group.

the dosage, instead of the case number, of concomitant medication was collected, would need further investigation. Shen [18] suggested that anxiolytics/hypnotics are over-prescribed while antidepressants are under-used. He thought that most Taiwanese patients with major depressive disorder and/or generalized anxiety disorder do not receive antidepressant therapy [18]. To collect further data is needed from psychiatric patients in Taiwan and cross-nationally to compare and to evaluate the potential of over-use of anxiolytics/hypnotics in Taiwanese schizophrenic patients.

Concomitant therapy prescriptions in the categories of anxiolytics/hypnotics, antidepressants, and mood stabilizers in this study (Table 2) remained almost constant for at the baseline and at 36 months. But the prescription of anticholinergic medications was increased from 34.0% to 47.4% from the beginning to the end of the study (Table 2). Maybe this prescription habit of anticholinergic drugs has been taught in generations in Taiwan although the use of anticholinergic drug does not have the data to prevent the antipsychotic-medicated patients from developing extrapyramydal symptoms [19].

As stated previously, effective antipsychotic treatment should be aimed to manage all aspects of the disease state including the positive, negative, depressive, and cognitive symptoms [20]. In this study, positive and negative symptoms were worse in severity than depressive symptoms at baseline (Table 3), with depressive symptoms being the least severe. Of the patients who remained on antipsychotic therapy for 36 months, many of them showed a clinical response to treatment in all of these domains, most notably in the positive and negative symptoms (Table 3). These results are significant because depressive symptoms have been associated with compromised quality of life [21], an increased risk of psychotic relapse, and suicide [22, 23] while impaired functional well-being, greater disability, and mortality may be attributed to or associated with negative symptoms [24].

Based on important clinical studies as the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) [25] and the European First Episode Schizophrenia Trial (EUFEST) [26], we also believe that the estimated time to medication discontinuation is an index of treatment effectiveness considering the influences of treatment efficacy, tolerability and adherence. The present study showed that patients treated with olanzapine had a lower risk (hazard ratio = 0.65, 95% CI 0.43, 0.99) of treatment discontinuation compared to those treated with other antipsychotic monotherapy (Figure 2). And the median time to discontinue is twice longer (36 months vs. 18 months) for olanzapine than other antipsychotics. These favorable outcome with olanzapine in treatment continuation may reflect choices of psychiatrists and their patients considering efficacy, tolerability and adherence. Although the reasons for longer continuation of treatment with olanzapine are still controversial, higher efficacy, acceptable improved tolerability and a good therapeutic alliance between physician and patient may be important reasons.

Treatment-emergent weight gain [27, 28] may affect compliance [29] and treatment satisfaction [30]. An initial, rapid weight gain was found in this study (Figure 3), with significantly greater weight gain occurring over the first 12 months (p=0.0129) in patients treated with olanzapine. Compared to those treated with other antipsychotic monotherapy. The differences in mean weight changes were not significant over the following two years, but a difference may not have been detected given the smaller number of patients available for follow-up after the first year.

Interpreting the data of this report should be cautious because this study has three limitations. (A) The patients in this study were systematically over-sampled for olanzapine use. Therefore, the data may not reflect the actual prescription of the antipsychotics in treating schizophrenia and limit the accuracy of outcomes associated with those being prescribed with other antipsychotic medications. (B) As in any longitudinal study, significant number of patients in this study was dropped out or lost to follow-up. Therefore, results at the end of the study may only represent those patients who remained enrolled. And (C) being an observational study, investigators and patients were not blinded and patients were not randomized into their treatment groups. Therefore, the study data may have potential bias inherited in such study design.

Clinical Implication

Longer time to discontinuation of treatment and more weight gain in the first 12 months for patients receiving olanzapine than other antipsychotics revealed in this study offer the clinicians information in considering choosing treatment for their patients. The incidental findings of the popularity of antipsychotic monotherapy and the potential over-prescription of anxiolytics/hypnotics in treating patients with schizophrenia in Taiwan warrant further investigation.

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