CNPT The Japanese Society of Clinical Neuropsychopharmacology
Clinical Neuropsychopharmacology and Therapeutics
scnp

Clinical and functional outcomes for patients with schizophrenia treated with olanzapine: One-year naturalistic outcomes for inpatients and outpatients in Japan

Haya Ascher-Svanum,* Wenyu Ye,† Jennifer Flynn,†
Shinji Fujikoshi,† Naohiro Nakahara,† Michihiro Takahashi†‡

**Eli Lilly and Company, Indianapolis, IN, USA*
†Eli Lilly Japan K.K., Kobe, Japan
‡Terauchi-Takahashi Psychiatric Clinic, Ashiya, Japan

ABSTRACT

Purpose: To assess the clinical and functional outcomes of olanzapine treatment for schizophrenia in a 1-year naturalistic study of inpatients and outpatients in Japan.
Methods: We used data from a large (N=1850), prospective, observational study of Japanese schizophrenia patients who were initiated on olanzapine. Clinical and functional outcomes of inpatients and outpatients were contrasted using chi-square tests, t-tests, and mixed models for repeated measures controlling for baseline demographics.
Results: At study entry, 43.2% were outpatients and 56.8% were inpatients. The mean (± SD) dosage for olanzapine was 11.4 ± 5.7 mg/day. Outpatients were significantly younger and more likely to be female. The most common reason for switching to olanzapine was poor medication efficacy (outpatients: 71.8%, inpatients: 74.3%), followed by medication intolerability (outpatients: 21.5%, inpatients: 28.0%). Most outpatients (63.8%) and inpatients (71.6%, p=.003) completed the study. Outpatients and inpatients experienced clinically and statistically significant improvements in global symptom severity, positive, negative, depressive, and cognitive symptoms, health-related quality of life, paid work, and social activities. Many outpatients (60.9%) and inpatients (50.5%, p<.001) demonstrated symptomatic response, with 51.0% of outpatients and 32.8% of inpatients (p<.001) experiencing remission. Mean weight gain was 2.06 kg, with 26.5% of patients experiencing clinically significant weight gain (≥ 7%).
Discussion: In this 1-year naturalistic study, inpatients and outpatients who initiated treatment with olanzapine experienced significant improvements in their clinical and functional outcomes. One-fourth of patients experienced clinically significant weight gain. Current findings highlight the favorable benefit to risk profile of olanzapine for the treatment of schizophrenia in Japan.

Keywords: Olanzapine, Schizophrenia, Treatment Outcome, Inpatients, Outpatients

Received April 5, 2011 / Accepted November 1, 2011 / Published November 25, 2011

INTRODUCTION

Schizophrenia can have a devastating impact on the afflicted person's ability to function normally. Naturalistic studies across different geographies have found that only a small proportion of individuals with this disorder are married [1,2] or competitively employed [1,3]. Although, both physical functioning and mental functioning are lower than population norms, the disorder's primary effects are on mental functioning [4]. The symptoms of schizophrenia interfere with the ability of most patients to live productive lives.

Antipsychotic medications represent the primary

Corresponding Author: Haya Ascher-Svanum, Lilly Corporate Center, Indianapolis, IN 46285 USA.
Tel: 1-317-277-8713 Fax: 1-317-276-7100 E-mail: haya@lilly.com

treatment for the core symptoms of schizophrenia [5-7]. The antipsychotics are often divided into two broad categories, based primarily on the timing of their development relative to clozapine: the first-generation or typical antipsychotics and second-generation or atypical antipsychotics (e.g., risperidone, olanzapine, quetiapine, perospirone, ziprasidone, and aripiprazole) [8]. Recent large scale publically funded clinical trials [9] and meta-analyses of randomized clinical trials [10,11] have shown that the atypical antipsychotics are a heterogeneous group of medications that vary in effectiveness and tolerability. In meta-analyses, olanzapine has been found to have greater efficacy in reducing the symptoms of schizophrenia than typical antipsychotics [12] and compared to other atypical antipsychotics, including ziprasidone, aripiprazole, quetiapine, and risperidone [10], but with potentially greater weight gain than these comparators [13]. Considering that treatment response also varies among individual patients, there is a need to tailor treatment to individual patients' needs, as some patients who do not respond to one antipsychotic may respond to a different one [14].

Prospective observational studies in Europe and the United States (US) have examined the outcomes for patients with schizophrenia treated with antipsychotics in usual clinical practice. The pan-European Schizophrenia Outpatient Health Outcomes (SOHO) study was a non-interventional study that enrolled over 10,000 outpatients in 10 European countries and followed them for 36 months [15-20]. The discontinuation rates for patients treated with olanzapine were significantly lower than for amulsipride, risperidone, quetiapine, and typical antipsychotics [15,16]. Medication discontinuation rate for any cause (or time to all-cause medication discontinuation) is considered a measure of overall medication effectiveness, as it encapsulates both efficacy and tolerability [21]. Consistent with findings on lower discontinuation rates, the SOHO study also found significantly better response rate [16], lower relapse rates [17], and greater functional improvement [16] for patients treated with olanzapine than for patients treated with risperidone, quetiapine, or typical antipsychotics. Similarly, in usual care in the US, patients treated with olanzapine stayed longer on therapy relative to haloperidol, risperidone, and quetiapine [22]. However, it is unclear whether these findings from usual care in Europe and the US generalize to patients with schizophrenia treated in Japan.

There is little observational research examining the effectiveness of olanzapine for schizophrenia in Japan. In addition to potential genetic variations across geographies, differences in healthcare systems have the potential to effect outcomes. Relative to many other geographies, patients with schizophrenia in Japan are more likely to be treated with typical antipsychotics [23-25] and with multiple antipsychotics [23,25]. Japan has also been reported to have the highest level of psychiatric inpatient beds per capita [26], reflecting more frequent use of inpatient facilities for a longer duration. The average length of hospital stay for treatment of schizophrenia in Japan was reported in 2008 to be 312.9 days [27], which is substantially longer than 11.5 days found in the US [28]. Due to marked variation in healthcare systems across world geographies, there is a need to assess the clinical and functional outcomes in the treatment of schizophrenia patients in Japan, and to understand how treatment outcomes may differ between Japanese inpatient and outpatients. It is also unclear whether treatment outcomes in usual clinical care settings in Europe and the US could be generalized to schizophrenia patients treated in Japan.

The objectives of this study were two-fold. The first objective was to assess clinical and functional outcomes following initiation of olanzapine in a 1-year naturalistic study of schizophrenia patients in Japan. The outcomes were assessed in five domains that are relevant to patients, clinicians, family members, and payers: medication persistence, symptom improvement, functional outcomes, relapse and hospitalization, and treatment-emergent adverse events. The second objective was to describe and contrast differences in these treatment outcomes for inpatients and outpatients. Results are discussed in the context of previously published treatment outcomes for schizophrenia patients treated in overseas global geographies outside of Japan, including Europe and the US.

METHODS

Study Procedures

A large (N=1,949) multicenter, naturalistic, 1-year study in Japan called the Olanzapine Post Marketing Surveillance (OPMS) study provided data for this analysis. The OPMS study was designed to assess the safety of olanzapine and the primary results were previously published in Japanese [29]. The primary eligibility criteria for the study were a diagnosis with schizophrenia based on DSM-IV criteria and initiation of treatment with olanzapine. The study enrollment began once the patient was initiated on olanzapine, which could have been a patient's first antipsychotic treatment, a switch from another antipsychotic, or an

augmentation of their current antipsychotic treatment. In this naturalistic, observational, and non-interventional study, all treatment decisions were left to the discretion of the treating physician. The study enrollment began in November 2003 and completed in July 2004 with the follow up period continuing for one year after enrollment or until the patient discontinued treatment with olanzapine. Data were collected at the baseline, 3-month, 6-month, and 12-month visits.

The internal review boards at each of the participating institutions approved the study procedures. Informed consent was obtained based on the rules at each participating medical facility.

Measures

The procedures for this observational study were designed to be minimally invasive, thus, cumbersome or invasive measures were not included in the study. Information on demographic characteristics, history of illness, and reasons for switching to olanzapine were collected at baseline, along with an inquiry about a history of the following medical complications: hypertension, hyperlipidemia, hepatic dysfunction, renal dysfunction, or other. The outcome measures covered five core domains: medication persistence, symptom improvement, functional level, relapse and hospitalization, and adverse events.

Medication Persistence

Time to and rate of all-cause medication discontinuation (persistence on medication) was based on medication information that was collected during the study including drug name, dose, route of administration, and start and stop dates. When a patient discontinued olanzapine they also discontinued their enrollment in the study. If the stop date for olanzapine was missing the study discontinuation date was used.

Symptom Improvement

The Clinical Global Impression – Schizophrenia (CGI-SCH) is a clinician-rated measure of global severity rating and 4 additional symptom clusters: positive, negative, cognitive, and depressive symptoms. The rating scale is anchored and ranges from no symptoms (0) to severe symptoms (6) [30]. The concurrent validity of the CGH-SCH subscales with the corresponding subscales from the more rigorous Positive and Negative Syndrome Scale (PANSS) [31] have been found to be moderate to high depending on the subscale. Correlation coefficients ranged from .86 for positive symptoms to .61 for depressive symptoms, with the remaining ranging from .75 to .80. Inter-rater reliability has been found to be high (interclass correlation coefficients ranging from .73 to .82 for all but the depressive subscale (.64) [30].

Symptomatic response and remission were defined based on previously published definitions for the CGI-SGH. Response was defined as a 2-point improvement in the CGI-SCH global severity rating for patients with a baseline rating of 4 to 6 points, or a 1-point improvement for patients with a baseline rating between 1 and 3 [16]. Symptomatic remission was defined as mild to no symptoms (score ≤ 2) on the CGI-SCH positive, negative, cognitive, and global severity scores [17].

Functional Outcomes

The European Quality of Life – 5 Dimensions (EQ-5D) is a generic measure of health related quality of life (HRQOL) [32]. The measure includes a patient rated Visual Analog Scale (VAS) rating from 0 to 100 of overall health and additional ratings of 5 specific dimensions of HRQOL: Level of Movement, Control of Environment, Normal Activities, Pain/Discomfort, and Anxiety/Depression. Utility values ranging from death (0) to perfect health (1) are assigned to different health states created from the ratings on the 5 dimensions. The construct validity of the EQ-5D has been evaluated in a sample of individuals with schizophrenia: utility scores were moderately correlated with the PANSS subscales (-.15 to -.67) and the World Health Organization Quality of Life – Brief Questionnaire subscales (.28 to .60) [33]. In addition to the EQ-5D, patients were also asked about their participation in social activities in the past four weeks and employment status.

Relapse and Hospitalization

Relapse was defined as an increase in CGI-SCH global symptom severity score of at least 2 points to at a score of at least 3 (“moderately ill”) for patients who met the criteria for response at an earlier visit. Relapse was also examined among patients who met the criteria for remission at an earlier visit using the same criteria. In addition to hospitalization status at each visit, the number of days hospitalized since the previous visit was also collected. Based on the hospitalization status at the time of olanzapine initiation, patients were grouped into two cohorts: inpatients or outpatients.

Adverse Events

Body weight was measured at each visit. Body mass index (BMI) was categorized based on the World Health Organization recommendations for Asians [34]. The categories included: underweight (<18.5), normal (≥18.5, ≤23), overweight (>23, ≤30), and obese (>30). Finally, the study included clinicians' ratings for dystonia/akathisia/parkinsonism, tardive dyskinesia, decreased libido, amenorrhoea/other menstrual dysfunction, erectile/sexual dysfunction, gynecomastia, and lactorrhea. A treatment-emergent adverse event was coded if the symptom was absent at baseline and present later during the study or if the symptom was rated as mild at baseline and increased in severity during the study.

Statistical Methods

Baseline comparisons between the inpatient and outpatient groups were completed with t-tests for continuous variables and chi-square tests for categorical variables. For the CGI-SCH and EQ-5D measures, the baseline comparisons were completed using the baseline contrasts from the outcome models. Mixed Models for Repeated Measures (MMRM), with baseline covariates for age, gender, duration of illness, and presence of any medical complication, were used to assess changes over time on the CGI-SCH and EQ-5D measures. Comparisons of categorical variables between baseline and endpoint were completed using McNemar's test with missing observations imputed using the last observation carried forward method. Survival curves for time to treatment discontinuation were constructed using unadjusted Kaplan-Meier estimates and a log-rank test was used to test the difference between inpatients and outpatients. All analyses were completed using SAS version 9.1.3 (SAS Institute, Inc., Cary, NC) with a significance level was set at $\alpha = .05$.

RESULTS

The OPMS study registered and enrolled 1949 patients, of which 1850 (94.9%) met all study entry criteria: 27 were excluded for contract or registration violations, 20 had no case report forms, 49 did not return after the initial visit, and 3 did not initiate treatment with olanzapine. At study entry, 43.2% (n = 800) were outpatients and 56.8% (n = 1050) were inpatients. The average dose of olanzapine during the study was 11.4 ± 5.7 mg/day, with higher doses for inpatients (12.9 ± 5.5 mg/day) than outpatients (9.3 ± 5.4 mg/day; $p < .001$). Table 1 presents the baseline characteristics for the study sample and contrasts the inpatients with the outpatients. The reasons for switching from the previous medication to olanzapine, which was primarily due to insufficient efficacy, are also given in Table 1. Only 847 patients (45.8%; outpatient: 55.0%; inpatient: 38.8%) were treated with olanzapine monotherapy throughout the study, with the remaining 1003 patients (54.2%) being treated with antipsychotic polypharmacy at some point during the study.

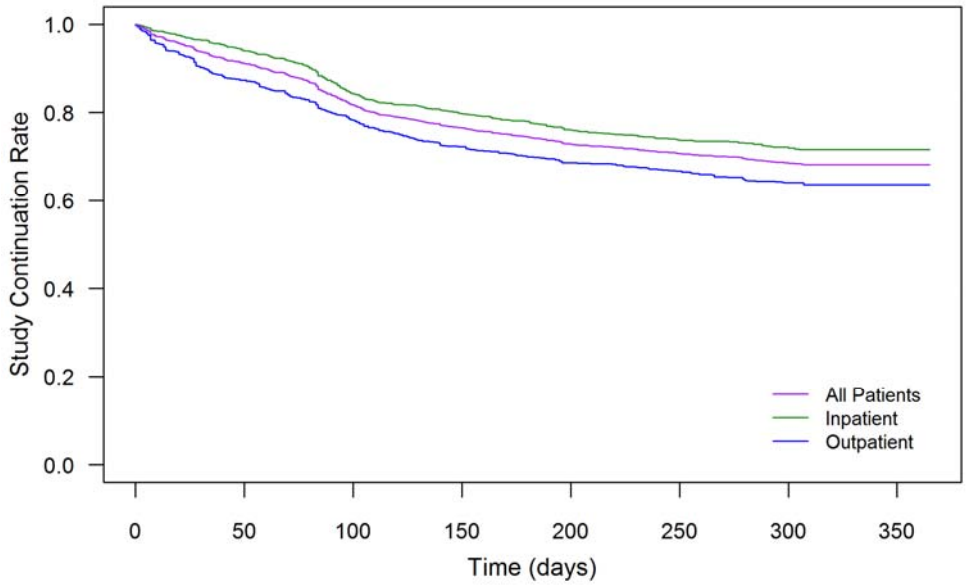

Figure 1. Time to all-cause discontinuation of olanzapine for all patients, inpatients, and outpatients. Time to all-cause discontinuation was significantly longer for inpatients than outpatients ($p = .003$).

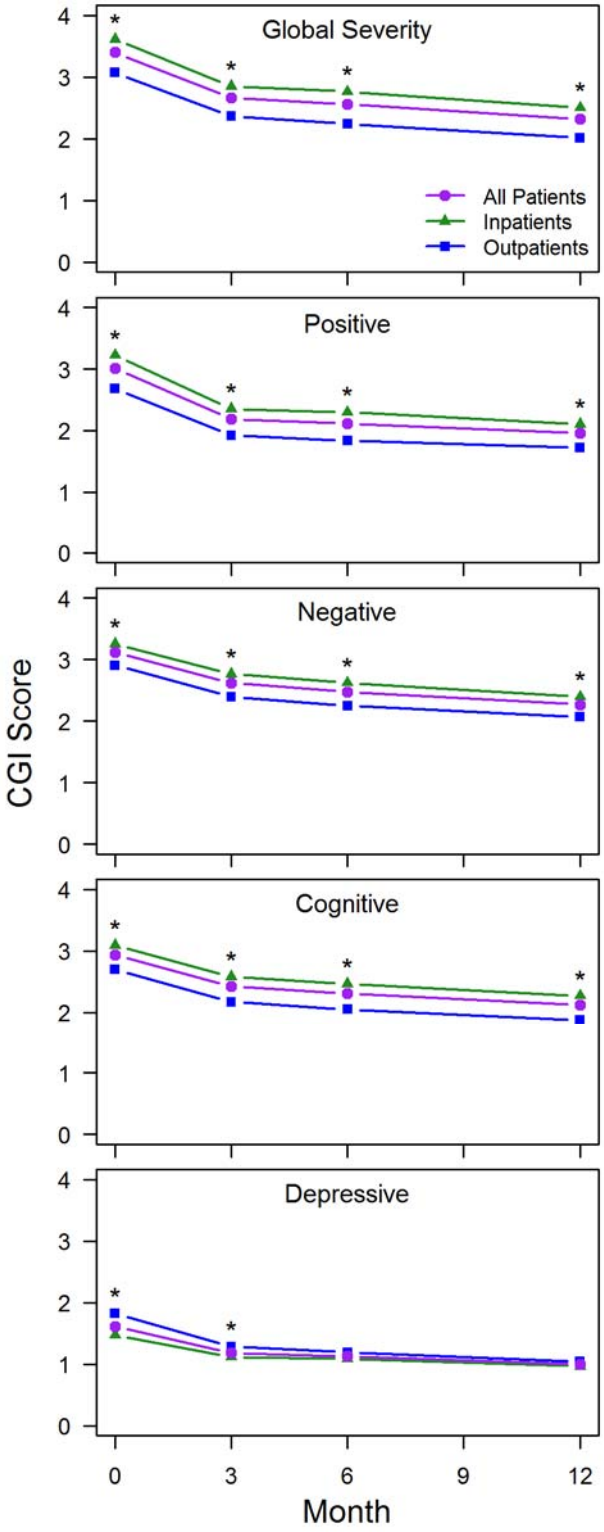

Figure 2. CGI-SCH scores over the 1-year study period. The CGI-SCH subscale scores changed significantly from study entry to post-baseline visits ($p < .001$) for all patients, outpatients and inpatients. The MMRM models were adjusted for age, gender, duration of illness, and presence of any medical complication. Asterisks indicate differences between inpatients and outpatients at each visit ($p < .05$).

Table 1. Baseline Characteristics

Characteristic	Total N	All Patients	Outpatients	Inpatients	p
Age (y), mean ± SD	1850	44.8 ± 15.5	38.3 ± 13.9	49.8 ± 14.8	<.001
Female (%)	1850	46.8	49.6	44.7	.03
Duration of illness (y), mean ± SD	1451	18.3 ± 14.7	11.4 ± 11.6	23.2 ± 14.8	<.001
Any medical complications (%)	1849	36.2	22.6	46.6	<.001
Working for pay (%)	1820	9.0	17.8	2.2	<.001
CGI-SCH global, mean ± SD	1822	3.4 ± 1.1	3.0 ± 1.0	3.7 ± 1.0	<.001
CGI-SCH positive, mean ± SD	1822	3.0 ± 1.5	2.6 ± 1.4	3.3 ± 1.5	<.001
CGI-SCH negative, mean ± SD	1822	3.1 ± 1.3	2.7 ± 1.2	3.3 ± 1.3	<.001
CGI-SCH cognitive, mean ± SD	1822	2.9 ± 1.3	2.6 ± 1.2	3.2 ± 1.3	<.001
CGI-SCH depressive, mean ± SD	1822	1.7 ± 1.4	1.9 ± 1.3	1.5 ± 1.4	<.001
EQ-5D VAS, mean ± SD	1815	47.7 ± 22.5	45.3 ± 20.0	49.5 ± 24.0	<.001
EQ-5D Utility Score, mean ± SD	1822	0.68 ± 0.18	0.70 ± 0.16	0.67 ± 0.19	0.94
BMI, mean ± SD	1638	22.6 ± 4.1	23.0 ± 4.1	22.3 ± 4.0	<.001
Reason for switch (%)	609				
Insufficient efficacy	445	73.1	71.8	74.3	.49
Medication intolerability	151	24.8	21.5	28.0	.06
Patient request	42	6.9	9.7	4.2	.01
Non-compliance	29	4.8	4.0	5.5	.40

Note. The p-value reflects the comparison of outpatients to inpatients.

Medication Persistence

Overall 68.2% of patients completed the study, including 63.8% of outpatients and 71.6% of inpatients (p <.001). The average time to discontinuation during the one year study was 265.5 ± 119.4 days (outpatient: 251.7 ± 127.7; inpatient: 276.0 ± 111.7). Figure 1 displays the discontinuation rates over the full study period for both inpatients and outpatients.

Symptom Improvement

On the CGI-SCH global severity score and the positive, negative, cognitive, and depressive symptom subscale scores, the patients significantly improved after initiating treatment with olanzapine (p < .001). Overall, symptom improvement appeared to be the more pronounced in the first 3 months of therapy. With the exception of the depressive subscale, the inpatients had statistically significant (p < .001) higher scores on all of the subscale at each time point (see Figure 2). On the depressive subscale, there was a significant time by hospitalization interaction in which the outpatients initially had higher scores.

Overall, the response rate was 54.8% and significantly higher for the outpatients (60.9%) than inpatients (50.5%; p < .001). Similarly 39.7% of patients demonstrated symptom remission at any time including 51.0% of outpatients and 32.8% of inpatients (p < .001).

Functional Outcomes

Health related quality of life improved from an EQ-5D VAS score of 47.9 at baseline to 65.3 at the 12 month visit (p < .001). At baseline, outpatients had statistically significantly lower scores than inpatients (45.3 vs. 49.5; p < .001), but similar VAS scores (within 2 points and p > .05) at all post-baseline visits. Utility scores from the EQ-5D improved from .679 at baseline to .801 at the 12-month visit and were comparable across time (within .02 points and p > .05).

The number of patients working for pay and engaging in social activities increased during the study. At baseline, 9.0% were working for pay, which improved to 10.5% at the end of the study (p = .001); with an improvement from 17.8% to 20.5% for outpatients (p = .01) and 2.2% to 3.4% for inpatients (p = .048). At baseline 28.3% of patients had engaged in at least 1 social activity during the previous 4-week period, which increased to 37.2% at endpoint (p < .001); with an increase from 42.0% to 52.2% for outpatients (p < .001) and 18.7% to 26.7% for inpatients (p < .001).

Relapse and Hospitalization

When relapse was assessed for patients who met the criteria for response, 13.3% (outpatients: 13.0%, inpatients: 13.6%, p = .80) relapsed prior to the end of the study. Alternatively, when relapse was assessed for patients who met the criteria for remission, 18.8%

(outpatients: 17.7%, inpatients: 19.9%, p = .56) relapsed prior to the end of the study. During the study, patients were hospitalized an average of 121.8 ± 144.3 days (outpatients: 7.7 ± 34.6, inpatients: 211.2 ± 134.1). Among the inpatients, 28.9% were discharged at some point during the study. At the study endpoint, 78.4% of the inpatients remained hospitalized, while 2.3% of the outpatients were hospitalized. Overall, the percent of patients who were hospitalized decreased from 56.8% at baseline to 45.8% at endpoint (p < .001).

Treatment Emergent Adverse Events

New onsets of the measured adverse events were relatively infrequent. There were 59 cases (3.2%) of new onset dystonia/akathisia/parkinsonism; 5 cases (0.3%) of new onset tardive dyskinesia; 11 cases (0.7%) of new onset decreased libido; 14 cases (2.1%) of new onset amenorrhoea/menstrual dysfunction; 6 cases (0.4%) of new onset erectile/sexual dysfunction; a single case of new onset gynecomastia (0.1%), and a single case of new onset lactorrhea (0.1%). The rates of these new onset adverse events were similar for inpatients and outpatients (within 0.2% and p > .05).

Mean weight gain was 2.06 kg (outpatients: 2.33 kg, inpatients 1.89 kg, p = .19), with about one-fourth of patients (26.5%, outpatients: 27.3%, inpatients: 26.0%, p = .57) experiencing clinically significant weight gain (≥ 7%). The patients' BMI categories increased for 17.1% of patients (outpatients: 16.4%, inpatients: 17.5%), decreased for 5.7% (outpatients: 3.8%, inpatients: 6.8%), and remained the same for 77.2% (outpatients: 79.8%, inpatients: 75.7%, p = .046).

Sensitivity Analysis

To evaluate whether the study's findings were possibly driven by the use of antipsychotic polypharmacy - the use of olanzapine with any other antipsychotic during this 1-year study, we conducted a sensitivity analysis, in which all the study analyses were repeated using only the 847 patients that were treated with olanzapine monotherapy throughout the study. Results of the sensitivity analysis, and its conclusions, remained nearly identical to the original analysis, except for two changes: (a) the originally significant improvement the percentage of inpatients reporting working for pay had become non-significant (despite an increase in the rate of working for pay from 5.2% to 6.4%, p = .39), and (b), the originally significant difference in response rate between outpatients (71.2%) and inpatients (65.1%) became non-significant (p = .09). All other findings remained statistically significant in the sensitivity analysis with only the olanzapine monotherapy treated patients.

DISCUSSION

This 1-year observational study of olanzapine treatment in schizophrenia documented the naturalistic outcomes of 1850 Japanese inpatients and outpatients across five core domains: medication persistence (a proxy measure of a medication's effectiveness [21]), symptom improvement (in global severity, specific symptom domains, and response and remission rates), functional outcomes (general HRQOL and the specific functional sub-domains of work and social activity), relapse and hospitalization (rates and hospitalized duration), and treatment-emergent adverse events. In usual clinical care in Japan, olanzapine treated patients experienced and maintained significant improvements in their clinical symptoms and functional status, with somewhat better outcomes for outpatients than inpatients. The clinical and functional benefits were accompanied, however, by a significant weight gain (≥ 7%) in about one-fourth of patients (26.5%). All other studied treatment-emergent adverse events were observed in only a very small proportion of the patients.

Positive outcomes were observed across the core outcome domains. Level of persistence on olanzapine therapy was high, as nearly 70% of patients remained on treatment for the full one-year study period, with significantly higher completion rates for inpatients than outpatients. In terms of symptom improvement, both inpatients and outpatients showed significant improvements in positive, negative, cognitive, and depressive symptoms. Overall, 54.8% responded to olanzapine treatment and 39.7% met the criteria for symptom remission, with significantly more outpatients responding and achieving remission than inpatients. Both inpatients and outpatients also demonstrated significant improvements in HRQOL, social functioning, and ability to gain competitive employment. Over one quarter of the patients (28.9%) who were hospitalized at the time of olanzapine initiation were discharged during the study. Finally, among the patients who responded to olanzapine treatment, only 13.3% had a symptomatic relapse. On average, both the inpatients and outpatients had positive outcomes across these core outcome domains.

The inpatients appeared to represent a meaningfully different subset of patients from the outpatients as there were multiple significant differences. In terms of demographics, the inpatients were older, more likely

to be male, and had a longer duration of illness. Across the study visits, the inpatients had more severe symptoms, lower remission rates, had lower HRQOL, were treated with higher doses of olanzapine, and were less likely to engage in social activities or competitive employment. The differences between inpatients and outpatients found in this population is consistent with other research showing that inpatients with schizophrenia have more severe symptoms, are treated with higher doses of antipsychotics, and have higher needs for care [35,36]. The greater depressive symptoms among outpatients rather than inpatients has also been reported previously [36], and may reflect higher levels of insight resulting in greater awareness of their functional disability or may reflect greater stresses from living in the community; however, the reasons could not be ascertained from the data in this study.

The rates of treatment emergent adverse events were relatively uncommon, ranging from 0.1% for gynecomastia or lactorrhea to 3.2% for dystonia/ akathisia/parkinsonism. The relatively low rates of these adverse events are consistent with meta-analytic reviews, which have found olanzapine to be associated with a lower incidence of extrapyramidal adverse events than typical antipsychotics [12] as well as the atypical antipsychotics risperidone and ziprasidone [11]. Consistent with some prior studies [9,13], 26.5% of the population experienced clinically significant weight gain (≥ 7% of baseline body weight) and the average weight gain after one-year was 2.06 kg. A recent meta-analysis of atypical antipsychotics reported that patients treated with olanzapine experienced more increases in weight, cholesterol, and glucose than most of the other atypical antipsychotics [13]. Consistent with research outside of Japan, the most commonly observed adverse event was weight gain.

In this one-year observational study of Japanese patients with schizophrenia, the benefit to risk profile of olanzapine appeared favorable. Moreover, despite differences in health care systems, the results from the OPMS study were found to be similar to findings in other world geographies.

Outcomes for Olanzapine Treatment Outside of Japan

The design of the OPMS study in Japan was similar to the SOHO study in Europe; the primary differences were that the SOHO study included only outpatients, enrolled over 10,000 patients, and had a duration of 3 years [18]. The baseline characteristics of the 5,377 outpatients initiated on olanzapine in the SOHO study appear similar to those of the outpatients in the OPMS study in terms of average age (40.0 ± 13.4 and 38.3 ± 13.9 years), gender (41.1% and 49.6% female), CGI-SH global severity in the moderately ill range (3.4 ± 1.0 and 3.0 ±1.0), paid employment rate (20.7% and 17.8%), and level of functioning as measured by the EQ-5D VAS (45.7 ± 21.1 and 45.3 ± 20.1, for the SOHO and OPMS studies, respectively) [16,20].

In addition to similarity in baseline characteristics, treatment outcomes for outpatients on the core outcome domains in the OPMS study were similar to those observed in the European SOHO study. The percent of patients remaining on treatment for one year was 63.8% for the outpatients in the current study and slightly higher at 70.3% in the SOHO study [37]. Symptomatic response rates were similar at 60.9% for outpatients in OPMS and 63.8% in the SOHO study [37]. In terms of global functioning, the EQ-5D VAS score of 65.3 observed in this study was remarkably similar to the 65.2 observed after 1-year in the SOHO study [37]. The paid employment rates were 20.5% after 1-year of treatment in the current study and 20.3% in the SOHO study [37]. Among outpatients who had responded to treatment the relapse rate was 13.0% in the current study and 7.0% when using a similar definition in SOHO [37]. Finally, the percentage of patients experiencing clinically significant weight gain (≥ 7%) after 1-year of treatment was 26.5% in OPMS and 28.0% in SOHO [37]. Across the core domains, the outcomes for outpatients treated with olanzapine in Japan appear largely consistent with the outcomes for olanzapine treated patients in a similarly designed observational study conducted in 10 European countries.

Limitations

This prospective observational study was designed to maximize the generalizability of results regarding the outcomes for Japanese patients with schizophrenia treated with olanzapine. Therefore, design considerations that favored external validity were given precedence over those that favored internal validity. Because this was a single arm prospective study, treatment effects of olanzapine cannot be separated from the improvements due to the passage of time. In addition, antipsychotic polypharmacy was common in this study, which is consistent with other studies of usual care in Japan [23,25]. Therefore, the treatment effects observed may not be due solely to the olanzapine treatment, but also include the effects other medications and psychosocial interventions. However, it is notable that findings from the current single cohort study appear consistent with those of SOHO, a

similar observational study that included several antipsychotic cohorts. The similarity in baseline patient characteristics and in treatment outcomes for the olanzapine-treated outpatients (when comparing OPMS outpatients to the SOHO study, which included only outpatients) suggest that findings from the current Japanese OPMS study reflect treatment effects rather than sheer study artifacts such as regression to the mean or the passage of time. Although baseline demographic differences were statistically controlled for in the analyses, there were other important baseline variables, potentially including unmeasured variables, which differed between inpatients and outpatients. Differences in outcomes between inpatient and outpatients may represent differences in patient characteristics rather than the effects of the treatment setting. Finally, dates of hospitalizations were not collected in this study. This prevented analyses of the time to discharge from psychiatric hospitalization among participants who were inpatients at study enrollment and among outpatients who were hospitalized during the study. However, data on hospitalization rates for both outpatients and inpatients were available at each assessment point, which provided some information about this important treatment parameter that appears to be relatively frequent among patients with schizophrenia in Japan.

CONCLUSIONS

In this 1-year prospective naturalistic study, inpatients and outpatients who were initiated on olanzapine therapy experienced and maintained significant improvements in their clinical and functional outcomes. These favorable outcomes were, however, accompanied by clinically significant weight gain among one-fourth of patients. Current findings highlight the favorable benefit to risk profile of olanzapine in the treatment of inpatients and outpatients with schizophrenia in Japan.

ACKNOWLEDGEMENTS

Funding for this study was provided by Eli Lilly and Company. Technical writing support was provided by Michael Stensland of Agile Outcomes Research Inc, Rochester, Minnesota, USA and Susan Dennett of Strategic Health Outcomes Inc, Carmel, Indiana, USA

CONFLICTS OF INTEREST

Haya Ascher-Svanum is a full-time employee of Eli Lilly and Company. Jennifer Flynn, Wenyu Ye, Shinji Fujikoshi, Naohiro Nakahara, and Michihiro Takahashi are full time employees of Eli Lilly Japan, K.K. All authors are minor stockholders in Eli Lilly and Company.

REFERENCES

[1] Rosenheck R, Leslie D, Keefe R, McEvoy J, Swartz M, Perkins D, Stroup S, Hsiao JK, Lieberman J. Barriers to employment for people with schizophrenia. Am J Psychiatry 2006; 163: 411-417.

[2] Lehman AF, Fischer EP, Postrado L, Delahanty J, Johnstone BM, Russo PA, Crown WH. The Schizophrenia Care and Assessment Program Health Questionnaire (SCAP-HQ): an instrument to assess outcomes of schizophrenia care. Schizophr Bull 2003; 29: 247-256.

[3] Karagianis J, Novick D, Pecenak J, Haro JM, Dossenbach M, Treuer T, Montgomery W, Walton R, Lowry AJ. Worldwide-Schizophrenia Outpatient Health Outcomes (W-SOHO): baseline characteristics of pan-regional observational data from more than 17,000 patients. Int J Clin Pract 2009; 63: 1578-1588.

[4] Fleischhacker WW, Rabinowitz J, Kemmler G, Eerdekens M, Mehnert A. Perceived functioning, well-being and psychiatric symptoms in patients with stable schizophrenia treated with longacting risperidone for 1 year. Br J Psychiatry 2005; 187: 131-136.

[5] Falkai P, Wobrock T, Lieberman J, Glenthoj B, Gattaz WF, Möller H. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia, Part 1: acute treatment of schizophrenia. World J Biol Psychiatry 2005; 6: 132-191.

[6] Falkai P, Wobrock T, Lieberman J, Glenthoj B, Gattaz WF, Möller H. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia, part 2: long-term treatment of schizophrenia. World J Biol Psychiatry 2006; 7: 5-40.

[7] Lehman AF, Lieberman JA, Dixon LB, McGlashan TH, Miller AL, Perkins DO, Kreyenbuhl J. Practice guideline for the treatment of patients with schizophrenia, second edition. Am J Psychiatry 2004; 161: 1-56.

[8] Leucht S, Kissling W, Davis JM. Second-generation antipsychotics for schizophrenia: can we resolve the conflict? Psychol Med 2009; 39: 1591-1602.

[9] Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RSE, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005 22; 353: 1209-1223.

[10] Leucht S, Komossa K, Rummel-Kluge C, Corves C, Hunger H, Schmid F, Asenjo Lobos C, Schwarz S, Davis JM. A meta-analysis of head-to-head comparisons of second-generation antipsychotics in the treatment of schizophrenia. Am J Psychiatry 2009; 166: 152-163.

[11] Komossa K, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S, Duggan L, Kissling W, Leucht S. Olanzapine versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev 2010; CD006654.

[12] Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet 2009 3; 373: 31-41.

[13] Rummel-Kluge C, Komossa K, Schwarz S, Hunger H, Schmid F, Lobos CA, Kissling W, Davis JM, Leucht S. Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: a systematic review and meta-analysis. Schizophr Res 2010; 123: 225-233.

[14] Suzuki T, Uchida H, Watanabe K, Nomura K, Takeuchi H, Tomita M, Tsunoda K, Nio S, Den R, Manki H, Tanabe A, Yagi G, Kashima H. How effective is it to sequentially switch among Olanzapine, Quetiapine and Risperidone?—A randomized, open-label study of algorithmbased antipsychotic treatment to patients with symptomatic schizophrenia in the real-world clinical setting. Psychopharmacology 2007 8; 195: 285-295.

[15] Haro JM, Suarez D, Novick D, Brown J, Usall J, Naber D. Three-year antipsychotic effectiveness in the outpatient care of schizophrenia: observational versus randomized studies results. Eur Neuropsychopharmacol 2007; 17: 235-244.

[16] Haro JM, Edgell ET, Novick D, Alonso J, Kennedy L, Jones PB, Ratcliffe M, Breier A. Effectiveness of antipsychotic treatment for schizophrenia: 6-month results of the Pan-European Schizophrenia Outpatient Health Outcomes (SOHO) study. Acta Psychiatr Scand 2005; 111: 220-231.

[17] Haro JM, Novick D, Suarez D, Alonso J, Lépine JP, Ratcliffe M. Remission and relapse in the outpatient care of schizophrenia: three-year results from the Schizophrenia Outpatient Health Outcomes study. J Clin Psychopharmacol 2006; 26: 571-578.

[18] Haro JM, Edgell ET, Jones PB, Alonso J, Gavart S, Gregor KJ, Wright P, Knapp M. The European Schizophrenia Outpatient Health Outcomes (SOHO) study: rationale, methods and recruitment. Acta Psychiatr Scand 2003; 107: 222-232.

[19] Novick D, Haro JM, Suarez D, Vieta E, Naber D. Recovery in the outpatient setting: 36-month results from the Schizophrenia Outpatients Health Outcomes (SOHO) study. Schizophr Res 2009; 108: 223-230.

[20] Haro JM, Edgell ET, Frewer P, Alonso J, Jones PB. The European Schizophrenia Outpatient Health Outcomes Study: baseline findings across country and treatment. Acta Psychiatr Scand Suppl 2003; 7-15.

[21] Stroup TS, McEvoy JP, Swartz MS, Byerly MJ, Glick ID, Canive JM, McGee MF, Simpson GM, Stevens MC, Lieberman JA. The National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project: schizophrenia trial design and protocol development. Schizophr Bull 2003; 29: 15-31.

[22] Ascher-Svanum H, Zhu B, Faries DE, Lacro JP, Dolder CR, Peng X. Adherence and persistence to typical and atypical antipsychotics in the naturalistic treatment of patients with schizophrenia. Patient Prefer Adherence 2008; 2: 67-77.

[23] Bitter I, Chou JC, Ungvari GS, Tang WK, Xiang Z, Iwanami A, Gaszner P. Prescribing for inpatients with schizophrenia: an international multi-center comparative study. Pharmacopsychiatry 2003; 36: 143-149.

[24] Chong M, Tan CH, Fujii S, Yang S, Ungvari GS, Si T, Chung EK, Sim K, Tsang H, Shinfuku N. Antipsychotic drug prescription for schizophrenia in East Asia: rationale for change. Psychiatry Clin Neurosci 2004; 58: 61-67.

[25] Shinfuku N, Tan C. Pharmacotherapy for

schizophrenic inpatients in East Asia--changes and challenges. Int Rev Psychiatry 2008; 20: 460-468.
[26] Oshima I, Mino Y, Inomata Y. How many long-stay schizophrenia patients can be discharged in Japan? Psychiatry Clin Neurosci 2007; 61: 71-77.
[27] Health Statistics Office, Statistics and Information Department, Vital and Health Statistics Division. Summary of Static/Dynamic Surveys of Medical Institutions and Hospital Report [Internet]. Tokyo, Japan: Ministry of Health, Labour and Welfare; 2008 [cited 2011 Feb 18]. Available from: http://www.mhlw.go.jp/english/database/db-hss/mih_report_2008.html
[28] Healthcare Cost and Utilization Project (HCUP). HCUP Nationwide Inpatient Sample (NIS), 2004 [Internet]. Rockville, MD: Agency for Healthcare Research and Quality; [cited 2010 Feb 3]. Available from: http://hcupnet.ahrq.gov/HCUPnet.jsp
[29] Kuramochi M, Ono H, Nakahara N, Takagaki N, Fujikoshi S, Fuchigami Y, Michihiro Takahashi. Health outcome survey of olanzapine therapy in patients with schizophrenia: Analytical results of the post-marketing special survey of olanzapine. Jpn J Clin Psychopharmacol 2009; 12: 71-89.
[30] Haro JM, Kamath SA, Ochoa S, Novick D, Rele K, Fargas A, Rodríguez MJ, Rele R, Orta J, Kharbeng A, Araya S, Gervin M, Alonso J, Mavreas V, Lavrentzou E, Liontos N, Gregor K, Jones PB. The Clinical Global Impression-Schizophrenia scale: a simple instrument to measure the diversity of symptoms present in schizophrenia. Acta Psychiatr Scand Suppl 2003; 16-23.
[31] Kay SR, Opler LA, Fiszbein A. Positive and Negative Syndrome Scale (PANSS) User's Manual. North Tonawanda, NY: Multi-Health Systems, Inc; 2000.
[32] The EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy 1990; 16: 199-208.
[33] Prieto L, Sacristán JA, Hormaechea JA, Casado A, Badia X, Gómez JC. Psychometric validation of a generic health-related quality of life measure (EQ-5D) in a sample of schizophrenic patients. Curr Med Res Opin 2004; 20: 827-835.
[34] WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004 10; 363: 157-163.
[35] Nakanishi M, Setoya Y, Kodaka M, Makino H, Nishimura A, Yamauchi K, Mimura M, Sato H, Arata H, Yukumi H, Amagasa T, Ueno H, Miyamoto Y, Sugie T, Anzai N. Symptom dimensions and needs of care among patients with schizophrenia in hospital and the community. Psychiatry Clin Neurosci 2007; 61: 495-501.
[36] Soni SD, Mallik A, Reed P, Gaskell K. Differences between chronic schizophrenic patients in the hospital and in the community. Hosp Community Psychiatry 1992; 43: 1233-1238.
[37] Eli Lilly and Company. Olanzapine over 12 months in the SOHO study: Data on File.