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Characteristics of Outpatients Initiated on Olanzapine versus Risperidone in the Treatment of Schizophrenia in Japan: A Healthcare Database Analysis

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ABSTRACT

Purpose: To compare the characteristics of outpatients who were initiated on olanzapine or risperidone in the naturalistic treatment of schizophrenia in Japan.
Methods: The Japan Medical Data Centre Database (JMDC) was used to identify patients diagnosed with schizophrenia or schizoaffective disorder using ICD-10 codes. Patients were required to be 20-65 years old, to have initiated olanzapine or risperidone therapy at an outpatient setting between January 2004 and July 2008, and to be continuously enrolled during the 6 months prior and 12 months post initiation date. Treatment groups were compared on demographics, medical and psychiatric comorbidities, prior medication use patterns, and prior health care resource utilization. Chi-square tests and t-tests were employed for univariate comparisons. Multivariate logistic regressions were used to assess the independent contribution of the predictors.
Results: In both the multivariate and univariate models, olanzapine-initiated patients (n=334) were more likely than risperidone-initiated patients (n=502) to have a history of treatment with antidepressants (56.6% vs. 43.8%, $p < 0.001$) and a history of prior manic episodes (59.3% vs. 51.6%, $p = 0.03$).
Discussion: Current findings suggest that in Japan, olanzapine and risperidone are not used interchangeably. Olanzapine appears to be used more often for schizophrenia patients with comorbid mood symptoms, as reflected by a prior diagnosis of manic episodes and prior treatment with antidepressants. Previous research has found that schizophrenia patients with depressive symptoms have a worse prognosis across a broad range of outcomes including the use of more relapse-related mental health services, higher rates of arrests, and suicidality, as well as poorer quality of life, mental functioning, family relationships, and medication adherence.

Keywords: olanzapine, risperidone, schizophrenia, epidemiologic studies

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INTRODUCTION

Schizophrenia is a chronic, disabling mental illness characterized by positive symptoms, such as hallucinations, delusions, and disorganized speech, and negative symptoms, such as blunted emotions and reduced goal-directed behavior [1]. Effective pharmacological treatments are available, particularly for management of the positive symptoms [2-5]. One of the primary challenges psychiatrists face in treating schizophrenia is identifying the most appropriate antipsychotic medication for a given patient at a given point in time.

Treatment guidelines separate the antipsychotics into two groups: the older first-generation or typical antipsychotics, and the newer second-generation or atypical antipsychotics [2-5]. Two of the more commonly used atypical antipsychotics in Japan are olanzapine and risperidone [6]. Although both are atypical antipsychotics, accumulating research

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indicates that these two medications are not interchangeable given the differences in efficacy and adverse event profiles [7]. Olanzapine has been shown to be more effective, but associated with greater weight gain and other metabolic effects [8-10]; whereas risperidone is associated with less weight gain, more dose dependent extrapyramidal symptoms [11-13], and greater prolactin elevations, particularly for females [14]. Differences between olanzapine and risperidone may lead clinicians to systematically use each drug with different types of schizophrenia patients.

When choosing an antipsychotic for a specific patient, guidelines, such as those developed by the World Federation of Societies of Biological Psychiatry, recommend that "The choice of anti-psychotic drug should be made jointly by the individual and the clinician responsible for treatment based on an informed discussion of the relative benefits of the drugs and their side-effect profile" [15] (p. 155). Although this statement is undoubtedly accurate, it fails to provide much in the way of specific guidance. The current evidence base for the process of choosing an antipsychotic for a given patient at a given time is limited.

Antipsychotic treatment patterns can vary between inpatients and outpatients with schizophrenia, in part due to the more complex patient profiles found with acutely ill inpatients. The inpatient-outpatient distinction is particularly relevant in the Japanese healthcare system, where long term inpatient care is common [16].

In Japan, little research has examined the factors that may contribute to the choice of olanzapine or risperidone in usual care for the treatment of patients with schizophrenia. The objective of this study was to compare the characteristics of outpatients who were initiated on olanzapine versus risperidone in the naturalistic treatment of schizophrenia in Japan.

METHODS

Data Source

The Japan Medical Data Centre Database (JMDC) was utilized for this analysis. JMDC is an employment-based administrative database that contains the medical and pharmacy claims from 10 different payers (insurance societies) that cover employed individuals and their family members. JMDC includes information on approximately 0.6 million enrolled members between August 2003 and June 2008.

The JMDC database is in compliance with the Japanese law for Protecting Personal Information and follows the guidelines for health insurance associations using their members' health data. The data is de-identified, commercially available to the public, and widely considered exempt from institutional review board/ethics committee approval. The members' inpatient and outpatient medical claims include the International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10) diagnosis codes [17]. The date of service information for medical claims is restricted to month and year. Pharmacy claims included the full dispensing date, the days of supply, and dosage information. Drugs are classified and identified based on The Anatomical Therapeutic Chemical Classification System (ATC) codes [18].

Sample Selection

The initial extract of data from the JMDC database included all of the diagnostic and prescription claims between August 2003 and July 2009 for patients who had at least one diagnosis of schizophrenia (F20.0 to F20.9). This initial data cut included 4,861 individuals.

The primary selection criterion for this analysis was the initiation of treatment with either olanzapine or risperidone before June 30, 2008. An index date was identified for each patient based on the date the patient had a first pharmacy claim for either risperidone or olanzapine (i.e., index drug). Initiation was identified based on a period of 3 months without a claim for the index drug prior to the index date. Patients were categorized into 2 mutually exclusive study cohorts based on the most recent initiation: risperidone or olanzapine.

In addition to initiation on risperidone or olanzapine, the study also used the following inclusion and exclusion criteria: (1) Patients were required to have at least one diagnosis of schizophrenia (F20.0 to F20.9) or schizoaffective disorder (F25.0 to F25.2, F25.9) in the 6 months prior to or in the 12 months following initiation on the index drug. (2) Patients were excluded from the study if they had ICD-10 diagnoses for any of the following conditions during the 6 months prior to or the 12 months following initiation of the index drug: organic mental disorders, organic brain disorders, dementia, or Alzheimer's disease. (3) Patients whose first claim was not at least 6 months prior to the index date and last claim was not at least 12 months following the index date were excluded from the analysis. This was used as a proxy for continuous enrollment. (4) The analysis was restricted to adults aged 20 to 65, inclusively. The

lower cutoff was used to restrict the population to adults and the upper cutoff was used in accordance with most prior schizophrenia research of adult populations [10, 19]. (5) Individuals who were inpatients at the time of the index date were excluded from the analysis.

Variable Definitions

This analysis focused on the data during 6 months prior to the initiation of either olanzapine or risperidone, including the index date. The ATC codes were used to identify previous treatment with different classes of drugs. Atypical antipsychotics were defined as olanzapine, risperidone, aripiprazole, blonanserin, clozapine, perospirone, quetiapine, and zotepine. Anticholinergic/antiparkinsonian drugs included amantadine, biperiden, levodopa, carbidopa/levodopa, selegiline, and trihexyphenidyl. Antidepressants included amoxapine, setiptiline, trimipramine, mirtazapine, amitriptyline, imipramine, clomipramine, trazodone, dosulepin, nortriptyline, maprotiline, mianserin, lofepramine, milnacipran, fluvoxamine, sertraline, and paroxetine. Finally, hypnotics and sedatives included amobarbital, secobarbital, barbital, phenobarbital, pentobarbital, passiflora, estazolam, quazepam, zopiclone, triazolam, trichlorethly phosphate, nitrazepam, nimetazepam, haloxazolam, flunitrazepam, flurazepam, brotizolam, bromvalerylurea, lormetazepam, flurazepam, rilmazafone, zolpidem, and choral hydrate. Mood stabilizers included only lithium. Use of each class of drug was coded with an indicator variable.

In addition to the drug class variables, several other variables were coded based on claims from the 6 months prior to the index date. Two indicator variables were coded one for prior use of risperidone and one for prior use of olanzapine. Antipsychotic polypharmacy was defined as at least 60 days of concurrent use of two or more antipsychotics. Based on the ICD-10 diagnostic codes indicators for the following comorbid conditions were coded: depression (F32 through F33), manic episodes (F30), and diabetes mellitus (E10 through E14).

Healthcare utilization variables were created to capture the costs and resources used by patients during the 6 months preceding the index date. Outpatient visits were measured as a count of the number of visits. An indicator variable was coded if a patient had utilized inpatient services. An indicator for antipsychotic adherence was designated if a patient had filled scripts for any antipsychotic on 80% or more of the days in the 6 months prior to the index date (i.e., Medication Possession Ratio ≥ .80). Finally, total healthcare costs were aggregated based on the amounts paid by the health plans for medical and prescription medications.

Statistical Methods

Univariate comparisons of characteristics between patients initiated on olanzapine or risperidone were conducted using chi-square tests or Fisher's exact tests for categorical variables and t-tests or Wilcoxon rank-sum tests for continuous variables. Multivariate logistic regressions were used to assess the independent and interactive effects of the multiple factors that could contribute to distinguishing olanzapine and risperidone initiators. Two logistic regression models were utilized. Both models included the patients' demographic characteristics (age and gender) and prior resource use variables (prior cost, prior outpatient visits, prior hospitalization, and antipsychotic adherence). The first model added prior comorbidities to this base model, and the second one added prior medication use variables. The models were separated because of potential multicollinearity between the comorbidities and medication use variables. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were used to show the associations with each significant predictor in the model. The significance level was set at $\alpha = 0.05$ and all analyses were conducted using SAS version 9.1.3 (SAS Institute, Inc., Cary, NC).

RESULTS

Figure 1 documents the application of the inclusion and exclusion criteria. Approximately two-thirds (3208/4861 = 66.0%) of the individuals with schizophrenia in the initial dataset had at least one pharmacy claim for olanzapine or risperidone. The majority of these patients had a claim with a diagnosis of schizophrenia (2829/3208 = 88.2%) in the 6 months preceding or 12 months following the index pharmacy claim. The continuous enrollment criteria resulted in the largest drop in the sample selection, reducing the total sample size by 46% from 2552 to 1378. After applying all inclusion and exclusion criteria, the analytic sample consisted of 836 individuals – 334 were treated with olanzapine and 502 treated with risperidone. The average age of the patients in the final sample was 36.9 years and 47.5% were male.

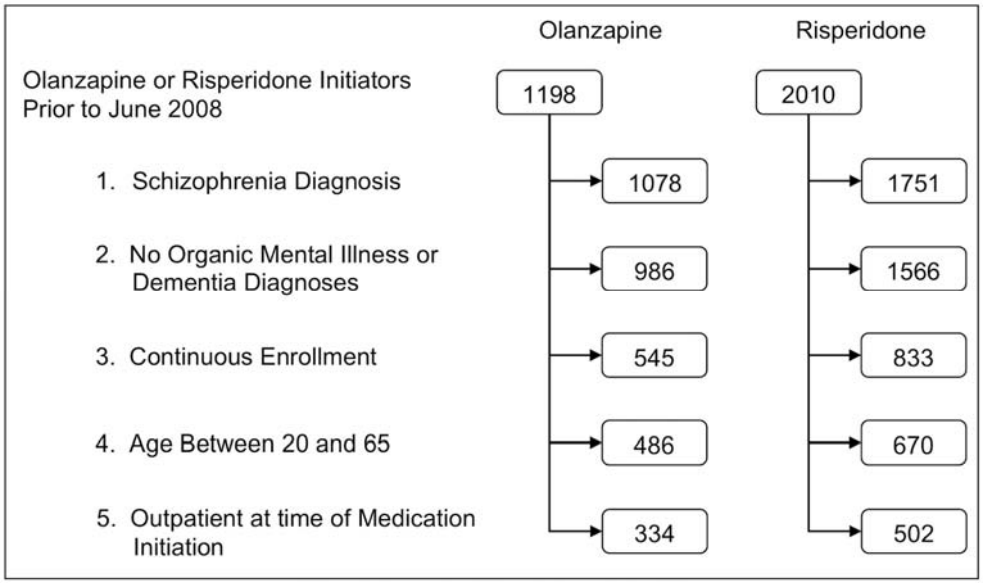

Figure 1. Patient Selection. The diagram displays the number of olanzapine and risperidone initiators remaining after each of the inclusion and exclusion criteria were applied.

Table 1. Baseline Characteristics for Olanzapine and Risperidone Initiators

Variable	Olanzapine (n = 334)	Risperidone (n = 502)	p
Demographics			
Age, mean (SD), y	36.5 (9.8)	37.2 (10.6)	.29
Gender (Male), % (n)	48.8% (163)	46.6% (234)	.53
Prior Resource Use			
Inpatient Service Use, % (n)	8.4% (28)	9.2% (46)	.70
Outpatient Visits, mean (SD)	16.0 (14.3)	16.5 (17.0)	.66
Total Treatment Cost, mean (SD), yen	209081 (334321)	235348 (338525)	.78
Antipsychotic Adherence, % (n)	28.4% (95)	34.5% (173)	.07
Prior Comorbidities			
Diabetes, % (n)	10.8% (36)	15.7% (79)	.04
Depression, % (n)	47.6% (159)	44.4% (223)	.37
Manic Episode, % (n)	59.3% (198)	51.6% (259)	.03
Prior Medication Use			
Atypical Antipsychotic Use, % (n)	43.4% (145)	47.6% (239)	.23
Typical Antipsychotic Use, % (n)	31.7% (106)	37.3% (187)	.10
Olanzapine Use, % (n)	15.6 (52)	18.3% (92)	.30
Risperidone Use, % (n)	22.5% (75)	23.5 (118)	.72
Antipsychotic Polypharmacy Use, % (n)	13.2% (44)	18.1% (91)	.06
Antidepressant Use, % (n)	56.6% (189)	43.8% (220)	<.001
Hypnotics/Sedative Use, % (n)	55.1% (184)	54.8% (275)	.93
Anticholinergic Use, % (n)	20.7% (69)	27.3% (137)	.03
Mood Stabilizer Use, %(n)	10.8% (36)	6.8% (34)	.04
Psychiatrist Prescribed, % (n)	40.1% (134)	37.5% (188)	.44

Table 1 provides the univariate comparison of the two cohorts on the demographic characteristics, prior resource use, prior medical and psychiatric comorbidities, and prior medication use during the 6 months preceding the initiation of olanzapine or risperidone. The risperidone initiators were more likely to have prior claims with diagnoses for diabetes mellitus and prior use of anticholinergic drugs. The olanzapine initiators were more likely to have prior claims with diagnoses for manic episodes, prior mood stabilizer use, and prior antidepressant use.

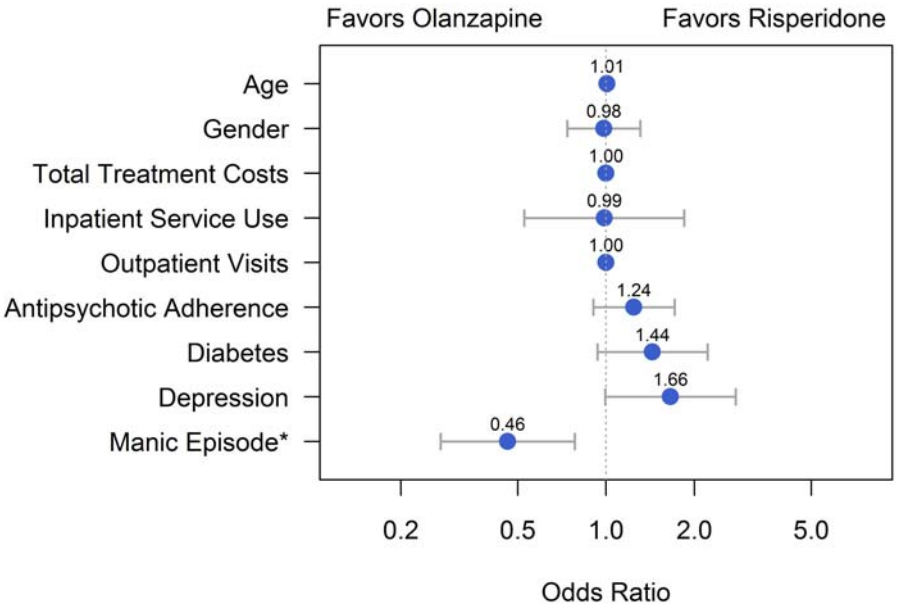

Figure 2. Prior Comorbidities Multivariate Logistic Regression Results. Age, Outpatient Visits, and Total Treatment Costs were continuous variables with confidence intervals narrower than the marker width. *p < .05.

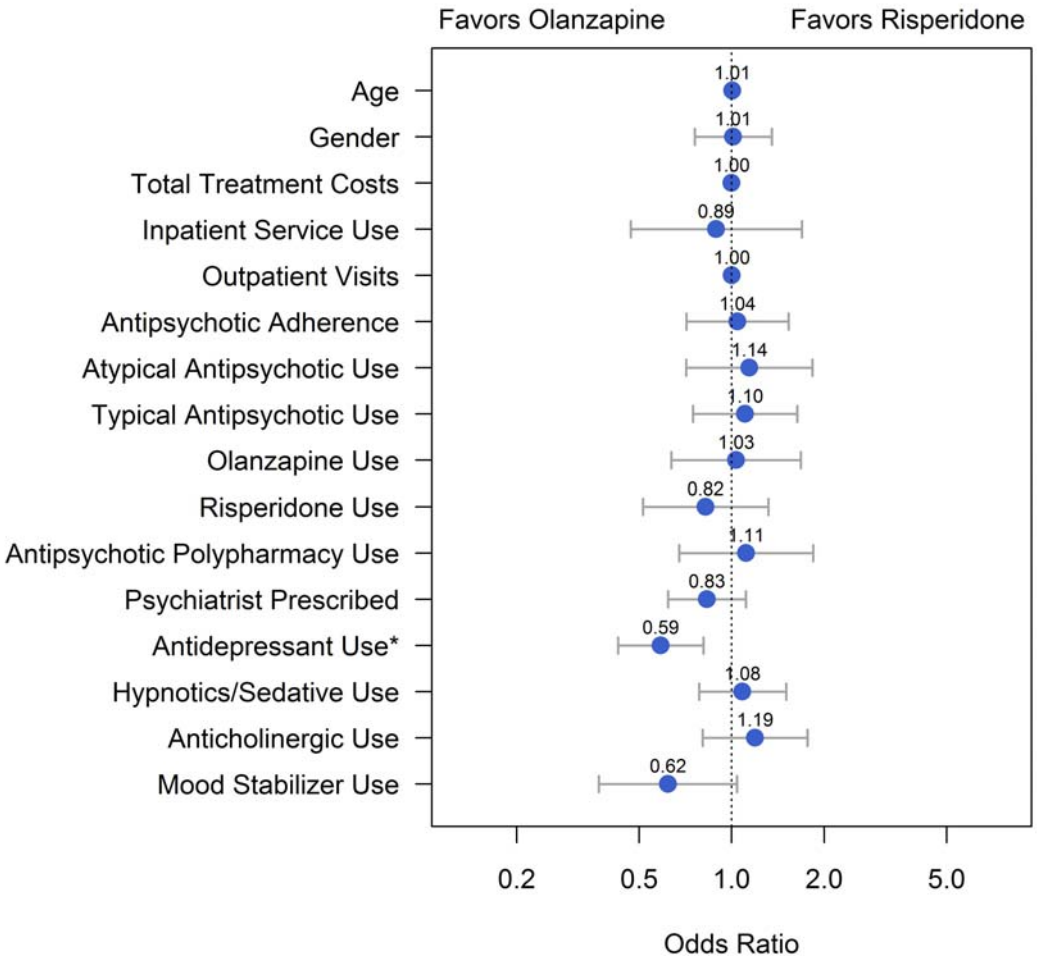

Figure 3. Prior Prescription Patterns Multivariate Logistic Regression Results. Age, Outpatient Visits, and Total Treatment Costs were continuous variables with confidence intervals narrower than the marker width. *p < .05.

Multivariate logistic regressions were used to assess the independent contribution of the different variables in predicting whether a patient would initiate treatment with olanzapine or risperidone. Two separate logistic regression analyses were conducted because of potentially collinearity

between medication treatments and comorbid diagnoses (e.g., those with depression diagnoses are likely to be treated with antidepressants). Figure 2 displays the odds ratios and confidence intervals for the likelihood of initiation with risperidone or olanzapine based on the demographics, prior resource use, and prior comorbid diagnoses. After correcting for background demographics and healthcare resource use, olanzapine initiators were more likely to have a history of manic episodes and a history of antidepressant use. Figure 3 displays the odds ratios and confidence intervals for the model based on prior prescription patterns.

DISCUSSION

The characteristics of patients that were treated with olanzapine or risperidone could be differentiated by historical information from the patients' administrative claims data in Japan. In both the univariate and multivariate analyses, olanzapine patients were more likely to have a history of manic episodes and a history of treatment with antidepressants.

To the authors' knowledge, this is the first study to contrast background differences between olanzapine and risperidone initiators in usual clinical practice in Japan; previous research examining this question has come primarily from the analysis of administrative claims databases in the United States. In the United States, olanzapine initiators were found to have more complex psychiatric histories than risperidone initiators including more pre-existing psychiatric comorbidities [20], more prior use of other classes of psychiatric medications [20,21], higher prior psychiatric inpatient costs [22], more previous treatment with clozapine [21,23,24], and more initial prescriptions from psychiatrists [24]. Consistent with these prior studies, olanzapine initiators in the current analysis were more likely to have diagnoses for manic episodes and had more prior antidepressant use. In the United States, risperidone was found to be initiated more often than olanzapine for patients with schizophrenia who have more physical comorbidities [20,22-25]. Consistent with these studies, the univariate analysis found that risperidone initiators were more likely to have previous claims for diabetes mellitus. Differences between the current study and these previous analyses may reflect differences in the healthcare systems, the study population, or the timing of the studies.

The implication of these findings is that physicians do not appear to use olanzapine and risperidone interchangeably, but rather use them for patients with different prior treatment and comorbidity profiles. The olanzapine initiated patients were more likely to have previous diagnoses for manic episodes and, in the univariate analysis, were more likely to have prior mood stabilizer use. Lithium was the only medication defined as a mood stabilizer in this analysis and this conservative definition may explain the difference in the rates of prior manic episodes and mood stabilizer use in Table 1. The most robust predictor of olanzapine initiation was a history of treatment with antidepressants. Antidepressant use is not necessarily indicative of depressive symptoms because antidepressants are also used to treat other conditions such as generalized anxiety disorder, social phobia, obsessive-compulsive disorder, and posttraumatic stress disorder. Previous research has found that schizophrenia patients with depressive symptoms have a worse prognosis across a broad range of outcomes including the use of more relapse-related mental health services, higher rates of arrests, and suicidality, as well as poorer quality of life, mental functioning, family relationships, and medication adherence [26-28].

Limitations

Administrative claims data are limited in detail, thus some important predictors may have been missing from the data. The predictors were only assessed in the 6 months preceding initiation of olanzapine or risperidone and do not reflect the patients full treatment history. Many conditions are not coded in claims and some comorbid conditions may have been under diagnosed. The percentage of patients with claims for diabetes mellitus was higher than the 8.6% prevalence rate reported for patients with schizophrenia in Japan from past chart review research [29]. Diabetes mellitus diagnoses may be coded on a claim any time a blood test (i.e., HbA1c) is conducted regardless of the status of the results leading to a potential over diagnosis. All diagnoses in administrative claims data are made based on information collected in usual clinical care and are coded for reimbursement purposes; therefore, they may not consistently reflect more thorough research diagnoses. Finally, despite the potential limitations in accuracy of the diagnoses, the information represents an unobtrusive view of usual clinical care in Japan. However, because the administrative data contained claims only for employees or their families, the sample was younger and may not be representative of the Japanese population as a whole.

CONCLUSION

Current findings suggest that in Japan, olanzapine and risperidone are not used interchangeably. Olanzapine appears to be used more often for schizophrenia patients with comorbid mood symptoms, as reflected by prior diagnoses of manic episodes and prior treatment with antidepressants. The antidepressant use may not reflect depressive symptoms as these medications are also used to treat other conditions such as anxiety disorders. Previous research has found that schizophrenia patients with depressive symptoms have a worse prognosis across a broad array of outcomes including more relapse-related mental health services, arrests, and suicidality, as well as poorer quality of life, mental functioning, family relationships, and medication adherence.

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CONFLICTS OF INTEREST

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

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