

Long-term safety of ziprasidone in schizophrenic patients: an open trial

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Abstract. – OBJECTIVES: The Authors report the safety results of the extension phase of three multicenter, phase III studies, which evaluated ziprasidone in schizophrenic patients switching from another antipsychotic agent or who required a transition from intramuscular to oral ziprasidone.

PATIENTS AND METHODS: A total of 331 patients were evaluated, with a mean follow-up of 22 months (range: 3-73 months).

RESULTS AND CONCLUSIONS: Ziprasidone appeared well tolerated; most adverse events were of mild or moderate severity. No new safety or tolerability issues emerged. However, the authors observed a high number of withdrawals, possibly associated with a lack of long-term compliance, which is a common feature in schizophrenic patients.

Key Words:

Antipsychotic agents, Safety, Schizophrenia, Ziprasidone.

Introduction

“Second generation” or “atypical” antipsychotic drugs (e.g.: risperidone, olanzapine, quetiapine, aripiprazole) represent a widely-used option for the treatment of schizophrenic patients¹. Overall, the different atypical antipsychotics present negligible differences in efficacy^{2,3}.

Of note, a remarkable proportion of schizophrenic patients will require life-long treatment, due to the chronic course of this disease⁴. Therefore, safety and tolerability represent a crucial issue when prescribing an antipsychotic drug⁵. A favourable safety profile, associated with a limited number of adverse events, may also increase patients’ compliance and therefore optimize the management of schizophrenia⁶.

Ziprasidone is an atypical antipsychotic with a characteristic neurotransmitter receptor-binding profile, a favourable benefit/risk ratio in schizophrenic patients, and is approved for the treatment

of this condition in US and Europe⁷⁻⁹. However, patients in therapy with ziprasidone carry a slightly increased risk of prolongation of heart rate-corrected QT (QTc) interval than subjects on other atypical antipsychotics¹⁰. Several studies demonstrated the efficacy and safety of ziprasidone over a short-term (up to 18 weeks) period¹¹⁻¹³. These results were also confirmed when switching from another antipsychotic agent¹⁴⁻¹⁵ or when evaluating the transition from intramuscular (IM) to oral formulation of ziprasidone^{11,16}.

Some clinical experiences indicated that the clinical benefits of ziprasidone are also sustained over a long-term (up to 52 weeks)¹⁷⁻²⁰. However, further evidence on the safety of ziprasidone, possibly from longer-term studies, may be desirable to provide a more complete picture of this drug.

We conducted three multicenter phase III studies (namely A1281028, A1281044, A1281045) to evaluate the efficacy and safety of ziprasidone in schizophrenic patients switching from another antipsychotic agent (A181028 and A1281044) or in those who require a transition from the intramuscular (IM) to the oral formulation (A1281045) (manuscripts submitted). Patients still on ziprasidone at the end of these studies could enter a long-term extension phase, during which they took oral ziprasidone. We report here the safety results of this extension phase.

Patients and Methods

Study Setting and Design

This was an open label, multicenter, flexible dose study designed to allow patients who completed one of the core studies (A1281028, A1281044, A1281045) on ziprasidone to continue treatment with this drug for at least one year (extension visits) or until the drug became commercially available (19th May 2009; extra extension visits). Protocol number was A1281061 and the trial is deposited in clinical-

trials.gov with the identifier NCT00139737. We conducted this study in 93 Italian centers specialized in the treatment of psychiatric disease, located throughout the country. The Local Ethical Committees of every involved center approved the study design, and we planned the study protocol in accordance with the Helsinki Declaration. Each patient signed an informed consent before the inclusion in the trial.

Patients

Adult (18-60 years) patients diagnosed with schizophrenia (DMS-IV definition) were eligible for this study if they had successfully completed one of the three core studies on ziprasidone listed above. Psychiatric exclusion criteria were: (a) immediate risk of committing harm to self or others; (b) need for concomitant treatment with anti-psychotic drugs other than ziprasidone; (c) need for treatment with antidepressants or mood stabilizers. Main general exclusion criteria applied in this study and in the core trials were: (a) history and/or diagnosis of clinically significant haematological, renal, hepatic, gastrointestinal, endocrine, pulmonary, dermatological, oncological, or neurological disease, with the exception of cured skin cancer or type 2 diabetes; (b) diagnosis of acute or chronic heart disease, clinically significant ECG abnormalities, QTc interval ≥ 450 msec, or concomitant treatment with medications that prolong QTc interval; (c) serum K⁺ or Mg²⁺ or any other laboratory parameter outside the normal range; (d) confirmed HIV, HBV or HCV infection; (e) inability to follow the study protocol; (f) pregnancy or breastfeeding; (g) hypersensitivity to ziprasidone or lactose.

Study Interventions

At study initiation, all patients maintained the same dose of oral ziprasidone (provided by Pfizer Italy s.r.l.) taken at the end of the core study. The dosage could then be adjusted within 20-40-60-80 mg bid, based on clinical status. Subjects were instructed to take medication together with food. Patients continued the treatment for 8 weeks since the initiation of the oral therapy. The initial dose was 40 mg bid. The treatment was continued for one year or until ziprasidone became commercially available.

Benzodiazepines and anticholinergic agents could be administered at the investigator's discretion as necessary. Subjects receiving stable dose of anticholinergic agents remained on their current dose for seven days; the dose was then re-

duced or treatment was suspended at the investigator's discretion. Propranolol could be administered for akathisia. Patients could not take any other psychoactive medications. Concomitant therapies for stabilized somatic disease (which did not prolong QTc) were allowed.

Study Evaluations and Assessments

Patients underwent monthly visits. The first visit (baseline) corresponded to the last visit of the core study in which the patient was enrolled.

At each visit, investigators assessed the percentage of adverse events, vital signs, body weight, ECG, onset of concomitant disorders, need for concomitant treatments and compliance. The severity of each adverse event (mild, moderate, severe or serious) and its potential correlation with ziprasidone were also assessed. A serious adverse event (SAE) was defined as any medical occurrence which resulted in death, was life-threatening, required patient hospitalization or prolongation of existing hospitalization, or resulted in persistent/significant disability/incapacity. Investigators treated all adverse events in line with best clinical practice. As all the subjects entered the present protocol at the end of a previous ziprasidone protocol, we defined the AEs occurring after the first intake of study drug in the present study as "treatment-emergent". Laboratory measurements were also performed at baseline and at the final visit.

Every three months, investigators measured the scores of the Drug Attitude Inventory scale (DAI) and of the Subject Well-being under Neuroleptic treatment scale (SWN). Each patient could withdraw from the study at any time and the investigator could discontinue the treatment at any time if deemed necessary.

In each center, every effort was undertaken in order to have the same trained investigator performing all the assessments.

Statistical Analysis

Due to the study design, no estimation of sample size was necessary. We performed the safety analysis on the safety population, which included all patients who received ≥ 1 dose of ziprasidone.

We analyzed all data by descriptive statistics and evaluated any difference in study variables between different timepoints by Student's *t* test for paired data. We also used a Pearson correlation analysis to assess any correlation between ECG changes throughout the study and ziprasidone dose. A *p* value < 0.05 was considered statistically significant.

Table I. Baseline characteristics and demographics.

	Number (%)	Mean $\pm$ SD	Range
Age, years			
18-44	238 (71.9)	NR	NR
45-64	93 (28.1)	NR	NR
Males, number	193 (58.3)		
Vital signs			
Weight (kg)	329	77.9 $\pm$ 16.1	38-136
Height (cm)	330	169.0 $\pm$ 9.2	146-190
Systolic blood pressure, sitting (mmHg)	327	122 $\pm$ 12	90-160
Diastolic blood pressure, sitting (mmHg)	327	79 $\pm$ 8	50-110
Heart rate, sitting (bpm)	326	77 $\pm$ 10	52-100

Bpm: beats per minute; NR: not reported; SD: standard deviation.

Results

Baseline Characteristics and Patient Disposition

In total, 344 subjects entered the study. Thirteen patients did not receive any dose of ziprasidone and were excluded from the safety population. Therefore, the safety population included 331 subjects (193 males; mean age 38.5 $\pm$ 9.6). Table I summarizes the baseline characteristics of patients enrolled in the study. Fifty-eight subjects (17.5%) had concomitant conditions (in most cases metabolism and nutrition disorders).

Figure 1 shows the disposition of patients through the study, until month 36. At this time-point, 36 patients (10.9%) were still participating in the study. The maximum follow-up was 73 months. Nearly half of the patients (164; 49.5%) withdrew from the study within 6 months. Reasons for study discontinuation are summarised in Table II.

The median exposure to study drug was 186 days. Almost A total of 158 subjects (47.7%) changed ziprasidone dose at least once, with a mean daily dose of 104.43 $\pm$ 41.9 mg over the entire study. The mean daily dose was 103.99 $\pm$ 42.7

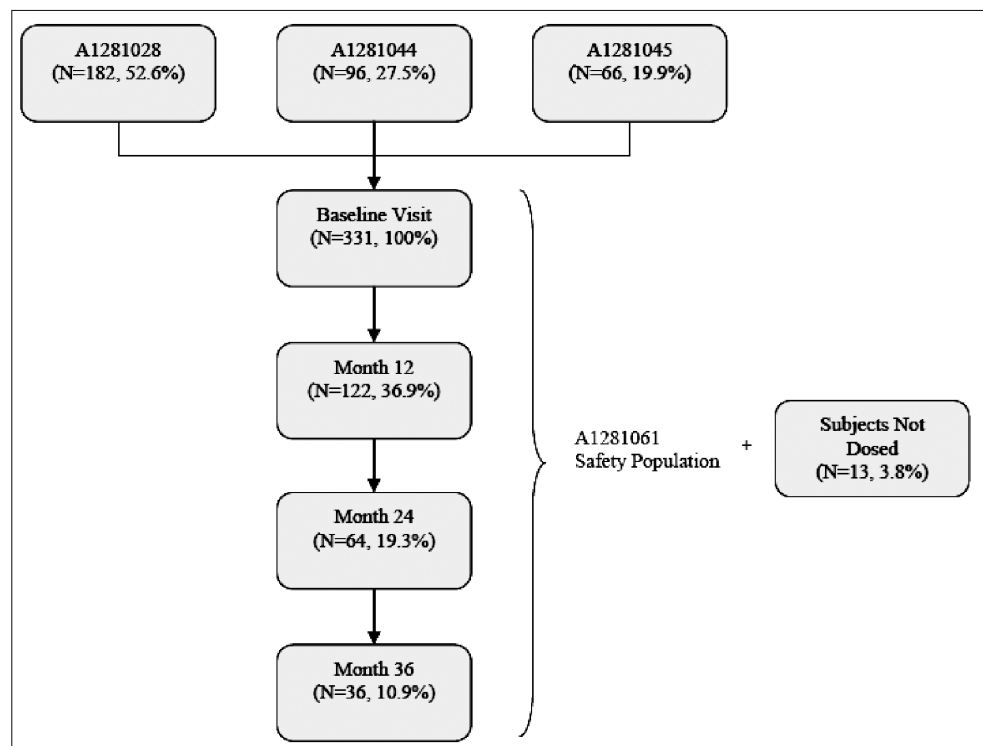


Figure 1. Subject disposition until month 36.

Table II. Reasons for study discontinuation.

	Number	%
Fatal event	3	0.9
Related to study drug	71	21.5
Adverse event	30	9.1
Laboratory abnormality	1	0.3
Lack of efficacy	40	12.1
Not related to study drug	254	76.7
Adverse event	28	8.5
Laboratory abnormality	1	0.3
Lost to follow-up	8	2.4
Other	27	8.2
Withdrawn consent	190	57.4
Total	328	99.1

mg/day and 103.02 ± 44.32 mg/day at start and at end of the study period, respectively.

Stratification according to the original core study did not disclose any significant difference in the above parameters.

Safety Analysis

Table III summarizes the percentage of adverse events and of study withdrawal/dose modification due to adverse events. In total, 198 patients (59.8%) experienced adverse events. Thirty-two subjects (9.7%) reported SAE, which were fatal in 3 patients.

Treatment Emergent Adverse Events

Twenty-four adverse events in 18 subjects were not considered treatment-emergent; among those, 9 were considered treatment-related from previous protocol (i.e. vomiting, agitation, salivary hypersecretion, insomnia, sleep disorder, prolonged QTc, interval, somnolence, gastritis). Therefore, 414 adverse events were treatment-emergent, 207 of which were treatment-related (Table III). Treatment-emergent and treatment-related adverse events by organ class are presented in Table IV.

The most frequent abnormality in investigations was prolonged QTc interval ($n=43$; 13.0%), reported as mild in 38 subjects and moderate in 5 subjects. Abnormal ECG was reported in 11 subjects (3.3%), mild in 8 subjects and moderate in 3 subjects. Five subjects had hyperprolactinemia (2 mild; 3 moderate), and 5 subjects experienced a transient increase in blood prolactin level (4 mild; 1 moderate).

The most frequent psychiatric disorder was insomnia, reported in 12 subjects (3.6%); mild ($n=8$) or moderate ($n=4$). Agitation and anxiety were reported in 8 and 7 subjects, respectively; only one patient experienced both events as severe. Somnolence (7 subjects) and extrapyramidal disorder (6 subjects) were the most frequent nervous system related adverse events.

Adverse Events Leading to Study Discontinuation or Dose Modifications

Most of the adverse events leading to discontinuation were psychiatric disorders, reported in 33 subjects (10.0%) and investigations (electrocardiogram and laboratories abnormalities) reported in 11 subjects (3%). When considering treatment-related adverse events leading to treatment discontinuation, psychiatric disorders were reported in 11 subjects (3.3%) and investigations in 7 subjects (2.1%). Among laboratory and vital signs measurements, 6 subjects had ECG abnormalities (5 prolonged QTc interval), and 1 subject showed weight decrease.

Twenty-five subjects (7.6%) had to reduce ziprasidone dose or to temporary interrupt due to treatment-related adverse events.

Serious Adverse Events

Three subjects died: an acute cardiac ischemia, a suicide and a cranial trauma due to accident. All the deaths occurred during study drug treatment and were judged by investigators as not re-

Table III. Adverse events and dose modifications thorough the study. All data are expressed as number (%).

	All adverse events	Treatment-emergent adverse events	Treatment related adverse events
Adverse events	438	414	207
Subjects with adverse events	198 (59.8)	188 (56.8)	131 (39.6)
Subjects with serious adverse events	32 (9.7)	32 (9.7)	3 (0.9)
Fatal events	3 (0.9)	3 (0.9)	0
Subjects with severe adverse events	30 (9.1)	30 (9.1)	6 (1.8)
Discontinuations due to adverse events	70 (21.1)	70 (21.1)	32 (9.7)
Subjects with dose reductions or temporary discontinuations due to adverse events	33 (10.0)	32 (9.7)	25 (7.6)

Table IV. Subjects with treatment-emergent adverse events by organ class (n = 331). All data are expressed as number (%).

	Treatment-emergent adverse events	Treatment related adverse events
Cardiac disorders	10 (3.0)	5 (1.5)
Endocrine disorders	6 (1.8)	5 (1.5)
Eye disorders	1 (0.3)	0
Gastrointestinal disorders	28 (8.5)	10 (3.0)
General disorders and administration site conditions	16 (4.8)	6 (1.8)
Hepatobiliary disorders	2 (0.6)	0
Infections and infestations	18 (5.4)	1 (0.3)
Injury, poisoning and procedural complications	9 (2.7)	0
Laboratory investigations and vital signs	73 (22.1)	64 (19.3)
Metabolism and nutrition disorders	8 (2.4)	6 (1.8)
Musculoskeletal and connective tissue disorders	3 (0.9)	2 (0.6)
Neoplasms benign, malignant and unspecified	2 (0.6)	0
Nervous system disorders	42 (12.7)	29 (8.8)
Psychiatric disorders	86 (26.0)	39 (11.8)
Renal and urinary disorders	1 (0.3)	1 (0.3)
Reproductive system and breast disorders	8 (2.4)	4 (1.2)
Respiratory, thoracic and mediastinal disorders	4 (1.2)	0
Skin and subcutaneous tissue disorders	7 (2.1)	2 (0.6)
Vascular disorders	6 (1.8)	3 (0.9)

lated to ziprasidone, while two of them were related to schizophrenia. Thirty-two subjects reported non-fatal SAE; among these, 3 patients (0.9%) had treatment-related SAE (epileptic seizures, agitation/aggressive behaviour, hypomania), which resolved after ziprasidone interruption and appropriate treatment.

ECG Measurements

Overall, 230 subjects out of 331 had a 12-lead electrocardiogram evaluation both at baseline and at one study visit. Changes from baseline in QTc interval are displayed in Table V. Increases in the QTc interval ≥ 30 msec were present in 21% of subjects (25% in women, 17% in men). Only two patients, one male and one female, had a value ≥ 500 msec. Statistical analysis did not disclose any correlation between ziprasidone dose and QTc changes.

Table V. Mean changes from baseline in QTc (baseline: 385 ± 37.3). All data are expressed as mean $\pm$ standard deviation.

Visit	N	Change from baseline (msec)
Baseline	317	NR
Month 3	174	-0.5 ± 31.4
Month 6	118	-1.5 ± 36.6
Month 9	101	-1.9 ± 31.6
Month 12	135	-5.2 ± 36.3
Final visit*	74	-2.1 ± 43.3

*Mean time = 22 months (range: 3-73). NR: not reported.

Laboratory Measurements and Vital Signs

Laboratory measurements were available at baseline and final visits for 127 patients. In total, 67 subjects (53% of evaluable subjects) with a normal laboratory test at baseline had ≥ 1 abnormality and 43 subjects (36%) with an abnormal laboratory test at baseline had at least one abnormality at study end. The greatest number of abnormalities was related to prolactin levels (n=20), proteinuria (n=15), urine blood (n=14), and neutropenia (n=11). There were no clinically significant changes between baseline and last observation in vital signs.

DAI and SWN Scales

Overall, the mean total score of DAI slightly increased until month 9; at month 12 and at subject's final visit a decrease was observed; no statistical differences were observed between different timepoints (Table VI). We observed a similar trend for the SWN scale, with a significant reduction at last visit versus baseline values (-5.9 ; $p \leq 0.05$).

Discussion

This study was the extension of three previous protocols which were designed to evaluate the efficacy and safety of ziprasidone in schizophrenic patients. Patients included in this study were, therefore, already treated with ziprasidone and

Table VI. DAI scale total score and changes in total score. Scores are expressed as mean±standard deviation.

Visit	N	Total score (range)
Baseline	316	15.8 ± 10.9 (–22–30)
Month 3	204	18.1 ± 10.1 (–18–30)
Month 6	148	18.3 ± 9.9 (–14–30)
Month 9	116	18.5 ± 10.2 (–10–30)
Month 12	147	16.1 ± 11.3 (–22–30)
Final visit*	115	15.5 ± 11.4 (–22–30)

*Mean time = 22 months (range: 3–73). NR: not reported.

took the drug for up to 73 months. However, most patients withdrew from the study during the first year of this extension study. At 36 months, only 36 patients were still on study drug. We must observe that in the wide majority of patients withdrew from the study for lack of consent and not for adverse events or insufficient efficacy. Since all patients were already involved in a clinical trial, we speculate that the long involvement in a clinical protocol could have played a role in the decision to withdraw consent. This hypothesis is in line with previous suggestions²¹, but we cannot exclude that the perception of adverse events and/or lack of efficacy by the patients may have played a part in this decision, as described in a long-term study on ziprasidone by Ratner et al²⁰. Moreover, a low compliance to psychiatric treatment is well-accepted in current literature²², and the analysis of DAI and SWN scales documented in our study may lend further support to a suboptimal compliance to ziprasidone, even if the large number of drop-outs may have biased this result.

Despite the high number of withdrawals, our findings provide a detailed picture, on a rather large sample size, of the safety of ziprasidone over a long-term period. To our knowledge, this is the longest follow-up described to date for ziprasidone treatment.

Overall, the frequency of adverse events was quite high, with around 40% of subjects experiencing a drug-related event. However, these events were, in the majority of cases, of mild/moderate severity and led to treatment interruption or dose modification in a low proportion of subjects (around 15%). This finding is in line with previous long-term studies, even with a shorter follow-up than ours^{17–20}.

No new safety concerns were reported over the long-term follow-up. In fact, the most frequently reported adverse events were prolongation of QTc interval, insomnia, agitation, anxiety, som-

nolence and extrapyramidal disorders, which have all already been associated with short- and long-term administration of ziprasidone^{11–14–20}. Of note, we did not observe any discontinuation due to prolactin elevation: this finding may be attributed to the high 5-HT_{2A}:D₂ binding ratio exhibited by ziprasidone²³. More recent studies confirm this data^{24–25}.

Prolongation of the QTc interval (calculated with the Bazett's formula) is a well-documented side-effect of ziprasidone¹⁰. We observed this event in about 15% of subjects and 5 patients had to withdraw from the study for this event. We cannot exclude, however, an over-reporting of QTc prolongation, due the high attention of clinicians to this event. Moreover, only two patients experienced large (> 500 msec) prolongation of QTc interval; overall, changes from baseline values were minor and in the negative direction, although the wide variability in this parameter (evidenced by a large standard deviation) does not allow us to reach any definite conclusion.

Our study has several limitations. They include the open label design and the lack of an active comparator. Moreover, patients were followed more closely than what commonly happens in clinical practice.

Taking these limitations into account, our study suggests that ziprasidone is generally well-tolerated, with most adverse events being of mild or moderate severity. No new safety or tolerability issues emerged over a long-term follow-up. However, the high number of withdrawals, possibly associated with a lack of long-term compliance, may represent a concern.

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References

- 1) VOHORA D. Atypical antipsychotic drugs: current issues of safety and efficacy in the management of schizophrenia. *Curr Opin Investig Drugs* 2007; 8: 531–538.
- 2) MOTLOVÁ L, SPANIEL F, HÖSCHL C, BALON R. Are there any differences in the efficacy among second

- generation antipsychotics in the treatment of schizophrenia and related disorders? *Ann Clin Psychiatry* 2007; 19: 133-143.
- 3) KOMOSSA K, RUMMEL-KLUGE C, HUNGER H, SCHWARZ S, BHOOPATHI PS, KISSLING W, LEUCHT S. Ziprasidone versus other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev* 2009; 4: CD006627.
- 4) SWAINSTON HARRISON T, SCOTT LJ. Ziprasidone: a review of its use in schizophrenia and schizoaffective disorder. *CNS Drugs* 2006; 20: 1027-1052.
- 5) THOMAS P, ALPTEKIN K, GHEORGHE M, MAURI M, OLIVARES JM, RIEDEL M. Management of patients presenting with acute psychotic episodes of schizophrenia. *CNS Drugs* 2009; 23: 193-212.
- 6) CAÑAS F. Management of agitation in the acute psychotic patient—efficacy without excessive sedation. *Eur Neuropsychopharmacol* 2007; 17(Suppl. 2): S108-114.
- 7) GREENBERG WM, CITROME L. Ziprasidone for schizophrenia and bipolar disorder: a review of the clinical trials. *CNS Drug Rev* 2007; 2: 137-177.
- 8) PFIZER INC. Geodon® (ziprasidone HCl) capsules; Geodon® (ziprasidone mesylate) for injection for IM use only: prescribing information [online]. Available from URL: http://www.pfizer.com/pfizer/download/uspi_geodon.pdf. Last accessed: 21th February 2011.
- 9) PFIZER INC. Pfizer's Zeldox receives approval in Europe to treat manic or mixed episodes associated with bipolar disorder [online]. Available from URL: <http://www.pfizer.com>. Last accessed: 21th February 2011.
- 10) HADDAD PM, SHARMA SG. Adverse effects of atypical antipsychotics: differential risk and clinical implications. *CNS Drugs* 2007; 21: 911-936.
- 11) BROOK S, WALDEN J, BENATTIA I, SIU CO, ROMANO SJ. Ziprasidone and haloperidol in the treatment of acute exacerbation of schizophrenia and schizoaffective disorder: comparison of intramuscular and oral formulations in a 6-week, randomized, blinded-assessment study. *Psychopharmacology (Berl)* 2005; 178: 514-523.
- 12) SACCHETTI E, GALLUZZO A, VALSECCHI P, ROMEO F, GORINI B, WARRINGTON L. MOZART STUDY GROUP. Ziprasidone vs clozapine in schizophrenia patients refractory to multiple antipsychotic treatments: the MOZART study. *Schizophr Res* 2009; 113: 112-121.
- 13) ADDINGTON DE, PANTELIS C, DINEEN M, BENATTIA I, ROMANO SJ. Efficacy and tolerability of ziprasidone versus risperidone in patients with acute exacerbation of schizophrenia or schizoaffective disorder: an 8-week, double-blind, multicenter trial. *J Clin Psychiatry* 2004; 65: 1624-1633.
- 14) WEIDEN PJ, SIMPSON GM, POTKIN SG, O'SULLIVAN RL. Effectiveness of switching to ziprasidone for stable but symptomatic outpatients with schizophrenia. *J Clin Psychiatry* 2003; 64: 580-588.
- 15) WEIDEN PJ, DANIEL DG, SIMPSON G, ROMANO SJ. Improvement in indices of health status in outpatients with schizophrenia switched to ziprasidone. *J Clin Psychopharmacol* 2003; 23: 595-600.
- 16) DANIEL DG, ZIMBROFF DL, SWIFT RH, HARRIGAN EP. The tolerability of intramuscular ziprasidone and haloperidol treatment and the transition to oral therapy. *Int Clin Psychopharmacol* 2004; 19: 9-15.
- 17) ADDINGTON DE, LABELLE A, KULKARNI J, JOHNSON G, LOEBEL A, MANDEL FS. A comparison of ziprasidone and risperidone in the long-term treatment of schizophrenia: a 44-week, double-blind, continuation study. *Can J Psychiatry* 2009; 54: 46-54.
- 18) SIMPSON GM, O'GORMAN CJ, LOEBEL A, YANG R. Long-term improvement in efficacy and safety after switching to ziprasidone in stable outpatients with schizophrenia. *CNS Spectr* 2008; 13: 898-905.
- 19) LOEBEL AD, KHANNA S, RAJADHYAKSHA S, SIU CO, GILLER E, POTKIN SG. Ziprasidone in treatment-resistant schizophrenia: a 52-week, open-label continuation study. *J Clin Psychiatry* 2007; 68: 1333-1338.
- 20) RATNER Y, GIBEL A, YORKOV V, RITSNER MS. Effectiveness, safety, and tolerability of ziprasidone for treating schizophrenia patients undergoing usual care: a 12-month, open-label, flexible-dose, naturalistic observational trial. *Prog Neuropsychopharmacol Biol Psychiatry* 2007; 31: 1401-1409.
- 21) FRANK E, NOVICK DM, KUPFER DJ. Beyond the question of placebo controls: ethical issues in psychopharmacological drug studies. *Psychopharmacology (Berl)* 2003; 171: 19-26.
- 22) VORUGANTI LP, BAKER LK, AWAD AG. New generation antipsychotic drugs and compliance behaviour. *Curr Opin Psychiatry* 2008; 21: 133-139.
- 23) COMPTON MT, MILLER AH. Antipsychotic-induced hyperprolactinemia and sexual dysfunction. *Psychopharmacol Bull* 2002; 36: 143-164.
- 24) KIM SW, SHIN IS, KIM JM, BAE KY, YANG SJ, YOON JS. Effectiveness of switching from aripiprazole to ziprasidone in patients with schizophrenia. *Clin Neuropharmacol* 2010; 33: 121-125.
- 25) CİTİL DY, SELÇUK E, KARLIDA R, UNAL S. Ziprasidone-induced hyperprolactinemia: A case report. *Prog Neuropsychopharmacol Biol Psychiatry* 2008; 32: 905-906.