Amisulpride Switching in Schizophrenic Patients Who Showed Suboptimal Effect and/or Tolerability to Current Antipsychotics in a Naturalistic Setting: An Explorative Study

Yongmin Kim 1, Sheng-Min Wang 1,2, Kyung-Phil Kwak 3, Ho-Kyoung Yoon 4, Chi-Un Pae 1,5, Jung-Jin Kim 1, Won-Myong Bahk 1

1 Department of Psychiatry, College of Medicine, The Catholic University of Korea, Seoul, 2 International Health Care Center, Seoul St. Mary’s Hospital, The Catholic University of Korea, Seoul, 3 Department of Neuropsychiatry, Dongguk University School of Medicine, Gyeongju, 4 Department of Psychiatry, Korea University College of Medicine, Seoul, Korea, 5 Department of Psychiatry and Behavioural Sciences, Duke University Medical Center, Durham, NC, USA

Objective: Despite numerous atypical antipsychotics (AAP) available, many patients with schizophrenia still experience lack of efficacy and persistent side-effects. Switching from one AAP to another with a different side-effect profile has become a common clinical strategy. We aimed to investigate effect of switching to amisulpride in patients who showed suboptimal effect and/or tolerability to current antipsychotics treatment.

Methods: This was a 6-week, prospective, multicenter, open-label, flexible-dose study in patients with schizophrenia. Switching to amisulpride was achieved using cross-titration within 7 days (day 1: 300 mg on day 1 then flexibly dosed 400–800 mg/day). The primary end-point measure was proportion of patients achieving improvement in clinical benefit at week 6 based on Clinical Global Impressions-Clinical Benefit (CGI-CB). Secondary endpoints included change in scores in CGI-CB, CGI-Severity (CGI-S), Subjective Satisfaction Scores (SSS), Brief Psychiatric Rating Scale (BPRS), and Simpson and Angus Rating Scale.

Results: Among 37 patients switched to amisulpride, 76% completed study and 56.8% had clinical benefit measure by CGI-CB. CGI-CB and CGI-S scores showed significant improvement at week 6 compared to baseline (mean changes of CGI-CB and CGI-S scores: $-1.7\pm1.0, p<0.0001$ and $-0.6\pm0.0, p=0.001$, respectively). SSS scores also improved significantly (mean change: $2.1\pm2.6, p<0.0001$). Mean weight of patients significantly lowered compared to baseline (mean change: $-1.2\pm2.0, p<0.0001$).

Conclusion: Patients with schizophrenia who showed suboptimal efficacy or tolerability with their current antipsychotics and thereby switched to amisulpride resulted in clinical benefit in terms of both improved efficacy and tolerability. The small sample size limits generalizability of the study results.

KEY WORDS: Antipsychotic agents; Switch; Amisulpride; Clinical benefit.

INTRODUCTION

Schizophrenia, which affects approximately 1% of the population, is a devastating illness with a chronic impact on social, vocational, and daily living functioning.1,2) Although development of atypical antipsychotics (AAP) has resulted in an important advance in the treatment of schizophrenia, many patients treated with these AAPs still frequently experience lack of efficacy and bothersome side-effects (SEs).3,4) In addition, despite numerous AAPs available, the question of which antipsychotic drug should be preferred is still controversial. Nevertheless, switching from one AAP to another with a different SE profile has become a common, and in fact a recommended, strategy aimed at improving clinical outcomes by increasing efficacy and minimizing the SEs of the antipsychotics.5,6) In order to do so, understanding the possible benefits and risks associated with switching between AAPs is critical when making an optimum decision.7)

Studies showed that patients with schizophrenia have higher risk of having medical morbidity and mortality risks than general population,8) and weight gain, in association with metabolic syndromes, has continuously reported to be an important contributing factor to this higher
morbidity and mortality of schizophrenia. Recent studies repeatedly showed concerns of metabolic SE profiles of AAPs, hence metabolic profile including weight gain became one of the most important reasons for switching AAP from one to another.

Amisulpride has a very selective and high affinity for dopamine (D3/D2) receptors. Amisulpride increases dopaminergic transmission at low doses via presynaptic receptor blockade and blocks dopaminergic transmission at higher dosage. Researches have shown that amisulpride is either more effective or equally effective relative to conventional antipsychotics with respect to positive symptoms for schizophrenia. It also showed superior efficacy than to placebo and conventional antipsychotics with respect to negative symptoms. It has no affinity for other receptor or transporter systems, it is therefore believed to have a lower risk of causing SEs. Studies further showed that amisulpride is associated with significantly less weight gain than other AAPs, and it does not increase body mass index as well as lipid profiles. More importantly, a meta-analysis comparing efficacy and tolerability of 15 antipsychotics (13 AAPs and 2 typical antipsychotics) showed that amisulpride showed the lowest all-cause discontinuation rates and risk of causing sedation. These characteristics suggested that amisulpride may be an alternative option in patients requiring a change in antipsychotic treatment due to lack of efficacy or SEs.

Evidence from both randomized clinical trials (RCTs) and naturalistic trials in routine practice settings is valuable and required in investigating effective pharmacological choices for patients having schizophrenia. RCTs may provide the strongest empirical support, but their biases in patient selection can limit generalizability. Blinded use of placebos also poses ethical controversy. Thus, the purpose of this study was to investigate effect of switching to amisulpride in patients who showed suboptimal effect and/or tolerability to current oral AAP in a naturalistic setting.

METHODS

Study Design

This was a 6-week, prospective, multicenter, open-label, flexible-dose study conducted in three centers in Korea (The Catholic University of Korea, Dongguk University, and Korea University). The study consisted of a switching phase (day 0) and an evaluation phase (week 6). Switching was achieved using cross-titration, with amisulpride in the evening at 300 mg on day 1 then flexibly dosed 400-800 mg/day. Previous antipsychotic medication was tapered to 50% within first 3 days then stopped before day 7. The study was conducted in accordance with Declaration of Helsinki and Good Clinical Practices. All participants provided written consent before participating in this study. The study’s protocol was approved by institutional review board of the each study sites. Concomitant ongoing medications including benzodiazepines, zolpidem, anticholinergic, and beta blockers were permitted. However, antidepressants, mood stabilizers, psychoactive medications, and antipsychotics other than amisulpride were not permitted during the study.

Subjects

The present study enrolled Korean outpatients suffering from schizophrenia. The inclusion criteria were as follows: (1) meeting Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) criteria of schizophrenia; (2) between 20 and 70 years old; (3) receiving an AAP other than amisulpride; and (4) inadequate effect and/or tolerability to current AAP based on clinical response and tolerability. Patients were excluded for any of the following: (1) medication-naive first-episode schizophrenia patients; (2) clinically significant comorbid mental disorders in acute conditions (less than 3 months of symptom stabilization); (3) history of organic mental or neurological disorder, or mental retardation; (4) comorbid substance (alcohol, amphetamine, and opioid) abuse or dependence in acute conditions (less than 3 months of meeting remission criteria); (5) being treated with clozapine; (6) past history of treatment-resistance; (7) having risk of harming self or others; and (8) past history of treatment incompliance.

Measures

Clinical benefit was evaluated using the Clinical Global Impressions-Clinical Benefit (CGI-CB) at baseline and week 6. The CGI-CB, based on the principles outlined in Clinical Global Impression (CGI) item 3 (Efficacy Index), can assess both clinical efficacy and tolerability (Table 1). The scale ranges from 1 to 10 with score of 1 indicating most benefit and 10 indicating no benefit from the treatment. CGI-Severity (CGI-S) scale was used to assess the severity of patients’ clinical condition.

The primary end-point measure was proportion of patients achieving improvement in clinical benefit at week 6 based on CGI-CB score. Improvement in clinical benefit was defined as a decrease (> 1 score) from baseline in CGI-CB at week 6. Secondary endpoints were change in
Table 1. Assessment of clinical benefit using the CGI-CB scale

| Therapeutic effect | Clinical burden of side effect |
|--------------------|--------------------------------|
|                    | No burden | No clinically significant burden | Clinically significant burden | Burden of side effect outweighs therapeutic effect |
| Marked             | 1         | 2                                | 5                             | 10                                      |
| Moderate           | 3         | 4                                | 6                             | 10                                      |
| Mild               | 7         | 8                                | 9                             | 10                                      |
| None               | 10        | 10                               | 10                            | 10                                      |

CGI-CB, Clinical Global Impressions-Clinical Benefit. The scale ranges from 1 to 10 with score of 1 indicating most benefit and 10 indicating no benefit from the treatment, for instance, CGI-CB points of 4 or less indicate that the patient has clinical benefit rather than side effect, while 5-9 and 10 suggests some or no clinical benefit due to harmful adverse events, respectively.

Table 2. Patient demographics and clinical characteristics (non-parametric variables)

| Variable         | Number (%) |
|------------------|------------|
| Demography       |            |
| Gender           |            |
| Male             | 16 (43.2)  |
| Female           | 21 (56.8)  |
| Religion         |            |
| Yes              | 9 (24.3)   |
| Occupation       |            |
| Yes              | 6 (16.2)   |
| Marital status   |            |
| Yes              | 13 (35.1)  |
| Living area      |            |
| City             | 36 (97.3)  |
| Economic status  |            |
| Upper            | 0 (0)      |
| Middle           | 22 (59.5)  |
| Low              | 14 (37.8)  |
| Clinical characteristic |        |
| Family history   |            |
| Yes              | 3 (8.1)    |
| Comorbid diseases|            |
| Yes              | 3 (8.1)    |
| Use of BZD       |            |
| Yes              | 32 (86.5)  |
| Previous APs     |            |
| Olanzapine       | 14 (37.8)  |
| Aripiprazole     | 8 (21.6)   |
| Paliperidone     | 5 (13.5)   |
| Quetiapine       | 4 (10.8)   |
| Blonanserin      | 3 (8.1)    |
| Risperidone      | 2 (5.4)    |
| SEs              |            |
| Headache         | 4 (10.8)   |
| Weight gain      | 16 (43.2)  |
| Decreased attention | 12 (32.4)  |
| Insomnia         | 6 (16.2)   |
| Dry mouth        | 4 (10.8)   |
| Memory impairment| 9 (24.3)   |
| Constipation     | 3 (8.1)    |
| Tremor           | 2 (5.4)    |

BZD, benzodiazepine; Aps, antipsychotics; SEs, side effects.

Table 3. Patient demographics and clinical characteristics (parametric variables)

| Variable         | Range | Mean | Standard deviation |
|------------------|-------|------|--------------------|
| Age (yr)         | 20.0-57.0 | 40.7 | 10.07              |
| Age of onset (yr)| 18.0-53.0 | 33.9 | 8.94               |
| Number of previous hospitalization | 1.0-3.0 | 2.2 | 0.75             |
| Age at first hospitalization (yr) | 20.0-46.0 | 37.0 | 11.60           |
| Satisfaction score | 0.0-6.0 | 3.8 | 1.68              |
| BARS             | 0.0-9.0 | 0.6 | 1.69               |
| SAS              | 0.0-5.0 | 0.2 | 0.87               |
| Weight (kg)      | 51.8-94.0 | 67.2 | 9.58              |
| CGI-S            | 3.0-6.0 | 4.2 | 0.74               |
| CGI-CB           | 5.0-10.0 | 7.1 | 1.29               |

BARS, Brief Psychiatric Rating Scale; SAS, Simpson and Angus Rating Scale; CGI-S, Clinical Global Impressions-Severity; CGI-CB, CGI-Clinical Benefit.

Statistical Analysis

For the analysis of all efficacy and safety measures, the intention-to-treat (ITT) population/safety population was used. Thus, patients who received at least one dose of the study medication were included using last-observation-carried-forward (LOCF) method. Kolmogorov-Smirnov test was used for verification of regular distribution of data. Student’s t-tests were used for the analysis of quantitative variables, and chi-square test or Fisher’s exact tests were used for categorical variables. All statistical analyses were conducted using the NCSS 2007 Power Analysis & Sample Size software (NCSS, Kaysville, UT, USA) with a two-tailed significance level of \( p < 0.05 \).

RESULTS

Patients and Medications

The baseline demographic and clinical characteristics of the 37 patients are provided in Tables 2 and 3. Slightly more females (n=21) than males (n=16) were recruited with mean age of 40.68±10.07 years. Majority of them...
were taking benzodiazepines. Ongoing antipsychotics before switching to amisulpride, were olanzapine, aripiprazole, paliperidone, blonaserin, and risperidone. All patients were experiencing more than 1 SE. The most common SEs were weight gain, decreased attention, and memory impairment. In average, patients were moderately ill at baseline (CGI-S, 4.17±0.74).

Effectiveness

The proportion of patients showing improvement in terms of clinical benefit as measured by the CGI-CB score at week 6 was 56.8% (21/37; 95% confidence intervals (CIs), 0.3949 to 0.729). The mean dose of amisulpride prescribed was 416.22 mg/day (±230.35). Changes in the frequency of each CGI-CB score at baseline and week 6 are presented in Figure 1. The most frequent score at baseline on CGI-CB was 7 (29.7%) followed by 8 (27.0%) indicating that the previous antipsychotics that patients were taking resulted in low treatment effect with clinically significant SEs. However, 21.6% of patients had score of 6 indicating treatment effect with some burden of SEs. After 6 weeks of treatment, the most frequent CGI-CB score became 3 (24.3%), and score of 4 increased from 0% to 13.5% indicating favorable treatment outcome after changing to amisulpride. However, the rates of 6 and 7 were also high (for both 18.9%) suggesting that significant number of patients still experienced either low treatment effect or mild treatment effect with some SE burden even after switching to amisulpride.

After changing to amisulpride, CGI-CB and CGI-S showed significant improvement at week 6 compared to baseline (mean changes of CGI-CB and CGI-S: −1.7±1.0, p < 0.0001 and −0.6±0.0, p=0.001, respectively). However, no symptom improvement was noted in BARS. SSS also improved significantly (mean change: 2.1±2.6, p<0.0001) (Table 4).

Tolerability

Amisulpride therapy was well tolerated, and 75.7% (28/37) of patients completed the study. After switching to amisulpride, mean weight of patients significantly lowered compared to baseline (mean change: −1.2±2.0, p < 0.0001). There was no significant change in extra-pyramidal side effect according to SAS (Table 4). Table 5 shows the treatment-emergent SEs identified by the SAFTEE. The most frequently reported SEs after switching to amisulpride were insomnia (24.3%) and cognitive decline (18.9%). Dry mouth, headache, and constipation were relatively common SEs (for all 10.8%).

### Table 4. Change in CGI-CB, CGI-S, SSS, BARS, SAS, and weight from baseline to week 6

| Parameter | Baseline | Week 6 | Mean change | p value* |
|-----------|----------|--------|-------------|----------|
| CGI-CB    | 7.1±1.3  | 5.4±2.1| −1.7±1.0    | <0.0001  |
| CGI-S     | 4.2±0.7  | 3.6±0.8| −0.6±0.9    | 0.001    |
| SSS       | 3.8±1.7  | 5.8±1.9| 2.1±2.6     | <0.0001  |
| BARS      | 0.6±1.7  | 0.1±0.4| −0.5±1.7    | 0.111    |
| SAS       | 0.2±0.9  | 0.1±0.5| −0.1±0.4    | 0.184    |
| Weight (kg)| 67.2±9.6| 66.0±8.7| −1.2±2.0  | 0.002    |

Values are presented as mean±standard deviation.

CGI-CB, Clinical Global Impressions-Clinical Benefit; CGI-S, CGI-Severity; SSS, Subjective Satisfaction Scores; BARS, Brief Psychiatric Rating Scale; SAS, Simpson and Angus Rating Scale.

*Paired t-test.

### Table 5. Side effects at week 6

| Side effects   | Number (%) |
|----------------|------------|
| Insomnia       | 9 (24.3)   |
| Cognitive decline | 7 (18.9)  |
| Dry mouth      | 4 (10.8)   |
| Headache       | 4 (10.8)   |
| Constipation   | 4 (10.8)   |
| Tremor         | 3 (8.1)    |
| Sedation       | 2 (5.4)    |
| Weight gain    | 2 (5.4)    |
| Neck pain      | 1 (2.7)    |
**DISCUSSION**

The present study investigated whether patients with schizophrenia who showed suboptimal efficacy or tolerability with their current antipsychotics benefit from a switch to amisulpride. More than half (56.8%) showed an improvement in CGI-CB score suggesting that switching to amisulpride resulted in clinical benefit. In line with previous studies, amisulpride was generally well tolerated with 24% discontinuation rate. Notably, patient’s mean body weight dropped by more than 1 kg while showing no worsening of EPS rated by SAS. Weight gain and its related metabolic syndrome are an important cause of long term morbidity and mortality of patient with schizophrenia, hence amisulpride may be a viable alternative option especially in patients who are in overweight due to ongoing AAP treatment.

Interestingly, patient’s SSS also showed a significant improvement after switching to amisulpride. The favorable SE outcome of amisulpride might have contributed to enhanced SSS because weight gain (43.2%) was the most common reported SE before switching. Nevertheless, the results suggested that switching to amisulpride has improved both objective and subjective scores of patients with schizophrenia.

The most common SEs by amisulpride were insomnia, cognitive decline, dry mouth, headache, and constipation. Above all, all SEs associated with amisulpride were mild to moderate in severity. High incidence of cognitive decline and dry mouth contradicted with previous findings because, having no muscarinic activities, amisulpride was known to have less anticholinergic SEs. Memory decline and dry mouth rates were high, 24.3% and 10.8% respectively, even before patients switched to amisulpride. Thus, it is not possible to distinguish whether these SEs are caused from previous AAP or amisulpride.

Despite amisulpride has not yet been approved for the treatment of mood and anxiety disorders, its clinical potential for the treatment of major depressive disorder/dysthymia as well as anxiety symptoms including obsession has been extensively investigated and proved in a number of clinical studies. Indeed selective modulation of dopaminergic system in the mesocorticolimbic area may account for improvement of depression and cognition. Hence its selective antagonism of dopamine D2-D3 receptors may partly explain about the antidepressant effect, while moderate to medium doses (100-400 mg/day) for negative symptoms of schizophrenia. However, these effects are still remains to be further explored.

Our study has several limitations. The study’s naturalistic open-label design could be a shortcoming, we were therefore not able to rule-out bias related to unblended-rating. With no control group, it was not possible for us to compare effects of switching to amisulpride with that of non-switching or switching to other AAP. However, we must also mention that evidence not only from RCTs but also from naturalistic trials are needed to best reflect real clinical practice settings. All patients recruited were from teaching hospital, so the results may not be generalized to all clinical settings. Small sample size is another huge limitation.

In conclusion, the study suggests that a majority of patients switched to amisulpride from other AAP experienced more clinical benefit in terms of both efficacy and tolerability. Thus, amisulpride may be an alternative treatment option in patients with schizophrenia who are experiencing suboptimal efficacy or tolerability with ongoing antipsychotics. Adequately-powered and well-controlled RCTs are warranted to support the present findings in near future.

**Acknowledgments**

This study was supported by Handok Pharmaceuticals (Prof. Pae). The funding source did not involve the study design, recruitment, study conduction, collection and interpretation of data, and manuscript drafting.

**REFERENCES**

1. Wang SM, Han C, Lee SJ, Patkar AA, Masand PS, Pae CU. Schizophrenia relapse and the clinical usefulness of once-monthly aripiprazole depot injection. Neuropsychiatr Dis Treat 2014;10:1605-1611.
2. Tiitinen J, Haukkka J, Taylor M, Haddad PM, Patel MX, Korhonen P. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. Am J Psychiatry 2011;168:603-609.
3. Jakubovski E, Carlson JP, Bloch MH. Prognostic subgroups for remission, response, and treatment continuation in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial. J Clin Psychiatry 2015;76:1535-1545.
4. Altamura AC, Glick ID. Designing outcome studies to determine efficacy and safety of antipsychotics for ‘real world’ treatment of schizophrenia. Int J Neuropsychopharmacol 2010;13:971-973.
5. Zhao Z, Namjoshi M, Barber BL, Loosbrock DL, Tunis SL, Zhu B, et al. Economic outcomes associated with switching individuals with schizophrenia between risperidone and olanzapine: findings from a large US claims database. CNS Drugs 2004;18:157-164.
6. Fagioli A, Alfonsi E, Amodeo G, Cenci M, Di Lella M, Farinella F, et al. Switching long acting antipsychotic...
medications to amisulpride long acting once-a-month: expert consensus by a panel of Italian and Spanish psychiatrists. Expert Opin Drug Saf 2016;15:469-455.

7. Hong I, Novick D, Brugnoli R, Karagianis I, Dossenbach M, Haro JM. Clinical consequences of switching from olanzapine to risperidone and vice versa in outpatients with schizophrenia: 36-month results from the Worldwide Schizophrenia Outpatients Health Outcomes (W-SOHO) study. BMC Psychiatry 2012;12:218.

8. Sicras-Mainar A, Mauriño J, Ruiz-Beato E, Navarro-Artieda R. Prevalence of metabolic syndrome according to the presence of negative symptoms in patients with schizophrenia. Neuropsychiatr Dis Treat 2014;11:51-57.

9. Andrade C. Cardiometabolic risks in schizophrenia and directions for intervention, I: magnitude and moderators of the problem. J Clin Psychiatry 2016;77:e844-e847.

10. Lee SY, Park MH, Patkar AA, Pae CU. A retrospective comparison of BMI changes and the potential risk factors among schizophrenic inpatients treated with amisulpride, olanzapine, quetiapine or risperidone. Prog Neuropsychopharmacol Biol Psychiatry 2011;35:490-496.

11. Kawabe K, Ochi S, Yoshino Y, Mori Y, Onuma H, Osawa Y. Kim, et al. Metabolic status and resistin in chronic schizophrenia over a 2-year period with continuous atypical antipsychotics. Ther Adv Psychopharmacol 2015;5:271-277.

12. Gupta A, Dadheech G, Yadav D, Sharma P, Gautam S. Metabolic issues in schizophrenic patients receiving antipsychotic treatment. Indian J Clin Biochem 2014;29:196-201.

13. Chen CY, Lane HY, Lin CH. Effects of antipsychotics on bone mineral density in patients with Schizophrenia: gender differences. Clin Psychopharmacol Neuropsychiatr 2016;14:238-249.

14. Weiden PJ, Miller AL, Lambert TJ, Buckley PF. The art and science of switching antipsychotic medications, part 2. J Clin Psychiatry 2007;68:e102.

15. Rátthelyi J, Sawalhe AD. [Comorbidity of metabolic syndrome, diabetes and schizophrenia: theoretical and practical considerations]. Orv Hetil 2011;152:505-511. Hungarian.

16. Kim KS, Pae CU, Chae JH, Bahk WM, Jun TY, Kim DJ, et al. Effects of olanzapine on prolactin levels of female patients with schizophrenia treated with risperidone. J Clin Psychiatry 2002;63:408-413.

17. Sparshatt A, Taylor D, Patel MX, Kapur S. Amisulpride dose, plasma concentration, occupancy and response: implications for therapeutic drug monitoring. Acta Psychiatr Scand 2009;120:416-428.

18. Delcker A, Schoon ML, Oczkowski B, Gaertner HJ. Amisulpride versus haloperidol in treatment of schizophrenic patients—results of a double-blind study. Psychopharmacol 1990;23:125-130.

19. Puech A, Fleurot O, Rehn W. Amisulpride, and atypical antipsychotic, in the treatment of acute episodes of schizophrenia: a dose-ranging study vs. haloperidol. Acta Psychiatr Scand 1998;98:65-72.

20. Danion JM, Rehn W, Fleurot O. Improvement of schizophrenic patients with primary negative symptoms treated with amisulpride. Amisulpride Study Group. Am J Psychiatry 1999;156:610-616.

21. Pailhère-Martino JL, Lecrubier Y, Martinot JL, Aubin F. Improvement of some schizophrenic deficit symptoms with low doses of amisulpride. Am J Psychiatry 1995;152:130-134.

22. Pani L, Villagrá JM, Kontaxakis VP, Alptekin K. Practical issues with amisulpride in the management of patients with schizophrenia. Clin Drug Investig 2008;28:463-477.

23. Komossa K, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S, Silveira da Mota Neto JI, et al. Amisulpride versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev 2010;(1):CD006624.

24. Bak M, Fransen A, Janssen J, van Os J, Drukker M. Almost all antipsychotics result in weight gain: a meta-analysis. PLoS One 2014;9:e94112.

25. Leucht S, Cipriani A, Spino L, Marvidis D, Orey D, Richter F, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet 2013;382:951-962.

26. Han C, Wang SM, Seo HJ, Lee BC, Jeon HJ, Kim W, et al. Amisulpride augmentation, antidepressant combination or switching therapy in patients with major depressive disorder who are partial- or non-responsive to current antidepressants: a multi-center, naturalistic study. J Psychiatr Res 2014;49:75-82.

27. Severus E, Seemüller F, Berger M, Dittmann S, Obermeier M, Pfenning A, et al. Mirroring everyday clinical practice in clinical trial design: a new concept to improve the external validity of randomized double-blind placebo-controlled trials in the pharmacological treatment of major depression. BMC Med 2012;10:67.

28. Kapatchik TJ. The double-blind, randomized, placebo-controlled trial: gold standard or golden calf? J Clin Epidemiol 2001;54:541-549.

29. Guy W. National Institute of Mental Health (US); Psychopharmacology Research Branch; Early Clinical Drug Evaluation Program. ECDEU assessment manual for psychopharmacology. Rockville, MD: US Dept. of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs; 1976.

30. Ventriglio A, Gentile A, Stella E, Bellomo A. Metabolic issues in patients affected by schizophrenia: clinical characteristics and medical management. Front Neurosci 2015;9:297.

31. Lin CC, Bai YM, Wang YC, Chen TT, Lai IC, Chen JY, et al. Improved body weight and metabolic outcomes in overweight or obese psychiatric patients switched to amisulpride from other atypical antipsychotics. J Clin Psychopharmacol 2009;29:529-536.

32. Carrière P, Bonhomme D, Lempière T. Amisulpride has a superior benefit/risk profile to haloperidol in schizophrenia: results of a multicentre, double-blind study (the Amisulpride Study Group). Eur Psychiatry 2000;15:321-329.

33. Kim SW, Shin IS, Kim JM, Yang SJ, Hwang MY, Yoon JS. Amisulpride improves obsessive-compulsive symptoms in schizophrenia patients taking atypical antipsychotics: an open-label switch study. J Clin Psychopharmacol 2008;28:349-352.

34. Kim SW, Shin IS, Kim JM, Lee SH, Lee JH, Yoon BH, et al. Amisulpride versus risperidone in the treatment of depression in patients with schizophrenia: a randomized, open-label, controlled trial. Prog Neuropsychopharmacol Biol Psychiatry 2007;31:1504-1509.

35. Wang SM, Han C, Lee SJ, Jun TY, Patkar AA, Masand PS, et al. Second generation antipsychotics in the treatment of major depressive disorder: An update. Chonnam Med J 2016;52:159-172.

36. Wang SM, Han C, Lee SJ, Patkar AA, Masand PS, Pae CU. Aripiprazole, olanzapine, iloperidone, lurasidone, and sertindole: distinctive clinical characteristics of 5 novel atypical antipsychotics. Clin Neuropharmacol 2013;36:223-238.
37. Han C, Wang SM, Kato M, Lee SJ, Patkar AA, Masand PS, et al. Second-generation antipsychotics in the treatment of major depressive disorder: current evidence. Expert Rev Neurother 2013;13:851-870.

38. Pani L, Gessa GL. The substituted benzamides and their clinical potential on dysthymia and on the negative symptoms of schizophrenia. Mol Psychiatry 2002;7:247-253.