Chung Shan Medical Journal 2019; 30:141-150

Original Article

Is Second-Generation Antipsychotic Treatment Continuity Associated with New Onset Diabetes Mellitus in Patients with Major Depressive Disorder?

Chun-Yuan Lin[1,2,3] Ming-Hong Hsieh[2,4], Chun-Te Lee[2,4], Yu-Hsiang Kuan[4,5], I-Chia Chien[1,7], Chin-Chih Chiou[3] and Chun-Hung Su[2,8*]

[1] *Tsaotun Psychiatric Center, Ministry of Health and Welfare, Nantou, Taiwan*
[2] *School of Medicine, Chung Shan Medical University, Taichung, Taiwan*
[3] *National Changhua University of Education, Changhua, Taiwan*
[4] *Department of Psychiatry, Chung Shan Medical University Hospital, Taichung, Taiwan*
[5] *Department of Pharmacology, School of Medicine, Chung Shan Medical University, Taichung, Taiwan*
[6] *Department of Pharmacy, Chung Shan Medical University Hospital, Taichung, Taiwan*
[7] *Department of Public Health and Institute of Public Health, National Yang-Ming University, Taipei, Taiwan*
[8] *Division of Cardiology, Department of Internal Medicine, Chung Shan Medical University Hospital, Taichung, Taiwan*

Background

Second-generation antipsychotics (SGAs) have been commonly used in patients with severe mental illness. The possible association of SGA treatment continuity with new onset diabetes mellitus (NODM) in major depressive disorder (MDD) patients is a concern. The aim of this study was to determine if there are differences in the risk of NODM between MDD patients receiving SGAs continuously for more than 8 weeks and MDD patients receiving SGAs irregularly.

Methods

From the National Health Insurance Research Database (NHIRD), 859 MDD patients treated with SGAs continuously for more than 8 weeks were analyzed in a 1:1 propensity-score-matched sample to patients treated with SGAs irregularly. Patients were followed up and the outcome was based on ICD-9 CM codes indicating NODM. Cumulative incidences of NODM were calculated and the Cox proportional hazards model with competing risk was used to determine the risk factors for NODM.

Results

After propensity-score matching, 55 (6.40%) of 859 patients treated with SGAs continuously for more than 8 weeks and 59 (6.87%) patients treated with SGAs irregularly developed NODM. Rates of NODM among all matched patients were similar. SGA treatment continuity showed no significant risk for NODM (hazard ratio [HR] = 0.677; 95% confidence interval [CI], 0.437-1.047; p value=0.079). However, elevated risk of NODM was associated with increased age (per year) (HR= 1.040; 95% CI, 1.026-1.054; p value <0.001), history of hypertensive disease (HR= 2.506; 95% CI, 1.399-4.488; p value =0.002), and history of hyperlipidemia (HR= 2.956; 95% CI, 1.782-4.905; p value <0.001).

Conclusions

SGA treatment continuity is not associated with significant risk of NODM in MDD patients. The results of this study are helpful for weighing the potential benefits against the potential side effects and treatment effects of SGAs in treatment-resistant depression.

Keywords: Depression, Second-generation antipsychotics, Diabetes Mellitus

* Corresponding Author: Chun-Hung Su, MD, PhD
School of Medicine, Chung Shan Medical University, Taichung, Taiwan
Tel: +886-4-24730022 ext. 11191
Fax: +886-4-23248130
E-mail: such197408@gmail.com

Introduction

Major depressive disorder (MDD) is a disease with high prevalence of comorbidity and disability [1,2]. Prior studies have shown that second-generation antipsychotics (SGAs) result in better treatment responses than antidepressants alone in difficult-to-treat patients [3].

Despite their effects on treatment-resistance MDD, little is known about the long-term safety of SGAs in MDD [4,5]. SGAs are first-line treatments for schizophrenia. However, increasing numbers of reports have raised concerns about the associations among SGAs and risks of weight gain, type II diabetes mellitus (DM) and related conditions [6], limiting their clinical use in depression [7]. Depression comorbid with cardiometabolic problems leads to poorer treatment efficacy [8]; hence the association between SGAs and DM in patients with depression deserves investigation.

We have reported no significant difference in the risk of developing type II DM in MDD patients with and without SGA exposure [9]. However, it is not well known if there is any difference in the risk of new onset diabetes mellitus (NODM) between MDD patients receiving SGAs continuously and MDD patients receiving SGAs irregularly. In this study, subjects were divided into two groups: MDD patients with continuous SGA treatment for 8 weeks or more and MDD patients with irregular SGA treatment. Their risks of NODM were analyzed.

Methods

Database

The Psychiatric Inpatient Medical Claim Dataset, a subset of the NHIRD, includes data of patients who received inpatient psychiatric treatment from January 1, 1996 to December 31, 2007 and follow-up care until December 31, 2012 [10]. This dataset contains patients' demographic data and psychiatric and other inpatient and outpatient health care utilization data including diagnostic codes and details of prescriptions, procedures, and surgeries [11].

Subjects

This study was approved by the Institutional Review Board. Flowchart of sample selection is shown in **Figure 1**. MDD subjects were screened based on International Classification of Diseases, Ninth Revision, and Clinical Modification (ICD-9 CM) codes. By ascertaining the diagnostic stability of MDD [12] and excluding patients with type I or type II DM diagnosis before the index date (the date when subjects started SGA treatment), 2579 MDD patients (ICD9-CM code 296.2 or 296.3) with psychiatric inpatient histories and SGA prescription records for more than 1 day from 1996-2012 were identified. Based on previous trials [3,5] and the stability of prescriptions, we defined subjects with continuous SGA treatment as MDD patients who received SGAs continuously for at least 8 weeks. There were 1179 MDD patients who received SGAs continuously for more than 8 weeks and 1400 MDD patients who did not. We used propensity score matching (PSM) to create groups with similar characteristics [13,14]. Based on PSM, 859 patients treated with SGAs continuously for more than 8 weeks (SGA continuous exposure group) and 859 patients who were not treated with SGAs continuously for more than 8 weeks (SGA irregular exposure group) were paired [9].

Outcome variable

In this study, a patient was considered an NODM case if he or she received ≥ 1 inpatient or ≥ 3 outpatient ICD-9 diagnostic codes (ICD9-CM code 250) for type II DM.

Demographic and clinical variables

The demographic and clinical variables included age, gender, comorbid physical and psychiatric disorders related to the outcomes of depression and cardiometabolic diseases [15,16] and treatments prior

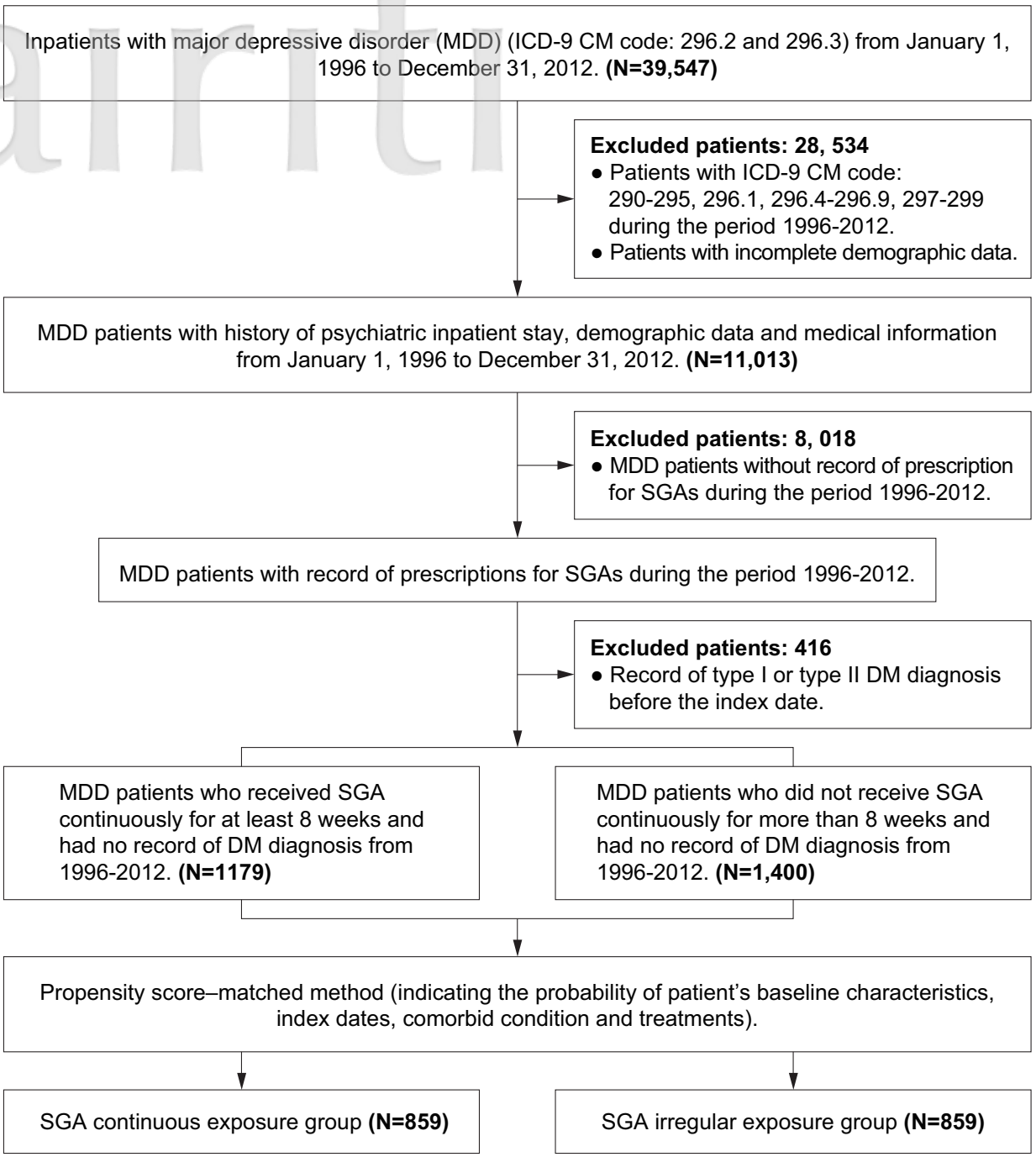

Figure 1. Flow chart of sample selection
Abbreviations:
MDD: Major depressive disorder
ICD-9 CM: International Classification of Diseases, Ninth Revision, Clinical Modification
DM: Diabetes mellitus
SGAs: Second-generation antipsychotics

to SGA [17]. A condition was coded as comorbid if it was accompanied by ≥ 1 inpatient or ≥ 3 outpatient relevant ICD-9 diagnostic codes prior to the index date. Treatments prior to SGA including antidepressants, first generation antipsychotics (FGA), anticonvulsants, lithium, stimulants, thyroid hormone, and electroconvulsive therapy (ECT) were defined as at least one record within one year prior to the index date [9].

Statistical Analysis

Continuous variables are expressed as mean (± standard deviation) and categorical variables are expressed as frequency (%). Differences between cohorts were analyzed by chi-square test for categorical variables and by independent t-test for continuous variables. The observation period started on the index date and continued until the development of NODM, death, or the end of 2012. Death prior to NODM occurrence was considered a competing risk event. Kaplan-Meier method and Gray method [18] were used to analyze cumulative rates of NODM and the differences between the curves were tested by the log-rank test. To provide adequate duration for examining the outcome while avoiding potential confounding factors over time, the observation period was set at 5 years [19, 20].We determined whether continuous SGA treatment for more than 8 weeks is a risk factor for NODM by the Cox proportional hazards (PH) model with competing risk and calculated hazard ratios (HRs) with 95% confidence interval (CI) of NODM. Patients' demographic and clinical variables were analyzed. Data management and HR calculations were carried out using the SAS system (version 9.2; SAS Institute, Cary, NC). Cumulative incidence estimation and Cox PH model fitting were implemented using the R software [21]. P< 0.05 was considered statistically significant.

Results

Demographic characteristics

Table 1 shows the characteristics of the two groups of MDD patients after PSM. PSM achieved good balance for nearly all the characteristics of the 859 pairs of patients.

Cumulative incidences of type II DM

After PSM, 55 (6.40%) patients treated with SGAs continuously for more than 8 weeks (mean follow-up period=5.93±2.64 years) and 59 (6.87%) patients treated with SGAs irregularly (mean follow-up period=5.56±2.79 years) developed NODM. Death before the occurrence of NODM was defined as competing mortality. The cumulative incidences of NODM after adjustment for competing mortality were similar (modified log-rank p-value=0.578, to the end of the data period; modified log-rank p-value=0.143, to the end of the 5th year).

Table 2 summarizes the risk of NODM after adjusting for competing mortality. SGA treatment continuity showed no significant risk for NODM (hazard ratio [HR] = 0.677; 95% confidence interval [CI], 0.437-1.047; p value=0.079). Elevated risk for NODM was associated with increased age (per year) (HR= 1.040; 95% CI, 1.026-1.054; p value <0.001), history of hypertensive disease (HR= 2.506; 95% CI, 1.399-4.488; p value =0.002) and history of hyperlipidemia (HR= 2.956; 95% CI, 1.782-4.905; p value <0.001).

Discussion

Metabolic abnormalities are adverse events of great concern for patients receiving long-term SGA treatment. Therefore, the potential benefits of SGA use in MDD should be carefully weighed against the potential for onset of abdominal obesity, insulin resistance, cardiovascular diseases and related conditions [6]. To our knowledge, this is the first population-based study to compare the risks of NODM in MDD patients receiving SGA treatment continuously for more than 8 weeks and MDD patients receiving SGA treatment irregularly.

Understanding of the long-term adverse metabolic effects of SGA use on MDD patients is insufficient. It is difficult to generalize adverse events such as NODM in clinical practice due to the small sample size, highly selected enrollees and short-term follow-up periods in most trials [4]. Although there has been no significant correlation between treatment-emergent blood glucose levels in trials longer than 12 weeks [22-24] , the decision to administer continuous SGAs must

Table 1. Characteristics of two groups of MDD patients after propensity matching

Characteristics	Matched Cohorts*		*p-value*
	SGA exposed continuously group	SGA exposed irregularly group	
	N=859	N=859	
Age when SGA began (or index date) (Mean, SD)	38.00±16.83	37.99±17.85	0.983
Gender (N %)			0.596
Male	419 (48.78)	431 (50.17)	
Female	440 (51.22)	428 (49.83)	
Comorbidity (N %)			
Psychiatric comorbidities (N %)			
Anxiety/Dysthymia	471 (54.83)	3 (8.6 %)	0.004
Alcohol abuse/dependence	40 (4.66)	32 (91.4%)	0.004
Substance abuse/dependence	31 (3.61)	32 (91.4%)	0.004
Intellectual disabilities	21 (2.44)	11 (31.4%)	0.75
Physical related with MDD outcome			
Neurologic disorders	101 (11.76)	112 (13.04)	0.464
Cardiac diseases	105 (12.22)	113 (13.15)	0.612
Endocrine disorders	175 (20.37)	9 (1.05)	>.999
Chronic liver disorders	175 (20.37)	163 (18.98)	0.504
Malignancy	33 (3.84)	36 (4.19)	0.806
Physical related with metabolic outcome			
Hypertensive disease	138 (16.07)	145 (16.88)	0.696
Hyperlipidemia	116 (13.50)	101 (11.76)	0.309
Other peripheral vascular disease	8 (0.93)	9 (1.05)	>.999
Prior cardiovascular events			
Ischemic heart disease	96 (11.18)	101 (11.76)	0.762
Cerebrovascular disease (stroke)	61 (7.10)	73 (8.50)	0.322
Heart Failure	80 (9.31)	82 (9.55)	0.934
Mediaction/Treatment beyond SGA (N%)			
Antidepressants uses			
Average daily dose (mg/day) (Mean, SD)	115.86+-53.87	115.73+-55.40	0.962
Prescription days (Mean, SD)	173.50+-120.33	169.62+-119.05	0.514
Kinds (N%)			0.973
0	47 (5.47)	49 (5.70)	
1 kind	398 (46.33)	395 (45.98)	

≧2 kinds	414 (48.20)	415 (48.31)	
First generation antipsychotics (FGA)			
Average daily dose (mg/day) (Mean, SD)	139.77±115.77	141.17±122.67	0.86
Prescription days (Mean, SD)	75.85±87.66	66.70±87.50	0.114
Kinds (N%)			0.555
0	404 (47.03)	398 (46.33)	
1 kind	288 (33.53)	307 (35.74)	
≧2 kinds	167 (19.44)	154 (17.93)	
Anticonvulsants (N%)	204 (23.75)	209 (24.33)	0.821
Lithium (N%)	28 (3.26)	24 (2.79)	0.673
Stimulant (N%)	14 (1.63)	14 (1.63)	>.999
Thyroid hormone (N%)	0	0	-
ECT (N%)	8 (0.93)	4 (0.47)	0.385

Note:
*Propensity score-matching
Definition of study groups and index dates:
SGA exposed continuously group: MDD patients who received SGA continuously for at least 8 weeks.
SGA exposed irregularly group: Propensity score–matched MDD patients without records of continuously SGA prescription.
Patients with records of type I or type II DM prior to the index dates were excluded. The index date of each patient in the SGA exposed group was assigned to the date of the first dispensing of a SGA. The index dates of patients in the unexposed group were assigned as the index dates of the corresponding SGA users.
Definition of comorbidity:
Comorbidity was coded if it showed up in the inpatient record once or in the outpatient records 3 times prior to the index day.
Comorbidities, listed by ICD-9 CM code, include anxiety/dysthymia (ICD 300), alcohol abuse/dependence (ICD 303, 305.0), substance abuse/dependence (ICD 304, 305.2-305.9), Intellectual disabilities (ICD 317-319), neurologic disorders (ICD 290, 310, 332, 340, 345, 430-438), cardiac diseases (ICD 428, 425, 678, 674, 410-414), endocrine disorders (ICD 244, 252), chronic liver disorders (ICD 570-572), malignancy (ICD 140-208), hypertensive disease (ICD 401), hyperlipidemia(ICD 272), other peripheral vascular disease (ICD 443.9), heart failure (ICD 402-404), Ischemic heart disease (ICD 410–414), Cerebrovascular disease (storke) (ICD 430–438), and Heart Failure (ICD 402-404).
Definition of treatment:
Usages of antidepressants, FGA, anticonvulsants, lithium, stimulant, thyroid hormone, or ECT were defined as at least 1 dispensation1 year prior to the index date. Antidepressant dosages were converted to imipramine-equivalent milligrams and antipsychotics dosages were converted to chlorpromazine-equivalent milligrams.
Abbreviations:
MDD: Major Depressive Disorder
SGA: Second generation antipsychotics
FGA: first generation antipsychotics
ECT: electroconvulsive therapy

Table 2. Risk of NODM after adjusting for competing mortality

	HR	95% CI	p value
Cohort- receiving SGA continuously≧ 8 weeks	0.677	0.437-1.047	0.079
age per year	1.04	1.026-1.054	<.001
Sex-male gender	1.354	0.830-2.209	0.225
Anxiety/Dysthymia	1.176	0.760-1.819	0.466
Alcohol abuse/dependence	1.214	0.468-3.147	0.691
Substance abuse/dependence	1.513	0.518-4.418	0.449
Neurologic disorders	0.511	0.200-1.307	0.161
Cardiac diseases	1.393	0.422-4.597	0.586
Endocrine disorders	0.474	0.052-4.278	0.506
Chronic liver disorders	1.309	0.823-2.083	0.255
Hypertensive disease	2.506	1.399-4.488	0.002
Hyperlipidemia	2.956	1.782-4.905	<.001
Ischemic heart disease	0.411	0.119-1.414	0.158
Cerebrovascular disease (stroke)	1.051	0.359-3.079	0.928
Heart Failure	0.702	0.343-1.435	0.332
Malignancy	0.655	0.244-1.758	0.401
Antidepressants dose	0.999	0.995-1.003	0.738
Antidepressants prescription days	1	0.998-1.002	0.926
First generation antipsychotics dose	1	0.998-1.002	0.886
First generation antipsychotics prescription days	0.999	0.996-1.002	0.658
Anticonvulsants	0.932	0.502-1.732	0.824
Lithium	0.387	0.073-2.069	0.267

Note:
The hazards ratios (HR) with 95% confidence intervals (CI) of new onset diabetes mellitus (NODM) were analyzed using the Cox proportional hazards (PH) model with competing risk. To provide adequate duration for examining the outcome and to avoid potential confounding factors over a longer period of time, the observation period was set to 5 years [19, 20] while we determined whether SGA treatment continuously for more than 8 weeks is a risk factor for NODM by the Cox proportional hazards (PH) model with competing risk.

Abbreviations:
NODM: new onset diabetes mellitus
HR: Hazards ratios
DM: Diabetes Mellitus
SGA: Second generation antipsychotics
FGA: First generation antipsychotics

be based on individual patient needs and consider the potential for metabolic changes.

In this study, MDD patients receiving SGAs continuously for more than 8 weeks did not demonstrate greater incidence of NODM than MDD patients receiving SGAs irregularly. However, NODM was associated with aging and history of hypertensive disease and hyperlipidemia. Possible explanations for our results include lower dose of SGAs in our patients, treatment adherence of our patients and efficacy of continuous SGA treatment. Prior research has suggested that the metabolic effects of SGAs are dose-dependent [23,25]. In our previous study, an average daily dose of chlorpromazine-equivalent 114.23±91.79 mg was administered to MDD patients, which is lower than that administered to mania or schizophrenia patients [6]. Impaired quality of life and poor adherence to metabolic control practice are very common in patients with depression [26,27]. Studies have shown that SGA augmentation results in better treatment response and higher rates of remission in MDD patients with treatment-resistant characteristics [3,28]. In the current study, some patients received SGA treatment continuously for more than 8 weeks indicating better adherence and tolerance to treatment, as well as benefit from SGAs. Since depression and metabolic dysfunction may be interrelated, the potential beneficial effects of SGAs on physical morbidity and life quality, including suitable exercise and nutrition in MDD, require comprehensive investigation.

Our results are consistent with the findings of previous reports [29] indicating elevated risk of NODM in association with hyperlipidemia, hypertension and increased age in MDD [30]. In addition, statin treatment for hyperlipidemia is a possible reason for increased risk of NODM [31,32]. For early detection and to determine consequent treatment, regular checks of metabolic syndrome profile are necessary. Moreover, SGA treatment should be conservative in patients who are older or with hyperlipidemia and/or hypertension.

The strengths of this study are its longer follow-up duration and investigation of all eligible patients in a nationwide sample. In addition, PSM was used to balance the groups. Moreover, the time course of SGA use and DM could be expounded. However, this study also has several limitations. Therefore, clinicians should interpret its results cautiously. Personal history, family history, lifestyle and records of metabolic parameters that could confound the outcomes were not available from the NHIRD. Bias may have existed due to the influence of unmeasured confounders. Selection bias was also a possibility since our subjects were MDD patients who had psychiatric inpatient stays indicating more severe psychopathology. Moreover, the data of patients whose initial psychiatric hospitalizations occurred in 2008-2011 were not available. There is a need for more studies using updated data in the future.

Conclusion

This study indicated that SGA treatment continuity is not associated with a significant risk of NODM in MDD patients. Although clinicians should interpret our results cautiously, this information is helpful for weighing the potential benefits against the side effects and treatment effects associated with SGAs in treatment-resistant depression.

Acknowledgement

Funding:

This study was supported by a Hospital and Social Welfare Organizations Administration Commission Grant (number 105-52).

Material support:

The present study was based in part on data from the NHIRD provided by the Ministry of Health and Welfare and managed by the National Health Research Institute..

Role of the Funders:

The sponsors were not involved in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

Conflicts of interest:

The authors declare that they have no potential

conflict of interest related directly or indirectly to the submitted research work.

Ethical standards:

This study has been approved by the Institutional Review Board of Tsaotun Psychiatric Center.

References

1. Greenberg PE, Fournier AA, Sisitsky T, Pike CT, Kessler RC. The economic burden of adults with major depressive disorder in the United States (2005 and 2010). *J Clin Psychiatry.* 2015;76(2):155-162.
2. Mauskopf JA, Simon GE, Kalsekar A, Nimsch C, Dunayevich E, Cameron A. Nonresponse, partial response, and failure to achieve remission: humanistic and cost burden in major depressive disorder. *Depress Anxiety* 2009;26:83-97.
3. Nelson JC, Papakostas GI. Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. *Am J Psychiatry.* 2009;166(9):980-991.
4. Chen J, Gao K, Kemp DE. Second-generation antipsychotics in major depressive disorder: update and clinical perspective. *Curr Opin Psychiatry.* 2011;24(1):10-17
5. Spielmans GI, Berman MI, Linardatos E, Rosenlicht NZ, Perry A, Tsai AC. Adjunctive atypical antipsychotic treatment for major depressive disorder: a meta-analysis of depression, quality of life, and safety outcomes. *PLoS Med.* 2013;10(3):e1001403.
6. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. *CNS Drugs.* 2005;19(Suppl 1):1-93.
7. Goldberg JF, Freeman MP, Balon R, et al. The American Society of Clinical Psychopharmacology Survey of Psychopharmacologists' Practice Patterns for the Treatment of Mood Disorders. *Depress Anxiety.* 2015;32(8):605-613.
8. Brown ADH, Barton DA, Lambert GW. Cardiovascular abnormalities in patients with major depressive disorder. *CNS Drugs.* 2009;23:583-602.
9. Lin CY, Wu YH, Wang HS, Chen PK, Lin YF, Chien IC. Risk of new onset Type II DM in MDD patients receiving second-generation antipsychotics treatment: a nationwide cohort study. *Depress Anxiety.* 2016;33(5):435-443.
10. Lin CY, Tsai GE, Wang HS, et al. Effectiveness of aripiprazole, olanzapine, quetiapine, and risperidone augmentation treatment for major depressive disorder: a nationwide population-based study. *J Clin Psychiatry.* 2014;75(9):e924-e931.
11. NHI. Information of medicines in NHI, Taiwan. 2014; http://www.nhi.gov.tw/english/index.aspx. Accessed January 1, 2014.
12. Sadock B, Sadock V. *Kaplan & Sadock's Synopsis of Psychiatry* 9ed. New York Williams & Wilkins; 2003.
13. Citrome L, Collins JM, Nordstrom BL, et al. Incidence of cardiovascular outcomes and diabetes mellitus among users of second-generation antipsychotics. *J Clin Psychiatry.* 2013;74(12):1199-1206.
14. Leon AC, Solomon DA, Li C, et al. Antiepileptic drugs for bipolar disorder and the risk of suicidal behavior: a 30-year observational study. *Am J Psychiatry.* 2012;169(3):285-291.
15. Kornstein SG, Schneider LS. Clinical features of treatment-resistant depression. *J Clin Psychiatry.* 2001;62(Suppl 16):18-25.
16. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. *Diabetes Care.* June 1, 2001 2001;24(6):1069-1078.
17. APA. American Psychiatric Association: Practice guidelines for the treatment of patients with major depressive disorder. 3rd edition. Arlington, VA.2010.
18. Song JW, Chung KC. Observational studies: cohort and case-control studies. *Plast Reconstr Surg* 2010;126(6):2234-2242.
19. Wu CY, Chen YJ, Ho HJ, et al. Association between nucleoside analogues and risk of hepatitis B virus–related hepatocellular carcinoma recurrence following liver resection. *JAMA.* 2012;308(18):1906-1913.
20. Henderson DC, Cagliero E, Gray C, et al. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five-year naturalistic study. *Am J Psychiatry* 2000;157(6):975-981.
21. Gray B. cmprsk: Subdistribution analysis of competing

risks. R package version 2.2-7 http://cran.r-project.org/web/packages/cmprsk/index.html: ; 2014.
22. Andersen SW, Clemow DB, Corya SA. Long-term weight gain in patients treated with open-label olanzapine in combination with fluoxetine for major depressive disorder. *J Clin Psychiatry* 2005;66(11):1468-1476.
23. Liebowitz M, Lam RW, Lepola U, Datto C, Sweitzer D, Eriksson H. Efficacy and tolerability of extended release quetiapine fumarate monotherapy as maintenance treatment of major depressive disorder: a randomized, placebo-controlled trial. *Depress Anxiety.* 2010;27(10):964-976.
24. Berman MI, Thase ME, Trivedi MH, et al. Long-term safety and tolerability of open-label aripiprazole augmentation of antidepressant therapy in major depressive disorder. *Neuropsychiatr Dis Treat.* 2011;7:303-312.
25. Simon V, van Winkel R, De Hert M. Are weight gain and metabolic side effects of atypical antipsychotics dose dependent? A literature review. *J Clin Psychiatry* 2009;70(7):1041-1050.
26. IsHak WW, Mirocha J, James D, et al. Quality of life in major depressive disorder before/after multiple steps of treatment and one-year follow-up. *Acta Psychiatr Scand* 2015;131(1):51-60.
27. Hoertel N, Limosin F, Leleu H. Poor longitudinal continuity of care is associated with an increased mortality rate among patients with mental disorders: results from the French National Health Insurance Reimbursement Database. *Eur Psychiatry* 2014;29(6):358-364.
28. Nelson JC, Thase ME, Trivedi MH, et al. Safety and tolerability of adjunctive aripiprazole in major depressive disorder: a pooled post hoc analysis (studies CN138-139 and CN138-163). *Prim Care Companion J Clin Psychiatry.* 2009;11(6):344-352.
29. Vancampfort D, Mitchell AJ, De Hert M, et al. Type 2 diabetes in patients with major depressive disorder: a meta-analysis of prevalence estimates and predictors. *Depress Anxiety.* 2015;32(10):763-773.
30. Buijsse B, Simmons RK, Griffin SJ, Schulze MB. Risk assessment tools for identifying individuals at risk of developing Type 2 diabetes. *Epidemiol Rev.* 2011;33(1):46-62.
31. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *The Lancet.* 2010;375(9716):735-742.
32. Waters DD, Ho JE, DeMicco DA, et al. Predictors of new-onset diabetes in patients treated with atorvastatin: results from 3 large randomized clinical trials. *J Am Coll Cardiol.* 2011/04/05/ 2011;57(14):1535-1545.