Effectiveness of Aripiprazole, Olanzapine, Quetiapine, and Risperidone Augmentation Treatment for Major Depressive Disorder: A Nationwide Population-Based Study

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ABSTRACT

Objective: Previous studies suggested that antidepressants augmented with second-generation antipsychotics (SGAs), including aripiprazole, olanzapine, quetiapine, and risperidone, resulted in better treatment response or higher rates of remission in patients with major depressive disorder (MDD). However, population-based study on SGA augmentation for patients with MDD remains limited. The purpose of this study was to investigate the effectiveness of SGA augmentation for treatment of MDD using the National Health Insurance Research Database in Taiwan.

Method: The subjects were patients with MDD (*ICD-9-CM* code: 296.2 and 296.3) who were initially admitted to psychiatric inpatient settings for the first time between January 1, 1996, and December 31, 2007, and could be tracked until December 31, 2011. To assess the treatment effect of SGA augmentation, 993 MDD patients who received aripiprazole, olanzapine, quetiapine, or risperidone augmentation treatment for 8 weeks or more were included in this 1-year mirror-image study. Outcome measures included length of psychiatric hospitalization and number of psychiatric admissions and emergency room (ER) visits.

Results: After patients received SGA augmentation treatment, key psychiatric service use (including length of psychiatric hospitalization [$P < .0001$], number of psychiatric admissions [$P < .0001$], and ER visits [$P = .0006$]) due to MDD diagnosis was significantly reduced. Subgrouping analysis for each SGA drug also showed significant reduction in number of psychiatric admissions for MDD patients who received aripiprazole ($P < .0001$), olanzapine ($P = .003$), quetiapine ($P < .0001$), and risperidone ($P < .0001$).

Conclusions: The study provides support that aripiprazole, olanzapine, quetiapine, and risperidone augmentation therapy could be effective in reducing psychiatric service utilization among MDD patients.

J Clin Psychiatry 2014;75(9):e924–e931

Submitted: *October 15, 2013; accepted March 14, 2014 (doi:10.4088/JCP.13m08843).*
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Major depressive disorder (MDD), a very common mental disorder with a lifetime prevalence reaching 16%,[1] heavily burdens individuals, families, and society. Pharmacotherapy has a limited role in the treatment for MDD. In general, antidepressant treatment is effective for only one-third of patients with MDD, partially useful for another third, and useless for the remaining third.[2] When the outcome is not optimal, patients tend to drop from treatment and, in turn, face detrimental risks such as disability and suicide.

Alternative antidepressants or augmentation therapies are common strategies if the first antidepressant treatment fails. For difficult-to-treat patients with MDD, the main augmentation therapies include combining 2 different antidepressants or combining antidepressant with an anticonvulsant agent, lithium, psychostimulants, or thyroid hormone.[2–5]

Recently, many clinical trials showed that antidepressant augmented with second-generation antipsychotics (SGAs), including aripiprazole,[6,7] olanzapine,[8] quetiapine,[9] and risperidone,[10,11] resulted in better treatment response or higher rates of remission than antidepressant monotherapy after 6–12 weeks of treatment. These clinical trials investigating SGA augmentation focused on treatment-resistant MDD, with an aim to improve the clinical symptoms of depression.[12] However, the long-term outcomes are unclear. Studies with longer term observation in population samples are helpful to investigate the efficacy of SGA augmentation treatment in patients with MDD.

No study to date has reported the characteristics of MDD patients using SGA augmentation treatment in the "real-world" setting,[13] and the study of the effect of SGA augmentation treatment on long-term outcomes (for example, psychiatric service uses, including number and length of psychiatric hospitalization, and utilization of emergency service) remains lacking.[12]

In the present study, the National Health Insurance Research Database (NHIRD) in Taiwan was used to understand the national trend of SGA utilization and to investigate the effectiveness of SGA augmentation treatment in MDD. The study subjects were MDD patients who had continuous SGA augmentation treatment (with aripiprazole, olanzapine, quetiapine, or risperidone) for 8 weeks or more. Using a 1-year mirror-image study design, the study examined the effect of SGA augmentation treatment on the need of subsequent service utilization, measured as the change in psychiatric inpatient and emergency room (ER) utilization before and after SGA augmentation treatment.

METHOD

Data Source

The NHIRD contains comprehensive health care data on more than 99% of the entire population of 23.74 million enrolled in the National Health Insurance (NHI) program in Taiwan. All diseases are

Clinical Points

- The real-world characteristics of patients with major depressive disorder (MDD) who received second-generation antipsychotic (SGA) augmentation are reported in this population-based study.
- This study investigates the treatment outcome of SGA augmentation in a different patient population than those who participated in the prospective clinical trials. The results show that SGA augmentation treatments have a positive role in clinical practice.
- Because of several limitations, clinicians should interpret the results cautiously.

covered under the NHI program, and patients' access to health services is nonrestrictive.[14] The NHIRD comprises information on demographic data, dates of clinical visits, diagnostic codes, and details of prescriptions, procedures, and surgeries. These datasets had been successfully used to evaluate the protective or risk factors for a variety of diseases in the population.[15,16] Our study population came from the Psychiatric Inpatient Medical Claim (PIMC) dataset, a subset of the NHIRD, which collected additional psychiatric information from 187,117 patients who received inpatient psychiatric treatment initially between January 1, 1996, and December 31, 2007, and their follow-up health care utilization data until December 31, 2011.

Study Subjects

Ethics approval was obtained from the Institutional Review Board of China Medical University Hospital for this study. The flowchart of study sample selection is shown in Figure 1. The MDD subjects were screened based on the *International Classification of Diseases*, *Ninth Revision*, *Clinical Modification* (*ICD-9-CM*) records. The list of *ICD-9-CM* codes of the diseases analyzed in the current study is shown in Supplementary eTable 1. The screening process identified 38,018 patients whose hospitalization to a psychiatric ward occurred between January 1, 1997, and December 31, 2010, with a primary diagnosis of MDD (*ICD-9-CM* code 296.2 or 296.3). In addition, so that the diagnostic stability of unipolar depression could be ascertained,[17] patients who had records of organic psychotic conditions, schizophrenia spectrum disorders, bipolar disorders, and affective psychosis were excluded.

To investigate the effectiveness of SGA augmentation treatment, we used prescription drug claims to identify the use of antidepressants, SGAs, and other medicines. The prescription drug claims contained the specific date, dose, and route of every prescription and the number of days supplied for each dispensed drug. All the prescriptions were reimbursed by the NHI. The list of medications analyzed in the current study is shown in Supplementary eTable 2. On the basis of previous clinical trials,[12,18] which found a mean treatment duration of 8 weeks, MDD patients who received antidepressants plus aripiprazole, olanzapine, quetiapine, or risperidone continuously for at least 8 weeks were defined as the study subjects. The index day was the day when the subjects started SGA augmentation treatment. Patients who could not be observed for a full 1-year service utilization before and after the index day were further excluded in order to calculate more valid outcome measures. The study comprised a final sample of 993 MDD patients with SGA augmentation therapy.

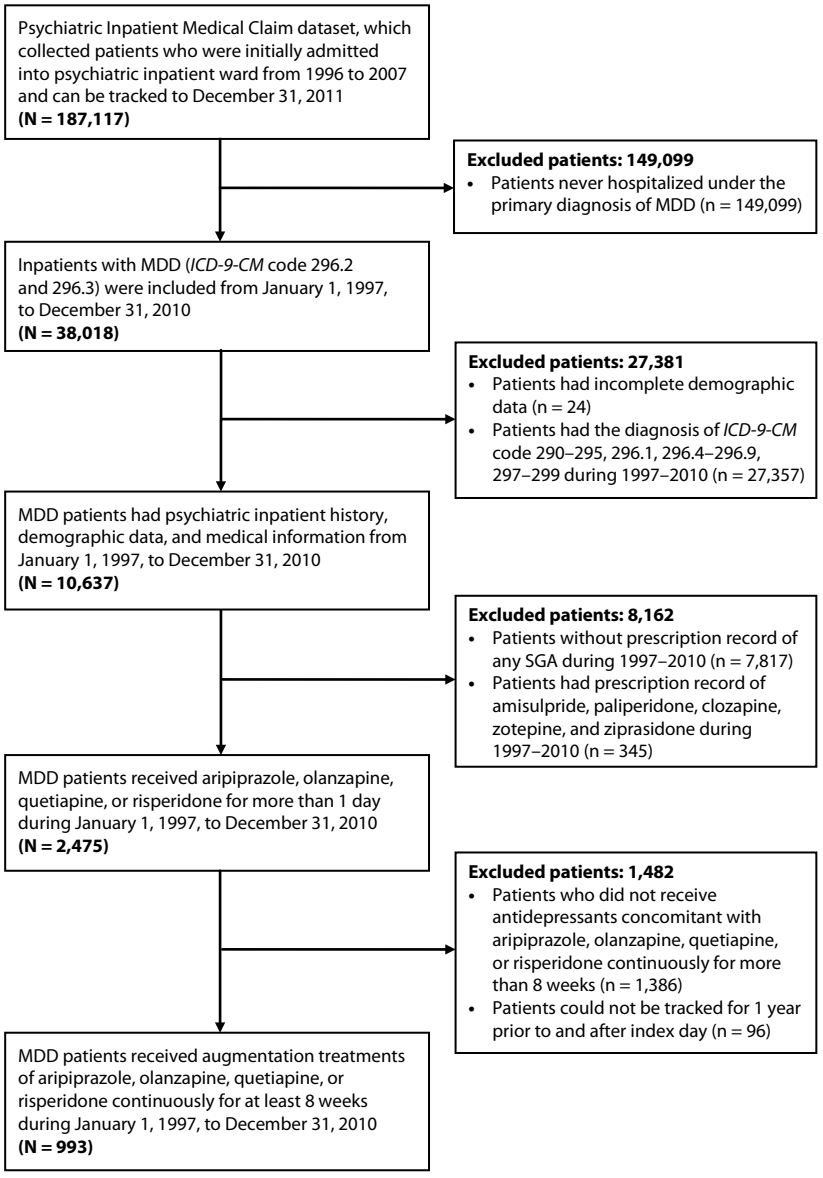
Outcome Variables

The present study applied a mirror-image study design to compare service utilization (length of psychiatric hospitalization and number of psychiatric admissions and ER visits) before and after SGA augmentation treatment among 993 MDD patients. Inpatient hospitalizations and ER visits had been successfully used to investigate prevalence[19] and treatment outcome[20] for psychiatric disorders using the national claims database. In the current study, number of psychiatric admissions and length of hospital stay were measured by using the PIMC inpatient records. In addition, if a patient was readmitted to the same hospital or transferred to another hospital within 3 days with the same diagnosis, the subsequent admission(s) was counted as part of the previous hospitalization. In addition to measuring key psychiatric services, 1-year change in concomitant treatment after SGA augmentation was also compared.

To compare the differences in the characteristics between MDD patients with SGA augmentation treatment and those without any SGA treatment, we selected a comparison group of patients. We identified 7,817 patients in the comparison group, defined as patients having the same diagnosis and hospitalization records, but who were never treated with any kind of SGA in Taiwan, including amisulpride, aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone, or zotepine. Since SGA augmentation is a new treatment strategy, there is a need to reduce the influence of time related to the underlying trend of the SGA use. Therefore, the patients not treated with any SGA were matched to the study subjects according to their first MDD admission dates, and these patients' index dates were assigned as the index dates of the corresponding subjects with SGA augmentation treatment.

For comparison of the pretreatment-posttreatment change in psychiatric service utilization among the 993 subjects against the general trend, the overall trend of psychiatric service utilization by MDD patients between 1996 and 2011 was provided. Average number of psychiatric admissions and average days of psychiatric hospitalization were calculated as total counts and days of psychiatric hospitalizations divided by the total number of MDD inpatients in each year. The main PIMC dataset does not contain new-onset patients admitted between January 1, 2008, and December 31, 2011, whose data have not been published yet. We applied alternative data for the trend analysis using the Longitudinal Health Insurance Database 2000 (LHID 2000), one of the subsets of the NHIRD. The LHID 2000 contains claims data of 1,000,000 randomly sampled patients from NHIRD.

Figure 1. Flowchart of Sample Selection



Abbreviations: *ICD-9-CM* = *International Classification of Diseases, Ninth Revision, Clinical Modification*; MDD = major depressive disorder; SGA = second-generation antipsychotic.

It has been shown that the demographic characteristics of sampled individuals in the LHID 2000 are representative of the general population in Taiwan.[21]

Demographic and Clinical Variables

The demographic and clinical information of the study subjects was analyzed. These variables included age, gender, comorbid physical and psychiatric disorders that frequently influence the outcomes of MDD patients,[22] antidepressant treatments, and other augmentation treatments.[3] Medical comorbidities included neurologic disorders, cardiac diseases, endocrine disorders, and chronic liver disorders. Psychiatric comorbidities included anxiety, dysthymia, and alcohol/substance misuse or dependence. The comorbid condition was coded as 1 if it appeared in the inpatient record once or in the outpatient records 3 times prior to the index day. Usage of antidepressants, first-generation antipsychotics (FGAs), anticonvulsants, lithium, stimulants, thyroid hormone, or electroconvulsive therapy was defined as having at least 1 record within 1 year prior to the index day. Antidepressant dosages were converted to imipramine-equivalent milligrams.[23]

Statistical Analysis

All data were expressed as mean ± SD for continuous variables and frequency (%) for categorical data. Independent *t* test or χ^2 test was used to test the differences in patient characteristics between patients receiving SGA augmentation

Table 1. Demographics of Patients With Major Depressive Disorder Receiving Second-Generation Antipsychotic (SGA) Augmentation Treatment Versus Patients Who Never Received Any SGAs

Demographic	Patients Receiving SGA Augmentation (n = 993)[a]	Patients Who Never Received Any SGAs (n = 7,817)[b]	*P* Value[c]
Age when SGA began, mean ± SD, y	43.81 ± 17.19	37.44 ± 18.47	< .0001
Gender, n (%)			
Male	370 (37.26)	4,849 (62.03)	< .0001
Female	623 (62.74)	2,968 (37.97)	
Comorbidity, n (%)[d]			
Neurologic disorders	173 (17.42)	856 (10.95)	< .0001
Cardiac diseases	184 (18.53)	918 (11.74)	< .0001
Endocrine disorders	29 (2.92)	89 (1.14)	< .0001
Chronic liver disorders	249 (25.08)	1,312 (16.78)	< .0001
Anxiety/dysthymia	761 (76.64)	4,226 (54.06)	< .0001
Alcohol abuse/dependence	52 (5.24)	262 (3.35)	.005
Substance abuse/dependence	41 (4.13)	100 (1.28)	< .0001
Treatments prior to SGA[e] augmentation			
Antidepressants			
Daily dose, mean ± SD, mg	155.76 ± 81.09	80.77 ± 84.58	< .0001
Prescription days, mean ± SD	189.20 ± 113.92	82.73 ± 102.91	< .0001
Kinds of augmentation therapies, n (%)			
0	0 (0.00)	2,569 (32.86)	< .0001
1	323 (32.53)	3,344 (42.78)	
≥ 2	670 (67.47)	1,904 (24.38)	
Other treatments, n (%)			
FGA	499 (50.25)	1,620 (20.72)	< .0001
Anticonvulsants	179 (18.03)	659 (8.43)	< .0001
Lithium	48 (4.83)	74 (0.95)	< .0001
Stimulants	24 (2.42)	29 (0.37)	< .0001
Thyroid hormone	0 (0.00)	1 (0.01)	> .9999
ECT	19 (1.91)	1 (0.01)	< .0001

[a]Patients who received aripiprazole, olanzapine, quetiapine, or risperidone augmentation treatment continuously for at least 8 weeks.
[b]Patients who never received any kind of SGAs available in Taiwan, including amisulpride, aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone, or zotepine. These patients who were never treated with any SGA were matched to the study subjects according to their first major depressive disorder admission dates, and these patients' index dates were assigned as the index dates of the corresponding subjects with SGA augmentation treatment.
[c]Independent *t* test or χ^2 test was used to test the differences.
[d]The comorbidity was coded as 1 if it showed up in the inpatient record once or in the outpatient records 3 times prior to the index day.
[e]Usage of antidepressants, FGAs, anticonvulsants, lithium, stimulants, thyroid hormone, or ECT was defined as having at least 1 record 1 year prior to the index day. Antidepressant dosages were converted to imipramine-equivalent milligrams.
Abbreviations: ECT = electroconvulsive therapy, FGA = first-generation antipsychotic, SGA = second-generation antipsychotic.

treatment and those never treated with any SGA. Wilcoxon signed rank test was used to assess the differences in length of psychiatric hospitalization and number of psychiatric admissions and ER visits between subjects before and after SGA augmentation treatment. The McNemar test was used to compare the 1-year difference of concomitant treatments in addition to the SGA treatment. Concomitant treatment records during the first 8 weeks of SGA augmentation therapy were excluded because, during the 8-week treatment period, the temporal concomitant medications were gradually phased out as SGA treatment began to take effect.[20] To examine the trend in total number and days of psychiatric hospitalizations, we performed linear regression analysis to assess changes in slopes of these measures by year.

All analyses were performed by using the SAS system (version 9.2; SAS Institute) and the STATA 11th edition (Stata Corp), and $P < .05$ was considered statistically significant.

RESULTS

Demographic Characteristics

Among MDD patients who had a history of psychiatric inpatient admission between 1997 and 2010, excluding those with other major psychiatric illness, the proportion of continuous 8-week SGA augmentation therapy is about 9.34% (Figure 1). The proportion of SGA augmentation in MDD grew steadily after 1999. The mean daily dosages of aripiprazole, olanzapine, quetiapine, and risperidone were 5.38 ± 2.83 mg, 4.60 ± 3.07 mg, 103.41 ± 84.18 mg, and 1.46 ± 1.21 mg, respectively. Older SGAs such as olanzapine, quetiapine, and risperidone were prescribed more widely than aripiprazole, the newer SGA in Taiwan.

Table 1 shows the demographic data, including age, gender, medical and psychiatric comorbidities, and treatments prior to the index date. The results showed some differences between

Table 2. Differences in 1-Year Psychiatric Service Utilization by Patients Before and After Receiving Second-Generation Antipsychotic (SGA) Augmentation Treatment[a]

Group	Before SGA	After SGA	Difference, %	*P* Value[b]
No. of psychiatric admissions				
Overall (n = 993)	805	365	−54.7	< .0001
Aripiprazole (n = 42)	53	17	−67.9	< .0001
Olanzapine (n = 135)	91	56	−38.5	.0030
Quetiapine (n = 604)	490	247	−49.6	< .0001
Risperidone (n = 212)	171	45	−73.7	< .0001
Days of psychiatric hospitalization				
Overall (n = 993)	20,293	18,283	−9.9	< .0001
Aripiprazole (n = 42)	1,318	967	−26.6	.0239
Olanzapine (n = 135)	2,579	2,806	8.8	.1906
Quetiapine (n = 604)	11,594	11,248	−3.0	< .0001
Risperidone (n = 212)	4,802	3,262	−32.1	.0002
No. of emergency room visits				
Overall (n = 993)	248	190	−23.4	.0006
Aripiprazole (n = 42)	13	6	−53.8	.1133
Olanzapine (n = 135)	24	27	12.5	.6891
Quetiapine (n = 604)	150	138	−8.0	.0981
Risperidone (n = 212)	61	19	−68.9	< .0001

[a]Patients who received aripiprazole, olanzapine, quetiapine, or risperidone augmentation treatment continuously for at least 8 weeks.
[b]Wilcoxon signed rank test was used to assess the differences.

Table 3. Differences in 1-Year Concomitant Treatments of Patients Before and After Receiving Second-Generation Antipsychotic (SGA) Augmentation Treatment[a]

Concomitant Treatment,[b] n	Before SGA	After SGA	Difference, %	*P* Value[c]
FGA	499	259	−24.17	< .0001
Anticonvulsants	179	191	1.21	.3989
Lithium	48	33	−1.51	.0489
Stimulant	24	20	−0.40	.5966
Thyroid hormone	0	0	0	NA
ECT	19	23	0.40	.5847

[a]Nine hundred ninety-three patients with major depressive disorder who received aripiprazole, olanzapine, quetiapine, or risperidone augmentation treatment continuously for at least 8 weeks.
[b]Usage of FGA, anticonvulsants, lithium, stimulant, thyroid hormone, or ECT was defined as having at least 1 record. Concomitant treatment records during the first 8 weeks of SGA augmentation therapy were excluded because, during the 8-week treatment period, the temporal concomitant medications were gradually phased out as SGA treatment began to take effect.
[c]McNemar test was used to compare the difference.
Abbreviations: ECT = electroconvulsive therapy, FGA = first-generation antipsychotic, NA = not applicable.

the 993 study subjects receiving SGA augmentation treatment and patients never treated with any SGA. Patients receiving SGA augmentation treatment were older (mean = 43.81 vs 37.44 years, $P < .0001$), were more likely to be female (62.74% vs 37.97%, $P < .0001$), and had a higher rate of observed comorbidity such as neurologic disorders ($P < .0001$), cardiac diseases ($P < .0001$), endocrine disorders ($P < .0001$), chronic liver disorders ($P < .0001$), anxiety/dysthymia ($P < .0001$), alcohol abuse/dependence ($P = .005$), and substance abuse/dependence ($P < .0001$). Patients with SGA augmentation treatment received more medications. For example, the subjects receiving SGA augmentation treatment had a higher mean daily dose of antidepressants compared to patients who never received any SGA ($P < .0001$). The subjects receiving SGA augmentation treatment were more likely to be treated by various kinds of augmentation therapies within the year prior to the SGA augmentation as well.

Psychiatric Services and Concomitant Treatments

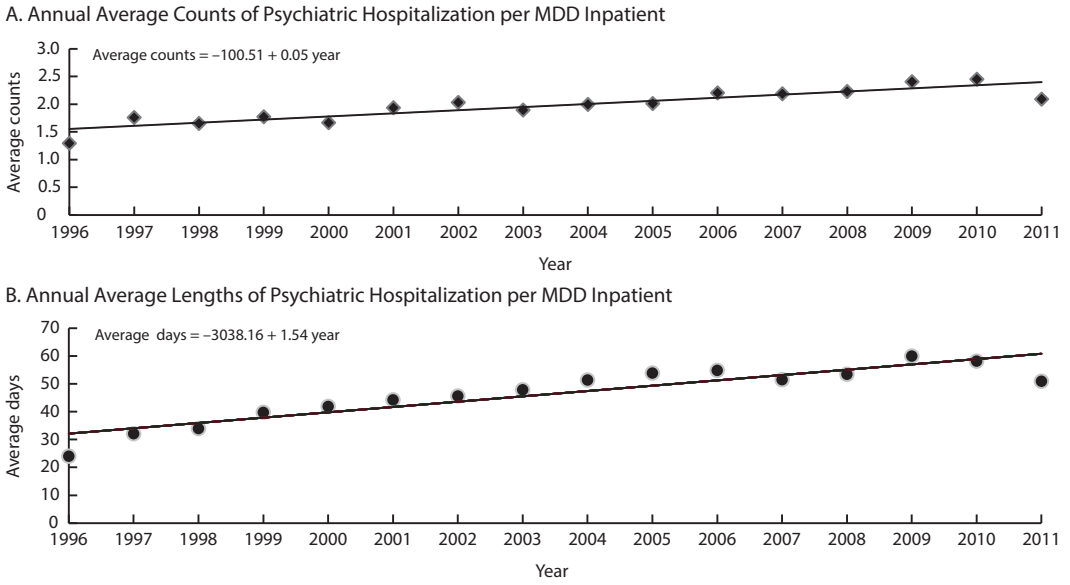
The pretreatment-posttreatment differences in psychiatric service utilization for 993 subjects receiving SGA augmentation treatment and the subanalysis by each SGA drug were performed in Table 2. Compared to the psychiatric utilization in the year before SGA augmentation treatment, total days of psychiatric hospitalizations in the posttreatment period were reduced by 9.9% ($P < .0001$), and total number of psychiatric admissions and ER visits was reduced by 54.70% ($P < .0001$) and 23.40% ($P = .0006$), respectively. The subgroup analysis revealed significant reductions in the number of psychiatric admissions for patients receiving aripiprazole (−67.9%, $P < .0001$), olanzapine (−38.5%, $P = .003$), quetiapine (−49.6%, $P < .0001$), and risperidone (−73.7%, $P < .0001$). Similarly, there were significant decreases in the days of psychiatric hospitalization for patients receiving aripiprazole, quetiapine, or risperidone and significant declines in ER visits for patients receiving risperidone. Although quetiapine was the most common SGA being administered, the reductions in overall service utilization did not appear to be driven by any 1 particular SGA drug. In addition, Table 3 provides the pretreatment-posttreatment differences in 1-year concomitant treatments for the subjects, suggesting that the use of FGAs was significantly reduced after 8-week SGA treatment ($P < .0001$).

It is possible that the observed pretreatment-posttreatment reduction in inpatient utilization among SGA subjects was related to a general trend of reduction in inpatient utilization, if there was such a trend, thus overestimating the effect of SGAs. To rule out this possibility, we analyzed the overall trend in psychiatric inpatient utilization for all MDD patients in the study period. We found that there was a general increasing trend in the number and length of psychiatric hospitalizations over the last 16 years between 1996 and 2011 in Taiwan (Figure 2). Estimates from linear regression showed a positive slope of 0.05 ($P < .0001$) for the number of admissions and 1.54 ($P < .0001$) for length of hospitalization, suggesting that the reduction in hospital utilization among the subjects receiving SGA therapy was in contrast to an underlying trend of increasing utilization.

DISCUSSION

To our knowledge, this is the first nation-wide population-based study to investigate the effectiveness of SGA augmentation treatment in MDD. We found that MDD patients being prescribed SGAs were most likely older and sicker patients than patients who never took SGAs, as indicated by higher rates of medical and psychiatric comorbidity and other augmentation treatments in the year prior to the SGA augmentation. Yet, after at least 8 weeks of SGA augmentation, including risperidone, olanzapine, quetiapine, and aripiprazole, length of psychiatric

Figure 2. Overall Trend of Psychiatric Service Utilization by Patients With Major Depressive Disorder (MDD) Between 1996 and 2011[a]



[a]Average number of psychiatric admissions and average days of psychiatric hospitalization were calculated as total counts and days of psychiatric hospitalizations divided by the total number of MDD inpatients in each year of the period 1996–2011 according to the Longitudinal Health Insurance Database 2000. Linear regression analysis was performed to assess changes in slopes of the number and days of psychiatric hospitalizations per MDD inpatient over years. Estimates from linear regression showed a positive slope of 0.05 ($P < .0001$) for the number of admissions and 1.54 ($P < .0001$) for lengths of hospitalizations during the study period, suggesting that there was a general increasing trend in the number and length of psychiatric hospitalizations over the last 16 years between 1996 and 2011.

hospitalization, number of psychiatric admissions and ER visits, and concomitant FGA treatment were significantly reduced. Moreover, subgrouping analysis for individual SGA drug showed significant reductions in the number of psychiatric admissions for all drugs.

Our findings demonstrate that SGA augmentation treatment was a new treatment choice for the MDD patients, with favorable outcomes in the clinical settings. Because many patients with MDD respond inadequately to antidepressant monotherapy, adjunctive therapies are commonly applied.[2,24] Similar to the increasing national trend of SGA augmentation for depression patients in the United States,[25] the proportion of SGA augmentation in MDD had grown steadily in Taiwan, while the number of clinical trials using SGA augmentation treatment for patients with MDD had also grown rapidly.[18,26] All SGA augmentation treatments were off-label uses in Taiwan before 2010. Aripiprazole and quetiapine were approved for MDD in Taiwan in December 2009 and October 2011, respectively.[27] However, off-label use of psychotropic medications was allowed by the evidence provided in scientific literature and patients' poor responses to approved treatments. The practice is consistent with American Psychiatric Association's *Practice Guideline for the Treatment of Patients With Major Depressive Disorder*,[3] wherein SGA augmentation is indicated for MDD patients who do not respond to antidepressant monotherapy. Evidently, older SGAs such as olanzapine, quetiapine, and risperidone were prescribed more commonly than aripiprazole. The daily dosage of aripiprazole, olanzapine, and quetiapine prescribed by clinicians in our data was lower than that used in MDD clinical trials. Moreover, the optimal dosage of SGAs for MDD is most likely lower than the effective dose for mania or schizophrenia, perhaps due to the reported effect that SGAs demonstrate nondopaminergic properties at low dosage.[12,28]

Although the decision of admission may depend on factors in addition to psychopathology, hospitalization is known to be a significant adverse event of psychiatric illness and serves as a valid outcome measure for the treatment of MDD.[29] The main reasons why MDD patients receive inpatient treatment are because of suicidal crisis, disease progression, relapse, or function deteriorating,[17,30] and reduced number and length of hospitalizations represent better treatment response of the illness. Similarly, reduced number of ER visits reflects decreases in the frequency of relapsed crises. The improvement in the length of psychiatric hospitalization and numbers of psychiatric admissions and ER visits suggested that SGA augmentation therapy played a positive role in the overall outcome of the MDD patients.

Overall, the subjects receiving SGA augmentation therapy had worse initial clinical condition and a higher number of comorbidities. There are potential biases this may cause, and we discuss 2 of them. First, sicker study subjects may be more likely to drop out due to suicide and death, and therefore biasing the inpatient and ER admission measures we used. However, because we included only subjects who had a full-year observation in utilization records before and after SGA treatment, this bias was minimized by the study design. Second, the sicker subjects might be hospitalized due to medical conditions and might reduce the need of separate psychiatric hospitalizations. This would bias our

estimated effect of SGA augmentation treatment. We tested this possibility by examining the change in all-cause, not just psychiatric cause, inpatient admissions and ER visits. Interestingly, the total number of hospitalizations and ER visits after SGA augmentation was still significantly lowered by −27.93% and −26.04%, respectively, even when we excluded MDD as the primary cause of utilization. While there could still be other potential confounders, our findings suggest a favorable effect of SGA treatment for MDD patients who began the study with more medical comorbidity and severe clinical conditions.

It was found that some study subjects receiving SGA augmentation treatment were also given FGAs. The concomitant use of FGA and SGA was most likely due to a "phase-in" effect of SGA during the study period. The use of FGAs was substantially reduced after SGA augmentation (−24.17%) (Table 3). When we excluded the subjects receiving any FGA, the estimates on all outcome measures remained similar. Therefore, the favorable outcome we observed in the SGA group was unlikely due to FGAs. Meanwhile, the effects of FGAs in MDD are controversial.[31] Despite the efficacy, FGAs have been discouraged due to the risk of tardive dyskinesia in MDD patients.[18]

There are several limitations in this observational study. First, one major limitation of our study is that, because of data limitation, we did not include outcome measures other than inpatient hospitalizations and ER visits. Our study was not meant to provide a full evaluation of the efficacy using a complete set of all possible outcome measures. Rather, we meant to provide a survey of how SGAs for MDD were implemented by clinicians in a real-world setting and to examine the effectiveness of such a treatment strategy using large-scale data. We acknowledge that other more refined outcome measures, such as severity of psychopathology, side-effect ratings, and quality of life, should be further examined in follow-up studies. Since we found significant reductions in hospitalizations and ER visits, which can be considered as measures of more severe adverse events, other more refined outcomes may reveal an even larger impact of SGA augmentation treatment. Second, some factors that may affect the outcomes of MDD, such as lifestyle, family history, previous number of depressive episodes, age at onset, and psychotherapy involvement that is self-pay, could confound the outcomes observed. However, the pretreatment-posttreatment mirror-image design could balance part of the bias arising from these confounders by comparing the pretreatment-posttreatment change of the same individual.

Third, some MDD patients with less pathology may not utilize inpatient services; therefore, selection bias may exist since our subjects were MDD patients who had psychiatric inpatients history. The study represented a subpopulation of MDD patients who had more severe psychopathology. In addition, patients whose initial psychiatric hospitalizations occurred in most recent years (2008–2011) were not available for our study; therefore, our study results may not be generalized. Since SGA augmentation in MDD is a recent treatment option, these patients deserve further investigation when the database is updated in the future. Fourth, we investigated only aripiprazole, olanzapine, quetiapine, and risperidone, all of which had shown efficacy in MDD augmentation treatment in previous clinical trials. There is a need for more studies on other less well-studied SGAs, such as amisulpride, clozapine, paliperidone, ziprasidone, and zotepine.

Fifth, the traditional mirror-image design using the starting date of SGA augmentation as the index day may underestimate the true impact of treatments. Patients usually receive the new therapy during crises in which more resources such as hospitalization or ER visits are utilized.[32] Moreover, patients do not respond immediately during the treatment period. Indeed, when we calculated hospital and ER utilization excluding the first 8 weeks of SGA augmentation treatment period, the 1-year differences in psychiatric hospitalization days and the numbers of psychiatric admissions and ER visits increased to −30.02%, −62.11%, and −27.02%, respectively ($P < .0001$), which implied a much greater impact of SGA, compared to −9.9%, −54.7%, and −23.4% when we included the first 8 weeks.

Finally, while SGA augmentation treatment for MDD appears to be effective, one needs to be cautious about the safety of such combination treatment strategy. We performed a test to examine the risk of cardiometabolic diseases between the 993 study subjects receiving SGA augmentation treatment and those never treated with any SGA. We found no statistical difference in the rate of newly onset hypertension, diabetes mellitus, disorders of lipoid metabolism, and ischemic heart diseases within 1 year from the index day when the SGA treatment was initiated. This finding was most likely due to the relatively low dose of and short duration of exposure to SGAs. In previous trials, the rate of discontinuation due to adverse events with SGAs occurred at a higher rate than that of placebo (9.1% versus 2.3%).[18] Moreover, the US Food and Drug Administration issued a black box warning in 2008 regarding the risks of both FGA and SGA use among elderly patients with dementia.[33] Because little is known about longer-term safety of the SGA augmentation treatment in MDD,[34] the use of SGA augmentation treatment should be more conservative for patients with a history cardiovascular diseases and for elderly patients. More studies focusing on the safety of SGA augmentation treatment in MDD are needed.

CONCLUSIONS

Our findings provide support that augmentation with SGAs, including aripiprazole, olanzapine, quetiapine, and risperidone, could be an effective way to reduce psychiatric service utilization in MDD patients. Findings from our observational population study affirm the positive findings from the randomized controlled clinical trials of SGAs in MDD patients.

Drug names: aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), imipramine (Tofranil, Surmontil, and others), lithium (Lithobid and others), olanzapine (Zyprexa and others), paliperidone (Invega), quetiapine (Seroquel and others), risperidone (Risperdal and others), ziprasidone (Geodon and others).

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Potential conflicts of interest: None reported.
Funding/support: Supported in part by a Changhua Hospital Research Grant (101-1) and by the Taiwan Department of Health Clinical Trial and Research Center of Excellence (DOH103-TD-B-111-004).
Role of the sponsors: The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.
Disclaimer: The interpretation and conclusions contained herein do not represent those of National Health Insurance Administration, Ministry of Health and Welfare or National Health Research Institutes.
Additional information: This study was based in part on data from the National Health Insurance Research Database (NHIRD) provided by the Bureau of National Health Insurance, Department of Health and managed by National Health Research Institutes (http://nhird.nhri.org.tw/en/index.htm). The use of NHIRD is limited to research purposes only. All applicants must follow the Computer-Processed Personal Data Protection Law and be reviewed for approval of data release.
Supplementary material: See accompanying pages.

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Supplementary material follows this article.

THE JOURNAL OF
CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Article Title: Effectiveness of Aripiprazole, Olanzapine, Quetiapine, and Risperidone Augmentation Treatment for Major Depressive Disorder: A Nationwide Population-Based Study

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DOI Number: 10.4088/JCP.13m08843

List of Supplementary Material for the article

1. **eTable 1** ICD-9-CM codes of the disease in the study

2. **eTable 2** Analyzed medicines in the study

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary eTable 1. ICD-9-CM codes of the diseases in the study

Diseases	Diseases/ICD-9-CM code
Major depressive disorder	ICD9-CM 296.2-296.3
Organic psychotic conditions	ICD9-CM 290-294
Schizophrenia-spectrum disorders	ICD9-CM 295, 297-299
Bipolar disorders	ICD-9-CM 296.0, 296.1, 296.4, 296.5, 296.6, 296.7, 296.8
Affective psychosis	ICD-9-CM 296.9
Physical comorbidities	
Neurologic disorders	Epilepsies(ICD-9-CM 345)
	Parkinson's disease(ICD-9-CM 332)
	Multiple sclerosis(ICD-9-CM 340)
	Cerebrovascular disease (ICD-9-CM 430-438)
	Traumatic brain injury (ICD-9-CM 310)
Cardiac disease	Ischemic heart disease(ICD-9-CM 410-414)
	Heart failure(ICD-9-CM 428)
	Cardiomyopathy (ICD-9-CM 425, 678, 674)
Endocrine disorders	Hypothyroidism(ICD-9-CM 244)
	Parathyroid disorders (ICD-9-CM 252)
Chronic liver diseases	Chronic liver disorders (ICD-9-CM 570-572)
Psychiatric comorbidities	
Anxiety	Anxiety states (ICD-9-CM 300.0, 300.00, 300.09,300.1, 300.15, 300.8, 300.89, 300.9)
	Panic disorder (ICD-9-CM 300.01)
	Agoraphobia with panic attacks (ICD-9-CM 300.21)
	Generalized anxiety disorder (ICD-9-CM 300.02)
	Social phobia (ICD-9-CM 300.23)
	Obsessive-compulsive disorders (ICD-9-CM 300.3)
	Neurasthenia (ICD-9-CM 300.5)
	Hypochondriasis (ICD-9-CM 300.7)
	Somatisation disorder(ICD-9-CM 300.81)
Dysthymia	Dysthymia (ICD-9-CM code: 300.4)

Alcohol/substances use	Alcohol misuse and dependence (ICD-9-CM 303, 303.9, 303.9X, 305.0X) Opioid misuse and dependence (ICD-9-CM 304.0X, 305.5X) Barbiturate misuse and dependence (ICD-9-CM 304.1X, 305.4X) Cocaine misuse and dependence (ICD-9-CM 304.2X, 305.6X) Cannabis misuse and dependence (ICD-9-CM 304.3X, 305.2X) Amphetamine misuse and dependence (ICD-9-CM 304.4X, 305.7X) Hallucinogen misuse and dependence (ICD-9-CM 304.5X, 305.3X))
Cardio-metabolic diseases	Hypertension(ICD-9-CM 401-405) Diabetes mellitus(ICD-9-CM 249-250) Disorders of lipoid metabolism(ICD-9-CM 272) Ischemic heart disease (ICD-9-CM 410-414)

Abbreviations:

ICD-9 CM: The International Classification of Diseases, Ninth Revision, Clinical Modification

Supplementary eTable 2. Analyzed medicines in the study

Mechanism	Ingredient
Antidepressants	
Tricyclic antidepressants (TCA)	Amitriptyline
	Clomipramine
	Chlordiazepoxide
	Dothiepin
	Doxepin
	Imipramine
	Maprotiline
Selective Serotonin Reuptake Inhibitor (SSRI)	Citalopram
	Escitalopram
	Fluoxetine
	Fluvoxamine
	Paroxetine
	Sertraline
Serotonin antagonist and reuptake inhibitor (SARI)	Trazodone
Serotonin-norepinephrine reuptake inhibitor (SNRI)	Duloxetine
	Milnacipran
	Venlafaxine
Norepinephrine-dopamine reuptake inhibitor (NDRI)	Bupropion
Monoamine oxidase inhibitor (MAOI)	Moclobemide
Noradrenergic and specific serotonergic antidepressants (NaSSA)	Mirtazapine
Second generation antipsychotics (SGAs)	Amisulpride
	Aripiprazole
	Clozapine
	Olanzapine
	Paliperidone
	Risperidone
	Quetiapine
	Ziprasidone
	Zotepine
First generation antipsychotics	Chlorpromazine
	Levomepromazine
	Fluphenazine
	Trifluoperazine

	Thioridazine
	Haloperidol
	Droperidol
	Flupentixol
	Clopenthixol
	Chlorprothixene
	Zuclopenthixol
	Pimozide
	Loxapine
	Sulpiride
Anticonvulsants	Valproic acid
	Carbamazepine
	Lamotrigine
Lithium	Lithium carbonate