Brand-name Antidepressants Outperform Their Generic Counterparts in Preventing Hospitalization for Depression: The Real-world Evidence from Taiwan

Chih-Wei Hsu, MD; Sheng-Yu Lee, MD, PhD; Yao-Hsu Yang, MD, PhD; Liang-Jen Wang, MD, MPH, PhD

Department of Psychiatry, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan (CWH); Department of Psychiatry, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan (SYL); Department of Psychiatry, College of Medicine and Hospital, National Cheng Kung University, Tainan, Taiwan (SYL); Health Information and Epidemiology Laboratory, Chang Gung Memorial Hospital, Chiayi County, Taiwan (YHY); Department of Traditional Chinese Medicine, Chang Gung Memorial Hospital, Chiayi County, Taiwan (YHY); School of Traditional Chinese Medicine, College of Medicine, Chang Gung University, Taoyuan, Taiwan (YHY); Department of Child and Adolescent Psychiatry, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan (LJW)
*Corresponding author:

Liang-Jen Wang, MD, MPH, PhD

Department of Child and Adolescent Psychiatry, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung city, Taiwan

No.123, Ta-Pei Road, Kaohsiung city, Taiwan.

Tel.: 886-7-7317123 ext. 8753; Fax : 886-7-7326817

E-mail: wangliangjen@gmail.com
Significance Statement

Generic antidepressants are approved on the market based on evidence of bioequivalence to their brand-name versions. However, whether generic antidepressants provide long-term effectiveness equivalent with the brand-name drugs in the real world remains unclear. In this study, Taiwan’s nationwide population-based data were used to examine whether generic antidepressants exert equal effectiveness as their brand-name counterparts for treating patients with depressive disorders. A total of 548,234 patients with depressive disorders were categorized into 10 antidepressants groups. The results revealed that patients treated with generic products of sertraline, paroxetine, escitalopram, venlafaxine, mirtazapine, and bupropion were at a higher risk of psychiatric hospitalization than those treated with their brand-name counterpart. We suggest that compared to most generic antidepressants, brand-name drugs exhibited more protective effects on psychiatric hospitalization for depressive patients. These findings could serve as an important reference for clinicians choosing an antidepressant for depressive patients.
Abstract

Background: Generic antidepressants are approved on the market based on evidence of bioequivalence to their brand-name versions. We aimed to assess whether generic antidepressants exert equal effectiveness as their brand-name counterparts for treating patients with depressive disorders.

Methods: In a nationwide population-based cohort in Taiwan from 1997 through 2013, patients with a diagnosis of depressive disorders and aged between 18 and 65 years, who were new users of antidepressant drugs were classified into either the brand-name group or the generic group. All patients were followed up until medication discontinuation or the end of the study period. We assessed risk for hospitalization as primary outcome and augmentation therapy, daily dose, medication discontinuation, or switching to another antidepressant as secondary outcomes.

Results: A total of 277,651 brand-name users (35.8% male; mean age: 41.2 years) and 270,583 generic users (35.8% male; mean age: 41.0 years) were divided into 10 different antidepressant groups (fluoxetine, sertraline, paroxetine, escitalopram, citalopram, venlafaxine, mirtazapine, moclobemide, imipramine, bupropion). We found that patients treated with the generic form of sertraline, paroxetine, escitalopram, venlafaxine, mirtazapine, and bupropion demonstrated significantly higher risks of psychiatric hospitalization (adjusted hazard ratios [HRs] ranged from 1.20 to 2.34) compared to their brand-name counterparts. The differences between brand-name antidepressants and their generic counterparts in secondary outcomes varied across different drugs.

Conclusions: Compared to most generic antidepressants, brand-name drugs exhibited more protective effects on psychiatric hospitalization for depressive patients. These findings could serve as an important reference for clinicians when encountering patients with depressive disorder.

Keywords: antidepressant; effectiveness; formulation; pharmacoepidemiology; psychiatry
Introduction

Depressive disorders (DD) are common psychiatric disorders and a growing public health issue. The lifetime risk is about 15%, and DD were estimated to be the third leading cause of worldwide disability in 2015 and are projected to rank first by 2030 (Vos et al., 2016; Malhi and Mann, 2018). Pharmacotherapy has been a pillar of depression treatments (Park and Zarate, 2019), and a recent network meta-analysis of 522 trials involving 21 antidepressants indicated that all the assessed drugs were more effective than placebo (Cipriani et al., 2018). Since the late 1930s, various brand-name antidepressants have been introduced to treat depression (Pereira and Hiroaki-Sato, 2018); however, as the patents of the original drugs expired, corresponding generic counterparts entered the market as competing options (Kesselheim et al., 2017). Current studies still debate whether brand-name and generic medications are clinically equivalent (Borgheini, 2003; Desmarais et al., 2011; Cessak et al., 2016). Therefore, understanding the treatment effectiveness of brand-name antidepressants and their generic products for patients with DD is crucial from the clinical aspect.

In 1984, the United States Food and Drug Administration was authorized to approve generic medications based on evidence of average bioequivalence, which is defined as the absence of a significant difference in the bioavailability of the active ingredient of the brand-name versions (Chow, 2014). Several studies from different countries and of different populations that have investigated branded and generic antidepressants have shown that their blood concentration or hemodynamics and participants’ tolerability or safety were almost identical (Chenu et al., 2009; Niyomnaitham et al., 2009; Shi et al., 2010; Zheng et al., 2012; Glowka et al., 2019). However, the populations of these studies were restricted to healthy subjects and thus many not extend to patients with DD. Although one study proved bioequivalence (plasma concentration) and therapeutic equivalence (depression symptoms) of brand and generic bupropion among patients with DD, its sample size was fewer than 100 people (Kharasch et al., 2019).

Furthermore, generic versions may still differ from brand-name products in peripheral features, such as excipients (inert binders or fillers) and appearance (pill shape or color) (Strom, 1987). Many patients and physicians continue to have negative perceptions of generic drugs and subjectively consider them less effective and safe than brand-name medications in clinical experience (Shrank et al., 2011; Kesselheim et al., 2016). A longitudinal case series in Canada revealed that patients had symptom re-emergence and developed new adverse events after switching to generic citalopram (Van Ameringen et al., 2007). One study of two databases in the United States found that generic users of escitalopram and sertraline had higher rates of psychiatric hospitalization (Desai et al., 2019). However, the antidepressants of these studies were limited to selective serotonin reuptake inhibitors (SSRIs) (Bolton et al., 2012); therefore, whether therapeutic inequivalence exists in other generic antidepressants remains unclear.
The objective of our study was to comprehensively determine the long-term therapeutic outcomes of brand-name and generic antidepressant patients with DD. We used a claims database consisting of the nationwide population, which should overcome the limitations mentioned above (only healthy participants, small sample sizes, and only SSRIs). We compared the risks of hospitalization, augmentation therapy, medication discontinuation, and switching to another antidepressant, as well as the average daily doses, between patients treated with brand-name antidepressants and their generic counterparts.

Methods

Ethical statement

The protocol for this study conformed to the Helsinki Declaration, and was approved by the Institutional Review Board (IRB) of Chang Gung Memorial Hospital. Patient records/information was anonymized and de-identified prior to analysis, and the need for written informed consent was waived by the IRB.

Data source

The Taiwan National Health Insurance (NHI) program was established in 1995 as the sole payer for healthcare services. As of 2010, approximately 23 million individuals were enrolled, covering 99% of Taiwan’s population. In this study, we used the National Health Insurance Research Database (NHIRD), which is derived from the reimbursement medical claims records of the NHI program. The NHIRD provides comprehensive information about the insured subjects, such as demographic characteristics (gender, date of birth, and income status) and claims data (clinical diagnostic codes, visiting medical institutions, outpatient and inpatient care, and such prescription records as prescription date, medication type of brand-name and generic form and dosage, and duration of drug supply). The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) was used for disease codes in this study. To protect individual privacy, all information from NHIRD that may have been used to identify individual patients or medical care institutions was anonymized to ensure confidentiality.

Study subjects
This cohort included all antidepressant users (with at least one antidepressant prescription) with a diagnosis of DD (ICD-9-CM: 296.2, 296.3, 300.4 or 311; diagnosed at least twice by psychiatrists based on their diagnostic interview and clinical judgment) that were registered in the NHIRD between 1 January 1997 and 31 December 2013; a similar definition was adopted in a previous study (Hsu et al., 2018). In this study, we used the code N06A from the Anatomical Therapeutic Chemical Classification System of the World Health Organization Collaborating Centre (WHOCC) for Drug Statistic Methodology in 2019 (https://www.whocc.no/atc_ddd_index/) to identify antidepressants, finding a total of 21 antidepressants in Taiwan. Patients with unknown gender status or a diagnosis of schizophrenia spectrum disorders (ICD-9-CM: 295) or bipolar disorders (ICD-9-CM: 296 except 296.2, 296.3) were excluded. In total, 943,493 antidepressant users with DD were identified.

The index date of this cohort study was defined as the date of the antidepressant prescription with a concurrent diagnosis of DD. We established the following exclusion criteria to eliminate the confounding effect of drug interactions and then categorized the remaining patients according to the selected antidepressant: 1) patients who had been prescribed the selected antidepressant before 1 April 1997 (at least a 90-day washout period); 2) patients who had been prescribed another antidepressant within 90 days before using the selected antidepressant (at least a 90-day washout period); 3) patients who had been prescribed the selected antidepressant after 2 October 2013 (at least a 90-day observation period); 4) patients who had been prescribed multiple antidepressant drugs at the index date (polypharmacy); 5) patients aged < 18 years or ≥ 65 years at the index date of the selected antidepressant prescription; 6) patients who received brand-name antidepressant prior to the date which its generic counterpart has been marketed.

Of the remaining patients that received the 21 selected antidepressants, some users received both brand-name and generic antidepressant treatment during the course of their diseases (mixed group). To eliminate any cross-over effect, we excluded patients with mixed use for further data analysis. The detailed case numbers of patients receiving the 21 antidepressants are listed in Supplementary Table S1. Afterward, those that met the following criteria were further excluded: 1) only the brand-name antidepressant but no generic form was available in Taiwan; 2) the sum of the selected antidepressant users who had been prescribed only a brand-name or generic drug was less than 10,000; and 3) the ratio of patients between the brand-name drug and generic counterpart was greater than 4. We ultimately narrowed down to a total of 10 antidepressants, and Figure 1 shows the flowchart of the participant selection procedure.

Demographics and potential confounders
In this cohort study, we evaluated the patients’ characteristics, which included gender, age, cohort entry date, medical comorbidities, psychiatric comorbidities, benzodiazepines use, socioeconomic status, and properties medical institution at the time of prescription. We employed the Charlson Comorbidity Index (CCI) as a proxy for medical comorbidities to determine general health status (Deyo et al., 1992), which was calculated using diagnostic codes from outpatient and inpatient records and has been widely applied for confounders in epidemiological research (Schneeweiss et al., 2001). Psychiatric comorbidities included substance use disorders (ICD-9-CM: 291, 292, 303, 304, 305 except 305.1, 357.5, 425.5, 535.3, or 571.0-571.3), anxiety disorders (ICD-9-CM: 300 except 300.4), and sleep disorders (ICD-9-CM: 307.4 and 780.5). We reported monthly income in New Taiwan dollar (NTD) to represent socioeconomic status, which was calculated according to the premium paid. In 2008, the approximate exchange rate of the NTD to the United States dollar (USD) was 31.5. Medical institution properties were grouped into two categories based on the accreditation level in Taiwan, which were hospital and clinic.

**Outcome variables**

All antidepressant users were observed from the index date of the selected antidepressant to its discontinuation date or 31 December 2013. The primary outcome of treatment effectiveness was hospitalization (overall and psychiatric) before discontinuation of the antidepressant. The secondary outcomes included the occurrence of augmentation therapy with another drug (another antidepressant, antipsychotic, or mood stabilizer) before discontinuation of the antidepressant, the average daily dose, discontinuation of the selected antidepressant, and switching to another antidepressant after discontinuing the initial antidepressant. We defined discontinuation of an antidepressant as the cessation of the selected brand-name or generic antidepressant for 90 days or longer. The average daily dose was defined as the dose of the last prescription before antidepressant discontinuation or the end of follow-up, which was also converted into a ratio of the average daily dose to the defined daily dose for standardization. We adopted the defined daily dose (DDD) determined by the WHOCC for Drug Statistics Methodology to assume the average maintenance dose per day for an antidepressant used for its main indication in adults (Sinnott et al., 2016). Switching was defined as changing to another antidepressant within 90 days after discontinuing the initial antidepressant.

**Statistical methods and sensitivity analyses**

We used descriptive statistics to compare patients’ characteristics and the average daily doses of different antidepressants. We used chi-square and independent t-tests to compare categorical and continuous variables, respectively, between the users of brand-name and generic antidepressants. For the treatment outcomes (hospitalization, medication discontinuation, antidepressant switching, augmentation
therapy), we constructed Cox proportional hazards regression models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the occurrence of such outcomes, which were further adjusted for potential confounders with gender, age, cohort entry date of the selected antipsychotic, CCI scores, psychiatric comorbidities, benzodiazepines use, income status, and prescription medical institution.

To minimize potential indication bias from the severity of DD, we performed subgroup analysis to evaluate the robustness of our results. We narrowed down this cohort study to antidepressant users who were diagnosed with major depressive disorders (MDD; ICD-9-CM: 296.2 or 296.3) and repeated the primary analysis. All analyses were conducted with SAS 9.4 software (SAS Institute) and MedCalc Statistical Software version 18.11.3 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2019). A two-tailed \( p < 0.05 \) was considered statistically significant.

**Results**

This study included a total of 548,234 patients with DD who received one of the following antidepressants in either brand-name or generic form: fluoxetine, sertraline, paroxetine, escitalopram, citalopram, venlafaxine, mirtazapine, moclobemide, imipramine, and bupropion. Table 1 summarizes the demographic data of the patients with DD treated with brand-name versus generic form of antidepressants pooled across all ten drugs. We found that the hospitals prescribed significantly more brand-name and less generic antidepressants compared to clinics (brand-name: hospital vs. clinic: 91.66% vs. 8.34%; generic: hospital vs. clinic: 41.79% vs. 58.21%; \( p <0.0001 \)). The individual drug comparison and the year by year information of characteristics of patients with DD and MDD are shown in Supplementary Table S2 and S3.

As the primary outcome, DD patients receiving the generic form of sertraline, paroxetine, escitalopram, venlafaxine, mirtazapine, and bupropion demonstrated significantly higher adjusted HR of psychiatric admission compared to those treated with their branded counterparts (HRs range: 1.20 to 2.34), as shown in Table 2. The subgroup analysis of only patients with MDD also indicated that those treated with the generic form of sertraline, paroxetine, escitalopram, venlafaxine, mirtazapine, moclobemide, and bupropion revealed significantly higher adjusted HR of psychiatric hospitalization than those treated with their brand-name counterparts (HRs range: 1.27 to 2.66). For admission due to all cause, those treated with the generic form of paroxetine, escitalopram, venlafaxine, and bupropion demonstrated a significantly higher risk of overall hospitalization than those treated with brand-name products. Furthermore, in the subgroup analysis, brand-name paroxetine, escitalopram, venlafaxine, and bupropion demonstrated a significantly higher risk of overall hospitalization than those treated with brand-name products.
moclobemide, and bupropion outperformed their generic counterparts in preventing all-cause hospitalization in MDD patients.

Table 3 provides the average daily dose, the ratio of the average daily dose to DDD, and the adjusted HR of augmentation therapies, antidepressant discontinuation, and antidepressant switching among the 10 antidepressants in patients with DD and MDD. We found that the users of generic sertraline were at a higher risk of receiving augmentation of a psychotropic medication, while those who receive the generic form of fluoxetine and escitalopram had a lower risk of receiving any psychotropic drug when compared to their brand-name counterparts. The detailed psychotropic drugs of augmentation therapies are provided in Supplementary Table S4.

In four of the studied antidepressants (fluoxetine, paroxetine, escitalopram, and imipramine), the daily doses of the generic drug were higher than those of the brand-name drug; in the other six antidepressants studied herein (sertraline, citalopram, venlafaxine, mirtazapine, moclobemide, and bupropion), the daily doses of the brand-name were higher than those of the generic version.

Regarding the adjusted HR of discontinuation, the users of generic sertraline were at a higher risk than the users of the brand-name form; however, the users of generic citalopram and mirtazapine had a lower risk than the users of the brand-name versions. As for the adjusted HR of switching, the generic drug users of four antidepressants (fluoxetine, escitalopram, citalopram, and mirtazapine) had a lower risk than the users of the brand-name product.

Discussion

This is the first study to compare the effectiveness between brand-name and generic antidepressants for depressive patients in Taiwan using real-world evidence. Compared to brand-name antidepressants, we found that patients with DD and MDD that received generic antidepressants were at a disadvantage with regard to preventing hospitalization, for both psychiatric admission and all-cause admission, after adjusting for potential confounders. Furthermore, DD and MDD patients treated with generic or brand-name antidepressants demonstrated heterogeneous findings in the risk for combining augmentation therapy, last average daily dose, discontinuation of antidepressants, and drugs switching, which varied across different drug products.

The occurrence of hospitalization was an important outcome for evaluating treatment effectiveness in psychiatric research using a database (Desai et al., 2019; Montastruc et al., 2019). Our results demonstrate that most brand-name antidepressants have an advantage in preventing psychiatric
hospitalization, a finding supported by previous studies (Wu et al., 2011; Desai et al., 2019). One nationwide study revealed that users of brand-name sertraline and escitalopram had a lower psychiatric hospitalization rate compared to those with generic products (Desai et al., 2019). Another retrospective analysis of the claims database showed that MDD patients who were switched from a brand-name SSRI to an alternative generic version had higher hospitalization rates (Wu et al., 2011). Compared to the aforementioned studies, this study has two strengths. First, we used a comprehensive nationwide database that provides a large sample size for longitudinal analysis. In the current study, we included 10 kinds of antidepressants (SSRIs and other classes of drugs) with 548,234 participants. Another strength is the direct comparison between brand-name drugs and their generic counterparts, which should yield more useful information than those that compare the differences between different antidepressants.

In the current study, we found the mean duration between the initial prescription to discontinuation was only 91.5 days and 94.8 days for brand-name and generic drugs in patients with DD, respectively; the difference in risk of discontinuation between brand-name and generic was less than 12% (Table 3). In addition, we found that 72.3% of the depressive patients who discontinued drug therapy did not switch to another antidepressant (Data not shown). The clinical practice guidelines recommended that the duration of antidepressant treatment for MDD should be at least 6 months (Lam et al., 2009). Our result was similar to a study using a United States database reported that only 27.6% of the patients continued antidepressant therapy for more than 90 days (Olson et al., 2006). The most common reasons for premature discontinuation were non-responsiveness or intolerance of side effects (Hodgkin et al., 2007). So we compared the risk of discontinuation between brand-name and generic antidepressants as another indication of effectiveness. It was suggested that generic medication may have lower proportion of adverse events compared to branded medication, which also lowered the risk of discontinuation (Takami et al., 2018). However, whether lower proportion of adverse events are related to lower efficacy still requires further study. Furthermore, high placebo response rates (ranging from 35% to 40%) in antidepressant users may also hinder the exploration of differences in efficacy between brand-name and generic versions (Furukawa et al., 2016).

If a first-line antidepressant cannot achieve satisfying treatment effects, several previous guidelines have suggested that switching to another antidepressant or augmentation therapy (combining two antidepressants or adding one antipsychotic/mood stabilizer to the original antidepressant) is a feasible strategy for physicians (Bayes and Parker, 2018). We found slight differences between brand-name and generic antidepressants with regard to the risk of switching to another antidepressant or augmentation with an antidepressant, antipsychotic, or mood stabilizer. The risks for switching and augmentation may also rely on clinical presentation and the prescribing physician’s medical resources, which were not
controlled for in the current study. Regarding the differences in average daily dose of the last prescription between brand-name and generic antidepressants, our results showed varied findings (higher doses in four kinds of generic antidepressants compared to their brand-name counterparts) with weak significance (the ratio of average daily dose to DDD was less than 0.12 in the same drugs and disorders group), as shown in Table 3.

Our study also has some limitations. First, it is subject to the usual limitations of retrospective analysis from reimbursement data. Although we attempted to control for potential confounding factors and adjust for observable baseline characteristics, unobserved confounders are not included in the current study, such as severity of depressive symptoms, residential area, support system, or drug compliance. Second, we make multiple comparisons for effectiveness (discontinuation, dose, switching, augmentation, and hospitalization) in this study. Third, patients who were allocated to generic or brand-name drugs were done so through clinical judgment in real-world settings but not through random assignment, so this study may have selection bias. Forth, the brand-name drugs were mostly prescribed by the doctors in hospitals, but not in clinics. The doctors in the hospital may provide better care than those in the clinic, and the medical resource in hospital may be more abundant than in the clinic. However, patients seeking treatment in hospital may suffered from greater severity of depression than their counterparts who received treatment in clinics. Although we adjusted the factor “medical institution” in the Cox proportional hazards regression models, the confounding effect may still exist. Finally, this study was only able to evaluate the effectiveness of 10 antidepressants, and our findings may not be generalized to other types of antidepressants.

Conclusions

The real-world evidence from Taiwan revealed that depressive patients treated with most generic antidepressants were at a higher risk of psychiatric admission compared to those treated with brand-name drugs. Furthermore, other clinical outcomes with regard to augmentation therapy, last average daily dose, medication discontinuation, and antidepressant switching were inconclusive in depressive patients treated with generic or brand-name antidepressants. These results could be an essential reference for clinical practices using antidepressants to treat depressive patients.

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Conflict of Interest

None reported.

Reference

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Figure legends

Figure 1. Flowchart showing the selection procedure of study subjects.
Figure 1

Patients diagnosed with depressive disorders and use of antidepressants from 1997 to 2013 (N = 1 023 126)

Remaining eligible patients (N = 943 493)

Excluded patients: N = 79 633
- Sex not documented (n = 700)
- A history of schizophrenia or bipolar disorders (n = 78 933)

Patients were grouped by type of antidepressant use (case numbers shown in the Supplemental Table 1)

Excluded criteria (detail shown in the Supplemental Table 1)
- Patients were prescribed selected antidepressant before 1997-04-01
- Patients were prescribed another antidepressant before using selected antidepressant < 90 days
- Observation period after initial prescription of selected antidepressant < 90 days
- Patients were prescribed more than one antidepressant at the index date
- Age at the index date of selected antidepressant prescription < 18 years or ≥ 65 years
- Patients who received brand-name antidepressant prior to the date which its generic counterpart has been marketed

Patients were classified by the status of prescription (brand-name drug only, generic drug only, or mixed use of two types)

Branded (N1), generic (N2), and mixed drug users (N3)
- Fluoxetine (N1 = 46 080, N2 = 88 221, N3 = 19 917)
- Sertraline (N1 = 64 548, N2 = 43 664, N3 = 9061)
- Paroxetine (N1 = 44 741, N2 = 27 911, N3 = 6883)
- Escitalopram (N1 = 32 934, N2 = 23 664, N3 = 3519)
- Citalopram (N1 = 15 802, N2 = 30 973, N3 = 3286)
- Venlafaxine (N1 = 24 328, N2 = 13 422, N3 = 3005)
- Mirtazapine (N1 = 12 895, N2 = 17 233, N3 = 2226)
- Moclobemide (N1 = 17 355, N2 = 10 888, N3 = 1941)
- Imipramine (N1 = 17 863, N2 = 10 338, N3 = 2096)
- Bupropion (N1 = 10 705, N2 = 4389, N3 = 525)
### Table 1 Characteristics of Patients with Depressive Disorders Treated with Brand-Name and Generic Formula of ten selected antidepressants in Taiwan, from 1997 to 2013

|                          | Brand-Name N = 277,651 | Generic N = 270,583 | p     |
|--------------------------|------------------------|---------------------|-------|
| **Sex (male/female)**    | 99,430/178,221 (35.81/64.19) | 96,897/173,686 (35.81/64.19) | NS    |
| **Age, years**           | 41.21 ± 13.04          | 40.03 ± 12.69       | ***   |
| **Charlson Comorbidity Index** | 1.41 ± 1.91          | 1.37 ± 1.81         | NS    |
| **Substance use disorders** | 16,278 (5.86)         | 17,395 (6.43)       | ***   |
| **Anxiety disorders**    | 123,134 (44.35)        | 126,749 (46.84)     | ***   |
| **Sleep disorders**      | 125,952 (62.68)        | 139,821 (65.08)     | ***   |
| **Benzodiazepines use**  | 174,024 (49.70)        | 176,092 (50.30)     | ***   |
| **Monthly income, NTD**  | 16,887 ± 17,869        | 16,180 ± 16,635     | NS    |
| **Medical institution (hospital/clinic)** | 254,499/23,152 (91.66/8.34) | 113,083/157,500 (41.79/58.21) | *** |

Abbraviations: NS, not significant; NTD, New Taiwan Dollar. Data were expressed as N (%) or mean ± standard deviation. Background color: ■ red means drug-G data is significantly higher than drug-B data; □ blue means drug-B data is significantly higher than drug-G data; □ white means drug-B and drug-G data are not significantly different. NS, ***, p <.0001
| Antidepressant | Group<sup>a</sup> | Subgroup<sup>b</sup> | Overall N (PY) | Overall aHR (95% CI)<sup>c</sup> | Psychiatric N (PY) | Psychiatric aHR (95% CI)<sup>c</sup> |
|----------------|-----------------|-----------------|----------------|-----------------|-----------------|-----------------|
| Fluoxetine     | DD              | Brand-Name      | 1192 (11 408) | 1.00 [Reference] | 828 (11 489)   | 1.00 [Reference] |
|                |                 | Generic         | 1631 (24 231) | 0.94 (0.87-1.01) | 1045 (24 407)  | 0.90 (0.82-0.99) |
|                | MDD             | Brand-Name      | 587 (5178)    | 1.00 [Reference] | 500 (5203)     | 1.00 [Reference] |
|                |                 | Generic         | 978 (14 256)  | 1.04 (0.94-1.16) | 814 (14 033)   | 1.06 (0.94-1.19) |
| Sertraline     | DD              | Brand-Name      | 1404 (13 945) | 1.00 [Reference] | 759 (14 117)   | 1.00 [Reference] |
|                |                 | Generic         | 652 (11 086)  | 1.03 (0.93-1.14) | 392 (11 613)   | 1.20 (1.05-1.37) |
|                | MDD             | Brand-Name      | 826 (6899)    | 1.00 [Reference] | 589 (6987)     | 1.00 [Reference] |
|                |                 | Generic         | 335 (4488)    | 1.10 (0.95-1.26) | 267 (4508)     | 1.27 (1.08-1.49) |
| Paroxetine     | DD              | Brand-Name      | 1081 (11 731) | 1.00 [Reference] | 666 (11 857)   | 1.00 [Reference] |
|                |                 | Generic         | 623 (7054)    | 1.55 (1.38-1.73) *** | 481 (7101)   | 1.82 (1.59-2.08) *** |
|                | MDD             | Brand-Name      | 628 (5259)    | 1.00 [Reference] | 494 (5302)     | 1.00 [Reference] |
|                |                 | Generic         | 387 (2583)    | 1.70 (1.46-1.97) *** | 360 (2593)   | 1.89 (1.61-2.22) *** |
| Escitalopram   | DD              | Brand-Name      | 828 (7999)    | 1.00 [Reference] | 508 (8066)     | 1.00 [Reference] |
|                |                 | Generic         | 305 (5332)    | 1.22 (1.05-1.42) * | 224 (5546)   | 1.39 (1.17-1.66) *** |
|                | MDD             | Brand-Name      | 495 (3261)    | 1.00 [Reference] | 383 (3288)     | 1.00 [Reference] |
|                |                 | Generic         | 189 (1712)    | 1.34 (1.11-1.61) * | 167 (1716)   | 1.42 (1.16-1.73) *** |
| Citalopram     | DD              | Brand-Name      | 427 (3744)    | 1.00 [Reference] | 239 (3739)     | 1.00 [Reference] |
|                |                 | Generic         | 396 (8588)    | 0.81 (0.69-0.96) * | 265 (8636)   | 1.01 (0.82-1.24) |
|                | MDD             | Brand-Name      | 242 (1887)    | 1.00 [Reference] | 179 (1902)     | 1.00 [Reference] |
|                |                 | Generic         | 185 (3081)    | 0.98 (0.79-1.23)  | 157 (3087)   | 1.14 (0.89-1.45) |
| Venlafaxine    | DD              | Brand-Name      | 635 (6392)    | 1.00 [Reference] | 360 (6482)     | 1.00 [Reference] |
|                |                 | Generic         | 223 (3058)    | 1.38 (1.15-1.64) ** | 158 (3074)   | 1.74 (1.39-2.16) *** |
|                | MDD             | Brand-Name      | 450 (3971)    | 1.00 [Reference] | 325 (4013)     | 1.00 [Reference] |
|                |                 | Generic         | 164 (1900)    | 1.30 (1.06-1.61) * | 142 (1903)   | 1.55 (1.23-1.96) *** |
| Mirtazapine    | DD              | Brand-Name      | 540 (2739)    | 1.00 [Reference] | 248 (2795)     | 1.00 [Reference] |
|                |                 | Generic         | 348 (3928)    | 0.96 (0.82-1.12)  | 224 (3958)   | 1.36 (1.11-1.68) *** |
|                | MDD             | Brand-Name      | 311 (1573)    | 1.00 [Reference] | 200 (1596)     | 1.00 [Reference] |
|                |                 | Generic         | 220 (1888)    | 1.18 (0.97-1.44)  | 172 (1903)   | 1.49 (1.18-1.88) *** |
| Moclobemide    | DD              | Brand-Name      | 277 (3778)    | 1.00 [Reference] | 110 (3830)     | 1.00 [Reference] |
|                |                 | Generic         | 128 (2576)    | 1.29 (0.97-1.70)  | 57 (2595)    | 1.48 (0.97-2.27) |
|                | MDD             | Brand-Name      | 90 (1415)     | 1.00 [Reference] | 70 (1417)      | 1.00 [Reference] |
|                |                 | Generic         | 53 (882)      | 1.93 (1.24-3.02) ** | 38 (986)    | 1.92 (1.14-3.21) ** |
| Imipramine     | DD              | Brand-Name      | 251 (3808)    | 1.00 [Reference] | 111 (3837)     | 1.00 [Reference] |
|                |                 | Generic         | 312 (2513)    | 0.99 (0.78-1.24)  | 41 (2564)    | 0.88 (0.61-1.27) |
|                | MDD             | Brand-Name      | 75 (922)      | 1.00 [Reference] | 56 (926)      | 1.00 [Reference] |
|                |                 | Generic         | 26 (493)      | 0.85 (0.54-1.33)  | 20 (494)     | 0.91 (0.54-1.54) |
| Bupropion      | DD              | Brand-Name      | 197 (2352)    | 1.00 [Reference] | 108 (2378)     | 1.00 [Reference] |
|                |                 | Generic         | 43 (833)      | 1.67 (1.16-2.41) * | 31 (835)    | 2.34 (1.51-3.62) ** |
|                | MDD             | Brand-Name      | 107 (978)     | 1.00 [Reference] | 76 (987)      | 1.00 [Reference] |
|                |                 | Generic         | 30 (269)      | 2.30 (1.45-3.64) ** | 27 (269)    | 2.66 (1.61-4.39) ** |

Abbreviations: aHR, adjusted hazard ratio; B: brand-name drug; CI: confidence interval; DD: depressive disorders; G: generic drug; MDD: major depressive disorders; N: numbers of hospitalization; PY: person-year of follow-up

Background color: ■ red means drug-G data is significantly higher than drug-B data; □ blue means drug-B data is significantly higher than drug-G data; ▪ white means drug-B and drug-G data are not significantly different. *, p < .05; **, p < .001; ****, p < .0001.

<sup>a</sup> Patients with the diagnosis of depressive disorders or major depressive disorders

<sup>b</sup> Patients treated with brand-name or generic drugs

<sup>c</sup> Adjusted for gender, age, entry year, Charlson Comorbidity Index, substance use disorders, anxiety disorders, sleep disorders, benzodiazepines use, monthly income, and medical institution
## Table 3 Comparison of Augmentation, Average Daily Dose, Discontinuation, Switching in Depressive Patients Treated with Brand-Name and Generic Formula of Ten Antidepressants

| Antidepressant | Group | Subgroup | Augmentation aHR (95% CI) | Dose, mg/day mean ± SD | Ratio, Dose/DDD | Discontinuation aHR (95% CI) | Switching aHR (95% CI) |
|----------------|-------|----------|---------------------------|------------------------|----------------|-----------------------------|------------------------|
| Fluoxetine     | DD    | Brand-Name | 1.00 [Reference]         | 21.62 ± 10.82          | 1.08          | 1.00 [Reference]              | 1.00 [Reference]         |
|                |       | Generic    | 0.91 (0.89-0.93) ***     | 22.62 ± 11.42          | 1.13 ***      | 1.00 (0.99-1.01)              | 0.93 (0.90-0.95) ***    |
|                | MDD   | Brand-Name | 1.00 [Reference]         | 22.97 ± 12.50          | 1.15          | 1.00 [Reference]              | 1.00 [Reference]         |
|                |       | Generic    | 0.93 (0.90-0.96) ***     | 23.68 ± 10.91          | 1.18 ***      | 0.99 (0.97-1.00)              | 0.89 (0.86-0.93) ***    |
| Sertraline     | DD    | Brand-Name | 1.10 (1.07-1.13) ***     | 49.00 ± 23.61          | 0.98 **       | 1.06 (1.04-1.07) ***          | 1.07 (1.04-1.10) ***    |
|                |       | Generic    | 1.11 (1.07-1.16) ***     | 54.94 ± 26.54          | 1.10 ***      | 1.06 (1.03-1.09) ***          | 0.93 (0.89-0.98) *      |
| Paroxetine     | DD    | Brand-Name | 1.00 [Reference]         | 17.65 ± 8.88           | 0.88          | 1.00 [Reference]              | 1.00 [Reference]         |
|                |       | Generic    | 1.01 (0.98-1.04)         | 17.98 ± 8.42           | 0.90 ***      | 1.05 (1.03-1.07) ***          | 1.02 (0.98-1.05)        |
| Escitalopram   | DD    | Brand-Name | 1.00 [Reference]         | 9.30 ± 4.37            | 0.93          | 1.00 [Reference]              | 1.00 [Reference]         |
|                |       | Generic    | 0.89 (0.86-0.92) ***     | 9.50 ± 4.16            | 0.95 ***      | 1.02 (1.00-1.05) ***          | 0.91 (0.86-0.95) ***    |
| Citalopram     | DD    | Brand-Name | 1.00 [Reference]         | 19.21 ± 9.19           | 0.96          | 1.00 [Reference]              | 1.00 [Reference]         |
|                |       | Generic    | 0.92 (0.89-0.95) ***     | 18.42 ± 8.35           | 0.92 ***      | 0.93 (0.91-0.95) ***          | 0.85 (0.81-0.88) ***    |
| Venlafaxine    | DD    | Brand-Name | 1.00 [Reference]         | 8.00 ± 4.73            | 0.85          | 1.00 [Reference]              | 1.00 [Reference]         |
|                |       | Generic    | 0.98 (0.94-1.03)         | 77.04 ± 41.69          | 0.77 ***      | 1.01 (0.98-1.04) ***          | 1.05 (1.03-1.11) *      |
| Mirtazapine    | DD    | Brand-Name | 1.00 [Reference]         | 96.27 ± 57.46          | 0.96          | 1.00 [Reference]              | 1.00 [Reference]         |
| Moelobemide    | DD    | Brand-Name | 1.00 [Reference]         | 321.08 ± 144.88        | 0.94          | 1.00 [Reference]              | 1.00 [Reference]         |
|                |       | Generic    | 0.93 (0.87-0.98) *       | 277.04 ± 127.13        | 0.92 ***      | 1.01 (0.98-1.05)              | 0.87 (0.82-0.94) *      |
| Imipramine     | DD    | Brand-Name | 1.00 [Reference]         | 29.80 ± 24.68          | 0.30          | 1.00 [Reference]              | 1.00 [Reference]         |
| Bupropion      | DD    | Brand-Name | 1.00 [Reference]         | 185.60 ± 79.71         | 0.62          | 1.00 [Reference]              | 1.00 [Reference]         |

**Abbreviations:** AHR, adjusted hazard ratio; CI: confidence interval; DD, depressive disorders; DDD, defined daily dose; MDD, major depressive disorders; SD, standard deviation. 

**Background color:** Red means drug-G data is significantly higher than drug-B data; blue means drug-B data is significantly higher than drug-G data; white means drug-B and drug-G data are not significantly different. *, p < 0.05; **, p < 0.01; ###, p < 0.0001.

* Patients with the diagnosis of depressive disorders or major depressive disorders

** Patients treated with brand-name or generic drugs

* Adjusted for gender, age, entry year, Charlson Comorbidity Index, substance use disorders, anxiety disorders, sleep disorders, benzodiazepines use, monthly income, and medical institution