Survey of Anticonvulsant Drugs and Lithium Prescription in Women of Childbearing age in Japan Using a Public National Insurance Claims Database

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ABSTRACT

Purpose: Pharmacological treatments with some anticonvulsants, including valproate, and lithium should be avoided where possible in childbearing-aged and pregnant women with epilepsy and bipolar disorder because they increase the risk of major congenital malformations. We surveilled real-world prescriptions of anticonvulsants and lithium in childbearing-aged female and male outpatients in Japan, using the first public National Insurance Claims Database of Japan.

Methods: We performed a summary statistical analysis of the numbers of the most prescribed 11 anticonvulsants and lithium tablets in female and male outpatients aged 15-29 (younger childbearing age), 30-49 (older childbearing age), and >50 (non-childbearing age) years from April 2014 to March 2015. We determined the association between anticonvulsant or lithium use and sex at childbearing age, and the odds ratio (OR) and 95% confidence intervals (CIs) were estimated using logistic regression analysis.

Results: Valproate (number of tablets = 273,135,937) was the most prescribed among the 12 investigated drugs, and 125,451,907 tablets were prescribed for women (younger, older, and non-childbearing ages, 19,296,528, 47,826,746, and 58,328,63, respectively), compared to 147,684,031 tablets for men (24,534,648, 57,229,981, and 65,919,402, respectively). Valproate prescription was only slightly lower in childbearing-aged women than in the same-aged men (i.e., 15-29 years of age, OR = 0.889 [95% CI, 0.888-0.890]; 30-49 years of age, OR = 0.944 [95% CI, 0.944-0.945]).

Discussion: This study demonstrated valproate was highly prescribed for childbearing-aged women in Japan in 2014-2015. Physicians should prescribe valproate with considerable caution in girls and childbearing-aged women.

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Introduction

Accumulating evidence demonstrates that treatments with certain anticonvulsants, such as valproate, and lithium, a mood stabilizer, should be avoided in childbearing-aged or pregnant women with epilepsy and bipolar disorder where possible, or implemented with extreme caution when their use is indispensable [1, 2]. This is because these drugs increase the risk of not only major congenital malformations but also neuropsychological and psychiatric complications [1-4]. However, anticonvulsant drugs are indispensable for treating epilepsy even in pregnant and childbearing-aged women as well as girls [2, 5]. The UK National Institute for Health and Care Excellence (NICE) number 192: antenatal and postnatal mental health clinical management and service guidance updated edition (NICE antenatal and postnatal mental health, 2017 antenatal and postnatal, 2017) [1], clearly recommends that physicians should not prescribe drugs with the potential to increase the risk of congenital malformations in pregnancy to not only female patients who are not pregnant or planning pregnancy, but also those of childbearing age at large [1].

Valproate is an anticonvulsant that was approved in the 1960s and is widely prescribed for the treatment of epilepsy and bipolar disorder [6]. It increases the risk of major congenital malformations, such as neural tube defects and intellectual disability of the offspring, when administered to pregnant women [2, 3]. According to the report of Kmiełtowicz [7], the Medicines and Healthcare Products Regulatory Agency of the UK advises that women and girls of childbearing potential should not be treated with sodium valproate unless it is unavoidably necessary.

In terms of pharmacological treatments for childbearing-aged women with bipolar disorder, lithium therapy also needs to be considered with very careful caution when they are planning a pregnancy or pregnant as well as other teratogenic anticonvulsants, valproate and carbamazepine as mood stabilizers, since fetal exposure to lithium in the first trimester leads to increasing risks of cardiac malformations such as Ebstein’s anomaly [1, 8].

The NICE antenatal and postnatal mental health, 2017 antenatal and postnatal, 2017 recommends that antipsychotics for women with bipolar disorder who are planning a pregnancy or become pregnant as a pharmacological therapy, unless antipsychotic treatments have not been effective for them [1].

Considering that at least ~40% of pregnancies are unplanned or unintended as indicated by several epidemiologic studies [9-11], physicians, neurologists, and psychiatrists consulting patients with epilepsy and bipolar disorder should avoid prescribing drugs with a high risk of teratogenicity, especially valproate, to girls and women of childbearing age. Therefore, determining the accurate rate of anticonvulsant and lithium prescription in women of childbearing age is critical.

The present study aimed to conduct a surveillance-based evaluation of the numbers and proportions of anticonvulsant and lithium prescriptions for childbearing-aged female outpatients compared to those for male outpatients of the same age in Japan. To this end, we used the publicly available National Insurance Claims Database (NDB) called “NDB Open Data Japan.” The NDB, which covers all insurance claims in Japan, has been managed by the Ministry of Health, Labour and Welfare (MHLW) of Japan [12]. The MHLW of Japan has provided the first NDB Open Data Japan report, which covers data for the fiscal year 2014 (from April 2014 to March 2015), in October 2016.

Methods

Design

A cross-sectional study design was used to comparatively assess the proportions of anticonvulsant and lithium prescriptions to all female outpatients of childbearing age and male outpatients of the same age, using the first NDB Open Data Japan. The survey protocol was reviewed and approved by the Institutional Review Board of the School of Medicine of Chiba University.

Data source

The NDB used in this study is a database developed by the MHLW of Japan in 2009. The MHLW
started operating the NDB as a free, publicly accessible database called "NDB Open Data Japan" on its websites [12]. The first NDB Open Data Japan consists of fundamental spreadsheets that summarize the claim data of the fiscal year 2014 (April 2014 to March 2015). The first NDB Open Data Japan provides free information on prescription drugs, such as numbers of prescribed tablets of the 30 top-ranking branded, but not generic drugs, based on various therapeutic classifications, such as anticonvulsant and psychotropic drugs.

The database accumulates health insurance claims monthly, resulting in one of the most exhaustive national healthcare databases worldwide, because the universal public pension insurance system in Japan has been extended to all citizens since 1961 [13]. The coverage rate of the NDB was 98.6% of the national health insurance claims of Japan as of May 2015 [12].

In this study, we used prescription data from April 2014 to March 2015 from the first NDB Open Data Japan. In addition to the numbers of whole tablets prescribed, the NDB also records prescriptions of half, one-third, and quarter tablets for each drug and, thus, the total data include decimal points. Therefore, the number of tablets prescribed was ultimately rounded to the nearest whole number in this study.

**Target drugs and definition of age ranges**
We examined the available prescription data of anticonvulsant drugs and lithium in female and male outpatients from the first NDB Open Data Japan. We categorized the data into total childbearing, younger childbearing, older childbearing, and non-childbearing age classifications at 15-29, 30-49, and ≥50 years, respectively.

**Primary outcomes**
The odds ratio (OR) was defined using the following method. The proportion of the number of tablets prescribed to women of childbearing age (15-29 and 30-49 years) to the number prescribed to women ≥50 years old was compared with the odds of the case group. Then, the proportion of the number of tablets prescribed to men of the same age as the childbearing groups to the number of tablets prescribed for men ≥50 years was compared with the odds of the control group.

The OR was finally calculated using the odds of the case and control groups. In addition, the 95% confidence interval (CI) of each OR was calculated. Specifically, a drug with an OR > 1.000 was prescribed at a higher rate to women of childbearing age than it was to men of the same age. In contrast, an OR < 1.000 indicated that the drug was prescribed at a lower rate to women of childbearing age than to men of the same age. The primary outcome was the identification of the proportion and OR of each anticonvulsant and lithium between males and females in the 15-29 and 30-49 age groups.

**Statistical analysis**
For the participant characteristics, we performed summary statistical analyses with frequencies and proportions for categorical data. To determine the association between anticonvulsants or lithium use, and sex at childbearing age, OR and 95% CI were estimated using logistic regression analysis. P < 0.05 was considered significant. All data analyses were conducted using the SAS software (ver. 9.4 SAS Institute Inc., Cary, NC, USA).

**Results**
Eleven anticonvulsants (valproate, carbamazepine, clonazepam, lamotrigine, phenytoin, levetiracetam, zonisamide, phenobarbital, gabapentin, topiramate, and clobazam) and lithium were available in the prescription data of female and male outpatients obtained from the first NDB Open Data Japan (Table 1). Table 1 shows the number of tablets of all investigated drugs prescribed to the female and male outpatients of younger (15-29-year-old), older (30-49-year-old), and non-childbearing age (≥50 years), respectively.

Valproate was the most frequently prescribed of the 12 investigated drugs in both female and male outpatients aged 15-29, 30-49, and ≥50 years (Table 1). Figure 1 shows the OR and 95% CI values of each investigated drug calculated to determine the association between anticonvulsants or lithium prescription and sex at childbearing age. Prescription rate of valproate was only slightly lower in childbearing-aged women (15-29 and 30-49 years) than in men of the same age (Figure 1A and B).

Additional notable findings were that the prescriptions of carbamazepine, phenytoin, and phenobarbi-
<table>
<thead>
<tr>
<th>Drug</th>
<th>Total number</th>
<th>Female patients (years)</th>
<th>Male patients (years)</th>
<th>Total</th>
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<tr>
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<td>474,353,500</td>
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<td>Clobazam</td>
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<tr>
<td>Zonisamide</td>
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<td>1,997,240,082</td>
<td>2,017,240,082</td>
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<td>7,000,000</td>
<td>10,000,000</td>
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<tr>
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</table>

Table 1. Numbers of prescribed tablets of each anticonvulsant and lithium and percentage based on sex and age groups.
Anticonvulsant and lithium prescription

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Figure 1. Associations between anticonvulsant or lithium prescription and sex in patients of childbearing age. **A** Ages (A) 15-29 and (B) 30-49 years. OR > 1.000 indicates the drug is prescribed at a significantly higher rate to female outpatients of childbearing age (15-29 or 30-49 years) than to male outpatients of the same age. Abbreviations: OR, odds ratio; CI, confidence interval; LMT, lamotrigine; LEV, levetiracetam; CNZ, clonazepam; TPM, topiramate; ZNS, zonisamide; CLB, clobazam; GBP, gabapentin; VPA, valproate; PHT, phenytoin; CBZ, carbamazepine; PB, phenobarbital; Li, lithium.

Discussion

In the present study, the number of valproate tablets prescribed to female outpatients of childbearing ages was only slightly lower than that to male outpatients of the same ages (15-29 and 30-49 years). This finding was based on data from the first publicly accessible NDB covering all insurance claims received in Japan in the fiscal year 2014. Moreover, the results of the OR analysis of each anticonvulsant and lithium between male and female outpatients showed that valproate prescription was only slightly lower in childbearing-aged women than in men of the same age, while carbamazepine and phenobarbital [2], which also both increase the risk of congenital malformations, were prescribed to childbearing-aged women at an obviously lower rate than they were to men of the same age.

These results are limited because the publicly accessible NDB records were based on the total num-
ber of prescribed valproate tablets and not the number of individuals prescribed valproate. However, the actual number and proportion of valproate prescription for girls and childbearing-aged women are thought to be a concern in terms of increasing the risk of congenital malformations such as neural tube defects [1], adverse neurodevelopmental effects, including intellectual disability [3], and autism spectrum disorders [4] in offspring who are antenatally exposed. Furthermore, valproate has the highest rate of congenital malformations among anticonvulsants [2, 14, 15]. The present findings suggest that in prescribing valproate to girls and women of childbearing age, considering the increased risk of congenital malformations in future pregnancies was an insufficient safety measure in the treatment of neuropsychiatric diseases, including epilepsy and bipolar disorder, in Japan during the fiscal year 2014 (April 2014 to March 2015).

Results of surveillance of valproate prescription in childbearing-aged or pregnant women vary among countries, although few studies have compared rates or patterns of valproate prescription in women of childbearing age with those in same-aged men. According to a survey of antiepileptic drug prescription in 978,957 women with 1,248,713 deliveries before, during, and after pregnancy using the healthcare databases of seven population-based regions in five European countries, including Denmark, Norway, the Netherlands, Italy (Emilia Romagna and Tuscany), and the UK (Wales and the rest), from 2004 to 2010, valproate was relatively frequently prescribed for pre-pregnant women in Tuscany and the Netherlands, compared to Denmark and Norway, and Emilia Romagna [16]. Furthermore, in terms of changing trends in valproate prescription for childbearing-aged women, Murphy et al. reported that the rate of valproate prescription in Ireland decreased between 2008 and 2013 in childbearing-aged women with epilepsy alone, but not in women with neuropsychiatric diseases such as bipolar disorder and other conditions [17]. Likewise, two studies in the United States revealed that valproate prescription declined in childbearing-aged or pregnant women with epilepsy, but not with non-epilepsy diseases such as bipolar disorder, between the 1990s and the 2000s [18, 19]. Given that valproate prescription for childbearing-aged women could be influenced by indications for non-epilepsy diseases represented by psychiatric disorders, physicians, especially when examining patients with psychiatric disorders, should prescribe valproate more cautiously for girls and childbearing-aged women and provide them with more appropriate information about the teratogenic risk of valproate and with contraceptive instructions than they do presently.

Recently, the joint task force of the Commission on European Affairs of the International League Against Epilepsy and the European Academy of Neurology has issued a statement on the need to limit the use of valproate in girls as well as women of childbearing-potential with epilepsy [5]. Regarding pharmacotherapy of bipolar disorders, the NICE guidelines recommend that valproate prescription should be avoided in all women of childbearing potential who are bipolar [1]. Further follow-up investigations of prescription patterns of valproate are needed after these guidelines and authorized statements.

Regarding other anticonvulsants, the results of this study showed that topiramate was nearly equally prescribed to female and male outpatients of younger age, and more prescribed to female outpatients of older childbearing age than to men of the same age. Previous studies have reported that first-trimester exposure to topiramate was an increased risk factor for major congenital malformations, such as cleft lip and palate [20-22]. Considering the present finding of a high prescription rate of topiramate to girls and women of childbearing age, physicians should be more careful in prescribing topiramate and valproate to these categories of patients in future.

In contrast, lamotrigine and levetiracetam were prescribed to girls and childbearing-aged women slightly more frequently than to men of the same age in this study. The prescription of levetiracetam and lamotrigine to girls and women of childbearing potential is preferred since the Cochrane review of Weston et al. [2] reported that fetal exposure to lamotrigine or levetiracetam has the overall lowest risk of congenital malformation among major anticonvulsants. Therefore, these findings indicate that prescriptions of lamotrigine and levetiracetam to childbearing-aged women during the fiscal year 2014 in Japan are preferable in terms of risk reduction.

As described above, this study showed that quite a few anticonvulsants, especially valproate, are prescribed for childbearing-aged women in Japan, similar to other countries. However, it is also true
that anticonvulsants, including valproate, are indispensable for some pregnant and childbearing-aged women with epilepsy. Therefore, the American Academy of Neurology and American Epilepsy Society recommends that women with epilepsy who are prescribed with anticonvulsants should take at least 0.4 mg of folic acid supplementation per day to reduce the risk of birth defects in their offspring [23]. Further studies on folic acid prescription in pre-pregnant women in Japan are needed.

Lithium prescription was only slightly lower in female outpatients of childbearing age than it was in male outpatients of the same age in the present study. Moreover, this study showed that lithium was significantly more frequently prescribed to female than to male outpatients of younger age (15-29 years). Fetal exposure to lithium in the first trimester is associated with increased risk of cardiac malformations such as Ebstein’s anomaly [8, 24]. However, lithium is one of the first recommended drugs for treatment in the maintenance phase for patients with bipolar disorder in most evidence-based guidelines [25-28]. For these reasons, lithium prescription in pregnancy is recommended for limited use in women with bipolar or other mood disorders who need lithium to prevent recurrent mood swing episodes [1].

Furthermore, while lithium is recommended for women planning pregnancy who do not clinically respond to other antipsychotics or mood stabilizers but do to lithium, it should be avoided in the first trimester according to the NICE antenatal and postnatal mental health guidelines [1]. A recent study reports that the relationship between lithium and cardiac malformations in humans is possibly dose-dependent and the risk increases by approximately threefold following fetal exposure to daily lithium doses ≥900 mg during the first trimester [29]. Therefore, physicians should be more careful in prescribing lithium to girls and women of childbearing potential by basing the determination of eligible patients in both categories on their proven need to continue daily lithium therapy.

This study has some limitations that are worth mentioning. First, the main and crucial limitation of this study was that the data presented were based on the numbers of prescribed anticonvulsant and lithium tablets obtained from the publicly accessible NDB, not on data on individual patients prescribed these drugs. The MHLW of Japan restricted the access of MHLW-authorized users to the prescription data of individual patients using a name-based aggregation method. However, our research group was not authorized. Further studies are needed to analyze the accurate data of individuals prescribed each drug following authorization from the MHLW of Japan.

Second, this study did not distinguish between prescription rates of drugs for each diagnosis because we did not have information linking each drug with each diagnosis, including the types of epilepsy, and bipolar and mood disorders, and other neuropsychiatric diseases such as migraine. Especially, information on the types of epilepsy or seizures is clinically essential for choosing anticonvulsants considering that valproate is one of the most effective agents for patients with idiopathic generalized tonic-clonic epilepsy. However, valproate is not recommended for girls and childbearing-aged women and, therefore, physicians should consider the importance of prescribing it very carefully for epilepsy treatment in this patient group. Third, the design of this study was a cross-sectional survey; further studies on longitudinal changes in prescription patterns on a yearly basis are needed. Fourth, prescription claims that we used in this study was not able to reflect real medical practices, that is, they never indicate that the medications were taken as instructed. Moreover, since blood levels were unavailable from the insurance claims, the degree of adherence is largely unknown. In addition, the present survey did not comprehend information on polypharmacy with multiple anticonvulsants in pregnancy that lead to a higher risk of negative consequences in terms of congenital malformations [30].

In conclusion, this study demonstrated that valproate was actually prescribed at a considerably higher rate to girls and women of childbearing age during the fiscal year 2014 in Japan. Considering that fetal exposure to valproate clearly has increased risks of teratogenicity and neurodevelopmental problems, physicians should alter their valproate prescription patterns by prescribing it more cautiously to girls and childbearing-aged women than they do presently.

**Conflict of Interest Statement**

Dr. Kensuke Yoshimura has received honoraria as a speaker/consultant from Sumitomo Dainippon
Pharma, Eli Lilly, Janssen Pharmaceutical, Otsuka, MSD, and received grants from Public Interest Incorporated Foundation and Pfizer Health Research Foundation; Dr. Tasuku Hashimoto has received grants/research supports from Astellas and Bracket global company; Dr. Takashi Takeuchi has received personal fees from Otsuka, GlaxoSmithKline, MSD, Dainippon-Sumitomo, Janssen, Eisai, Eli Lilly, Daiichi-Sankyo, Shionogi, and Tanabe-Mitsubishi; Prof. Takeshi Terao has received honoraria from GlaxoSmithKline K.K. and Taisho Toyama Pharmaceutical Co., Ltd. for advice regarding lamotrigine and lithium, respectively; Prof. Iyo has received consultant fees from Janssen, Eli Lilly, Otsuka, Meiji Seika Pharma and has reported honoraria from Janssen Pharmaceutical, Eli Lilly, Otsuka, Meiji Seika Pharma, Astellas, Dainippon Sumitomo, Ono, Mochida, MSD, Eisai, Daichi-Sankyo, No-vartis, Teijin, Shionogi, Hisamitsu and Asahi Kasei; Dr. Aiko Sato, Dr. Yasunori Sato, Prof. Hiroyuki Watanabe, and Prof. Michiko Nakazato report no conflicts of interest in this work.

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