Prescribing trend for female bipolar patients in childbearing age among psychiatrists in Japan

（全国の精神科医を対象とした妊娠可能年齢にある双極性障害女性患者に対する処方行動に関する研究）

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Abstract

Background: Accumulating evidence has shown that valproate has the greatest teratogenic potential, increasing the risk of major congenital malformations, such as neural tube defects, cleft palate, and neurodevelopmental disability. Some global guidelines state that valproate should not be used for girls or women of childbearing age with bipolar disorder, although valproate is a pharmacological option for acute mania and is used as a stabilization drug for patients with bipolar disorder. We investigated patterns in psychiatrists' prescription of valproate for female patients of childbearing age with bipolar disorder in Japan.

Methods: We conducted a questionnaire survey about psychiatric practice as it relates to major depression and bipolar disorder throughout women's life cycles with respect to psychiatrists from all prefectures in Japan from March to May 2018. The questionnaire had two parts: (1) assessment of participating psychiatrists' backgrounds and attitudes toward patients and (2) their patterns of prescription of psychotropics for female patients with mood disorders across generations and periods of pregnancy. Each question item had four response options: "not at all," "rarely," "sometimes," and "frequently." We examined patterns of prescription for childbearing-age women (late adolescence/young adulthood aged 18-24 years, childbearing-age, older adults aged 25-49 years) and during pregnancy periods.

Results: In total, 571 psychiatrists (427 males, 123 females, and 21 unknowns) responded appropriately to the questionnaire, including 320 who examined at least one or more late adolescence/young adulthood bipolar women. Approximately 70% of psychiatrists answered that they frequently or sometimes prescribe valproate for bipolar women of childbearing age [late adolescence/young adulthood: not at all, n = 23 (7.5%); rarely, n = 69 (22.5%); sometimes, n =116 (37.8%); and frequently, n = 99 (32.2%); childbearing-age, older adults: not at all, n = 13 (2.7%); rarely, n = 67 (13.8%); sometimes, n = 185 (38.1%); and frequently, n = 220 (45.4%)]. The proportion of general hospital psychiatrists who answered "not at all" or "rarely" to the frequency of their valproate prescriptions was higher than that of psychiatrists working in other medical facilities ($\chi^2(3) = 18.2$, $p < 0.001$).

Conclusion: Most psychiatrists frequently or sometimes prescribe valproate for women of childbearing age in Japan.

Key words: bipolar disorder, childbearing age, congenital malformations, pharmacoepidemiology, pregnancy, valproate

1. Introduction

Bipolar disorder frequently emerges in late teenagers and young adults (1-3) and its prevalence in males and females is the same (4). The nature, course and prognosis of bipolar disorder include a tendency towards remission and recurrent mood episodes (5), frequent comorbidities such as substance use and anxiety disorders (6), decreased quality of life and neurocognitive functioning in various domains such as work and family life (7, 8), and high mortality characterized by not only suicide (9, 10), but also general medical conditions (11). Therefore, the burden of this illness is serious in young bipolar patients that need continuous, ongoing management.

Pharmacological treatment plays a crucial role in the continuous management of patients with bipolar disorder in the form of therapies for any mood episodes, including mania and depression, and as continued treatment for the prevention of any episodes in the maintenance phase, according to several worldwide guidelines (12-14). However, in the case of girls, women of childbearing age and pregnant women with bipolar disorder, continuous medication is frequently difficult to successfully administer and the pharmacological strategy for these patients must be different from that for other patients, because newborns and children face risks of congenital malformations. Several guidelines for the management of bipolar disorder such as the National Institute for Health and Care Excellence: bipolar disorder: assessment and management [CG185] (NICE), last updated April 2018 (NICE 185 guideline) (15), the International College of Neuro-Psychopharmacology (CINP) treatment guidelines for Bipolar disorder in adults (CINP-BD-2017) (12), and the Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for management of bipolar disorder (CANMAT-Bipolar Guidelines-2018) (14), commonly state that valproate should not be used for women of childbearing age due to its teratogenic potential.

Although valproate is one of the pharmacological options for the treatment of acute mania and the maintenance of stabilization in patients with bipolar disorder, accumulating evidence has shown that valproate, among pharmacological treatments for bipolar disorder, has the greatest teratogenic potential as it increases the risk of major congenital malformations, such as neural tube defects, cleft palate (16, 17) and neurodevelopmental disability (18, 19). The CINP-BD-2017 states that valproate is not suitable for women of childbearing age. Moreover, the NICE 185 guideline and the UK National Institute for

Health and Care Excellence Clinical Guideline 192: antenatal and postnatal mental health clinical management and service guidance, last updated April 2018 (NICE 192 guideline) (20), state that valproate treatment must not be used for women, including young girls prior to puberty, unless alternative medications are not suitable or women are in a pregnancy prevention program.

Our recent study that investigated the top 11 best-selling anticonvulsants and lithium using the National Insurance claims database in Japan, showed that valproate was the most prescribed major anticonvulsant for female outpatients of childbearing age, and was prescribed only slightly less than these, compared to the same-aged men using the National Insurance claims database from April 2014 to March 2015. However, the data preceded the publication of the above-mentioned guidelines (21). The results of our study stir concern with regard to whether most psychiatrists or physicians in Japan properly prescribe valproate for childbearing-aged women, who must be cautioned with regard to its high teratogenic potential, and given adequate instruction with regard to their methods of contraception during treatment. Based on the findings of our previous study, we hypothesized that most psychiatrists and physicians do not pay close attention to the possibility of pregnancy, or the method of contraception, when they prescribe valproate for childbearing-aged women, and that psychiatrists who pay attention to patients' reproductive potential in their clinical practice only very cautiously consider prescribing valproate to bipolar women of childbearing age.

The aim of the present study was to identify psychiatrists' patterns of prescribing valproate for female patients with bipolar disorder of childbearing age (in their late adolescent years and late forties), compared to those who are pregnant, in Japan. Moreover, we also investigated the relationship between characteristics and reproduction-related interviews in the consultation of psychiatrists and their frequency of valproate prescription. To assess this, this study was performed with the data from a questionnaire survey that we conducted about psychiatric practice in major depression and bipolar disorder throughout the woman's life cycle by psychiatrists in all prefectures in Japan from March to May 2018. This study also examined the frequency of prescription of other mood stabilizers (lithium, carbamazepine, and lamotrigine), antipsychotics, and antidepressants in bipolar women of childbearing age and in the pregnancy period to compare them with prescriptions for valproate.

2. Materials and methods

Study design and participants

A cross-sectional study was conducted with psychiatrists who belong to the following associations: Association of Japan Psychiatric Clinics: Tokyo branch and Chiba branch, Association of Japan Psychiatric Hospitals: Ibaraki branch, Chiba branch and Tokyo branch, JSGHP; Japanese Society of General Hospital Psychiatry in 2018.

A total of 1414 medical institutions (963 General hospitals, 343 mental clinics, and 108 psychiatric hospitals) were chosen from the list of cooperation association and 4816 questionnaires were mailed through the postal service between March and May 2018. There were 571 respondents (427 male, 123 female, and 21 unknowns; mean age = 45.9 years, SD = 10.8). Psychiatrists who did not see patients of childbearing age (18 to 49 years) were excluded. Of 571 respondents, 320 (56.0%) psychiatrists met the eligible criteria for evaluating the prescribing action of female bipolar patients in late adolescence/young adulthood, ages 18–24 years. Of 571 respondents, 497 (87.0%) psychiatrists met the eligible criteria for evaluating the prescribing action of female bipolar patients in early or middle age. Of 571 respondents, 571 (100.0%) psychiatrists met the eligible criteria for evaluating the prescribing action of female bipolar patients who were pregnant.

At the beginning of the questionnaire, we declare the objectives of the study and our commitment to the confidentiality of respondents. Therefore, completing and mailing back the questionnaire was considered to reflect informed consent regarding participation in this study. The study's protocol was approved by the ethics committees of the Graduate School of Medicine and School of Medicine, Chiba University (20 November 2017).

Measures

Sociodemographic characteristics and prescription patterns of participants

The questionnaire was used to assess participating psychiatrists' backgrounds, attitudes towards patients, and prescribing behavior. With regard to psychiatrists' backgrounds, participants were asked about their demographic data, including sex, age, years of

clinical experience, hospital facility, and the number of patients with depression and bipolar disorder they treat per month. With regard to attitudes toward patients, the psychiatrists rated how often they focus on problems specific to life stages when counseling their patients. The question was followed by four response options: “not at all,” “rarely,” “sometimes,” and “frequently.” In the present study, we focused measurements of psychiatrists’ attitudes toward patients’ fertility by asking how often psychiatrists inquire about the following: any menstrual disorder, whether patients want to bear children, methods of contraception, and feelings of rejection for medication during pregnancy and breast-feeding periods. In their prescribing behavior, psychiatrists were requested to indicate how often they prescribe 16 types of medicine, depending on patients’ life stages. The life cycle was divided into 7 stages: ages 0–11 corresponding to childhood, ages 12–17 corresponding to pubescence, ages 18–24 corresponding to late adolescence/young adulthood, ages 25–49 corresponding to early middle age, ages 50–59 corresponding to late middle age, ages 65 and over 65 corresponding to senium, and the pregnancy period. We focused on childbearing age and the pregnancy period in this study. We defined childbearing age as being from 18 to 49 years and considered it to correspond to late adolescence and early middle age stages in this study.

The 16 types of drugs were of four types: antidepressants, mood stabilizers, antipsychotics, and Kampo. A full list of the medications is as follows: Antidepressants: SSRI (Selective Serotonin Reuptake Inhibitors), SNRI (Serotonin and Norepinephrine Reuptake Inhibitors), Mirtazapine, Tricyclic antidepressants, Tetracyclic antidepressants. Mood stabilizer: Lithium carbonate, Sodium Valproate, Carbamazepine and Lamotrigine. Antipsychotics: Typical antipsychotic, Atypical antipsychotic; Risperidone, Olanzapine, Quetiapine, Aripiprazole and others atypical antipsychotics. Kampo (herbal medicine).

Statistical analysis

We first performed a Chi-squared test (χ^2-test) for categorized variables to analyze categorical data between the current and previous affiliations of psychiatrists (i.e. general hospitals or other medical facilities) and the frequency of prescription of valproate for female bipolar patients among late adolescence/young adulthood. In addition, we calculated the partial correlations, controlling for sex, between years of

clinical experience, valproate prescription, and psychiatrists' attitude toward bipolar patients of childbearing age and during pregnancy. For all tests, a two-tailed $p < 0.05$ was considered statistically significant. All analyses were conducted using SPSS 22 (Arbuckle, 2013).

3. Results

Psychiatrists' trends for prescribing psychotropic drugs for female bipolar patients of childbearing age

A total of 320 psychiatrists participated in the assessment of prescription trends for female, late adolescent/young adulthood patients with bipolar disorder. A total of 497 psychiatrists participated in the assessment of prescription trends for bipolar female, early middle age patients. A total of 571 psychiatrists participated in the assessment of the prescription trends for pregnant patients. The participants demographic characteristics are shown in Table 1.

In general, the psychotropic drug we chose was prescribed more for female bipolar patients of childbearing age than for pregnant patients. Among female patients of childbearing age, early middle age patients got more psychotropic drug prescriptions than late adolescence/young adulthood patients, as shown in Table 2. Among female patients of childbearing age, early middle age patients got more psychotropic drug prescriptions than did late adolescent/young adulthood patients. Psychiatrists prescribed valproate for female late adolescence/young adulthood patients with bipolar disorder; 23 psychiatrists responded not at all, n = 23 (7.5%); rarely, n = 69 (22.5%); sometimes, n =116 (37.8%); and frequently, n = 99 (32.2%). Psychiatrists prescribed valproate for childbearing-age, older female patients with bipolar disorder; 13 psychiatrists responded not at all, n = 13 (2.7%); rarely, n = 67 (13.8%); sometimes, n = 185 (38.1%); and frequently, n = 220 (45.4%). While they avoided prescribing of VPA for pregnant patients, 387 psychiatrists responded "not at all" (75.3%) while 126 responded "rarely"–"frequently" (24.7%).

Table 1. Social and demographic characteristics of participants (*N* = 571)

	n (%)
Male	427 (74.8)
Female	123 (21.5)
Unknown	21 (3.7)
Age (years)	
Mean	45.9
Standard deviation	10.8
Years of clinical experience	
<11 years	181 (33.1)
11 years to under 21	180 (32.9)
21years to under 31years	111 (20.3)
More than 30 years	61 (13.7)
Unknown	24 (4.2)
Facilities	
general hospital	307 (53.8)
psychiatric hospital	151 (26.4)
clinic	62 (10.9)
others	7 (1.2)
Unknown	21 (3.7)
Specialized clinical department	
Psychiatry (general)	537 (94.0)
Psychosomatic medicine	27 (4.7)
Child psychiatry	33 (5.8)
Others	7 (1.2)

Table 2. Row point questionnaire answers regarding prescriptions for female bipolar patients

	Childbearing age								Pregnant women (*N* = 571)			
	Late adolescence/Young adulthood (18-24 years; *N* = 320)				Childbearing-age, older adults (25-49 years; *N* = 497)							
	Not at all	Rarely	Sometimes	Frequently	Not at all	Rarely	Sometimes	Frequently	Not at all	Rarely	Sometimes	Frequently
	n (%)				*n* (%)				*n* (%)			
Mood stabilizers												
Valproate	23 (7.5)	69 (22.5)	116 (37.8)	99 (32.2)	13 (2.7)	67 (13.8)	185 (38.1)	220 (45.4)	387 (75.3)	79 (15.4)	31 (6.0)	16 (3.1)
Lithium carbonate	15 (5.8)	54 (17.5)	125 (40.6)	111 (36.2)	7 (1.4)	42 (8.7)	181 (37.3)	255 (52.6)	382 (74.0)	77 (14.9)	37 (7.2)	20 (3.9)
Carbamazepine	109 (35.9)	102 (33.6)	74 (24.3)	19 (6.3)	122 (25.5)	157 (32.8)	148 (30.9)	52 (11.9)	402 (77.9)	78 (15.2)	30 (5.8)	3 (0.6)
Lamotrigine	32 (10.5)	57 (18.7)	126 (41.3)	90 (29.5)	40 (8.4)	75 (15.7)	209 (43.6)	155 (32.4)	221 (42.9)	119 (23.1)	124 (24.1)	51 (9.9)
Antidepressants												
SSRIs [a]	136 (44.2)	115 (37.3)	43 (14.0)	14 (4.5)	137 (28.2)	186 (38.3)	124 (25.5)	39 (8.0)	288 (55.7)	167 (32.3)	50 (9.7)	10 (1.9)
SNRIs [b]	108 (35.2)	120 (39.1)	63 (20.5)	16 (5.2)	184 (37.9)	173 (35.6)	96 (19.8)	32 (6.6)	323 (62.5)	152 (29.4)	34 (6.6)	8 (1.5)
Mirtazapine	122 (39.7)	117 (38.1)	55 (17.9)	13 (4.2)	168 (34.8)	167 (34.6)	121 (25.1)	27 (5.6)	324 (62.8)	146 (28.3)	39 (7.6)	7 (1.4)
Tricyclic antidepressants	233 (76.4)	61 (20.0)	10 (3.3)	1 (0.3)	341 (70.6)	106 (21.9)	33 (6.8)	3 (0.6)	455 (88.5)	53 (10.3)	5 (1.0)	1 (0.2)
Tetracyclic antidepressants	216 (70.4)	65 (21.2)	24 (7.8)	2 (0.6)	309 (63.8)	118 (24.4)	51 (10.5)	6 (1.2)	423 (82.1)	74 (14.4)	17 (3.3)	1 (0.1)
Antipsychotics												
Risperidone	54 (17.7)	102 (33.4)	121 (39.7)	28 (9.2)	64 (13.3)	150 (31.2)	208 (43.2)	59 (12.3)	200 (38.8)	190 (36.8)	106 (20.5)	20 (3.9)
Olanzapien	20 (6.5)	79 (25.7)	144 (46.9)	64 (20.8)	20 (4.2)	93 (19.3)	242 (50.3)	126 (26.2)	161 (31.0)	180 (34.7)	144 (27.7)	33 (6.4)
Quetiapine	17 (5.5)	71 (23.1)	147 (47.9)	71 (23.1)	20 (4.1)	73 (15.1)	250 (51.9)	139 (28.8)	144 (27.7)	165 (31.8)	160 (30.8)	50 (9.6)
Aripiprazole	10 (3.3)	47 (15.6)	164 (53.6)	85 (27.8)	11 (2.3)	54 (11.2)	264 (54.8)	153 (31.7)	110 (21.3)	177 (34.3)	180 (34.9)	49 (9.5)
Other atypical antipsychotics	109 (36.2)	109 (36.2)	66 (21.9)	17 (5.6)	170 (36.1)	150 (31.8)	120 (25.5)	31 (6.6)	286 (56.5)	148 (29.2)	65 (12.8)	7 (1.4)
Typical antipsychotics [C]	171 (57.2)	69 (23.1)	42 (14.0)	17 (5.7)	229 (48.8)	124 (26.4)	85 (18.1)	31 (6.6)	342 (67.2)	114 (22.4)	43 (8.4)	9 (1.8)
Kampo medicine (Harbal medicine)	99 (32.7)	98 (32.3)	79 (26.1)	27 (8.9)	156 (33.0)	134 (28.3)	144 (30.4)	39 (7.8)	211 (41.1)	152 (29.6)	111 (21.6)	39 (7.6)

[a] SSRI: selective serotonin reuptake inhibitors (e.g., Paroxetine hydrochloride hydrate, Sertraline hydrochloride, Escitalopram oxalate, and Fluvoxamine maleate)

[b] SNRI: serotonin noradrenalin reuptake inhibitors (e.g., Duloxetine hydrochloride, Milnacipran hydrochloride, and Venlafaxine hydrochloride)

[c] Typical antipsychotics: eg., Chlorpromazine hydrochloride, Haloperidol, Levomepromazine maleate, Sultopride hydrochloride, Timiperone, and Zotepine

Affiliation of psychiatrists and prescription of valproate for female bipolar patients among late adolescence/young adulthood

The χ^2-test showed that there were significant differences in the current affiliation of psychiatrists and valproate prescriptions for female bipolar patients among late adolescence/young adulthood, as shown in Table 3 ($\chi^2(3) = 18.2$, $p < 0.001$). A Haberman-type residual analysis showed that the number of psychiatrists working for general hospitals who reported that they prescribed valproate either "Not at all" or "Rarely" was higher than that of psychiatrists working for other medical facilities and hospitals. In addition, the number of psychiatrists working for general hospitals answered "Frequently" with regard to valproate prescription much less than psychiatrists working for other medical facilities or hospitals. In their previous affiliations, however, there were no differences between general hospitals and other medical facilities in terms of valproate prescriptions.

Partial correlation between valproate prescribing action and psychiatrists' backgrounds

We calculated the partial correlations, controlling for sex, between years of clinical experience, valproate prescription, and psychiatrists' attitude toward bipolar patients of childbearing age and in pregnancy (Table 4). The psychiatrists' years of experience was found to be positively and significantly correlated with a valproate prescription in late adolescence/young adulthood (18-24 years) ($r = 0.13$, $p < 0.05$). In childbearing-age, older adults (25-49 years) and pregnant women, on the other hand, there is no relationship between the two variables. There is no relationship between the contents of reproductive-related medical interviews and valproate prescriptions in childbearing age or pregnancy.

Table 3. Affiliation of psychiatrist and valproate prescription for female bipolar patients among late adolescence/young adulthood (18-24 years of age)

	Prescription of Valproate				χ^2	p
	Not at all	Rarely	Sometimes	Frequently		
	n (%)					
Current Affiliation					**18.2**	**0.001**
General Hospitals	20 (11.3)	49 (27.7)	57 (32.2)	51 (28.8)		
Other medical facilities	6 (4.2)	19 (13.2)	61 (42.4)	58 (40.3)		
Previous Affiliation					5.3	0.2
General Hospitals	24 (8.1)	67 (22.7)	106 (35.9)	98 (33.2)		
Other medical facilities	2 (7.7)	1 (3.8)	12 (46.2)	11 (42.3)		

Note . p value was calculated by the χ^2-test.

Table 4. Partial Correlation between valproate prescription and psychiatrists' attitude toward bipolar patients of childbearing age and during pregnancy

	Prescription of Valproate		
	Younger adults (18-24 years)	Elder childbearing-age adults (25-49 years)	Pregnant women
Years of clinical experience	**.13** *	-.01	.01
Reproductive-related medical interview			
Abnormal menstruation	-.02	-.03	-.04
Having desire to bear children	-.03	.03	-.04
Method of contraception	.02	.01	.08
Internal medicine avoiding during pregnancy and breast feeding	.09	.06	-.05

Note . Partial Correlation coefficients were controlled for sex. $^{*}p < .05$.

4. Discussion

In this study, three important findings about psychiatrists' prescription patterns of valproate for female bipolar patients of childbearing age in Japan deserve to be mentioned. First, the present study demonstrates that 70% of psychiatrists responding to the questionnaire sheet answered that they frequently or occasionally tended to prescribe valproate for women of childbearing age in Japan, although most answered that they did not for women who were pregnant. Specifically, 32% of psychiatrists answered that they frequently prescribed valproate for women aged 18 to 24 years, and 38% of those occasionally prescribed it for same-aged women. Thirty percent of psychiatrists answered they rarely tended to prescribe valproate, or that they did not at all prescribe it. Second, psychiatrists affiliated with general hospitals answered that they tended to refrain from prescribing valproate for childbearing-age women compared to those affiliated with other medical facilities such as psychiatric hospitals or private clinics. Third, the frequencies of reproductive-related medical interviews were not correlated with the tendency to prescribe valproate to women of childbearing age, although years of psychiatric experience was positively correlated with this.

This questionnaire study conducted from March to May 2018 reveals the possibility that more than half of psychiatrists frequently or occasionally tend to prescribe valproate for women of childbearing age in Japan. This finding is consistent with our previous study investigating prescribed tablets for childbearing-aged outpatients in Japan (21). On April 6, 2017, in reference to pharmacological treatments of women in perinatal periods, the Japanese Society of Perinatal Mental Health published the Perinatal Mental Health Consensus Guide 2017 on the website (http://pmhguideline.com/: in Japanese only) that states that valproate should not be prescribed to women of childbearing age. However, the society has been as small as the number of psychiatrists, and there were only 20 regular members at that time, while midwives constitute a large proportion of the regular members of the society (over 100 people). In other countries, such as Finland (22), Ireland (23), and Germany (24), valproate prescription has tended to slightly decline, although the data from these studies are not limited to pharmacological treatments of bipolar disorder. In the UK, at the same time as the last updated NICE 192 guideline, in April 2018, the Medicines and Healthcare Products Regulatory Agency (MHRA) stated that valproate use would be rigidly regulated and that valproate treatment must not be used for women, including young girls prior to puberty, unless alternative medications are not

suitable and unless women are part of a pregnancy prevention program (25). Considering that fetal exposure to valproate in the first trimester must be avoided, and that approximately 40% of pregnancies are unplanned or unintended (26), psychiatrists and physicians should not prescribe valproate for girls and childbearing-age women with bipolar disorder, in principle. Furthermore, the societies, associations, and related guidelines that directly influence psychiatrists or physicians are expected to clearly share warnings with regard to valproate prescriptions for girls and childbearing-age women with bipolar disorder in Japan and other countries, because changes in valproate prescription patterns among these countries may be slow.

In the present study, psychiatrists working at general hospitals answered that they tended to refrain from prescribing valproate to childbearing-age women compared to those affiliated with other medical facilities, such as psychiatric hospitals and private clinics. There are two main possible interpretations of this result. Freudenreich and Kontos report that consultation-liaison psychiatrists have better opportunities and situations for learning other medical specialties through their interdisciplinary collaborative work (27). This may make sense considering that psychiatrists working at general hospitals, compared to other institutions, have better chances and experience with regard to consulting pregnant women with psychiatric diseases at their hospitals which either have a birth center or obstetricians working in them. There are other reasons, too, for which psychiatric diseases and symptomatic and social severities of patients are different across general hospitals and other institutes. For instance, in/outpatients consulting psychiatrists in psychiatric hospitals may have more severe symptomatology, impaired social ability such as due to long-term hospitalization, and compromised cognitive performance, including in the form of intellectual disability, than those of general hospitals. Therefore, it is so difficult for such patients to become pregnant that psychiatrists prescribe valproate to them. However, in the real-world, women with severe mental illness such as schizophrenia and autism are fertile and do get pregnant and have newborns (28). Therefore, the societies and associations that largely influence any psychiatrists, regardless of any kinds of medical institutes, should provide warnings with regard to valproate prescription for girls and women of childbearing age.

In addition, the frequencies of reproductive-related medical interviews were not correlated with the tendency to prescribe valproate to women of childbearing age, although years of psychiatric experience was positively correlated with this. These results

were unexpected because our hypothesis was that psychiatrists who usually pay attention to future conceptions in their consultations of childbearing-age women would not, in general, have prescribed valproate to these women. The interpretation of this result was that there may be two groups of psychiatrists with regard to pregnancy, consisting of the ones refraining from prescribing valproate to childbearing-age women, and the other ones prescribing it with caution. It is difficult to interpret the positive correlation between years of psychiatric experience and the tendency to prescribe valproate to childbearing-age women. This result is limited because of the lack of surveillance with regard to real-world childbearing-aged women prescribed valproate, and with regard to the lack of assessment of each psychiatrist's valproate prescription dosage. Therefore, senior psychiatrists with enough clinical experience may have the opportunity to examine childbearing-age women with more refractory bipolar disorder than junior ones. Further studies are needed to clarify this.

With regard to other psychotropics, especially lithium and carbamazepine prescriptions, with regard to which the NICE 192 guideline cautions against girls and childbearing-age women (20), frequencies of lithium prescriptions were similar to those of valproate; approximately 77% of responding psychiatrists answered that they frequently or sometimes tended to prescribe it for bipolar women of childbearing age in Japan, and carbamazepine was not as frequently prescribed. These findings are consistent with our previous study (21). Fetal exposure to lithium in the first trimester is associated with increased risk of cardiac malformations (29). According to the NICE guideline, unless lithium is recommended for women planning pregnancies who do not clinically respond to other antipsychotics or mood stabilizers, but do respond to lithium, it should be avoided in the first trimester (20). However, it was clarified that the adverse effects of lithium use on the fetus are dose-dependent (30). Therefore, psychiatrists should be more careful when continuously prescribing lithium to girls and women of childbearing potential.

We acknowledge that there are several limitations to this study. First, we were unable to measure the real-world valproate prescriptions (including the dosage) of the responding psychiatrists. Given that some of female patients with bipolar disorder who consulted each responding psychiatrist were expected to have various comorbidities, intellectual disabilities, and complications, including epilepsy, early menopause, and bilateral ovarian ablation, a valproate prescription may be adequate for them with caution.

Second, the response rate of 11.8% was low, although 571 psychiatrists responded to this questionnaire in Japan. Third, the items with regard to reproductive-related medical interviews were relatively scarce in the questionnaire, which may have influenced the correlations between the answers and frequencies of valproate prescriptions.

Conclusion

The present study demonstrates that the majority of psychiatrists frequently or occasionally tend to prescribe valproate for women of childbearing age in Japan, although almost all answered they did not prescribe valproate to pregnant women. Specifically, 70% of psychiatrists answered that they frequently or sometimes prescribed valproate for women aged 18 to 24 years. Considering that fetal exposure to valproate in the first trimester must be avoided and that the high rate of pregnancies that are unplanned or unintended, psychiatrists, in principle, should not prescribe valproate to girls and women of childbearing age with bipolar disorder.

CRediT authorship contribution statement

Masumi Tachibana: Data curation, Formal analysis, Investigation, Methodology, Writing- original draft. **Tasuku Hashimoto:** Conceptualization, Methodology, Project administration, Formal analysis, Writing – original draft. **Mami Tanaka:** Formal analysis, Methodology, Software, Writing- original draft. **Hiroyuki Watanabe:** Conceptualization, Data curation, Investigation, Methodology. **Yasunori Sato:** Conceptualization, Methodology, Writing – review & editing. **Takashi Takeuchi:** Conceptualization, Data curation, Investigation, Methodology. **Takeshi Terao:** Conceptualization, Supervision, Investigation, Methodology, Writing – review & editing. **Shou Kimura:** Data curation, Investigation, Methodology. **Akio Koyama:** Data curation, Investigation, Methodology, Supervision. **Sachie Ebisawa:** Data curation, Investigation, Methodology. **Yuichiro Shizu:** Data curation, Investigation, Methodology. **Terunobu Nagase:** Data curation, Investigation, Methodology, Project administration. **Junichi Hirakawa:** Data curation, Investigation, Methodology. **Kotaro Hatta:** Data curation, Investigation, Methodology, Writing – review & editing. **Michiko Nakazato:** Conceptualization, Investigation, Methodology. **Masomi Iyo:** Investigation, Methodology, Supervision, Writing – review & editing. All authors have approved of the final manuscript.

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Conflict of interest

Dr. Hashimoto reported personal fees from research support of a clinical trial that the signant health (former, blacket global) company manages. Dr Hatta has received lecture honoraria for Dainippon-Sumitomo, Janssen, Meiji Seika, MSD, Otsuka, Takeda, and

Tanabe-Mitsubishi, and has served as a consultant for Dainippon-Sumitomo, MSD, and Meiji Seika. Dr. Iyo received consultant fees from Janssen, Elilly, Otsuka, and Meiji Seika Pharma and reports honoraria from Janssen, Eli Lilly, Otsuka, Meiji Seika Pharma, Astellas, Dainippon Sumitomo, Ono, Mochida, MSD, Eisai, Daiichi-Sankyo, Novartis, Teijin, Shionogi, Hisamitsu, and Asahi Kasei.

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