Use of Valproate in Women:
An Audit of Prescriptions to 10,001 Psychiatry, Neurology, and Neurosurgery Outpatients

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ABSTRACT

Background: Gestational exposure to valproate is associated with an unacceptably high risk of major congenital malformations, neurodevelopmental disorders, and other adverse outcomes. Prescription of valproate to reproductive-age women is therefore strongly discouraged in many parts of the world. To our knowledge, there is no pharmacoepidemiologic study of the prescription of valproate to women in a developing country.

Methods: During September to November 2019, we examined the prescriptions of 10,001 consecutive outpatients issued by about 250 medical professionals from the Departments of Psychiatry, Neurology, and Neurosurgery at the National Institute of Mental Health and Neurosciences, Bangalore, India (this is a large, tertiary care referral center and a designated institute of national importance, the largest of its kind in the country). We examined the prescriptions for inclusion of any formulation of valproate in women and men separately. For comparison purposes, we also extracted data on the prescription of carbamazepine.

Results: A large proportion of women (647/3,837; 16.9%) received a prescription that included valproate (mean dose = 898 mg/d); the age band 15–45 years accounted for 460 (71.1%) of these prescriptions. In comparison, 403 (10.5%) of 3,837 women received a prescription that included carbamazepine, and 289 (71.7%) of these were in the 15-to-45–year age band. Women were more likely to receive a prescription for valproate in the Departments of Neurology and Neurosurgery than in the Department of Psychiatry (29.1% vs 14.4%, respectively).

Conclusions: Female outpatients of childbearing age who consulted for disorders related to psychiatry, neurology, and neurosurgery were found to have a high exposure to valproate. If these findings can be generalized to other practices in the country, and to other developing countries, they suggest a pressing need for regulatory guidance regarding the avoidance of prescription of valproate to women of childbearing age. This is a public health matter of global importance.

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In several parts of the world, sodium valproate, valproic acid, and formulations thereof (referred to as *valproate* in the rest of this article) are approved for a number of indications, such as the treatment and/or prevention of seizure disorders, mood disorder, and migraine. Valproate is also used for many off-label indications, including the treatment of anxiety, aggression, neuropathic pain, behavioral and psychological symptoms of dementia, tardive movement disorders, cyclical vomiting, and others.[1]

The use of valproate during pregnancy is strongly discouraged. This is because gestational exposure to valproate is associated with a high risk of morphological teratogenicity,[1–4] fetal loss,[3,5] and neurodevelopmental disturbances such as lower IQ, cognitive delay, language delay, psychomotor delay, and autism spectrum disorder.[1,6,7] Women often have unplanned pregnancies. This could make it unsafe for a woman to use valproate during her reproductive lifespan. Regulatory restrictions have therefore been placed on the use of valproate in women.[1]

How well are the restrictions followed? Data are available from developed countries, mainly in Europe and North America.[8–13] However, there are no data from population-dense, developing countries, such as India, where the failure to limit valproate prescription to women could have important adverse public health consequences. We therefore conducted an audit of prescriptions of valproate to women in the largest tertiary care hospital in India that caters exclusively to psychiatry, neurology, neurosurgery, and related disciplines.

METHODS

Study Design and Setting

This study was conducted between September and November 2019 in the outpatient department of the National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India. NIMHANS is designated by an Act of Parliament as an institute of national importance and is the only one of its kind in the country. The institute conducts postgraduate training and research and provides clinical services across a wide range of disciplines. The institute hospital is a tertiary care center; whereas the primary catchment area is the populous city of Bangalore, a sizeable number of patients come from surrounding districts in the state of Karnataka, and referrals are received from the rest

Clinical Points

- Gestational exposure to valproate carries a high risk of birth defects and neurodevelopmental disorders.
- At a major center in India, 17% of 3,837 women received a prescription for valproate, and 71% of those prescriptions were to women aged 15–45 years.
- Regulatory guidance is necessary to proscribe the prescription of valproate to women of childbearing age.

of the country as well. At the time of the study, the hospital had about 930 inpatient beds and received about 1,300–1,500 outpatients a day.

The study was conducted as a pharmacovigilance activity, through prescription audit, by the Department of Clinical Psychopharmacology and Neurotoxicology, NIMHANS. The purpose of the study was to ascertain the frequency of prescription of valproate to women and to determine what variables, extractable from a prescription, may be associated with prescription of the drug to women. The study was approved by the Director of NIMHANS, and permission to publish the results was obtained from the Institute Ethics Committee, Basic Sciences and Neurosciences Division.

Sample

The sample comprised (the prescriptions of) all outpatients who were seen at the hospital during official working hours on official working days. These prescriptions were issued by approximately 250 junior residents, senior residents, and faculty members, working on different days by rotation. The sample was drawn from two locations. One location was the free drugs counter, which provides medicines, without charge, to patients who have a "below poverty line" card issued by the state government or to eligible patients with an income certificate issued by a competent authority. The other location was the Janatha Bazaar pharmacy, which provides medicines for purchase at a discounted price. Mood stabilizers and anticonvulsants available at the free drug counter include lithium, carbamazepine, valproate, phenobarbitone (phenobarbital), and phenytoin. All commonly prescribed mood stabilizers and anticonvulsants are available at the Janatha Bazaar pharmacy.

Data Extraction

Teams of pharmacovigilance assistants were stationed at both sampling locations. These assistants scrutinized all prescriptions (that were complete and legible) after the medicines were dispensed. There was no interaction with patients, and all data were obtained only from the prescriptions. About 90% of the prescriptions scrutinized in this study were obtained from the free drug counter; the rest were obtained from the Janatha Bazaar pharmacy.

Information was extracted from the prescriptions for the following variables: age and sex of the patient; the issuing clinical department; whether or not the prescription contained any formulation of valproate; the dose of valproate if valproate was prescribed; the frequency of dosing during the day; and the other drugs in the prescription, with special reference to carbamazepine.

Statistical Methods

We planned to examine approximately 10,000 prescriptions; this number was arbitrarily chosen. Mental health is the dominant discipline at NIMHANS, and the data for the Department of Psychiatry, the largest medical department in the institute, are presented separately from the data for the Departments of Neurology and Neurosurgery. The data for the latter two departments are pooled partly because of the smaller numbers and partly because whereas psychiatry patients receive valproate mostly for mood disorders, neurology and neurosurgery patients receive the drug for seizure disorder and (less commonly) for other neurologic disorders.

We analyzed the data with a view to understand the frequency of prescription of valproate to women, relative to men, with carbamazepine as a comparison drug. We attempted to understand what variables might be associated with a higher frequency of valproate prescription to women. We were particularly interested in the frequency of prescription of valproate to women who were of reproductive age, operationalized as age 15–45 years. There were no prespecified hypotheses; the analyses were exploratory.

We present our results chiefly as descriptive statistics: mean and standard deviation (SD) or frequency and percentage. In exploratory analyses, we compared means using the independent-sample *t* test and proportions using the χ^2 test. The α for statistical significance was set at .05.

RESULTS

We scrutinized the prescriptions of 10,001 unique patients. The mean (SD) age of these patients was 37.7 (13.6) years. The sample was 38.4% female. No other sociodemographic or clinical data were available in the prescriptions. The prescriptions were issued from the Departments of Psychiatry (79.9%) and Neurology/Neurosurgery (20.1%). Because of occasional missing data, all numbers for sample size do not necessarily add up to 10,001.

Use of Valproate in the Whole Sample

As many as 2,528 patients (25.3% of the sample) received valproate. The prescription of valproate was significantly lower for patients seen by the Department of Psychiatry than for those seen by the Departments of Neurology and Neurosurgery (1,689/7,995 [21.1%] vs 839/2,004 [41.9%]; $\chi^2_1 = 364.89$, $P < .001$).

Use of Valproate Among Men and Women

The prescription of valproate was significantly lower among women than among men (647/3,837 [16.9%] vs 1,879/6,159 [30.5%]; $\chi^2_1 = 233.13$, $P < .001$).

When only data from women were examined, the use of valproate was significantly higher among women seen

Table 1. Prescription of Valproate to Men and Women in Different Age Bands[a,*]

Age, y	Men (n = 1,879)	Women (n = 647)
< 18	242 (12.9)	76 (11.7)
18–29	489 (26.0)	137 (21.2)
30–39	492 (26.2)	179 (27.7)
40–49	432 (23.0)	167 (25.8)
50–59	152 (8.1)	53 (8.2)
60 and above	72 (3.8)	35 (5.4)

[a]Values are shown as n (column %).
*$\chi^2_5 = 9.90$, $P = .08$.

by the Departments of Neurology and Neurosurgery than among those seen by the Department of Psychiatry (190/654 [29.1%] vs 457/3,183 [14.4%]; $\chi^2_1 = 83.56$, $P < .001$).

Use of Valproate in Different Age Bands

The use of valproate in different age bands is presented in Table 1. The mean (SD) age of men who were prescribed valproate was 33.9 (13.8) years; the value was 35.8 (14.0) years in women ($t_{2,524} = 3.00$, $P < .003$). The age band 15–45 years accounted for 460 (71.1%) of the prescriptions of valproate to women.

Valproate Dosing

The mean (SD) valproate dose was 962.5 (338.5) mg/d in men and 897.9 (327.8) mg/d in women ($t_{2,524} = 4.22$, $P < .001$). Among women seen by the Department of Psychiatry, valproate was dosed at 904.0 (318.5) mg/d. Among women seen by the Departments of Neurology and Neurosurgery, the dose was 883.2 (349.7) mg/d. The difference in dosing between departments was not statistically significant ($t_{645} = 0.74$, $P = .46$).

Carbamazepine

There were 403 women who received carbamazepine, comprising 10.5% of the women in the sample. About a third of these prescriptions were from the Department of Psychiatry, and the rest were from the Departments of Neurology and Neurosurgery. As with valproate, most (n = 289; 71.7%) of the women prescribed carbamazepine were in the 15-to-45–year age band.

DISCUSSION

We found that a quarter of the 10,001 outpatient prescriptions that we examined included a formulation of valproate; that nearly 17% and 31% of prescriptions to women and men, respectively, contained valproate; and that 71% of the prescriptions of valproate to women were to women in the 15-to-45–year age band, that is, to women of potential childbearing age.

To our knowledge, this study is the first pharmacoepidemiologic study of the prescription of valproate to women in a third world country. How do these findings compare with data from other parts of the world? Wisner et al[8] studied 40,526 subjects with active prescriptions for non-antipsychotic mood stabilizers, based on information obtained from the New York State Medicaid database. They found that valproate was the most commonly prescribed drug among young women (23.4%). Based on data for the United States, the US Food and Drug Administration (FDA)[9] stated that "in the outpatient retail setting in 2012, approximately 1.5 million patients received a dispensed prescription for valproic acid and derivative products, and approximately 22% (341,000 patients) of total patients were women of reproductive potential age (13–45 years)."

In Finland, the use of valproate in women of reproductive age (15–44 years) showed only marginal decline—from 50 per 10,000 to 40 per 10,000—between 2012 and 2016.[10] In an audit of 648 clinical teams from 55 mental health trusts in the UK (period of study not stated), Paton et al[11] found that valproate had been prescribed to 24% of 2,364 women. In Switzerland, Spoendlin et al[13] reported that the use of valproate dropped marginally from 28 in every 10,000 women in 2014 to 21 in every 10,000 women in 2018. In a questionnaire-based survey of 571 psychiatrists in Japan, Tachibana et al[12] found that 70% of respondents stated that they sometimes or frequently prescribed valproate to bipolar women of childbearing age.

We were unable to find previous pharmacoepidemiologic data for the use of valproate in women of childbearing age in India or, for that matter, in any other population-dense third world country. We believe that our study may be the first of its kind for this part of the world.

Global Implications

It appears that, globally, an unacceptably high number of women of childbearing age diagnosed with mental health or neurologic disorders receive a prescription for valproate; this is of public health importance because gestational exposure to valproate is associated with a high risk of major congenital malformations, neurodevelopmental disorders, and other adverse outcomes.[1–7,14,15] There are 2 possible explanations for this pharmacoepidemiologic finding. One is that, especially in nonacademic practices, there may not be an adequate awareness of the risks associated with gestational exposure to valproate. The other is that, despite awareness, the need to avoid valproate in such situations may not be receiving sufficient priority; medical practitioners may believe that it could suffice to counsel women about the risks and the need for contraception.

Limiting the prescription of valproate only to women who are practicing contraception and only after appropriate counseling is not a good solution because of the possibility of contraceptive failure and/or unplanned pregnancy. With regard to planned pregnancy, should women stabilized on valproate wish to conceive, switching from valproate to another mood stabilizer or anticonvulsant could destabilize the disorder being treated. The best approach, therefore, would be to avoid the use of valproate altogether in women of childbearing age unless the woman cannot conceive because, for example, she has undergone a procedure such as tubectomy or hysterectomy. This message must be delivered widely, to all health care providers, through appropriately

designed educational programs. Region-specific regulatory guidance should also be prepared and issued.

Regulatory Guidance

In many developed countries, the state has taken responsibility for the health of the unborn child, and regulatory guidance has been issued to restrict the prescription of valproate to women of childbearing age.[1] As an example, the US FDA[9] issued a drug safety communication that contraindicated the prescription of valproate for the prevention of migraine to pregnant women. The safety communication noted that valproate should be prescribed to pregnant women with epilepsy or bipolar disorder only if other treatments did not provide adequate symptom control or were otherwise unacceptable. The safety communication also noted that valproate should not be administered to women of childbearing age unless the need for the drug was considered essential. Finally, the safety communication stated that women who are planning a pregnancy should be advised about the benefits and risks of valproate use during pregnancy and that alternative therapeutic options should be considered for such women.

The French National Agency for the Safety of Medicines and Health Products prohibited the prescription of valproate to girls and women who are diagnosed with bipolar disorder and who are either pregnant or of childbearing age and are not using an efficient form of contraception. Guidance also exists to discourage the prescription of valproate to girls and women who are of reproductive age and who are diagnosed with seizure disorder unless the use of the drug is unavoidable.[16] In the UK, the Medicines and Healthcare Products Regulatory Agency (MHRA) has prohibited the prescription of valproate to all women of childbearing potential who have not enrolled in a pregnancy prevention program. The National Institute for Health and Care Excellence (NICE) guidelines have been modified to include this regulatory change.[17]

The European Medicines Agency[18] advises doctors not to prescribe valproate for epilepsy or bipolar disorder during pregnancy, or even to girls or women who can become pregnant, unless other interventions are not tolerated or do not work; if valproate does need to be prescribed, patients should be advised about the need for contraception and should be supervised by an experienced doctor.

The Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders state that valproate is not recommended for use among women of childbearing age.[19] Regrettably, the Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines[20] include divalproex as a first-line treatment for a manic episode and for the maintenance treatment of bipolar I disorder. A saving grace is that the guidelines state in table footnotes that divalproex and carbamazepine should be used with caution in women of childbearing age, and in a section on pregnancy as a special situation, the guidelines discourage the use of divalproex during pregnancy. Other regulatory responses were summarized by Angus-Leppan and Liu.[21]

Strengths and Limitations

Our study has many important strengths. We examined 10,001 outpatient prescriptions from about 250 medical professionals in 3 medical departments; the data were prospectively collected across a 2-month period; and the study was conducted in a designated institution of national importance, the largest academic, research, tertiary care, and referral center of its kind in the country. The findings are therefore important given the quantity of the data and the importance of the center from which the data were collected.

Our study has an important limitation: we examined data from only one center, and so the generalizability of the findings to other centers in the country is limited. However, we believe that if 17% of women seen by neurologists, neurosurgeons, and psychiatrists in this center were prescribed valproate, then the prescription of valproate to women seen in these departments in other institutions, and in private medical practice, could be higher if only because the awareness of the risks could be less. We do not know, however, whether the use of valproate in this institute is high because it is a referral center that manages many difficult-to-treat patients in whom the risk-benefit ratio for use of valproate may have tilted the scales toward prescription of the drug. A better understanding of circumstances would require careful scrutiny of case files and/or discussion with the prescribers, neither of which was possible given the methods of this study.

As part of our pharmacovigilance responsibilities, we only scrutinized prescriptions. We did not examine case files or speak with patients. So, we do not know how many women who were prescribed valproate were practicing contraception or had had a tubectomy performed and, of those at risk of pregnancy, how many had been counseled regarding risks related to valproate exposure during pregnancy and hence the need to avoid conception. This information, however, is also unavailable in other prescription audit and pharmacoepidemiologic studies. As a side note, because about 90% of the patients we sampled belonged to low income categories, their health literacy may have been low; so, even had women been counseled about risks, the implications may not have been fully understood.

CONCLUSIONS

The use of valproate is strongly discouraged in women of childbearing age; there is formal regulatory guidance on the subject, with strict prescribing restrictions specified, in Europe and in the UK.[1] Nevertheless, we found that a high proportion of women outpatients of childbearing age, consulting in the Departments of Neurology, Neurosurgery, and Psychiatry at the National Institute of Mental Health and Neurosciences, Bangalore, India, received a prescription that included valproate. We hope that the publication of these findings will stimulate audits at other centers in third world countries and elsewhere in the world; our findings could serve as a yardstick for measuring, guiding, and evaluating improvement.

We also hope that our findings will stimulate a regulatory response from statutory bodies, such as the Central Drugs Standard Control Organization, Government of India; there is no regulation, currently, that applies to the prescription of valproate to women in India. We note that the regulatory response may need to consider locally relevant pharmacoeconomics as well as sociocultural practices related to temporary and permanent contraception. Given the importance of the subject to the mental health of women and children, regulatory responses are necessary in other developing countries, as well; the subject, in fact, is of global importance. Finally, the effectiveness of risk minimization strategies needs to be studied, as has been done, for example, in Europe.[22,23]

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REFERENCES

1. Andrade C. Valproate in pregnancy: recent research and regulatory responses. *J Clin Psychiatry*. 2018;79(3):18f12351.
2. Weston J, Bromley R, Jackson CF, et al. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. *Cochrane Database Syst Rev*. 2016;11(11):CD010224.
3. Veroniki AA, Cogo E, Rios P, et al. Comparative safety of anti-epileptic drugs during pregnancy: a systematic review and network meta-analysis of congenital malformations and prenatal outcomes. *BMC Med*. 2017;15(1):95.
4. Andrade C. Major congenital malformations associated with exposure to antiepileptic drugs during pregnancy. *J Clin Psychiatry*. 2018;79(4):18f12449.
5. Andrade C. Adverse pregnancy outcomes associated with gestational exposure to antiepileptic drugs. *J Clin Psychiatry*. 2018;79(4):18f12467.
6. Gentile S. Risks of neurobehavioral teratogenicity associated with prenatal exposure to valproate monotherapy: a systematic review with regulatory repercussions. *CNS Spectr*. 2014;19(4):305–315.
7. Veroniki AA, Rios P, Cogo E, et al. Comparative safety of antiepileptic drugs for neurological development in children exposed during pregnancy and breast feeding: a systematic review and network meta-analysis. *BMJ Open*. 2017;7(7):e017248.
8. Wisner KL, Leckman-Westin E, Finnerty M, et al. Valproate prescription prevalence among women of childbearing age. *Psychiatr Serv*. 2011;62(2):218–220.
9. US FDA. FDA Drug Safety Communication: valproate anti-seizure products contraindicated for migraine prevention in pregnant women due to decreased IQ scores in exposed children. US Food and Drug Administration website. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-valproate-anti-seizure-products-contraindicated-migraine-prevention. Accessed on April 2, 2021.
10. Virta LJ, Kälviäinen R, Villikka K, et al. Declining trend in valproate use in Finland among females of childbearing age in 2012-2016: a nationwide registry-based outpatient study. *Eur J Neurol*. 2018;25(6):869–874.
11. Paton C, Cookson J, Ferrier IN, et al. A UK clinical audit addressing the quality of prescribing of sodium valproate for bipolar disorder in women of childbearing age. *BMJ Open*. 2018;8(4):e020450.
12. Tachibana M, Hashimoto T, Tanaka M, et al. Patterns in psychiatrists' prescription of valproate for female patients of childbearing age with bipolar disorder in Japan: a questionnaire survey. *Front Psychiatry*. 2020;11:250.
13. Spoendlin J, Blozik E, Graber S, et al. Use of valproate in pregnancy and in women of childbearing age between 2014 and 2018 in Switzerland: a retrospective analysis of Swiss healthcare claims data. *Swiss Med Wkly*. 2021;151:w20386.
14. Hogan CS, Freeman MP. Adverse effects in the pharmacologic management of bipolar disorder during pregnancy. *Psychiatr Clin North Am*. 2016;39(3):465–475.
15. Balon R, Riba M. Should women of childbearing potential be prescribed valproate? a call to action. *J Clin Psychiatry*. 2016;77(4):525–526.
16. Casassus B. France bans sodium valproate use in case of pregnancy. *Lancet*. 2017;390(10091):217.
17. Iacobucci G. MHRA bans valproate prescribing for women not in pregnancy prevention programme. *BMJ*. 2018;361:k1823.
18. European Medicines Agency. Valproate and related substances. European Medicines Agency website. https://www.ema.europa.eu/en/medicines/human/referrals/valproate-related-substances. Accessed on April 1, 2021.
19. Malhi GS, Bell E, Bassett D, et al. The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. *Aust N Z J Psychiatry*. 2021;55(1):7–117.
20. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord*. 2018;20(2):97–170.
21. Angus-Leppan H, Liu RSN. Weighing the risks of valproate in women who could become pregnant. *BMJ*. 2018;361:k1596.
22. Toussi M, Isabelle B, Tcherny-Lessenot S, et al. Effectiveness of risk minimisation measures for valproate: a cross-sectional survey among physicians in Europe. *Pharmacoepidemiol Drug Saf*. 2021;30(3):283–291.
23. Toussi M, Shlaen M, Coste F, et al. Effectiveness of risk minimisation measures for valproate: a drug utilisation study in Europe. *Pharmacoepidemiol Drug Saf*. 2021;30(3):292–303.

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