INTRODUCTION

Socioeconomic disparities in epilepsy care have been reported across countries and healthcare systems. Persons with epilepsy and low socioeconomic status (SES) seem to have more severe epilepsy, higher rates of emergency visits, hospitalizations, and breakthrough seizures\(^1,2\) compared to persons with high SES. Regarding access to care, low SES has been associated with longer time to

1

Received: 12 November 2020 | Revised: 19 December 2020 | Accepted: 15 January 2021

DOI: 10.1111/ane.13397

ORIGINAL ARTICLE

Valproic acid and socioeconomic associations in Swedish women with epilepsy 2010–2015

Klara Andersson\(^1,2,3\) | Anneli Ozanne\(^2,3\) | Kristian Bolin\(^4\) | Torbjörn Tomson\(^5\)

Johan Zelano\(^1,3,6\)

Abstract

Objective: We investigated the correlation between socioeconomic status and the prescription of Valproic acid (VPA) in women of fertile age in Sweden.

Methods: This is a registered-based cohort study including all women living in Sweden aged 18-45 years in the years 2010–2015, with a diagnosis of epilepsy and no intellectual disability (n = 9143). Data were collected from the National Patient Register, the Drug Prescription Register, and the Longitudinal integration database for health insurance and labor market studies (LISA).

Results: Women with only 9 years of school were more often prescribed VPA than women with a University degree (12.9% compared to 10.7% in 2015 [\(p = 0.015\)]). Similar differences were seen between the lowest and highest income group (16.6% compared to 12.7% in 2015 [\(p < 0.001\)]). The odds of having a VPA prescription in 2015 was 1.59 (\(p < 0.001\)) in women with 9 years of school compared to women with a University degree, and 1.60 (\(p < 0.001\)) in the lowest income group relative to the highest income group after adjusting for age. From 2010 to 2015, the proportion with VPA prescription in the whole cohort diminished with an absolute reduction of −2.2% (\(p < 0.001\)). The decrease was similar among the different education and income groups (\(p = 0.919\) and \(p = 0.280\)).

Significance: The results indicate that the increased knowledge on VPA teratogenicity was implemented across socioeconomic strata in the Swedish healthcare system. Women with lower income or education level remained more frequent VPA users. Whether this difference reflects epilepsy type or severity, or socioeconomic disparities, merit further study.

KEYWORDS

epilepsy, public health, socioeconomic status, valproic acid
epilepsy surgery\textsuperscript{3} and lower access to a neurologist\textsuperscript{1,4,5} which may influence the prescription of anti-seizure medication (ASM). In Sweden, it was found that neurologists more commonly prescribed lamotrigine and levetiracetam compared to non-neurologists and persons with epilepsy and high SES were more commonly prescribed lamotrigine and less commonly prescribed valproate (VPA, valproic acid) than persons with lower SES.\textsuperscript{5} A study in Scotland found that women with epilepsy and low SES were more likely to be prescribed VPA, less likely to be on ASM monotherapy, and more likely to be on higher doses of VPA than women with higher SES.\textsuperscript{6} A major concern with VPA use in women is its teratogenic potential. In a systematic review of 31 studies of pregnancy outcomes, children prenatally exposed to VPA had 5.69 times increased risk for major congenital malformations (MCM) compared to children to mothers without epilepsy, 3.13 times higher risk than children to mothers with untreated epilepsy and significantly higher risk than children exposed to other antiepileptic drugs (AEDs).\textsuperscript{7} Pre-natal VPA exposure also has negative long-term effects with a higher risk of attention-deficit hyperactivity disorder\textsuperscript{8} and poorer school performance compared to children exposed to other or no ASM.\textsuperscript{9}

In 2014, the risks of MCM and cognitive delay associated with intrauterine VPA exposure caused regulatory agencies, the US. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), to restrict usage and VPA is now contraindicated for women of fertile age in the European Union unless all conditions of a certain pregnancy prevention program are met.\textsuperscript{10} Previous studies have evaluated the effects of the restricted recommendations on the prescription of VPA among fertile women in different European countries\textsuperscript{11,13,14} and reported coherent findings of decreased use\textsuperscript{11,13,14} or ceased increase\textsuperscript{12} in VPA prescriptions after 2014. However, previous studies lack analysis of whether the observed decrease in VPA prescription is general or differs among socioeconomic groups. The aim of this study was to investigate if socioeconomic position is associated with use of VPA in Sweden, and whether the regulatory changes of recent years have been equally implemented across different socioeconomic groups.

\section{MATERIALS AND METHODS}

\subsection{Registers}

This is a national cohort study based on the Swedish National patient register (NPR). The NPR has information on diagnoses from all admissions to inpatient care and all hospital-based outpatient care registered individually on a 12-digit personal number unique for all Swedish citizens. To assess SES, data on income and education were collected from the Longitudinal integration database for health insurance and labor market studies (Statistics Sweden, LISA). The Swedish prescribed drug register provided information of prescribed ASM. Information of deaths was collected from the Swedish cause of death register. The National Board of Health and Welfare Data cross-referenced and anonymized all data prior to analysis.

\subsection{Definitions}

Epilepsy was defined as occurrence of ICD-10-code G.40 in the NPR.\textsuperscript{15} A single prescription of the code N03AG01 in each year was used to define VPA prescription in the Swedish prescribed drug register for that specific year. To assess SES, variables were created for the highest attained levels of income and education with data from LISA. Information of education level was grouped into a variable with three categories. The first category includes all persons with 9 years of school or less. The second category includes persons with 2 or 3 years of high school. The third category includes all persons with some registered university degree. Income levels 1–4 were created from quartiles of yearly income for healthy age and gender matched controls to the whole population of adults with epilepsy in Sweden.

\subsection{Study population}

All adult women were included who had an epilepsy diagnosis registered in the NPR in 2000–2015, no diagnosis of intellectual disability (ICD-9 317-319 or ICD-10 F70-F79), and who were alive and 18–45 years old in 2010–2015.

\subsection{Statistical analyses}

No imputations were made for missing data. The statistical tests applied were Mantel–Haenszel chi-squared test, sign test and logistic regression. For different analyses, we used different selection criteria considering age. For the analyses of VPA prescription and age, women aged 18–45 years were selected for each specific year. In the sign test, only women with age >17 years in 2010 and <46 years in 2015 were included for a consistent sample. Multiple comparison correction was performed according to Benjamini–Hochberg correction with a false discovery rate of 5%. In the regression analysis, the cohort consisted of women with the age 18–45 years in 2015. All analyses were computed in the 23rd version of SPSS. The data that support the findings of this study are not publicly available due to privacy or ethical restrictions but available on request from the corresponding author.

\subsection{Ethical approval}

This study was approved by the regional ethics committee in Gothenburg, approval number 839-16 and conforms to the recognized standards of the journal.
3 | RESULTS

3.1 | Socioeconomic characteristics

The cohort consisted of 9143 women with epilepsy and no intellectual disability. The sociodemographic characteristics are presented in Table 1. As expected, it was more common to have lower income and education in the lower age groups (Mantel–Haenszel chi-squared test, \( p < 0.001 \)).

3.2 | VPA prescription and age

For every year in 2010–2015, there was a significant trend of VPA prescriptions being more common in the higher age groups (Figure 1). In 2010, 13.6% of 18–24 year olds had VPA compared to 18.5% of 40–45 year olds (Mantel–Haenszel chi-squared test, \( p < 0.001 \)). Except for in the youngest age group (18–24 years old), the proportion of VPA prescription diminished in all age groups from 2010 to 2015.

3.3 | VPA prescription and SES

We next assessed the association between VPA prescription, education level, and income level (Table 2). For each year in 2010–2015, VPA prescriptions were numerically more common among women with only 9 years of school compared to women with university education. In 2014, 15.0% of women with 9 years of school had VPA prescriptions compared with 11.8% of women with university education (Mantel–Haenszel chi-squared test, \( p = 0.001 \)). After correcting for multiple comparisons, all differences were significant except those in 2010. Similarly, VPA prescriptions were most common in the lowest income level. These differences were significant for all years, also with multiple comparison correction.

3.4 | Regression models

The odds of being prescribed VPA in 2015 was assessed with logistic regression (Table 3). Income and education were associated with VPA use in a univariable model and then adjusted for age. The odds of having a VPA prescription increased with lower education and income level. For women with only 9 years of school, the odds ratio of VPA prescription was 1.59 (95% CI 1.32–1.92 \( p < 0.001 \)) compared to women with university education. For women in income level 4, the odds ratio of VPA prescription was 1.60 (95% CI 1.25–2.04 \( p < 0.001 \)) compared to women in income level 1.

3.5 | Time trends in VPA prescriptions

To assess temporal trends, a sign test was conducted to investigate whether there was a significant difference in VPA prescription from 2010 to 2015 (Table 4). In a dependent sample of all women aged >17 years in 2010 and <46 years in 2015 \( n = 7873 \), each case was either prescribed VPA (=1) or not (=0) in 2010 and 2015. In the sign test, the difference in VPA prescription (2015–2010) was analyzed and each case resulted either in +1 (=VPA prescriptions started during the study period), 0 (=no difference in VPA prescriptions during the study period) or −1 (=VPA prescriptions stopped during the study period). In this dependent sample there was a significant absolute decrease (sign test, \( p < 0.001 \)) in the proportion of women with VPA prescriptions from 2010 to 2015 of −2.2%. No significant difference was found between income or education groups (Mantel–Haenszel chi-squared test, \( p = 0.919 \) and \( p = 0.280 \)).

| TABLE 1 | Cohort: Women aged 18–45 years old in 2015, with epilepsy and no intellectual disability |
|----------|---------------------------------------------------------------------------------|
| N = 9143 | Mean: 31.98 ± 7.755, median 32.0 |
| Age (y) | 18–24 years, \( n \) (%) | 25–29 years, \( n \) (%) | 30–34 years, \( n \) (%) | 35–39 years, \( n \) (%) | 40–45 years, \( n \) (%) | \( p \)-value (Mantel–Haenszel chi-squared test) |
| Education (missing = 798) | | | | | | |
| School (9 years) | 1486 (86.5) | 313 (19.6) | 252 (16.5) | 267 (17.9) | 342 (17.0) | <0.001 |
| High school (9+3 years) | 225 (13.1) | 920 (57.8) | 666 (43.6) | 578 (38.7) | 942 (46.8) | |
| University (9+3+?) | 7 (0.4) | 360 (22.6) | 611 (40.0) | 649 (43.4) | 727 (36.2) | |
| Total | 1718 (100) | 1593 (100) | 1529 (100) | 1494 (100) | 2047 (100) | |
| Income (missing = 110) | | | | | | |
| Level 1 | 1434 (72.0) | 857 (48.9) | 639 (38.9) | 601 (37.5) | 653 (31.9) | <0.001 |
| Level 2 | 447 (22.5) | 521 (29.8) | 478 (29.1) | 370 (23.1) | 511 (25.0) | |
| Level 3 | 104 (5.2) | 319 (18.2) | 394 (24.0) | 432 (27.0) | 573 (28.0) | |
| Level 4 | 6 (0.3) | 54 (3.1) | 131 (8.0) | 199 (12.4) | 310 (15.1) | |
| Total | 1991 (100) | 1751 (100) | 1642 (100) | 1602 (100) | 2047 (100) | |
In the present study, VPA use was found to be more common in women of childbearing age with low education and low income throughout all studied years. There was a significant decrease in VPA prescriptions over the study period, but no differences in the magnitude of this decrease across different education or income groups. This is an important observation, indicating that the restriction on VPA in the studied patient group has been equally well disseminated in Sweden and also reached persons of relatively low socioeconomic standing.
The overall aim of our project is to investigate how different socioeconomic standing influences access to epilepsy care in Sweden. With universal access to health care and relatively high degrees of economic equality, Scandinavian countries offer interesting settings for studies of socioeconomic disparities in access to care. If health care is free, remaining disparities indicate that universal access is not sufficient to close the socioeconomic treatment gap.

One cannot draw conclusions about access to care based simply on proportion of VPA users among women with different education or income; such an analysis is potentially confounded by both epilepsy type and epilepsy severity. For instance, generalized epilepsies for which VPA is used have an earlier age of onset than focal epilepsies and may interfere with education as well as earning capacity. Similarly, a high seizure frequency necessitating VPA use may affect education or income. The relatively small but significant differences in VPA proportions observed in this large cohort may well reflect differences in epilepsy severity between socioeconomic groups. The most interesting analysis with regard to unequal access to care is instead whether changes in VPA is detectable in all or only some socioeconomic groups during the time of increased knowledge on VPA teratogenicity.

We therefore focused on changes in VPA treatment. The proportion of women using VPA decreased in all education and income levels during the studied time period. When 2015 was compared to 2010, sign test analysis showed that VPA use decreased with −2.2% between these 2 years in the total cohort and there was no significant difference between education or income groups.

Our results are in line with previous reports that VPA use is decreasing in women with epilepsy of childbearing age. A large cohort study of VPA prescription in the UK, France, and in Italy used interrupted time series logistic regression found that the odds of being prescribed VPA compared to another AED decreased from 0.94 to 0.72 in France, from 0.87 to 0.80 in the UK, and from 1.05 to 0.85 in Tuscany Italy. A Swedish study used segmented logistic regression analysis and found a negative trend change $N = -8.57$, $p = 0.01$ among women with epilepsy aged 0–45 years from 2014 to 2016. A Finnish study of women with epilepsy aged 15–44 years found a decrease from 50 to 40 VPA users per 10,000 inhabitants from 2012 to 2016.

Importantly, our findings do not mean that socioeconomic disparity in the use of VPA does not exist. VPA use is more common in persons of lower socioeconomic standing. However, while 91% of those with an epilepsy diagnosis in the NPR fulfill epilepsy criteria on validation, epilepsy type, and severity are difficult to derive from register data, which must be considered before drawing any firm conclusions. Also, our data do not hold information about SES of the partners living in the same households, which is important to consider since it is likely to reflect upon the SES of the cases studied. Since socioeconomic disparities in VPA prescription among women risk to propagate socioeconomic disadvantages to the next generation, it is of great importance to further investigate why VPA is more commonly used in lower education and income groups.

**Acknowledgements**

The authors would like to thank Per Ekman for valuable discussions and statistic consultation.

**Conflict of Interest**

Dr. Tomson has received support from Eisai, GSK, UCB, Bial, Sanofi, Sun Pharma, Sandoz, EU, Stockholm County Council and CURE, outside the submitted work. Dr. Zelano has received support from the Swedish society of medicine during the conduct of the study and from UCB, Eisai, Bial, SK life science, GW pharma and UCB outside the submitted work. The remaining authors have no conflicts of interest.

**ORCID**

Klara Andersson: https://orcid.org/0000-0001-5907-8636
Anneli Ozanne: https://orcid.org/0000-0003-1737-3359
Kristian Bolin: https://orcid.org/0000-0003-1682-295X
Johan Zelano: https://orcid.org/0000-0001-9445-4545
REFERENCES

1. Begley CE, Basu R, Reynolds T, Lairson DR, Dubinsky S, Newmark M, et al. Sociodemographic disparities in epilepsy care: results from the Houston/New York City health care use and outcomes study. Epilepsia. 2009;50(5):1040–1050.

2. US Centers for Disease C, Prevention Epilepsy P. About one-half of adults with active epilepsy and seizures have annual family incomes under $25,000. Epilep Behav. 2016;58:33–34.

3. Rubinger L, Chan C, Andrade D, Go C, Smith ML, Snead OC, et al. Socioeconomic status influences time to surgery and surgical outcome in pediatric epilepsy surgery. Epilep Behav. 2016;55:133–138.

4. Andersson K, Ozanne A, Edelvik Tranberg A, Chaplin EJ, BolinK, MalmgrenK, et al. Socioeconomic outcome and access to care in adults with epilepsy in Sweden: a nationwide cohort study. Seizure. 2020;74:71–76.

5. Mattsson P, Tomson T, Eriksson O, Brannstrom L, Weitoft GR. Sociodemographic differences in antiepileptic drug prescriptions to adult epilepsy patients. Neurology. 2010;74(4):295–301.

6. Campbell E, Hunt S, Kinney MQ, Guthrie E, Smithson WH, Parsons L, et al. The effect of socioeconomic status on treatment and pregnancy outcomes in women with epilepsy in Scotland. Epilep Behav. 2013;28(3):354–357.

7. Weston J, Bromley R, Jackson CF, Adab N, Clayton-Smith J, Greenhalgh J, et al. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Cochrane Database Syst Rev 2016:11(1):CD010224.

8. Christensen J, Pedersen L, Sun Y, Dreier JW, Brikell I, Dalsgaard S. Association of prenatal exposure to valproate and other antiepileptic drugs with risk for attention-deficit/hyperactivity disorder in offspring. JAMA Netw Open. 2019;2(1):e186606.

9. Elkjaer LS, Bech BH, Sun Y, Laursen TM, Christensen J. Association between prenatal valproate exposure and performance on standardized language and mathematics tests in school-aged children. JAMA Neurol. 2018;75(6):663–671.

10. Agency SMP. Läkemedelsbehandling av epilepsi- behandlingsrekommendation. Swedish Medical Products Agency. 2019. [updated 3 October 2019; cited 2020 22 February 2020]. https://lakemedelsverket.se/upload/halso-och-sjukvard/behandlingsrekommendationer/191003-Behandlingsrekommendation-Epilepsi.pdf

11. Charlton R, Damase-Michel C, Hurault-Delarue C, Gini R, Loane M, Pierini A, et al. Did advice on the prescription of sodium valproate reduce prescriptions to women? An observational study in three European countries between 2007 and 2016. Pharmacoepidemiol Drug Saf. 2019;28(11):1519–1528.

12. Kurvits K, Laius O, Uusküla M, Haldre S, Rakitin A. Valproic acid prescription trends among females of childbearing age in Estonia: a 14-year nationwide prescription database study. Seizure. 2020;76:28–31.

13. Virta LJ, Kälviäinen R, Villikka K, Keränen T. 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.

14. Karlsson Lind L, Komen J, Wettermark B, von Euler M, Tomson T. Valproic acid utilization among girls and women in Stockholm: impact of regulatory restrictions. Epilepsia Open. 2018;3(3):357–363.

15. Sveinsson O, Andersson T, Mattsson P, Carlsson S, Tomson T. Clinical risk factors in SUDEP: a nationwide population-based case-control study. Neurology. 2020;94(4):419–429.

How to cite this article: Andersson K, Ozanne A, Bolin K, Tomson T, Zelano J. Valproic acid and socioeconomic associations in Swedish women with epilepsy 2010–2015. Acta Neurol Scand. 2021;143:383–388. https://doi.org/10.1111/ane.13397