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FULL-LENGTH ORIGINAL RESEARCH

Valproic acid utilization among girls and women in Stockholm: Impact of regulatory restrictions

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Summary

Objective: **In November 2014, the European Medicines Agency (EMA) strengthened restrictions on the use of valproic acid in girls and women of childbearing potential. The objective of this study was to determine whether there has been a change in initiations of valproic acid treatment to females after the regulatory restrictions and to assess if such changes differed between indications (epilepsy and psychiatric disorder).**

Methods: **An interrupted time-series analysis was conducted using all initiations of valproic acid in Stockholm, Sweden. from January 2011 to June 2017. Female and male patients aged 0–45 years with a recorded diagnosis of epilepsy and/or a psychiatric disorder were compared.**

Results: **Before the EMA warning, a decline in trend of valproic acid initiations was seen in patients with epilepsy. After the warning, a significant decrease of valproic acid initiations was seen in women with a psychiatric disorder, but not in women with epilepsy.**

Significance: **The regulatory warning appeared to have significantly influenced valproic acid initiations in women of childbearing age with a psychiatric disorder. No effect was seen in women with epilepsy, probably because the decline had started long before.**

KEY WORDS: **Regulatory warnings, Interrupted time series, Epilepsy, Psychiatric disorder, Sex differences.**

Valproic acid has been a widely used antiepileptic drug (AED), in particular in the treatment of generalized epilepsies,[1] and is also used for treatment of bipolar disorder, particularly with mania.[2] Valproic acid use in pregnancy has been associated with a higher risk of malformations than most other AEDs[3] and more recently evidence has emerged concerning an association with impaired cognitive development of children exposed in fetal life.[4,5] Based on these data, the European Medicines Agency (EMA) in November 2014 strengthened its restrictions for use of valproic acid in girls and women,[6,7] stating that valproic acid should not be prescribed in girls or in women of childbearing potential "unless alternative treatments are ineffective or not tolerated." The new recommendations were sent as a 'Dear healthcare professional letter' to healthcare professionals in the EU.[7] As in many other countries, the EMA warning was highlighted in academic press and reported in the national media in Sweden.[8,9] The restrictions have raised some concerns, since valproic acid is the most effective treatment for some epilepsies, for some women the only effective drug,

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Key Points

- During the years before EMA restrictions, initiation of valproic acid had increased in women with psychiatric diseases
- A steady decline in initiation of valproic acid was seen years before the EMA restrictions in women with epilepsy
- The EMA restrictions were followed by reduced initiations of valproic acid in girls and women with a psychiatric disorder but not epilepsy

and because uncontrolled seizures can have serious, sometimes fatal, consequences.[1]

The objectives of this study were to determine whether there has been a change in initiations of valproic acid treatment to women over time, particularly after the regulatory restrictions were published, and to assess if such changes differed between indications, that is, epilepsy and bipolar disorder.

Methods

Study design

An interrupted time-series (ITS) design of valproic acid prescription claims was used to evaluate the change in AED prescription before and after the EMA warning. The ITS analysis design is suitable for evaluating the impact of a population-level health intervention that occurs in a well-defined point in time. Population-level data were collected over time at equal intervals, and regression techniques were used to establish an underlying trend, which is 'interrupted' by an intervention at a known point in time.[10]

Data source

This study used data from the Stockholm regional healthcare data warehouse VAL (Vårdanalysdatabasen), an administrative health data register containing anonymized data for all 2.2 million inhabitants of Stockholm County, Sweden.[11] Vårdanalysdatabasen includes dispensed prescriptions, diagnoses from primary and secondary care, hospitalizations and other healthcare consultations, as well as information about the patient's sex, age, migration, and death. Diagnoses are available for secondary care since 1993 and for primary care since 2003.

The study was approved by the Regional Ethical Review Board in Stockholm (EPN 2016/517-32).

Study population

We identified all patients who claimed at least one prescription of valproic acid (ATC-code N03AG01) between January 2011 and June 2017. We hypothesized that the EMA warning would have the greatest effect on initiations of valproic acid and thus the analysis focused on new users of valproic acid. New users were defined as patients who had not been dispensed valproic acid in the past 365 days. Thus a patient could become a new user in multiple study months if he or she met the criterion of having no valproic acid use in the prior 365 days.

Patients initiated on valproic acid were stratified into diagnostic groups to determine whether the EMA warning had different effects depending on diagnosis. The diagnoses included in this study reflect the approved indications for valproic acid in Sweden: epilepsy and bipolar disorder. The specific indication for which valproic acid was prescribed is not available in the drug prescription database; therefore, we included all International Classification of Diseases, Tenth Revision (ICD-10) diagnoses that were recorded for consultations or hospitalizations for these patients during 5 years prior to the first valproic acid dispensation. Selected diagnoses were those associated with epilepsy (G40-41) or psychiatric conditions (F30-39, F40-48, F10, F55, F50, and F60). Patients with none of these diagnoses were categorized as "other." Indications were identified by analyzing history of diagnoses at different time windows of 1 year, 2 years, and 5 years prior to dispensing date. The 5-year time window reference measurement was compared to measurements at 1 year and 2 years as a sensitivity analysis.

Intervention

The intervention was the month when the EMA warning was issued (November 2014), creating three segments in a time series: (1) before the EMA warning (Jan 2011 to October 2014), (2) during the EMA warning (November 2014), and (3) after the EMA warning (December 2014 to June 2017).

Statistical analysis

For each calendar month, we defined the number of patients who were new users of valproic acid. For the analysis restricted to a certain diagnosis, we looked at the number of patients initiated each quarter instead of each month, due to insufficient number of initiations for an ITS when using a monthly interval. Segmented logistic regression analyses were used to calculate a trend (rate of change) in each segment of the time series. A step function was used to determine whether there was a change in number of new users on valproic acid directly after the intervention period compared with before (level effect), based on the assumption of an underlying linear relationship between the time and the number of initiations in each month. The segmented regression model controls for baseline levels and trends, and thereby we could estimate the numbers of users if the intervention would not have occurred.[10] We tested the residuals for first-order autocorrelation with the Durbin-Watson statistic and by graphical analyses of the autocorrelation and partial autocorrelation plots.[12]

The primary outcome was the change in the number of valproic acid initiations after the EMA warning. We conducted separate segmented regression models for men and women; for males and females 0–45 years of age; and for males and females 0–45 years of age with epilepsy or psychiatric disorder(s). Females 0–45 years with a diagnosis code for both epilepsy and a psychiatric disorder in the 5 years prior to inclusion were excluded as there were too few of them.

The statistical package IBM SPSS Statistics version 23.0 was used for all statistical analyses. Data extraction was done using SAS EG 6.1 (SAS Institute Inc., Cary, NC, U.S.A.).

Results

In total, 7402 patients were initiated on valproic acid between January 2011 and June 2017. Of these, 541 patients were initiated twice during the time period. Characteristics of the study population are presented in Table 1. The study population was mainly adults (mean age 41.3 years). The majority of patients were diagnosed with psychiatric disorder(s) (43.9%). An epilepsy diagnosis was found in 24.9% of the patients and <5% had a diagnosis of both epilepsy and a psychiatric disorder. A quarter of the patients had no registered diagnosis of either epilepsy or a psychiatric condition during the last 5 years (26.7%).

Time trends

During the study period, a decrease in total number of valproic acid initiations was observed. Figure 1 shows the pattern of valproic acid initiations in men and women throughout the study period regardless of diagnosis. Slightly more women than men (2293 vs. 2198) were initiated on valproic acid during the prewarning period (January 2011 and October 2014), while fewer women than men were initiated after the warning (1300 women vs. 1516 men, December 2014 and June 2017).

Table 1. Characteristics of the study population initiated on valproic acid between January 2011 and June 2017

Characteristic	N	%
Sex		
Men	3760	50.8
Women	3642	49.2
Age group		
0–18	856	11.6
19–45	3468	46.9
≥46	3078	41.6
Diagnostic group		
Epilepsy diagnosis only	1843	24.9
Epilepsy and psychiatric disorder	334	4.5
Psychiatric disorder only	3252	43.9
No diagnosis of epilepsy or psychiatric disorder	1973	26.7

N = 7402.

Interrupted time series analysis

No significant immediate changes in valproic acid initiations were observed in men or women at the time of the EMA warning in November 2014 (Table 2). However, after 2 years, there was a significant change in trend for females 0–45 years of age (−8.57, p = 0.01), whereas no significant change was observed for males of the same age (−1.29, p = 0.72).

In epilepsy, there were fewer initiations in women than in men (Fig. 2), while the opposite was observed in patients with psychiatric disorder (Fig. 3). Before the EMA warning, a decline in trend was observed in epilepsy patients, while an increase was seen in patients with a psychiatric disorder (Fig. 2). After the warning, no significant changes in valproic acid initiations were seen in men or women with epilepsy (Table 2). In psychiatric disorders, the trend increased before the warning (Fig. 3). After the warning, a significant decrease in trend was observed in females 0–45 years of age (−1.85, p = 0.05) (Table 2). The effect was even more pronounced after 2 years (−21.96, p = 0.01).

Sensitivity analysis

A sensitivity analysis was conducted using different time windows for a recorded diagnosis of epilepsy or a psychiatric disorder prior to inclusion in females 0–45 years. Changing the time window to 2 years or 1 year did not result in any changes on the trend (data not shown).

Discussion

In the present population-based ITS analysis, we found that the EMA warning was associated with a change in initiations of valproic acid in women with a psychiatric disorder but not in epilepsy. This difference between the indications can have several explanations. Our data (Figs. 2 and 3) suggest that the initiations of valproic acid to women with epilepsy have declined steadily long before the EMA warning. This is in contrast to utilization for psychiatric disorders where a gradual increase was seen up to 2014 (Fig. 3). A recent publication based on Finnish registry data found prevalent use in women of childbearing age to diminish similarly regardless of indication between 2012 and 2016.[13] However, data from other countries show findings similar to ours, before the EMA alert, a reduced use of valproic acid for epilepsy in pregnancy[13] and in women of childbearing age,[14] but a rise in its use for psychiatric conditions.[13] There are 2 main differences between the present study and the Finnish study. First, we studied initiations of valproic acid, whereas the Finnish study analyzed prevalent use. Second, we used an ITS design while they studied temporal trends.

It is likely that neurologists managing women with epilepsy have gradually adjusted their prescribing of valproic acid to the emerging evidence of the teratogenic effects long before the EMA warnings in 2014.[4,5] In Stockholm, the Drug and Therapeutic Committee recommended other

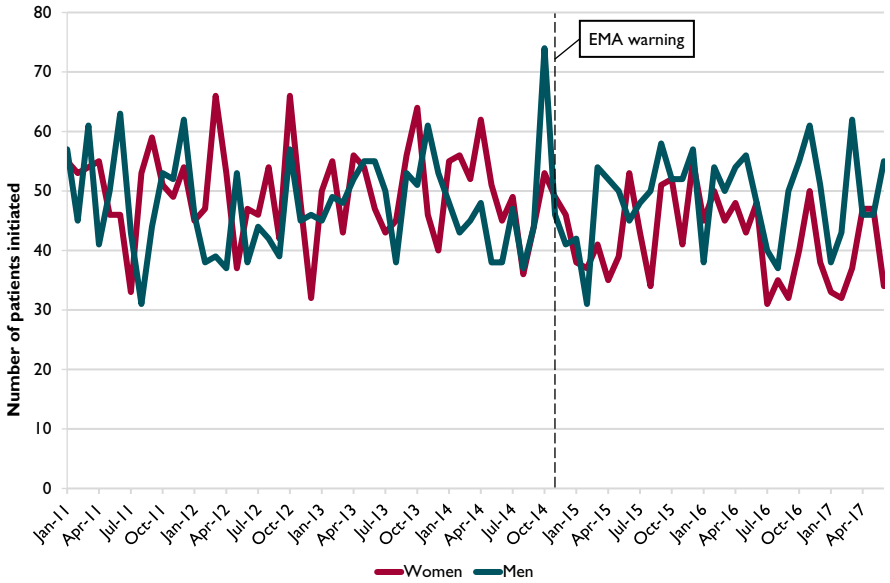

Figure 1.
Initiations of valproic acid in men and women regardless of diagnosis
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Table 2. Associations between the EMA warning and change in total number of valproic acid initiations

	Trend change (n)	Level effect (n)	Effect after 2 years (n)
All	0.03 (p = 0.91)	−6.06 (p = 0.29)	−5.39 (p = 0.45)
Women	−0.12 (p = 0.50)	−4.95 (p = 0.16)	−7.55 (p = 0.09)
Men	0.15 (p = 0.43)	−1.11 (p = 0.77)	2.16 (p = 0.65)
Females 0–45 years	−0.22 (p = 0.09)	−3.78 (p = 0.15)	−8.57 (p = 0.01)**
Males 0–45 years	0.00 (p = 1.00)	−1.29 (p = 0.66)	−1.29 (p = 0.72)
Females 0–45 years of age with epilepsy only	0.54 (p = 0.42)	−1.45 (p = 0.75)	2.35 (p = 0.69)
Females 0–45 years of age with psychiatric disorder only	−1.85 (p = 0.05)*	−9.01 (p = 0.15)	−21.96 (p = 0.01)**
Males 0–45 years of age with epilepsy only	0.90 (p = 0.27)	4.71 (p = 0.39)	11.00 (p = 0.12)
Males 0–45 years of age with psychiatric disorder only	0.60 (p = 0.49)	−10.17 (p = 0.09)	−6.00 (p = 0.42)

*p < 0.05. **p < 0.01.

drugs than valproic acid for girls and women of fertile age in the "Wise List" in 2005, for patients with epilepsy. For patients with bipolar disorder, a similar recommendation was first introduced in 2012.[15] The Wise List contains evidence-based recommendations for prescribers and have high adherence and impact on drug prescribing.[16,17] A potential additional explanation to drug increased valproic acid initiations may be an increased incidence of bipolar disorder. The incidence of diagnosed bipolar disorder in Sweden has increased over the last 20 years and was around 4–6/10,000 individuals per year in 2010, with higher numbers in women.[18] The incidence of epilepsy is 3–5/10,000 individuals per year in Sweden.[19,20] The incidence of epilepsy in the Northern countries has remained constant[21] or declined[22,23] in most age groups. Differences in changes in prescription patterns could also reflect availability of treatment alternatives for epilepsy and bipolar disorders. For some epilepsy types, valproic acid may be the most effective treatment and treatment alternatives are few.[1] Thus, it is possible that the women with epilepsy who are receiving valproic acid could not switch to alternative treatments. However, treatment alternatives for bipolar disorder include several different pharmacological and nonpharmacological treatment options.[24] Valproic acid has been shown to be effective in prevention of acute mania, but lithium remains the gold standard for long-term treatment.[25] Also olanzapine[26] and aripiprazole[27] have been shown to be efficacious for treating acute mania. Therefore, the women with psychiatric disorders in our study may have switched to alternative treatments more easily and rapidly than the women with epilepsy.

Regulatory safety warnings could have an impact on clinical practice but are difficult to measure. A survey among U.S. neurologists showed that 20% were not aware of U.S. Food and Drug Administration (FDA) warnings about general safety risks for AEDs.[28] Only notifications from

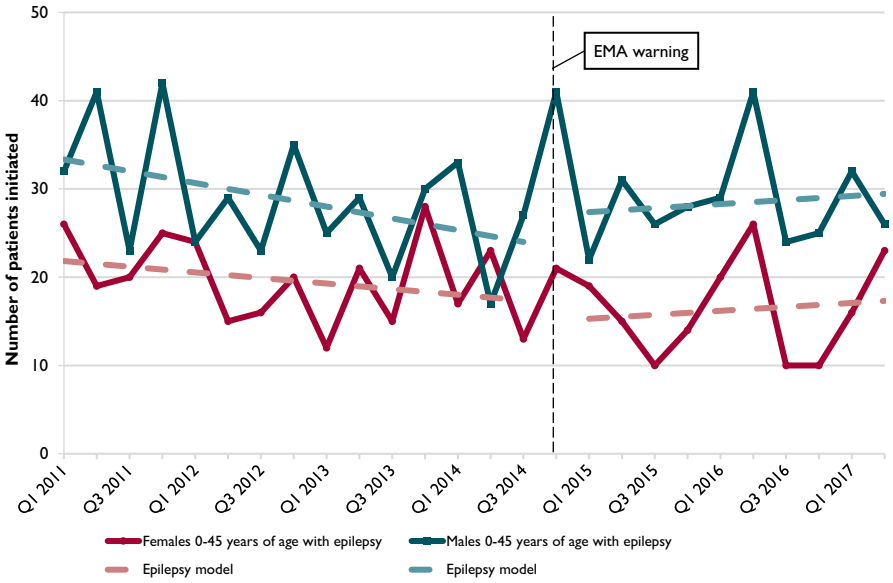

Figure 2.
Patterns of valproic acid initiations in males and females 0–45 years of age diagnosed with epilepsy from January 2011 through June 2017
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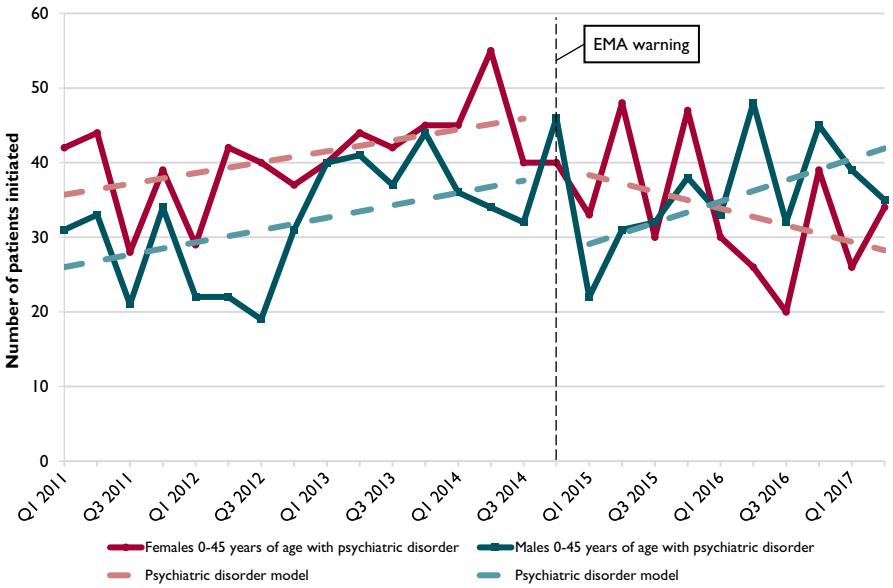

Figure 3.
Patterns of valproic acid initiations in males and females 0–45 years of age diagnosed with psychiatric disorder from January 2011 through June 2017
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specialty organizations were associated with accurate knowledge of AED safety warnings. Social and psychological factors among physicians are also necessary to consider when communicating risks of medical products.[29]

Strengths and limitations

This is the first study to examine the association between the EMA warning on valproic acid and the initiations of valproic acid using an ITS design. The ITS design is the best available method to evaluate the impact of policy changes where a control groups is not possible.[30] The ITS design cannot assume causality, and it is possible that other external factors unrelated to the EMA warning and media coverage may have affected the utilization pattern of valproic acid during the study period, such as advertising from pharmaceutical companies and competing communications by

professional organizations. These factors could not be accounted for in this study.

This study has some important limitations. Vårdanalysdatabasen database is a large regional dataset of healthcare records and represents the Stockholm population. Our findings may thus not be generalizable to the whole Swedish population or beyond. The actual indication for which valproic acid was prescribed was not known. Because VAL does not include information about the underlying clinical diagnosis for prescription of drugs, we estimated possible indications based on the approved indications of the AEDs. Therefore, it is an uncertainty in the association between diagnoses and prescriptions. In addition, we had data available for only a limited number of months after the intervention, limiting the timescale over which we could detect effects. There could be a potential lag period between the implementation of the EMA warning and the prescribing physicians' response to it.

Conclusion

In conclusion, the effect of the regulatory recommendations was notable in the prescribing of valproic acid in women of childbearing age with a psychiatric disorder. In epilepsy, the decline in use in women of childbearing age had started earlier and thus the declining use just continued. This could reflect an earlier higher level of awareness of the risk of fetal exposure in the neurology community.

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Disclosure of conflicts of interest

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