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Valproate utilisation trends among girls and women from 2013 to 2018

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ABSTRACT

Purpose: To evaluate the change in the number of female valproate users in Lithuania from 2013 to 2018 and determine the presumed impact of two distinct European Medicines Agency (EMA) regulatory interventions on the observed trend.

Method: An interrupted time series analysis was performed using reimbursement data from the National Health Register Fund to detect changes in user trends after a selected regulatory event in time.

Results: The absolute number of female patients under 50 using valproate is seen decreasing over time. After an EMA regulatory procedure in 2014, there was only a delayed decrease in female valproate users under 15 (a change in trend of -4.83, 95%CI = -9.45 to -0.22, P = 0.041, a decrease in level 15 months post-intervention of -40.06, 95%CI = -79.26 to -0.86, P = 0.046). An increase in new prescriptions for patients with epilepsy was noted post-intervention (change in trend 13.75, 95%CI = 6.03–21.48, P = 0.004). The EMA referral procedure in 2017–2018 was followed by a lasting decrease in female valproate users of reproductive age and older (level effect 3 months post-intervention: -201.28, 95%CI = -310.61 to -91.96, P = 0.001 and -170.60, 95%CI = -287.73 to -53.48, P = 0.007, respectively). However, the rate of new initiations on valproate for patients with either epilepsy or mood disorders remained constant.

Conclusions: The number of female patients under 50 using valproate is decreasing over time. The 2018 EMA referral procedure was followed by a notable reduction in female valproate users.

1. Introduction

In the occurrence of pregnancy, valproate use among girls and women has been linked to foetal risks, such as congenital malformations and neurodevelopmental problems [1–9]. The latter include an increased risk of autism and attention deficit hyperactivity disorder (ADHD) [10–12]. Existing and emerging evidence pointing to the mentioned risks provoked both discussions in the scientific community and actions undertaken by European regulatory agencies [6,8]. The European Medicines Agency (EMA) assessed the safety of valproate and related substances during the years 2013–2014 and afterwards issued recommendations to strengthen valproate-related warnings with the aim to diminish valproate initiations in girls and women of childbearing age [13]. After national data showed unsatisfactory effects of such guidelines, the French Agency for the Safety of Health Products (France ANSM) triggered a new procedure, which ended in approval of renewed restrictive measures in May 2018 [14,15]. The measures include a contraindication of valproate in most cases of pregnancy, a pregnancy prevention programme, educational material distribution and changes in the product's information. Recent studies from Europe and other continents report mostly signs of ongoing decrease in valproate use among females of reproductive age [16–25]. However, these findings often arise after prevalent use is compared at different time points, but only rarely information about the effectiveness of a specific regulatory event is collected [26]. Lithuania is a country in the European Union with a population of about 2.8 million, a prevalence of epilepsy (including status epilepticus) in women of 5.9 per 1000 inhabitants and an incidence of 1.4 women per 1000 inhabitants in 2018 [27].

Our aims were:

Abbreviations: ARIMA, autoregressive integrated moving average; CMDh, The Coordination Group for Mutual Recognition and Decentralised Procedures – Human; EC, European Commission; EMA, European Medicines Agency; France ANSM, French Agency for the Safety of Health Products; ITS, interrupted time series; MHRA, UK's Medicines and Healthcare products Regulatory Agency; PRAC, The Pharmacovigilance Risk Assessment Committee

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1 To observe the trend of valproate use among female patients in different age groups in Lithuania from 2013 to 2018.
2 To evaluate, whether there is any change in trends of valproate utilisation after two distinct EMA interventions took place.
3 To compare trends of new female patient initiations on valproate in two diagnostic groups (epilepsy and mood disorders).
4 To detect a change in the trend of new prescriptions after EMA regulatory events.

2. Methods

2.1. Study design

We sought to evaluate change over time in the number of patients using valproate, thus the analysis of an interrupted time series (ITS) model was chosen. ITS is a quasi-experiment, which enables retrospectively analysing a change in a secular trend in respect to a defined intervention at the population level [26,28]. The output of this method consists of both the change in level (the difference between regression line prognosis and observed levels at a post-intervention point) and the change in trend (the difference between the pre- and post-intervention slopes) in regard to the outcome (defined as number of patients in this study) [26].

2.2. Study data

All data studied was received from the National Health Register Fund of Lithuania and consisted of patient reimbursement information (drug quantity, value, number of patients reimbursed) for valproate (ATC code N03AG01). Lithuania employs a compulsory health insurance model, where permanent residents are covered by insurance and are eligible for reimbursement of valproate if indicated (our study did not include valproate users that buy the drug without reimbursement). The number of individual girls and women in three different age groups (0–14, 15–49 and older than 50) reimbursed each quarter from 2013 to 2018 represented the outcome in the time series. We chose to analyse quarterly data as patients using long-term drug packages (for 3 or 6 months) would more likely be included either every or every two quarters, thus creating only a first-order autocorrelation, which could be adjusted. Other reasons for quarterly data extraction included expected small sample size and a gradual change in outcome, which would not require minor intervals. In this part of the analysis, there was no differentiation among diagnoses.

Data available for newly initiated patients with diagnoses of either epilepsy (ICD-10-AM code G40) or mood disorders (codes F30-39) was used in a separate part of the analysis. Initiations of girls and women aged under 50 were collected for every half-year from 2013 to 2018. Anticipation of small sample size prompted adoption of longer time intervals. Such a specific age group was selected both because of data retrieval system constraints and a distinction in EMA recommendations, where a joint guideline target-group of both girls and women of reproductive age might be discerned [13,14,29]. New initiations are recorded when the patient has received no prescription for valproate for at least one year.

Events representing separate intervention points chosen did not affect data collection in any way. As there was no retrieval of individual patient data or records, we did not seek approval from the local bioethics committee.

2.3. Intervention points

Four different year quarters represented distinct “intervention points” for analysis of change in the absolute number of valproate users. Due to methodological constraints (three data points required around an intervention), only two half-years (one for each EMA referral procedure) corresponded intervention points for data of newly initiated patients. All outcome data points were identical when analysing separate interventional points as there is a recommendation to include a long pre-intervention period for more statistical power [26].

The first intervention point was the fourth quarter of 2013 (Q4 2013) when the UK’s Medicines and Healthcare products Regulatory Agency (MHRA) started a referral procedure to assess the benefits and risks of valproate in October 2013 [13].

The second intervention was in October/November 2014 as The Pharmacovigilance Risk Assessment Committee (PRAC) published conclusions regarding valproate risks and The Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) agreed to a strengthened warning (Q4 2014) [13,29]. The State Medicines Control Agency released a translated informational letter to doctors in Lithuania in late November of the same quarter. This intervention of 2014 (represented as the second half of 2014) was included for the analysis of new initiations.

Another intervention point represented the EMA procedure triggered by France ANSM in March 2017 (Q1 2017) [14]. The first half of 2017 was available for analysis of newly initiated patients as well.

The CMDh endorsed new measures in March 2018 (with a public letter to local doctors sent out in September 2018 in Lithuania), thus the first quarter of 2018 was chosen as the last available point of intervention (Q1 2018) [14]. The European Commission (EC) approved the measures in May 2018, but this date was excluded because of the limitations of the statistical method [15].

We chose to evaluate referral procedures’ starting points in addition to the assessments’ ending points (thus broadening the conceptual bounds of a regulatory process) because of possible gradual changes in valproate prescription patterns due to ongoing scientific discussions and media coverage [18].

2.4. Statistical analysis

A non-seasonal autoregressive integrated moving average (ARIMA) model with adjustment for first-order autocorrelation was applied. For consensus, the technical part of data evaluation was performed following recommendations presented in Cochrane Effective Practice and Organisation of Care (EPOC) resources [30].

The IBM SPSS Statistics (Version 23.0 IBM Corp., Armonk, NY, USA) statistical package and Microsoft Excel (Version 16.0, Microsoft Corp., Redmond, WA, USA) were used for all statistical analyses.

3. Results

A gradual decrease in the absolute number of patients over the years is seen in patients younger than 15 (-8.04 per quarter, 95% confidence interval, CI = -9.12 to -6.96, $P < 0.001$) and those aged 15–49 (-33.38, 95% CI = -39.82, -26.93, $P < 0.001$).

The only significant results after the assessment procedure of 2013–2014 were observed in the group of girls under the age of 15. A significant difference between slopes (-4.83, 95% CI = -9.45 to -0.22, $P = 0.041$) was found after new regulatory measures had been established in 2014. Additionally, there was a decrease in level delayed by 15 months (level effect at 15 months -40.06, 95% CI = -79.26 to -0.86, $P = 0.046$).

The impact on the number of reimbursed patients of the more recent referral procedure of 2017–2018 is presented in Fig. 1 and Appendix A-Table 1. With the start of the assessment procedure, a significant change in trend is seen both in women of reproductive age and women older than 50 (-48.28, 95% CI = -68.07 to -28.49, $P < 0.001$ and -50.61, 95% CI = -74.02 to -27.19, $P < 0.001$, respectively). Additionally, significant level effects were found 9 months (-96.12, 95% CI = -165.15 to -27.10, $P = 0.009$) and 15 months (-131.45, 95% CI = -221.19 to -41.71, $P = 0.006$) post-intervention for these two age groups, respectively. The effect lasted during subsequent months. Except for the level change at 9 months post-intervention, significant

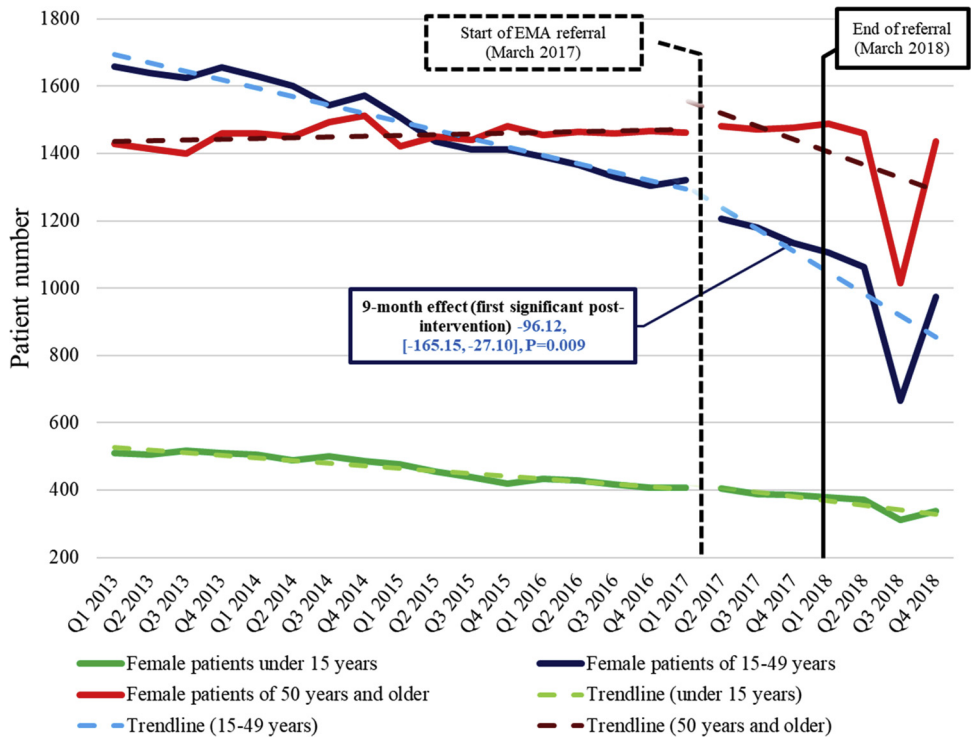

Fig. 1. Female patients using valproate from 2013 to 2018 and a time series interruption (represented by a gap) at the start of the 2017–2018 referral procedure. EMA – European Medicines Agency.

findings overlapped in time with accordant results after the final stage of the procedure in March 2018 (just before its official EC approval of May 2018) in these two groups.

Initiation data is presented in Fig. 2 and Appendix A-Table 2. There is an increase in initiations for patients diagnosed with epilepsy a year after EMA recommendations of 2014 (32.54, 95% CI = 3.39–61.69, P = 0.033) and later, combined with a positive change in trend (a trend of decrease in the absolute number of initiations in epilepsy is present, however). No significant impact is found after the start of the 2017 referral. Both selected intervention points at respective half-years had no detectable influence for the underlying trend of newly initiated patients diagnosed with mood disorders.

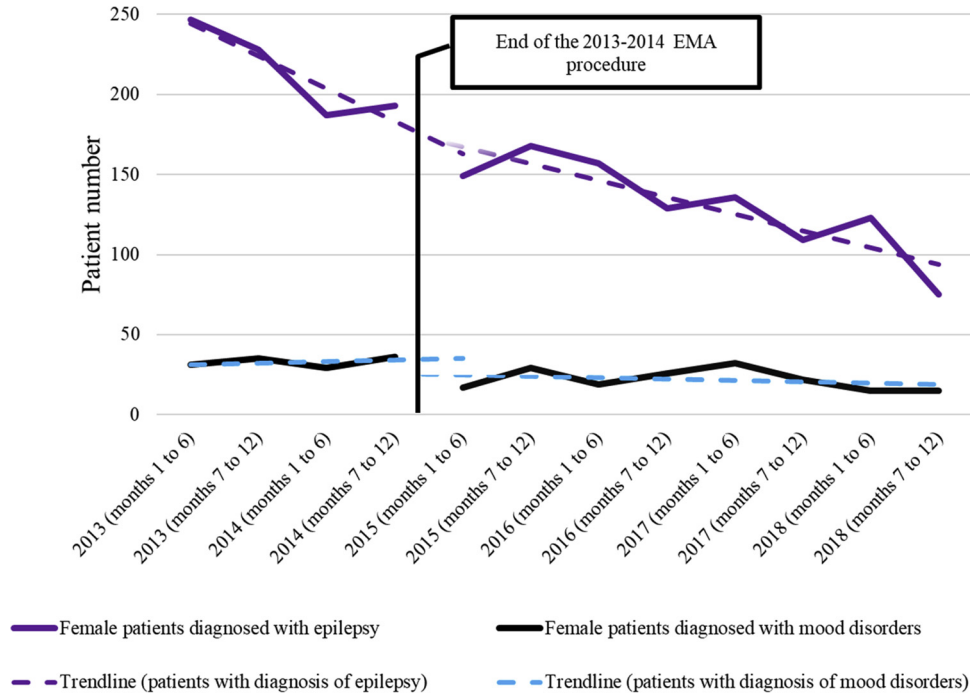

Fig. 2. Female patients younger than 50 years newly initiated on valproate from 2013 to 2018 with time series interruption (represented by a gap) at the end of the 2013–2014 referral procedure. EMA – European Medicines Agency.

4. Discussion

4.1. Basic findings

A general decrease in female patients under 50 using valproate was observed in our study. Probably due to an improving understanding of valproate risks, various other studies report a decrease in valproate users, especially those with epilepsy [17,19–25]. Our data for newly initiated patients points to a seemingly comparable decrease in prescribing for epilepsy patients, and a more stable trend for patients with mood disorders, who received fewer prescriptions. Such results differ from reports of higher valproate use for psychiatric disorders than for epilepsy and could be determined by differences in psychiatric care in distinct healthcare systems [18,31,32]. Based on national disease prevalence data we could estimate that in every age group roughly a third of women with epilepsy received valproate at the end of 2018, thus presenting a need to continue active utilisation reduction among women of reproductive age.

4.2. The effects of the 2013–2014 EMA procedure

Our study does not show any significant impact of the 2013–2014 valproate assessment procedure on the total number of patients using the drug, except for a delayed effect in girls under 15. A long period of delay post-intervention could indicate a slow change in prescription patterns or some coinciding event. However, there is a lack of significant change in the targeted group of patients of reproductive age and this could relate to a certain ineffectiveness of EMA guidelines. Additionally, ITS analysis of newly initiated patients points to an increase in prescriptions for patients with epilepsy and no effect for those diagnosed with mood disorders. A similar study on the population of Stockholm found no influence of the intervention for girls and women being initiated on valproate except the group aged under 45 and diagnosed with psychiatric disorders [18]. While sporadic study results are contrasting and often consist of prevalent use comparison, the strengthened warning by EMA in 2014 was overridden by a stricter regulation in 2018 after a new review process, thus indicating possibly insufficient prior action to reduce valproate prescriptions in European health systems [17–19,23,33].

4.3. The impact of the 2017–2018 valproate assessment and related restrictions

Findings of the ITS model for the 2017–2018 restriction indicate a possible reaction to the ongoing discussion and intermediate stages of the procedure: there is a negative change in secular trend at the beginning of the procedure and a decrease in the number of patients even before the final exertion of new regulations. It is noteworthy that the lowest value of female patients using valproate was during the third quarter of 2018. The timing of this seemingly outlying data point (which could have a significant impact on the trend) would correspond to a follow-up of the final EC approval in May 2018 with subsequent implementation of new restrictions. However, the ITS model does not provide causation for observable changes, thus the actual reasons underlying this point may only be speculated. A lack of additional reduction of new initiations could indicate that discontinuation of valproate, rather than non-initiation caused an observable decrease in the total number of patients. The surge in the number of users at the end of the time series could indicate unsuccessful valproate discontinuation cases during Q3 2018 (an increase in seizure frequency, for example) and reinitiation on the drug. For future analysis, especially when observing new prescriptions, it would be necessary to include more post-interventional data points. They could help indicate the long-term impact of the finally approved 2018 EMA restrictions and their exertion.

Ongoing discussions reflect the complexity of valproate use among female patients and the notion that valproate is an effective drug despite its risks in pregnancy [6,16]. Opinions arguing that valproate is useful in many female patients of younger age (for example, those with an intellectual disability or not wishing to conceive) reveal that a fast and total decrease in valproate prescriptions is probably not feasible or might even be unnecessary [6,16,34–36]. The pregnancy prevention programme included in EMA guidelines presents options that potentially minimise the occurrences of foetal exposure to valproate and should be implemented when valproate remains the best treatment option [14,37,38].

Our study shows that, in the case of valproate, the course of an EMA regulatory process might have implications in itself. Some decrease in valproate use is detected earlier than legally binding decisions or changes in marketing took place. This could be determined by better communication to the public (for example, several local media outlets covered issues concerning valproate teratogenicity and findings by France ANSM in 2017, but not during a similar drug review in 2013–2014), improved access of information about the ongoing referral or a strengthened tone of restrictions. In case of additional favourable data from other studies, future referral processes could rely on similar methods for external communication. To our knowledge, the local reaction to new international (EMA's, The Food and Drug Administration's) and national (the State Medicines Control Agency's) guidelines is also facilitated by an active epilepsy specialist and patient community, which operates by organising meetings and discussions.

5. Study limitations

The study is limited by being retrospective and therefore lacking causal assessment of the selected interventions. Few data points post-intervention were available, especially for more recent intervention points in the time series, as well as for data of newly initiated patients. A thorough analysis of a longer timeline of valproate use could indicate a different influence of the same regulation in the future. Another limitation is that the selected interventions did not take place at an instantaneous well-defined time point, and involved public hearings, media coverage, separate review, conclusion, endorsement and approval statements distributed over time. There is also no knowledge of how changes in demographic factors, disease incidence or prevalence influenced the observable trends.

6. Conclusions

A decrease of valproate use was found in Lithuania for female patients younger than 50. New initiations on valproate are more frequent for epilepsy than for mood disorders. In respect to findings of regulatory agencies in France, there was no local decrease in the use of valproate after EMA strengthened corresponding warnings in November 2014. The latest regulatory EMA procedure during the years 2017–2018 likely influenced a decline in the total number of female patients who use valproate, but did not significantly affect the rate of new initiations. Our results indicate a good local reaction to European restrictions concerning valproate. In order to ensure foetal risk prevention, future studies should monitor long-term changes in valproate prescription patterns and a more extensive decrease in valproate use is required.

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Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.seizure.2019.07.001.

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