CPRD STUDY MONITORING THE USE OF VALPROATE IN GIRLS AND WOMEN IN THE UK: January 2010 to December 2019

KEY MESSAGES:

MHRA has been monitoring trends in the prescribing of sodium valproate to assess the impact of evolving regulatory recommendations and introduction of the pregnancy prevention programme using primary care data from the Clinical Practice Research Datalink GOLD database for Scotland, Wales, and Northern Ireland and the AURUM database for England (CPRD; https://www.cprd.com/).

As of April 2018, valproate medicines must not be used in women and girls of childbearing potential unless the conditions of the Pregnancy Prevention Programme are met and only if other treatments are ineffective or not tolerated, as judged by an experienced specialist.

Both new and repeat prescribing of valproate in girls and women of childbearing age has declined over the period January 2010 to December 2019 across the UK. Data on valproate prescribing in pregnancy up to December 2019 has been analysed which shows that prescribing has continued to decline across the whole of the UK with new prescribing in women aged 18-45 years in the second half of 2019 at the lowest levels seen in the study period.

There has been a slight increase in the rate of new initiations observed in 2019 in girls under 18. However, this is based on low absolute numbers and should be interpreted with caution.

Although trends for decreasing use of valproate in female patients are in line with NICE and regulatory recommendations for the treatment of epilepsy and bipolar disorder, prescribing in pregnancy is still occurring.

There are some changes to the analyses presented in this report compared to earlier reports. Data from the CPRD AURUM database have been additionally used due to the decreasing coverage of English GP practices within CPRD GOLD. All analyses have been stratified by dataset. Given differences in the coding systems used across the two databases, analyses by indication for treatment have not been included.
Figure 1: Incidence rate of first prescriptions for valproate in females by age group in Scotland, Wales and Northern Ireland (rate per 10,000 female patients, data source: CPRD GOLD).
Figures 1 and 2 shows the incidence rate of first prescriptions of valproate (based on the earliest record for a valproate prescription in a patient’s available GP record) in Scotland, Wales and Northern Ireland; and in England, respectively. There has been a general decline in the rate at which valproate is started in girls and women in all regions. In England, there was an overall decline of approximately 87% reduction in new use in women of child-bearing age in the second half of 2019 compared with that in the first half of 2010 (0.54 vs. 4.04 per 10,000 women aged 14-45 years, respectively). In comparison, in Scotland, Wales and Northern Ireland there was an overall decline of approximately 84% reduction in the second half of 2019 compared with that in the first half of 2010 (0.96 vs. 5.83 per 10,000 women aged 14-45 years, respectively). The sharp decline in new use within adolescent girls seen in early 2015 had been maintained into 2019 and new prescribing in women aged 18-45 is at its lowest level of the study period. New prescribing in younger girls is slightly higher than in the preceding 6 months but the absolute number of girls with a prescription identified is very low and these analyses should be treated with caution.

Figures 2: Incidence rate of first prescriptions for valproate in females by age group in England (rate per 10,000 female patients, data source: CPRD AURUM).
Figure 3: The prevalence of prescribing of valproate in females by age band in Scotland, Wales and Northern Ireland (rate per 10,000 female patients, data source: CPRD GOLD)
Figures 3 and 4 shows the overall rate of prescribing of valproate in women, including repeat prescriptions in Scotland, Wales and Northern Ireland, and in England, respectively. There has been an overall decline in valproate prescribing in girls and women of child-bearing age in the UK. In England, there was a 53.7% decrease in prescribing in women of child-bearing age in the second half of 2019 compared to beginning of 2010 (11.4 vs. 24.7 per 10,000 women aged 14-45 years, respectively). In comparison, in Scotland, Wales and Northern Ireland, there was a 49.6% decrease in prescribing in the second half of 2019 compared to beginning of 2010 (16.9 vs. 33.6 per 10,000 women aged 14-45 years, respectively). There was some acceleration in the decreasing rate of prescribing of valproate in the first half of 2019. However, the rate of prescribing in the second half of 2019 has decreased at a slower rate from the previous 6-months by 6.7% in England and 1.1% in Scotland, Wales and Northern Ireland.
Use of Valproate during pregnancy

Figure 5 shows that there has been change in the level of prescribing during pregnancy from 2010 to 2019. Overall, a total of about 650,000 pregnancies (including ongoing pregnancies and those with an unknown outcome) were detected in the CPRD GOLD database between January 2010 and December 2019. In 489 pregnancies, the woman received a prescription for valproate (<0.08% of all eligible pregnancies). Prescribing of valproate in pregnancy declined by 77.8% (from 11.09 per 10,000 pregnancies [95% confidence interval (CI) 9.12 to 13.48] in 2010 to 2.46 per 10,000 pregnancies [95% CI 1.25 to 4.86]) in 2019. There has been an estimated 47% reduction in the rate of exposure to valproate in pregnancy in 2019 compared to 2018. However, it should be noted that the data for 2019 includes ongoing pregnancies where exposure may yet occur, and all analyses are based on small numbers of exposed pregnancies meaning there is substantial uncertainty in the data. Analyses for the prescribing in pregnancy are not available for CPRD AURUM as the pregnancy register for that database is still under development.

Figure 5: The rate of prescribing of valproate in pregnancy (rate per 10,000 pregnancies and with 95% confidence intervals (CIs), time period: 2010 – 2019, data source: CPRD GOLD)

Technical notes

- The CPRD primary care databases contain the anonymised, longitudinal medical records of patients registered with contributing primary care practices across the UK. CPRD contains patient registration information, and all care events that general practice staff record. This includes demographic information, medical diagnoses, and prescriptions issued in primary care. The data have been extensively used in observational research including studies of drugs in pregnancy.

- In previous reports, valproate prescribing rates were derived the CPRD GOLD database. In this report, due to under-representation of England in CPRD GOLD database, the CPRD AURUM database was used to derive
valproate prevalence and incidence prescribing rates for England. Prescribing rates for Scotland, Wales and Northern Ireland were derived from data from CPRD GOLD database, and prescribing rates for England from CPRD AURUM.

- CPRD AURUM consists of data from practices that use the EMIS GP software, and CPRD GOLD consists of data from practices that use the Vision GP software. CPRD GOLD database includes a number of derived variables to facilitate research in the data, such as the up-to-standard date at which the practice data is deemed of research quality. The CPRD AURUM database does not include the up-to-standard date. A number of GP practices that previously contributed data to CPRD GOLD are now supported by the EMIS software and have agreed to contribute data to CPRD AURUM. Duplicate historical data for such practices will be held in both GOLD and AURUM databases. Therefore, differences in trends and rates between England and the other regions in this report may be due to the differences between the two databases and not due to different prescribing practices in England.

- Women were eligible for inclusion in the analysis for each 6-month period if they were alive and in active follow-up for the whole period. To be eligible for the analysis of new (ie, incident) use of valproate, at least 1 year of follow-up prior to the relevant 6-month period was required. The CPRD/LSHTM Pregnancy algorithm was used to detect pregnancies between 2010–2019 within the CPRD GOLD database and estimate the pregnancy-related dates. Women could contribute more than one pregnancy to the study and each unique pregnancy outcome was considered separately. However, pregnancies overlapping in dates were excluded from the analysis. The pregnancy algorithm is not available for CPRD AURUM.

- A different approach to derive prescribing rate in pregnancy was used compared to previous reports (published prior to 2019). The rates here were based on the year pregnancies started and included ongoing pregnancies, whereas previous analyses derived rates based on the year the pregnancies ended or excluded ongoing pregnancies. Therefore this report includes additional pregnancies deemed ongoing at the time of the report, and additional information on the outcome of pregnancies started in 2018 but that were ongoing at the time of the January 2010 - December 2018 report update, resulting in different prescribing rate in pregnancy in 2018 from what has been reported last year.

- Furthermore, CPRD is a dynamic database with new data being added retrospectively when new practices start contributing data and data being withdrawn in case practices leave and withdraw their patients’ data in between monthly database updates. Therefore, numbers and rate estimates for the same time periods will vary by data build. This can result in different prescribing trends from what has been reported previously.

- There are several key limitations of the CPRD data that need to be considered when interpreting these figures:

  1. Only prescriptions made in primary care will be captured and the estimates will also include prescriptions that were never dispensed or were dispensed but not adhered to. In the UK, prescribing of valproate will be initiated by a specialist but will usually transfer to primary care within one or two prescriptions so the vast majority of prescribing should be captured.

  2. The CPRD GOLD database has seen a decrease in the number of practices that are contributing data in recent years and there are now a limited number of practices from certain geographical regions. The data on pregnancy should be interpreted with caution due to lower numbers in the most recent years. The algorithm used to identify pregnancies in CPRD may under-ascertain or over-ascertain pregnancies for which outcomes have not been correctly coded at the GP practice (which is particularly likely for early pregnancy loss and pregnancies solely followed by specialists or at hospitals) and the representativeness of the pregnancies identified is unknown.

- The information presented here is based in part on data from the Clinical Practice Research Datalink obtained under licence (Independent Scientific Advice Committee approved study protocol: 14_013A2). However, the interpretation and conclusions contained in this report are that of MHRA alone.
These data have been produced by the Vigilance and Risk Management of Medicines Division of the Medicine and Healthcare products Regulatory Agency (MHRA), an executive agency of the Department of Health and Social Care. If you wish to contact MHRA about this report, please email info@mhra.gov.uk