



CPRD STUDY MONITORING THE USE OF VALPROATE IN GIRLS AND WOMEN IN THE UK: January 2010 to June 2018

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 (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 and in pregnancy have declined over the period January 2010 to June 2018.

A slightly larger decline was observed in the rate of new valproate prescriptions, with sustained low initiation in adolescent girls, although this is based on lower absolute numbers and should be interpreted with caution.

Valproate is most commonly prescribed for epilepsy but is still used in patients with migraine despite not being indicated for this in the UK.

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.

Monitoring of CPRD will continue, and updated data will be presented on the MHRA website as it becomes available on a six-monthly basis. The next data will be available in March 2019.

Figure 1: Incidence rate of first prescriptions for valproate in females by age group (rate per 10,000 female patients, data source: CPRD GOLD).

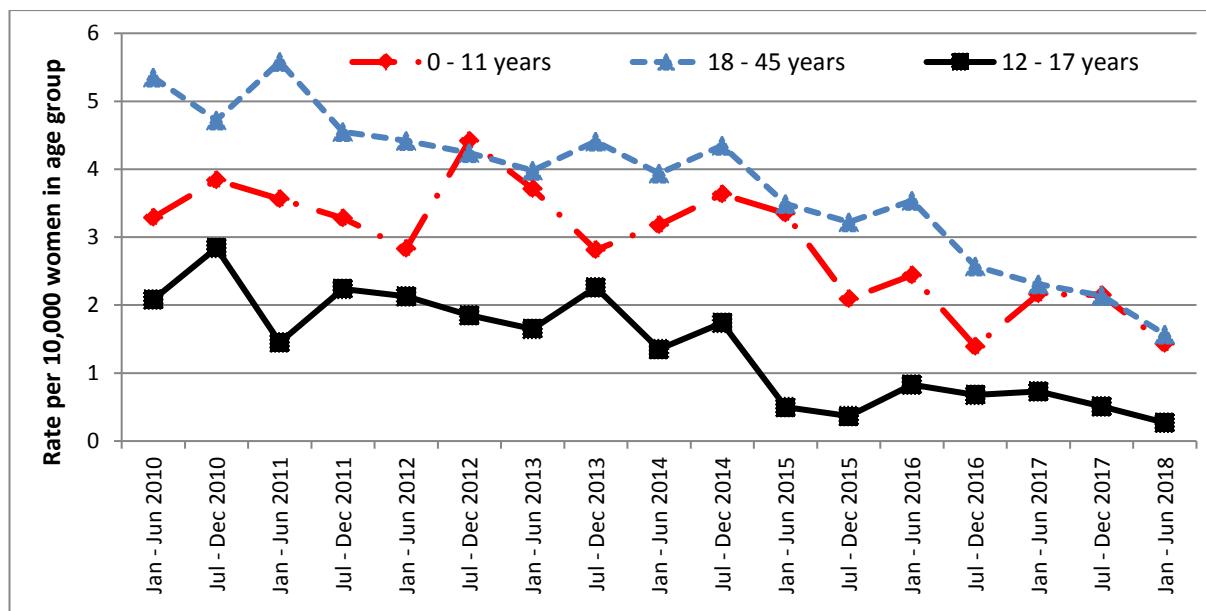


Figure 1 shows the incidence rate of first prescriptions of valproate (based on the earliest record for a valproate prescription in a patient's available GP record). There has been a general decline in the rate at which valproate is started in girls and women, with an overall decline of approximately 72% reduction in new use in the first half of 2018 compared with that in the first half of 2010 (4.93 vs. 1.37 per 10,000 women aged 45 years and younger, respectively). The sharp decline in new use within adolescent girls seen in early 2015 has been maintained into 2018.

Figure 2: The prevalence of prescribing of valproate in females aged 14-45 years by indication (rate per 10,000 female patients, data source: CPRD GOLD)

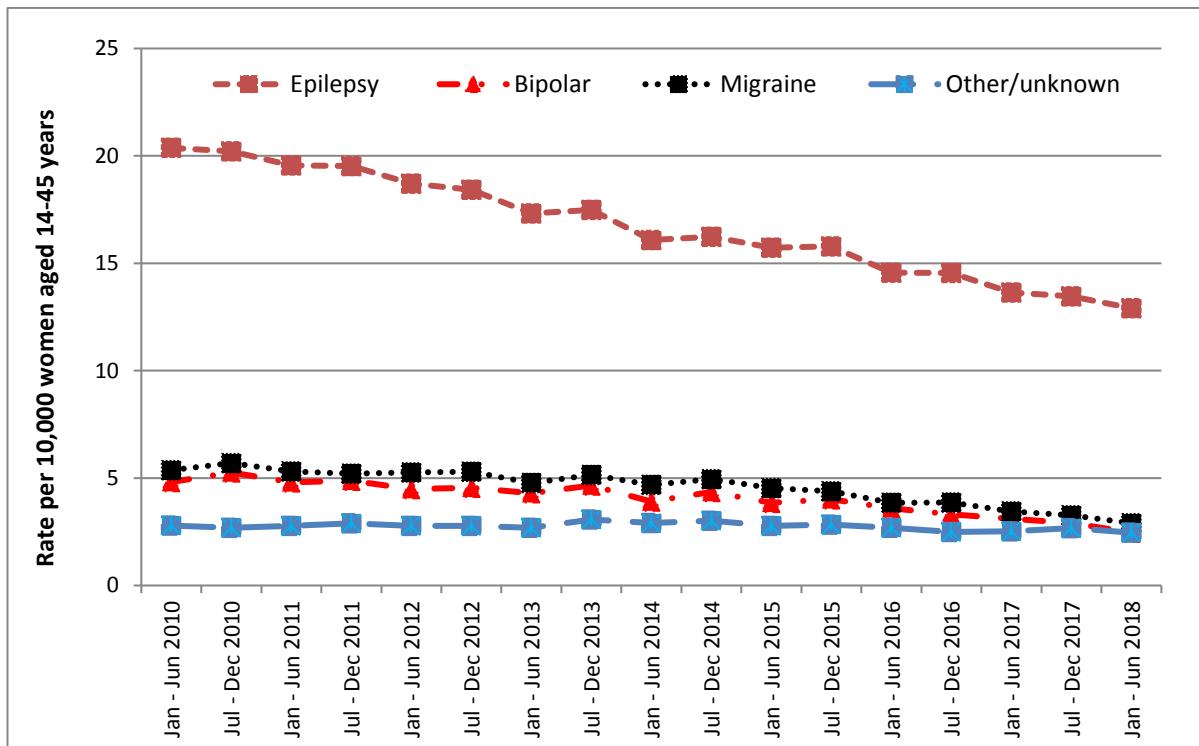
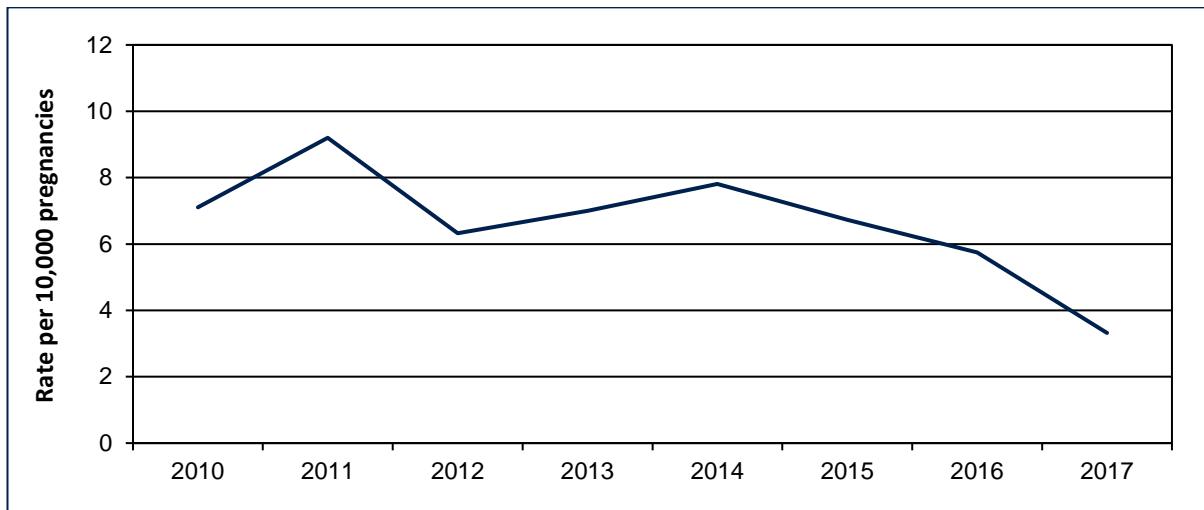


Figure 2 shows the overall rate of prescribing of valproate in women aged 14-45 years, including repeat prescriptions. There has been an overall decline in valproate prescribing, with a 37% decrease in prescribing in the first half of 2018 compared to 2010 (18.34 vs. 29.28 per 10,000 women aged 14-45 years, respectively). As would be expected, the most common indication for treatment with valproate is epilepsy. The decline in prescribing of valproate in women is observed across conditions (with a decrease of 37%, 49%, and 46% in patients with epilepsy, bipolar disorder, and migraine respectively during the study period).

Figure 3 shows that there has been change in the level of prescribing during pregnancy over the study period. Overall, a total of 600,000 pregnancies were detected in the CPRD between January 2010 and December 2017. In 415 pregnancies, the woman received a prescription for valproate (<0.07% of all eligible pregnancies). Prescribing of valproate in pregnancy declined by 47% (from 0.07% to 0.03%) between 2010 and 2017.

Figure 3: The rate of prescribing of valproate in pregnancy (rate per 10,000 pregnancies, data source: CPRD GOLD)



Technical notes

- The CPRD primary care database contains 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.
- 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 2010–2017 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.
- 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) In CPRD data, prescriptions are not directly linked to a specific diagnosis meaning that the medical record must be searched for possible indications. Indication was inferred using patient clinical diagnosis and referral records. In the analysis presented here, a strict list of terms was used to define indication, and a record at any time in the patient's medical record was considered as a potential indication. Indication was defined as bipolar disorder if the patient had a clinical record recording a diagnosis of bipolar disorder, mania, or a manic episode at any time in their record. Women could contribute towards more than one group. The rather crude approach of examining the entire patient record, not just the record prior to the primary diagnosis, has been conducted here and therefore results should be interpreted with caution.
 - (3) 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