Prescribing data related to the use of valproate in females and males in England

1 KEY MESSAGES

2 Patient safety is the MHRA's highest priority, and the Agency have introduced several measures to reduce the potential harms of valproate* use in both females (since 2018) and males (since 2024). See MHRA website for more information on valproate safety measures.

3 This analysis of data from the Clinical Practice Research Datalink (CPRD) aimed to describe the prescribing trends of valproate, along with lines of treatment and switching, in females and males in England to support the monitoring of prescribing following the safety measures. Prescribing information on valproate is available from several sources, but CPRD enables more in-depth, patient-level analysis than aggregate data alone. Inclusion of clinical diagnoses means that prescribing can be analysed by condition, and patient-level prescribing records mean that switching to alternative medicines can be tracked. This publication describes the results of these analyses.

4 Between January-March 2018 and April-June 2024, the proportion of females aged 16-44 newly prescribed valproate fell by 77% (from 2.8 to 0.63 per 100,000), and the overall proportion prescribed valproate declined by 56% (from 143.5 to 63.8 per 100,000).

5 Since the MHRA's National Patient Safety Alert in November 2023, which introduced measures related to valproate prescribing in females under age 55, new prescribing in females aged 16-44 has fallen by 17% (from 0.76 to 0.63 per 100,000), and overall prescribing has fallen by 7% (from 68.6 to 63.8 per 100,000).

6 The proportion of females, aged 16 to 44 years, newly prescribed valproate as a first line treatment (i.e. as the first medication being used to treat their condition) has decreased from 15% prior to end of April 2018 to 3% from May 2018 to 16 September 2024 in epilepsy and from 9% prior to end of April 2018 to 1% from May 2018 to 16 September 2024 in bipolar disorder.

7 29% of female patients, aged 16-44, who were prescribed valproate as a first line treatment for epilepsy prior to end of April 2018 switched to either lamotrigine or levetiracetam without subsequently switching back to valproate. Similarly, 26% of female patients, aged 16-44, who were prescribed valproate first line for bipolar disorder during the same time period switched to either quetiapine or olanzapine and did not return to valproate.

* Valproate refers to all valproate containing medicines: Belvo, Convulex, Depakote, Dyzantil, Epilim, Epilim Chrono or Chronosphere, Episenta, Epival, and Syonell▼

8 Between January-March 2018 and April-June 2024, the proportion of males aged 16-44 newly prescribed valproate fell by 78% (from 6.86 to 1.48 per 100,000), and the overall proportion prescribed valproate declined by 14% (from 323.2 to 277.4 per 100,000).

9 Specifically, there was a 63% decrease in new valproate prescribing in males since the introduction of new measures in November 2023 related to new prescribing of valproate in male patients under age 55 years of age.

10 The proportion of males, aged 16 to 44 years, newly prescribed valproate as a first line treatment (i.e. as the first medication being used to treat their condition) has decreased from 29% prior to end of January 2024 to 4% from February 2024 to 16 September 2024 in epilepsy and from 11% prior to end of January 2024 to 2% from February 2024 to 16 September 2024 in bipolar disorder.

11 19% of male patients, aged 16-44, who were prescribed valproate as a first line treatment for epilepsy prior to end of January 2024 switched to either lamotrigine or levetiracetam without subsequently switching back to valproate. Similarly, 16% of male patients, aged 16-44, who were prescribed valproate first line for bipolar disorder during the same time period switched to either quetiapine or olanzapine and did not return to valproate.

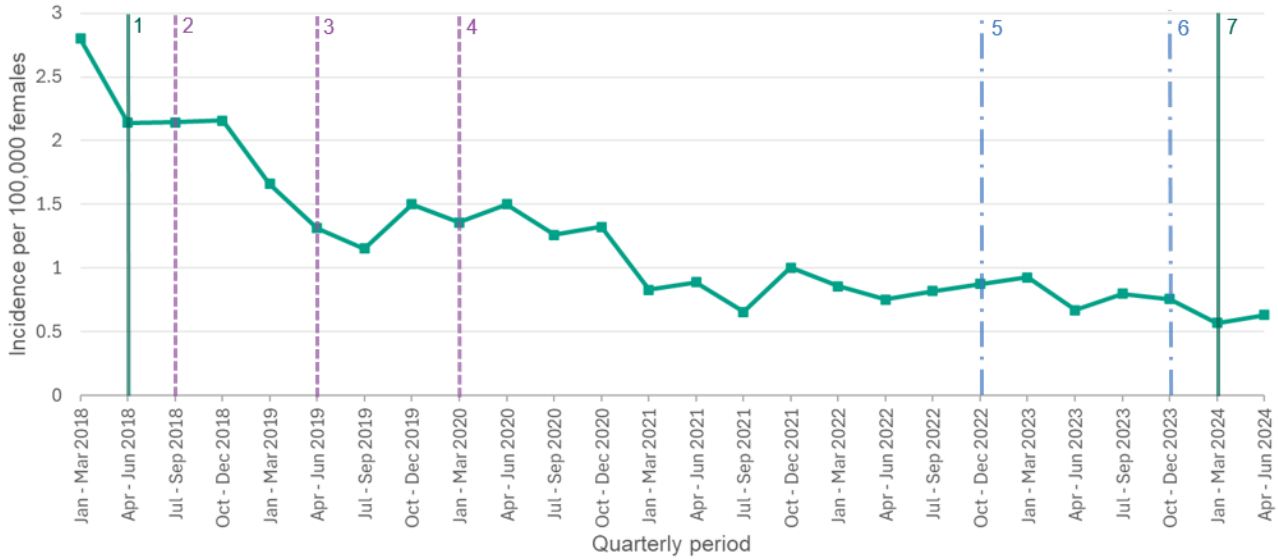
12 While CPRD Aurum has been demonstrated to be representative of the UK general population the data does not cover the whole country. There are other data sources available to monitor valproate prescribing at a national level, including prescribing in pregnancy. Links for these are provided below.

13 In this report, data in all trend graphs are presented by quarterly time periods. Where data on incident prescribing (where patients are newly prescribed valproate) is presented, this is based on a patient's earliest recorded valproate prescription during January 2018 to June 2024. To try to ensure this is a patient's first prescription they must have at least one year of prior available data without a valproate prescription.

14 Valproate prescribing will continue to be monitored using CPRD data, with updates published every six months as new data becomes available.

Valproate prescribing in females

Figure 1: Cumulative incidence of females, aged 16-44 years, newly prescribed valproate in England (per 100,000 females, data source: CPRD Aurum)



New measures come into force
Publication of new educational materials/updates to materials
Communication of upcoming measures

Note: Vertical lines indicate the timing of regulatory measures. Their inclusion is for reference only and should not be interpreted as evidence that these measures directly caused changes in prescribing; 1. 24 April 2018 – valproate Pregnancy Prevention Programme introduced for women and girls of childbearing potential; 2. September 2018 – online and hardcopy materials for Pregnancy Prevention Programme available; 3. 16 April 2019 – updates to Annual Risk Acknowledgement Form and clinical guidance to support compliance with Pregnancy Prevention Programme; 4. January 2020 – updated educational materials sent to healthcare professionals to support the Pregnancy Prevention Programme; 5. 12 December 2022 – announcement that new safety measures will be introduced in the coming months to put in place two-prescriber review for new female and male patients under 55 years old; 6. 28 November 2023 – National Patient Safety Alert asking organisations to put a plan in place to implement two-prescriber review for new female and male patients under 55 years old; 7. January 2024 – deadline for two-prescriber review requirements and new safety and education materials introduced.

Figure 1 shows the cumulative incidence of females, aged 16-44, in England newly prescribed valproate. There has been a decline in new valproate prescribing in females in this age group over the whole time period, falling by around 77% - from 2.8 per 100,000 females in January-March 2018 to 0.63 per 100,000 females in April-June 2024. There was a 17% decrease in new prescribing among females aged 16-44 since the MHRA issued a National Patient Safety Alert in November 2023 to introduce measures related to new and existing prescribing of valproate in females under age 55 years of age.

New valproate prescribing also declined in other age groups (0-11, 12-15, 45-54 and 55+) and had reached its lowest level across most of the age groups by the end of the study period (data not presented).

Figure 2: Cumulative incidence of females, aged 16-44 years, newly prescribed valproate by indication in England (per 100,000 female patients, data source: CPRD Aurum).

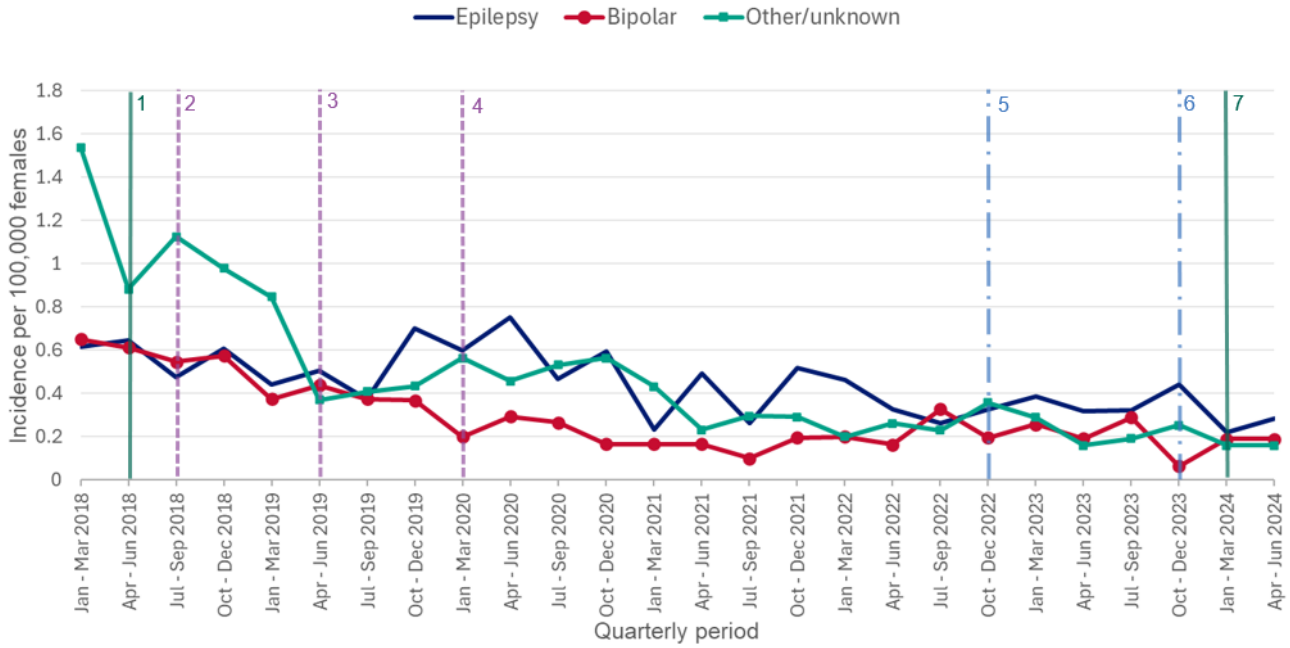


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Figure 2 shows the cumulative incidence of females, aged 16-44 years, newly prescribed valproate in England, broken down by licensed indication (epilepsy or bipolar disorder). It is important to note that due to the small numbers of females newly prescribed valproate the cumulative incidence may appear to fluctuate, also to note that a strict definition was used to identify indication. The “other/unknown” group includes females for whom indication was not able to be identified using the strict definition and may therefore represent cases where indication might not have been recorded or where valproate might be being used for an indication other than epilepsy or bipolar disorder (see Technical Notes for limitations related to indications).

A decline in new prescribing is observed across all indications with a decrease by around 54% for epilepsy and 71% for bipolar disorder from January-March 2018 to April-June 2024.

Figure 3: Prevalence of valproate prescribing in females, aged 16-44 years, in England (per 100,000 female patients, data source: CPRD Aurum)

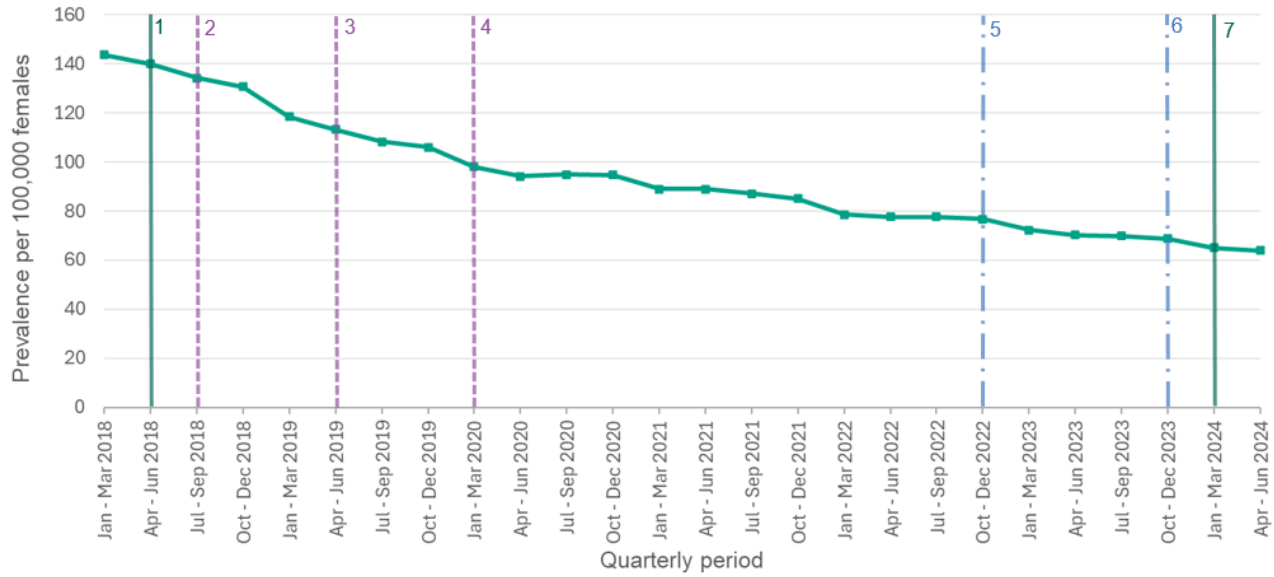

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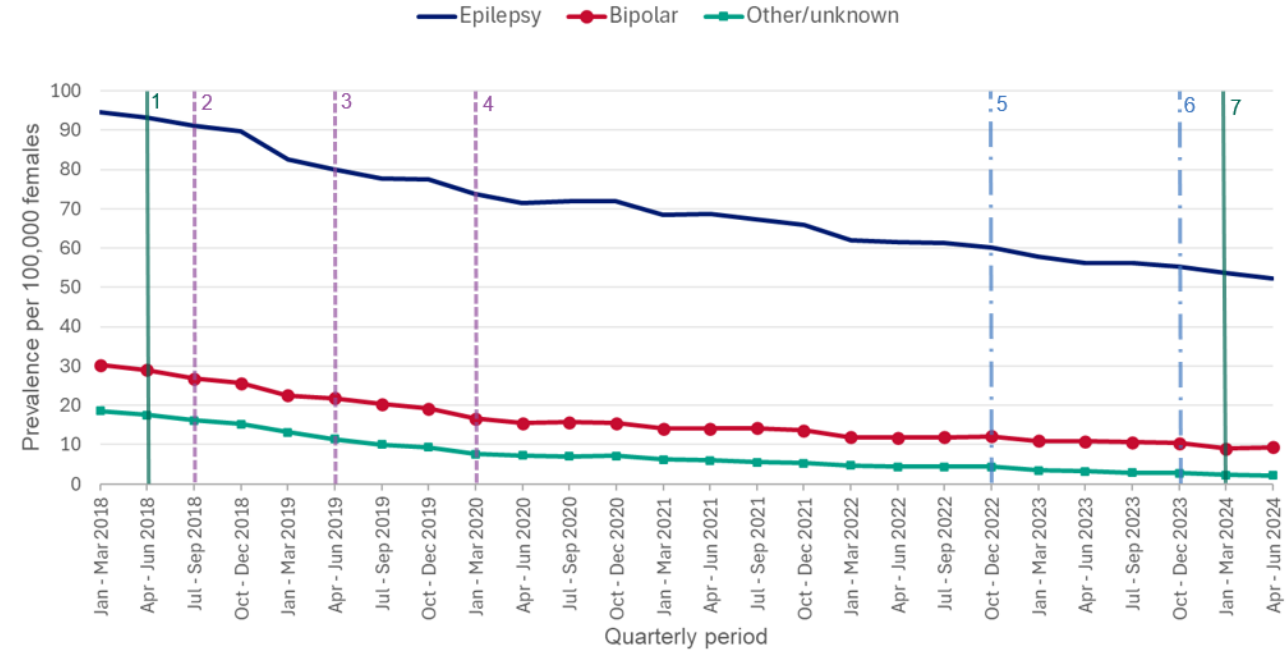
Figure 3 shows the prevalence of valproate prescribing in females, aged 16-44, over the time period in England. Prescribing fell by around 56% - from 143.5 per 100,000 females in January-March 2018 to 63.8 per 100,000 females in April-June 2024.

Valproate prescribing was greater among females aged 55 years and over and females aged 45 to 54 years. Prescribing in all age groups declined over the study period and by the end of the time period, overall valproate prescribing had reached its lowest level across all age groups (0-11, 12-15, 45-54 and 55+, data not presented).

Figure 4a: Prevalence of valproate prescribing in females, aged 16-44 years, by indication in England (per 100,000 female patients, data source: CPRD Aurum).



Note: Vertical lines indicate the timing of regulatory measures. Their inclusion is for reference only and should not be interpreted as evidence that these measures directly caused changes in prescribing; 1. 24 April 2018 – valproate Pregnancy Prevention Programme introduced for women and girls of childbearing potential; 2. September 2018 – online and hardcopy materials for Pregnancy Prevention Programme available; 3. 16 April 2019 – updates to Annual Risk Acknowledgement Form and clinical guidance to support compliance with Pregnancy Prevention Programme; 4. January 2020 – updated educational materials sent to healthcare professionals to support the Pregnancy Prevention Programme; 5. 12 December 2022 – announcement that new safety measures will be introduced in the coming months to put in place two-prescriber review for new female and male patients under 55 years old; 6. 28 November 2023 – National Patient Safety Alert asking organisations to put a plan in place to implement two-prescriber review for new female and male patients under 55 years old; 7. January 2024 – deadline for two-prescriber review requirements and new safety and education materials introduced.

Figure 4 shows the overall prescribing of valproate by indication in females in England, aged 16-44 years. A decline in overall prescribing is observed across all indications, prescribing decreased by about 45% for epilepsy and 69% for bipolar disorder from January-March 2018 to April-June 2024.

Lines of treatment in females with epilepsy

Details on lines of treatment and the limitations in their calculation are stated in the Technical notes. The time periods presented were chosen to align with the communication of the main valproate regulatory recommendations for females at end of April 2018.

Figure 5: Sunburst plots showing lines of treatment for females with epilepsy aged 16-44 years old in England, stratified by two time periods (data source: CPRD Aurum; limited to 3 lines of treatment)

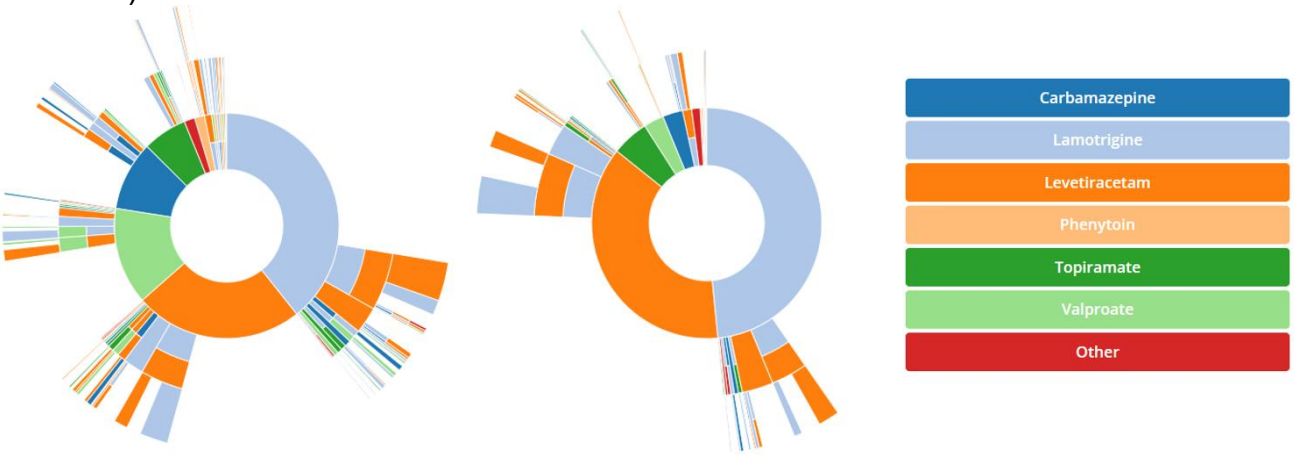


Figure 5a: until end of April 2018

Figure 5b: from start of May 2018

Note: Figure 5a includes patients with incident prescriptions from 01/01/2010 to 30/04/2018. Figure 5b includes patients with an incident prescription from 01/05/2018 to 16/09/2024.

From Figure 5a, valproate was prescribed to approximately 15% of females aged 16-44 as their first treatment for epilepsy before the end of April 2018. This dropped off to around 3% after start of May 2018 (Figure 5b). Two other medications - lamotrigine and levetiracetam - became more common as first treatments after the start of May 2018. During this period, about 50% of females were prescribed lamotrigine and 39% were prescribed levetiracetam as first treatments, compared to around 41% and 26%, respectively, before end of April 2018 (this could include possible combination therapy).

Furthermore, among females who started treatment with valproate before end of April 2018, approximately 15% switched to levetiracetam, and 14% switched to lamotrigine, as their second treatment without subsequent prescriptions for valproate. For females who started treatment with valproate after start of May 2018 approximately 20% switched to either lamotrigine or levetiracetam, without subsequent prescriptions for valproate, however the numbers are very low. Of note, even if a female's first prescription of valproate was before end of April 2018, since their treatments were followed up over time it could be that their second line treatments were prescribed after start of May 2018 and these are still included. Also, some females may have been prescribed a combination of treatments, which is shown by the horizontal segment dividers in the sunburst plots, but it is challenging to estimate the number with confidence due to the way the data was collected.

Lines of treatment in females with bipolar disorder

Figure 6: Sunburst plots showing lines of treatment for females with bipolar disorder aged 16-44 years old in England, stratified by two time periods (data source: CPRD AURUM; limited to 3 lines of treatment)

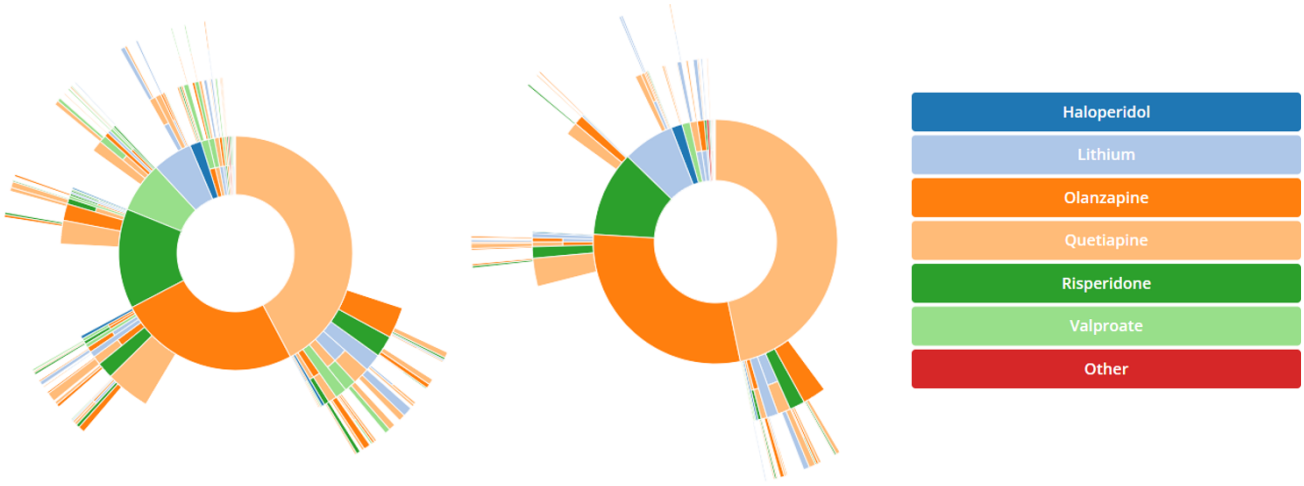


Figure 6a: until end of April 2018

Figure 6b: from start of May 2018

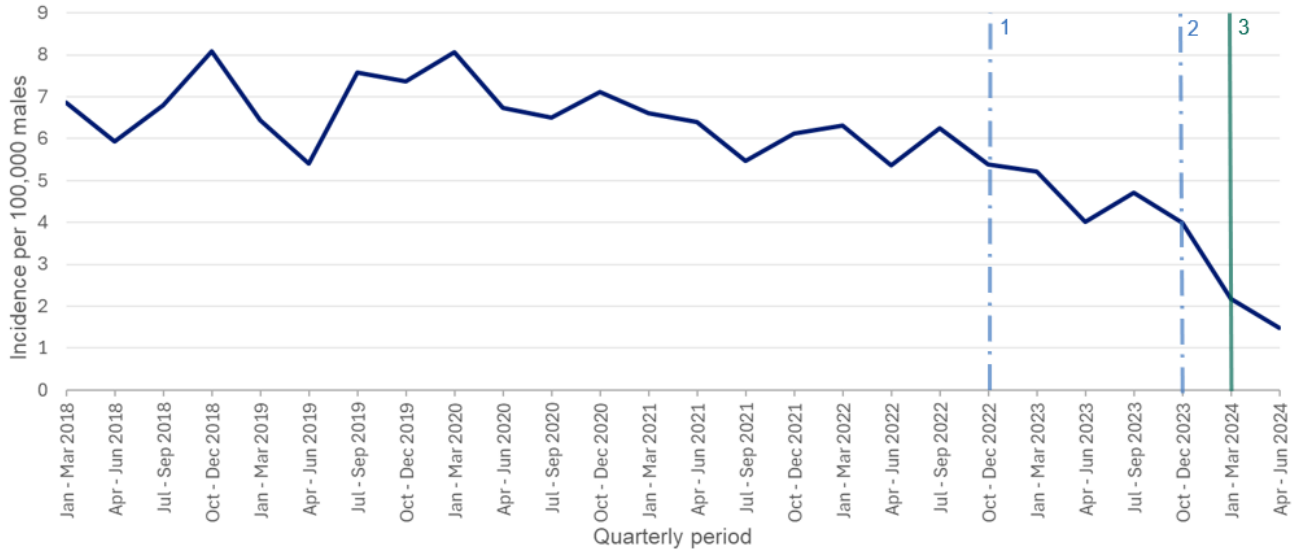
Note: Figure 6a includes patients with incident prescriptions from 01/01/2010 to 30/04/2018. Figure 6b includes patients with an incident prescription from 01/05/2018 to 16/09/2024.

From Figure 6a, valproate was prescribed to approximately 9% of females aged 16-44 as their first treatment for bipolar disorder before the end of April 2018. This decreased to around 1% after start of May 2018 (Figure 6b). Two other medications - quetiapine and olanzapine - became more common as first treatments after the start of May 2018. During this period, about 48% of females were prescribed quetiapine and 31% were prescribed olanzapine as first treatments, compared to around 44% and 27%, respectively, before end of April 2018 (this could have included possible combination therapy).

Furthermore, among females who started treatment with valproate before the end of April 2018, approximately 18% switched to quetiapine, and 8% switched to olanzapine, as their second treatment without subsequent prescriptions for valproate.

Valproate prescribing in males

Figure 7: Cumulative incidence of males, aged 16-44 years, newly prescribed valproate in England (per 100,000 male patients, data source: CPRD Aurum)

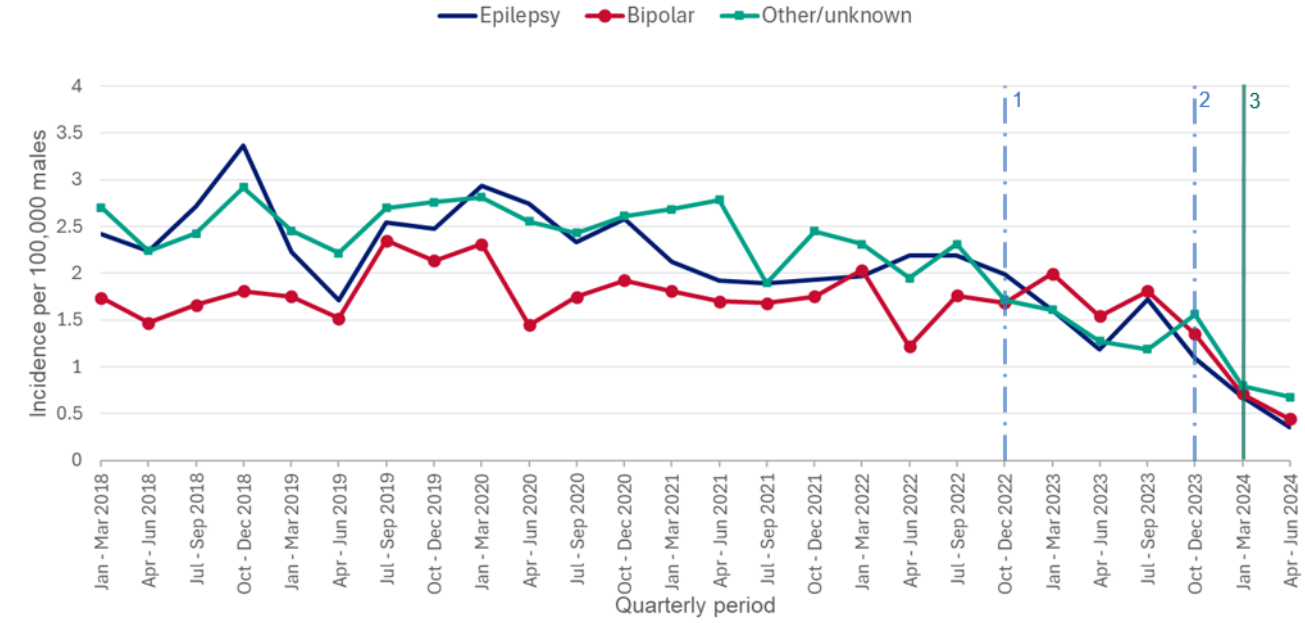


Note: Vertical lines indicate the timing of regulatory measures. Their inclusion is for reference only and should not be interpreted as evidence that these measures directly caused changes in prescribing; 1. 12 December 2022 – announcement that new safety measures will be introduced in the coming months to put in place two-prescriber review for new female and male patients under 55 years old; 2. 28 November 2023 – National Patient Safety Alert asking organisations to put a plan in place to implement two-prescriber review for new female and male patients under 55 years old and existing patients who are women and girls of childbearing potential; 3. January 2024 – deadline for two-prescriber review requirements and new safety and education materials introduced.

Figure 7 shows the cumulative incidence of males, aged 16-44 years, in England newly prescribed valproate. Prescribing trends have fluctuated but declined over the time period. In this age group new prescribing fell by around 78% - from 6.86 per 100,000 males in January-March 2018 to 1.48 per 100,000 males in April-June 2024. Specifically, there was a 63% decrease in new valproate prescribing in males since the introduction of new measures in November 2023 related to new prescribing of valproate in male patients under age 55 years of age. Also, for the last two quarters of the time period there was a decline of around 32% - from 2.19 per 100,000 males in January-March 2024 to 1.48 per 100,000 males in April-June 2024.

New valproate prescribing in males also declined in other age groups (0-11, 12-15, 45-54 and 55+) and had reached its lowest level across most of the age groups by the end of the study period (data not presented).

Figure 8: Cumulative incidence of males, aged 16-44 years, newly prescribed valproate by assumed indication in England (per 100,000 male patients, data source: CPRD Aurum).



Communication of upcoming measures
New measures come into force

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Figure 8 shows the cumulative incidence of males, aged 16-44 years, newly prescribed valproate in England, broken down by licensed indication (epilepsy or bipolar disorder). It is important to note that a strict definition was used to identify indication. The “other/unknown” group includes males for whom indication was not able to be identified using the strict definition and may therefore represent cases where indication might not have been recorded or where valproate might be being used for an indication other than epilepsy or bipolar disorder (see Technical Notes for limitations related to indications).

Prescribing trends have fluctuated across all indications with new prescribing decreasing by around 85% for epilepsy and 75% for bipolar disorder from January-March 2018 to April-June 2024. Towards the end of the time period, new prescribing for epilepsy is observed to be similar to new prescribing for bipolar disorder.

Figure 9: Prevalence of valproate prescribing in males, aged 16-44 years, in England (per 100,000 male patients, data source: CPRD Aurum)

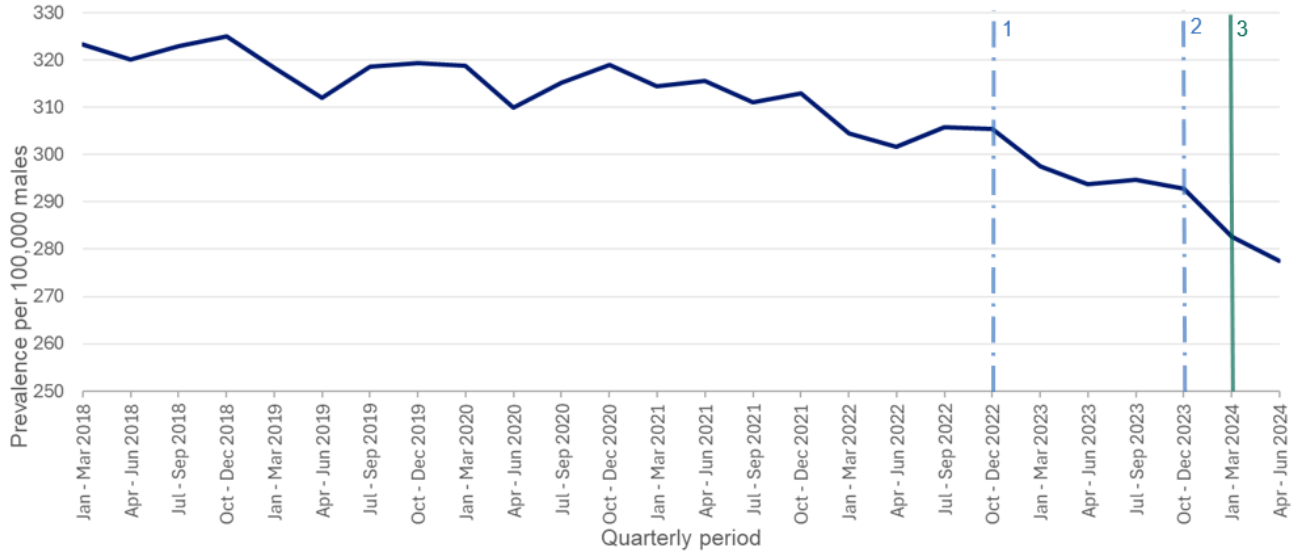

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Figure 9 shows the prevalence of valproate prescribing in males, aged 16-44 years, over the time period in England. There has been a 14% decrease in valproate prescribing among males aged 16-44 years from 323.2 per 100,000 in Jan-Mar 2018 to 277.4 per 100,000 in Apr-Jun 2024.

Valproate prescribing was greater among males aged 55 years and over and males aged 45 to 54 years. Prescribing in all age groups (0-11, 12-15, 45-54 and 55+) declined over the study period (data not presented).

Figure 10: Prevalence of valproate prescribing in males, aged 16-44 years, by indication in England (per 100,000 male patients, data source: CPRD Aurum)

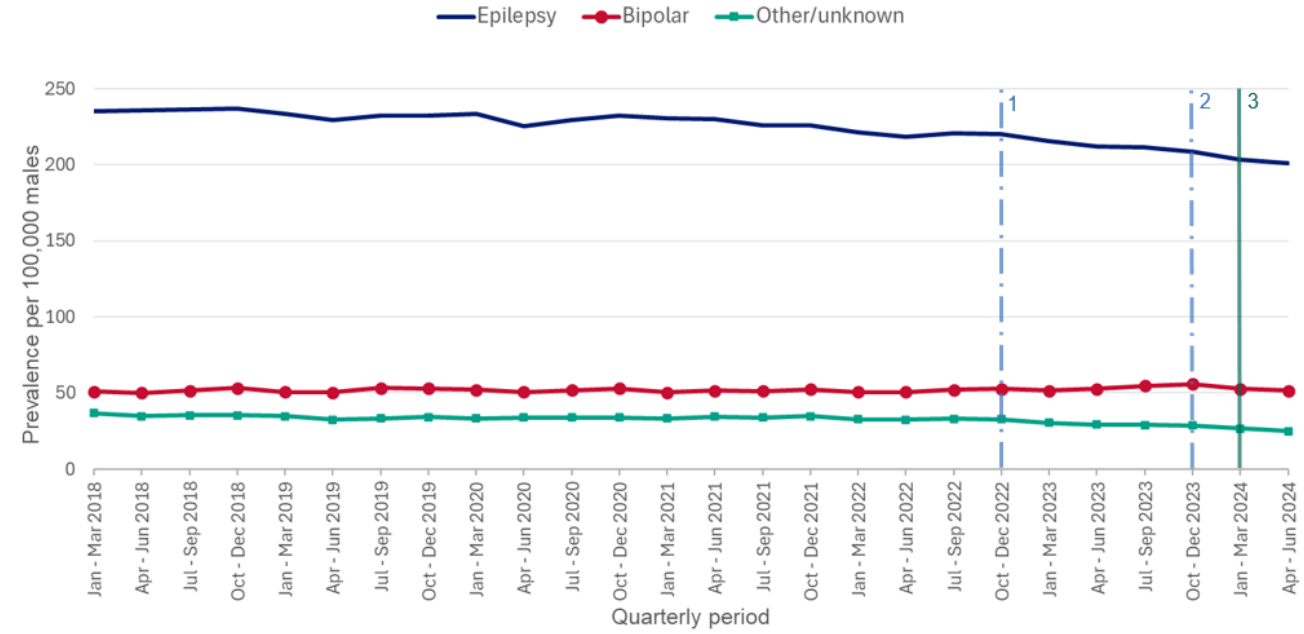

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Figure 10 shows the overall prescribing of valproate by indication in England, in males aged 16-44 years. Prescribing decreased by about 15% for epilepsy from January-March 2018 to April-June 2024, whereas prescribing for bipolar disorder appears to have stayed relatively stable over the same time period.

Lines of treatment in males with epilepsy

Details on lines of treatment and the limitations in their calculation are stated in the Technical notes. The time periods presented were chosen to align with the communication of the main valproate regulatory recommendations for males at the end of January 2024.

Figure 11: Sunburst plots showing lines of treatment for males with epilepsy aged 16-44 years old in England, stratified by two time periods (data source: CPRD Aurum; limited to 3 lines of treatment)

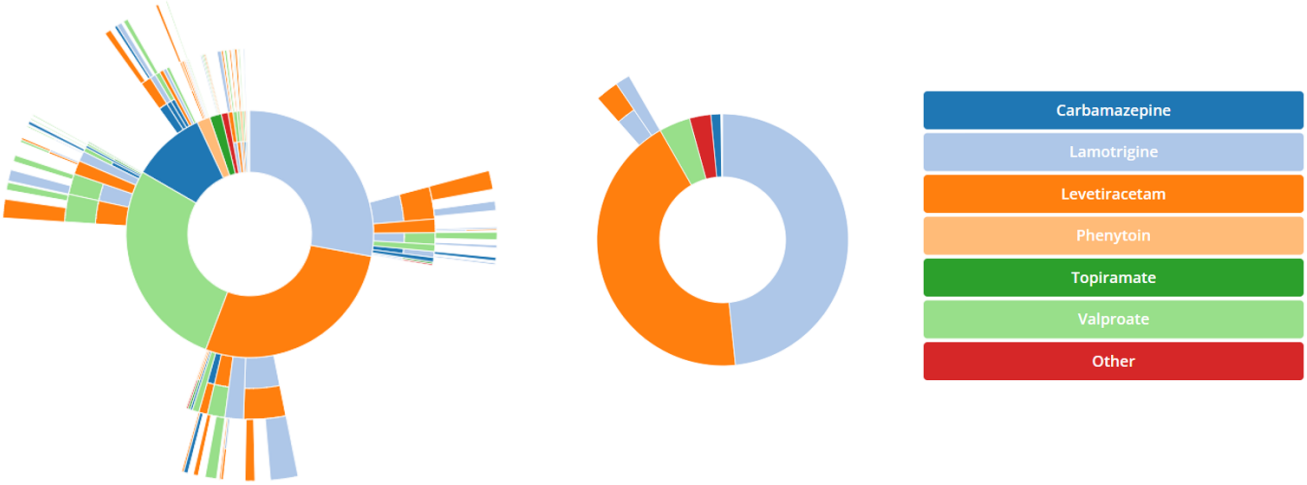

Figure 11a: until end of January 2024

Figure 11b: from start of February 2024

Note: Figure 11a includes patients with incident prescriptions from 01/01/2010 to 31/01/2024. Figure 11b includes patients with an incident prescription from 01/02/2024 to 16/09/2024.

From Figure 11a valproate was prescribed to around 29% of males aged 16-44 as their first treatment for epilepsy before the end of January 2024. This decreased to about 4% after start of February 2024 (Figure 11b). Two other medications - lamotrigine and levetiracetam - became more common as first treatments after start of February 2024. During this period, about 49% of males were prescribed lamotrigine and 44% were prescribed levetiracetam as first treatments, compared to around 29% and 30%, respectively, before end of January 2024.

Furthermore, among males who started treatment with valproate before end of January 2024, approximately 11% switched to levetiracetam, and 8% switched to lamotrigine as their second treatment, without subsequent prescriptions for valproate. There are no switches in treatment for males with an incident valproate prescription after start of February 2024 due to limited follow-up time, therefore further lines of treatment are not yet observed.

Lines of treatment in males with bipolar disorder

Figure 12: Sunburst plots showing lines of treatment for males with bipolar disorder aged 16-44 years old in England, stratified by two time periods (data source: CPRD Aurum; limited to 3 lines of treatment)

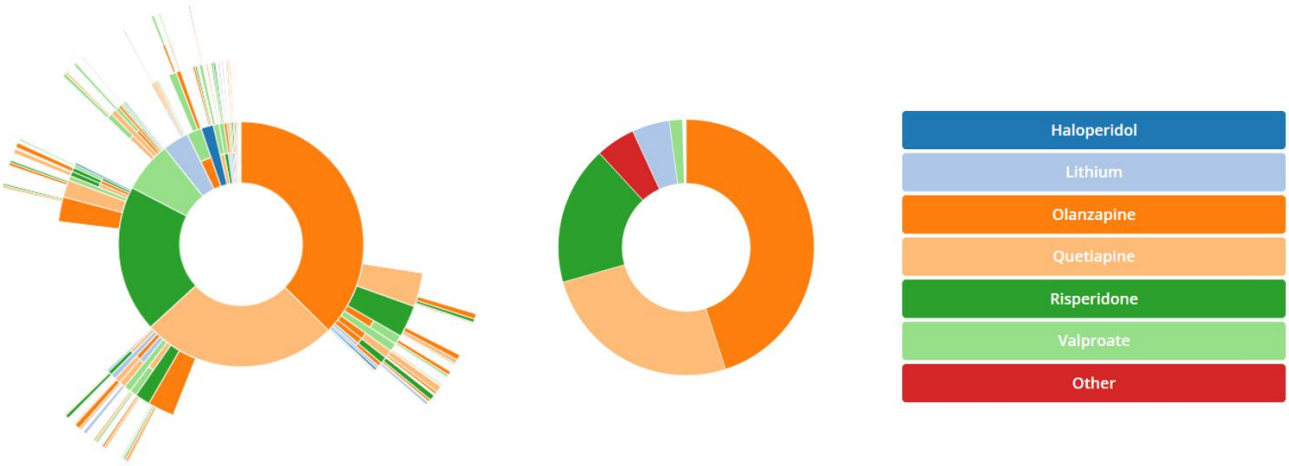

Figure 12a: until end of January 2024 Figure 12b: from start of February 2024

Note: Figure 12a includes patients with incident prescriptions from 01/01/2010 to 31/01/2024. Figure 12b includes patients with an incident prescription from 01/02/2024 to 16/09/2024.

From Figure 12a valproate was prescribed to approximately 11% of males aged 16-44 as their first treatment for bipolar disorder before the end of January 2024. This decreased to 2% after start of February 2024 (Figure 12b). Another medication - olanzapine - became more common as a first treatment with about 45% of males prescribed after start of February 2024 compared to 40% before end of January 2024.

Furthermore, among males who started treatment with valproate before end of January 2024, approximately 9% switched to quetiapine and 7% switched to olanzapine as their second treatment, without subsequent prescriptions for valproate. Similarly to the epilepsy cohort there is very limited follow-up for those patients with an initial prescription after start of February 2024.

Technical notes

- The Clinical Practice Research Datalink (CPRD) Aurum primary care database contains anonymised computerised longitudinal records of patients registered with contributing primary care practices across England. CPRD Aurum contains patient registration information, demographic information, medical diagnoses, and prescriptions issued in primary care. CPRD Aurum consists of data from practices that use the EMIS GP software. It has been shown to be representative of the general UK population. At the time of this analysis (Dec 2024 build, https://doi.org/10.48329/qfkt-kb64) CPRD Aurum covered approximately 16.5 million current patients, which is around 24% of the UK population.

- CPRD is a dynamic database with historical data being added retrospectively when new practices start contributing data. Therefore, incidence and prevalence estimates for the same time periods can vary depending on the data version and may differ from previously reported figures.

- Cumulative incidence and prevalence of prescribing were calculated per quarter (3-month periods), starting from January – March 2018 and ending April – June 2024 (the last available full quarter). Data on prescribing prior to 2018 can be found here Valproate – reproductive risks - GOV.UK. Patients were eligible for inclusion in the analysis for each 3-month time period if they were alive and registered with a practice for the whole quarter. The number of patients in the whole of CPRD AURUM were used as a denominator to calculate cumulative incidence and prevalence of valproate per 100,000 patients (females and males separately). For a patient to be eligible for the analysis of new (i.e., incident) use of valproate, at least 1 year of follow-up prior to first recorded prescription in the time period was required.

- Sunburst plots were generated using patient's incident/new prescriptions in the time period 1st January 2010 to 16th September 2024, this end date is the latest data collection date as unlike the prescribing trends graphs the sunburst plot does not rely on including full quarters of data. The sunburst plots are used to try to ascertain which AEDs/bipolar disorder drugs patients were prescribed as first-line treatment per indication cohort. For each of the time periods a patient's incident AED/bipolar disorder drug prescription was determined based on a patient's earliest record for an AED/bipolar disorder drug prescription within the study period, with a minimum of one-year prior prescription free follow-up. The patient's treatment was then followed up over the time period to ascertain treatment episodes and hence possible lines of treatment. Of note, if a patient's first prescription of an AED/bipolar disorder drug occurred during the first time period (prior to end of April 2018 or end of January 2024 for females and males respectively) it could be that their second/third line treatments were prescribed after the end of the time period, and these are still included within the analysis.

- The sunburst plots compare patients who initiate treatment in two different time periods. These were chosen to be in line with the time periods when the main valproate regulatory recommendations were communicated and enables monitoring of trends of prescribing before and after these time points. For males these are split

into patients with a first prescription prior to the end of January 2024 and those after start of February 2024. For this reason, there is a smaller sample size and limited follow-up available for the males in the subsequent period, and therefore this data should be interpreted cautiously.

- There are several key limitations of the CPRD data that need to be considered when interpreting the 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 taken. 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 majority of prescribing should be captured.

    2. CPRD includes the year of birth for all the patients, however it only includes month of birth for those aged under 16 years. In addition, the date of the month is not provided. Therefore, for all patients the day was assumed to be the 1st of the month, and the month was assumed to be January if not provided. This may cause minor age misclassification.

    3. In CPRD data, prescriptions are not directly linked to a specific diagnosis, so indications were inferred from medical records. A strict list of terms was used to define indications. For the prescribing trends analysis, the closest record prior to the first prescription per quarter per patient was considered as a potential indication for that patient. Some patients had both epilepsy and bipolar disorder events recorded and the term closest (but prior) to the prescription record was kept, however these could have been recorded many months/years prior. Epilepsy was given priority if both indications were recorded on the same date closest (but prior) to the date of the prescription record. The 'Other/unknown' indication group includes those with neither of these licensed indications recorded as per the criteria above and may include possible unlicensed indications. It is challenging to estimate the actual proportion of patients who were prescribed for each of the licensed indications due to the limitations of the data and the assumptions made, and hence the prescribing trends by indication graphs in this report should be interpreted in light of these limitations.

       For the sunburst plots showing lines of treatments a different approach was taken to define indication. This was in part because patients were identified by their indication as opposed to a prescription, as per the prescription trends analysis described above, where indication was specific to prescriptions within in each quarter. Using a similar, more restrictive, approach looking only for records of indication prior to the incident prescription per patient, would have resulted in a far smaller cohort in which line of treatment could be explored in the sunburst plots. Therefore, the indication specific cohorts, i.e. epilepsy and bipolar disorder cohorts, included patients with at least one recorded code for epilepsy or bipolar disorder respectively at any time in their medical record and at least one incident prescription of the relevant drugs. Patients could have

contributed to both groups if they had both the indications recorded. It could be that an 'indication' medical code is not recorded in a patient's medical record hence that patient would not be included in the cohort. Therefore, the indication specific cohorts would not include all eligible patients, and some patients might not be in the correct indication cohort. Hence, the results for indications should be interpreted with caution and in light of all these limitations.

4. Although sunburst plots are useful to assess patterns in sequential treatment data, there are some limitations to be aware of: a) if there are a large number of individual treatments and therefore segments generated this can lead to visual clutter and be challenging to interpret, b) the segment size becomes smaller in the outer rings and visually determining proportions accurately might become difficult, c) the plots can oversimplify complexities present within the data, d) the plots will only be based on the data available hence many of the other limitations stated above will apply, e) some patients may have been prescribed a combination of treatments, shown by the horizontal segment dividers in the plots, but it is challenging to estimate the number with confidence due to way the data was collected.
   Of note, the number of lines of treatments (rings) have been limited to the first 3 treatments due to disclosure control of data as the number of patients gets very low with further lines (rings) of treatments.
   The AEDs included within the sunburst plots were selected based on the NHS England Medicines in Pregnancy Register (Workbook: Meds&Preg). For bipolar disorder, the included drugs were selected based on the NICE guidelines for management of non-depressive symptoms of bipolar disorder (Overview | Bipolar disorder: assessment and management | Guidance | NICE). The AEDs with the lowest usage have also been combined as 'Other' to avoid visual clutter. These AEDs include: Cenobamate, Oxcarbazepine, Phenobarbital and Zonisamide. For both epilepsy and bipolar disorder, the 'Other' category also includes segments for which patient counts would otherwise be fewer than 5 due to disclosure control of data.

5. Treatment episodes were generated to produce sunburst plots as patients could have had multiple exposures over the study time period. Date, duration and quantity of prescriptions for the antiepileptic drugs (AEDs) and bipolar disorder drugs were used to derive the start and stop dates for treatment episodes. However, the duration and quantity variables within CPRD are not always accurate and/or are subject to missingness, therefore some assumptions were applied when deriving treatment episodes. The duration variable was preferentially used but where this was not appropriate quantity was used instead; this value was then added to the prescription start date and a lag of 28 days was added to this to account for possible delays in the patient starting the prescription or gaps due to missed doses. A treatment episode of a particular drug continued for as long as subsequent prescriptions were issued before the end of the duration plus the 28-day lag. Therefore, a new treatment episode for a patient was defined when the start date of a new prescription was later than the previous prescription date + duration/quantity + 28 days. Further assumptions include a) the first prescription in the data is the patient's true first prescription b) the patient took the entirety of the prescription. As a result of

these assumptions and limitations the sunburst plots should be interpreted with care.

The information presented here is based in part on data from the Clinical Practice Research Datalink obtained under licence (Research Data Governance approved study protocol: 22_002036). The interpretation and conclusions contained in this report are that of MHRA alone.

Other key national data sources for monitoring valproate prescribing trends

England

- The NHS England Medicines and Pregnancy Register (NHSE MPR) provides data on women of childbearing age prescribed valproate and valproate exposed pregnancies in England (Medicines and Pregnancy Registry - NHS England Digital; Dashboard: Workbook: Meds&Preg).
- The NHS Business Service Authority (NHSBSA) routinely publishes a dashboard on valproate dispensing for females, based on NHS England prescriptions in community pharmacies (Valproate safety dashboard | NHSBSA).

Scotland

- The Public Health Scotland Anti-Seizure Medicines in Pregnancy registry provides similar data for Scotland, including prescribing trends for males (Anti-Seizure Medicines in Pregnancy 1 April 2025 - Anti-Seizure Medicines in Pregnancy - Publications - Public Health Scotland; Dashboard - Anti-Seizure Medicines in Pregnancy 1 April 2025 - Anti-Seizure Medicines in Pregnancy - Publications - Public Health Scotland)

Northern Ireland.

- The Northern Ireland HSC Business Services Organisation and Statistics and Research Agency also publish valproate monitoring reports, detailing the number of male and female patients prescribed and dispensed valproate (Sodium Valproate Monitoring - Business Services Organisation (BSO) Website).

Wales

- The All Wales Therapeutics and Toxicology Centre, National Prescribing Indicators 2024–2025 – Analysis of Prescribing Data to December 2024 (published April 2025) includes number of female patients aged 14-55 years with a prescription for sodium valproate. wttc.nhs.wales/files/national-prescribing-indicators/national-prescribing-indicators-2024-2025-analysis-of-prescribing-data-to-december-2024-pdf/