This article has been accepted for publication in BMJMEDICINE following peer review.

The definitive copyedited, typeset version is available online at

10.1136/bmjmed-2023-000760

Evaluating the use of sodium valproate and other anti-seizure medication in nationwide linked electronic health records in England and Wales

Caroline E Dale*[1], Rohan Takhar*[1], Yat Yi Fan[1], Fatemeh Torabi[2], Michail Katsoulis[3], Samuel Kim[4], Andrew Lambarth[5], Christopher Tomlinson[6], Tim Wilkinson[7], Tanja Mueller[8], Amanj Kurdi[8,9], Mark Ashworth[10], Mamas A Mamas[11], Kamlesh Khunti[12], Ashley Akbari[2], Andrew D Morris[13], Munir Pirmohamed[1], Anthony G Marson[1,14], David Williams[15], David Hunt[7], Cathie Sudlow[13,16], Reecha Sofat[1,16], on behalf of the CVD-COVID-UK/COVID-IMPACT Consortium

* *Both authors contributed equally*

Corresponding author: r.sofat@liverpool.ac.uk

Affiliations

1. Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, UK.
2. Swansea University Medical School, Swansea University, Swansea, Wales, UK.
3. MRC Unit for Lifelong Health and Ageing, University College London, UK.
4. Royal Free NHS Foundation Trust.
5. St Georges University Hospitals NHS Foundation Trust.
6. Institute of Health Informatics, University College London, UK.
7. Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK.
8. Strathclyde Institute of Pharmacy & Biomedical Sciences, University of Strathclyde, Glasgow, UK.
9. Department of Clinical Pharmacy, College of Pharmacy, Hawler Medical University, Erbil, Kurdistan Regional Government, Iraq.
10. School of Life Course and Population Sciences, King's College London.
11. Centre for Prognosis Research, Keele University, Keele, UK.
12. Diabetes Research Centre, University of Leicester, Leicester, UK.
13. Health Data Research UK, London, UK.
14. The Walton Centre NHS Foundation Trust, Liverpool, UK.
15. UCL EGA Institute for Women's Health, University College London Hospitals NHS Foundation Trust, London, UK.
16. British Heart Foundation Data Science Centre, Health Data Research UK, London, UK.

Key words

Sodium valproate, electronic health records, pregnancy

Abstract

Objective:
Sodium valproate is an evidence-based treatment for idiopathic generalised epilepsy (IGE), and is also used for bipolar affective disorder. Sodium valproate is known to have teratogenic effects and has been subject to regulatory changes. Key policy statements in 2018 aimed at women of childbearing potential and introducing the pregnancy prevention programme (PPP) were followed by the onset of the Covid-19 pandemic. We investigated the use of sodium valproate in England and Wales during the period 2019 to 2023, including by women during pregnancy, comparing with other anti-seizure medications (ASMs) in comprehensive national level electronic health records.

Methods and Analysis:
Prevalent (current) and incident (new) uses of sodium valproate and other ASMs before and during the Covid-19 pandemic (January 2019 - December 2023) were identified using NHS England's Secure Data Environment and the SAIL Databank, covering the whole population of England and Wales respectively. Use was stratified by age-bands and sex. Annual rates were calculated for 2019-2022. Rates of dispense by Local Authority District (LAD) per 10,000 women of child-bearing potential (CBP; aged 15-49 years) were also calculated. We assessed pregnancy rates per 1000 women aged 15-49 dispensed ASMs and examined the timing and dose of sodium valproate dispensed during pregnancy. Rates of disease indication (epilepsy, bipolar affective disorder) per 1000 women dispensed sodium valproate were calculated. We investigated trends in epilepsy-related deaths between 2015 to 2022 using time series analysis.

Results:
Use of sodium valproate in women of CBP decreased whilst use of most other ASMs increased between 2019 and 2023. New initiation of sodium valproate per 100,000 women fell from 7 to 5 in women aged 15-19, 11 to 7 in women aged 20-29 and 14 to 7 in women aged 30-39 between 2019 and 2022. Incident use also declined in men of the same age but remained at much higher levels (from 53 to 43 in men aged 15-19, 59 to 47 in men aged 20-29 and 57 to 42 in men aged 30-39 per 100,000 men). Pregnancy rates fell from 6.0 to 5.2 per 1000 women of CBP dispensed sodium valproate over the same period. The number of pregnant women with evidence of a sodium valproate dispense during the pregnancy period fell from 140 in 2019 to 85 in 2023. Epilepsy was the most common indication, followed by bipolar affective disorder (751 and 193 per 1,000 women of CBP dispensed sodium valproate respectively in 2023). There was no clear evidence that epilepsy-related deaths increased in women aged 15-49 during 2015-2022; but there was some evidence for a slight increase in men aged 15-49 during the later period between April 2018 and December 2022.

Conclusion:
Using comprehensive national records, we have tracked changes in the prescribing of ASMs in response to regulatory actions. We demonstrated that rates of use of sodium valproate by women, including during pregnancy, fell before and continued to slowly decline during the Covid-19 pandemic. Incident use also declined in men but remained at much higher levels than in women. This approach linking national dispensing data to health records at the individual level facilitates the possibility of monitoring changes to medicines affected by regulatory changes, including in specific population groups such as pregnant women, and their potential impact on health outcomes.

Research in context

What is already known on this topic:

- Sodium valproate is an effective anti-seizure medication (ASM) but is known to be teratogenic; it is associated with a range of adverse neurodevelopmental effects.
- Sodium valproate has been the subject of review and regulatory action by the MHRA and other regulatory agencies since 1971 because of these teratogenic effects. Policy changes in 2018 strengthened the regulatory position on sodium valproate limiting prescriptions in women of childbearing potential and introducing the pregnancy prevention programme (PPP).
- Existing data have not yet been detailed enough to give a comprehensive picture of change in use of sodium valproate by women of childbearing potential, including during pregnancy, disease indications associated with its use, as well as the broader implications of policy changes and the impact of the Covid-19 pandemic on their implementation.

What this study adds:

- Linking information from across electronic health record (EHR) data sources, we have defined nationwide pregnancy episodes to address exposure to ASMs during pregnancy, including dose and timing of use.
- The study shows that rates of use of sodium valproate by women of childbearing potential, including during pregnancy, fell before and continued to slowly decline during the Covid-19 pandemic, despite disruption to most services.
- We also examine epilepsy-related mortality in the population during the period 2015 to 2022, finding no clear evidence that epilepsy-related deaths increased in women but some evidence for a slight increase in men after April 2018. However, more research would be required to establish any causal association with sodium valproate.

How this study might affect research, practice or policy:

- With improved access to electronic health data with coverage of the whole population, the impact of policy changes and their consequences can be more reliably tracked. This approach evaluates the use of sodium valproate in the population which can be used to inform future regulatory changes.

Introduction

Sodium valproate is an evidence-based, anti-seizure medication (ASM) for newly diagnosed idiopathic generalised epilepsy (IGE).[1,2] It is also used in other forms of epilepsy and bipolar affective disorder, as well as in migraine and other conditions. The teratogenic effects of the drug are well known, and when used during pregnancy it can be associated with a range of adverse effects, including increased risk of spontaneous abortion, birth defects and neurodevelopmental disorders (autism, autism spectrum disorder, attention deficit/hyperactivity disorder and reduced IQ).[3-8] Major physical malformations are seen in approximately 10% of babies, with evidence for a dose response effect.[8] Guidelines caution against the use of sodium valproate in women of child-bearing potential (CBP), although they emphasise balancing this risk with effective treatment of life-threatening epilepsy.[9]

In 2013, the Medicines and Healthcare products Agency (MHRA) tightened its advice, stating that sodium valproate was "not for use in pregnancy unless there is no effective alternative" and again in 2018, stating that "sodium valproate must no longer be used in any woman or girl able to have children unless she has a pregnancy prevention programme (PPP) in place".[9,10] In their advice the MHRA highlighted that other effective medicines are available for epilepsy and bipolar affective disorder. The Cumberlege report 'First do no Harm' published in July 2020,[11] in the midst of the Covid-19 pandemic, reinforced advice on use of sodium valproate in women of CBP, and presented sodium valproate as an example of how the health system fails to respond when patients and their families raise concerns about the safety of treatments. In December 2022, the Commission on Human Medicines (CHM) advised the MHRA to extend reducing the use of sodium valproate in men, based on a full safety review of reproductive toxicity in males including pre-clinical and clinical data.[12-14] The guidance now states that sodium valproate should not be started in new patients (male or female) below the age of 55, unless two specialists independently consider and document there are no effective alternative treatments or there are reasons that the reproductive risks do not apply. A second specialist signature is also needed for continuation of sodium valproate in women and girls of childbearing potential at their next annual specialist review. This is in addition to current safety measures, including the sodium valproate pregnancy prevention plan, which remains in place for any girls and women of childbearing potential.[12]

The direct and indirect effects of Covid-19 on routine care and actioning of clinical pathways have been well documented, for which a 'catch up' is required. What has not been demonstrated is the effect, if any, on ongoing regulatory advice, and if implementation of this also slowed. In this study we describe the use of sodium valproate across the population of England and Wales during the study period of January 2019 to December 2023 where medicines data linked to health care data were available, to investigate if Covid-19 impacted the ongoing use of sodium valproate by women of childbearing potential, in light of the publication of the Cumberlege Report and the Government's response to it and following earlier regulatory changes. Our aims were therefore to (1) describe the use of sodium valproate across the population of England and Wales during the period 2019-2023, following MHRA policy changes (April 2018), the Covid-19 pandemic (March 2020), the publication of the Cumberlege report (July 2020) and the Government's response to it (2021); (2) to put the use of sodium valproate in the context of other ASMs (lamotrigine, levetiracetam, carbamazepine, topiramate), and to benchmark use in women against men; (3) to describe geographical variation in the rate of use of sodium valproate by women of CBP (age 15-49) by local authority district; (4) to describe in detail the use of sodium valproate amongst women of CBP, including disease indications associated with use, and dose and timing of use during pregnancy; and (5) to explore the wider impact of policy changes, using epilepsy-related mortality as an example.

Materials and Methods

Data

We studied de-identified individual-level population-scale data accessed through the NHS England's Secure Data Environment (SDE) service for England, via the BHF Data Science Centre's CVD-COVID-UK/COVID-IMPACT Consortium, and the SAIL Databank for Wales.[15,16] Details are included in the Supplementary Material.

England:
Within the NHS England SDE service the NHS Business Service Authority (NHSBSA) dispensing data are updated on a monthly basis and include prescriptions for all medications dispensed in the community in England.[17] Dates in NHSBSA reflect the month in which the script was submitted for payment rather than the date a medication was dispensed to the patient. The first available month of NHSBSA data in the English SDE was April 2018. Data on indications, concurrent pregnancy, and counselling are drawn from the General Practice Extraction Service (GPES) extract Data for Pandemic Planning and Research (GDPPR), including data from 98% of all English general practices.[15]

Wales:
For Wales linked population-scale patient-level data was accessed through the Trusted Research Environment known as SAIL Databank.[16] Dispensing data are from all community pharmacies in Wales available within the Welsh Dispensing Data Set (WDDS),[18] which is updated on a monthly basis and covers records from January 2016 onwards. Within SAIL upon each monthly release of WDDS, a research ready data asset (RRDA) is created and maintained[19] based on Covid-19 population e-cohort RRDA,[16] which enhances the dispensing data for research purposes with mapping to additional coding classifications and meta-data. Welsh data are presented separately (e.g. disease indications; due to non-comparability of mapped codes) and/or excluded from some analyses (e.g. pregnancy; due to insufficient sample size).

Analyses

Prevalent and incident dispensings of sodium valproate & other ASMs over time and variation by sex
We analysed trends in prevalent (current) and incident (new) uses of sodium valproate before and during the Covid-19 pandemic period (1st January 2019 to 31st December 2023 in England; 1st January 2019 to 30th June 2022 in Wales). We compared this with the dispensing of other commonly used ASMs, including lamotrigine, levetiracetam and brivaracetam, carbamazepine and carbamazepine like compounds (oxcarbazepine, eslicarbamazepine) and topiramate (**Appendix A**). We defined CBP women as age bands 15-19, 20-29, 30-39, 40-49, and included men of equivalent ages for comparison. Code lists are provided in the **Supplementary Material**.

We identified incident (newly dispensed) users of sodium valproate, and also identified if sodium valproate was the first of any ASM used from those included in these analyses. To calculate person-level incident medication, we identified the first recorded occurrence of dispensed sodium valproate during the study period. We allowed an initial clearance window for the first nine months of data availability to permit monthly incidence counts to stabilise from the high levels of artefact "incidence" associated with records first becoming available for analysis. April 2018 (the start of NHSBSA data in the English SDE) was used in both English and Welsh data.

Through the linkage of medicines dispensing data to individual characteristics derived from linked primary and secondary care datasets,[20] we investigated how the dispensing of ASMs varied by age and sex. We counted items of sodium valproate and other ASMs dispensed to men and women by month in England and Wales during the period January 2019 to December 2023 (to June 2022 in Wales). We calculated annual age-specific rates of sodium valproate use per 100,000 women of CBP by referencing the relevant mid-year populations for England available from the Office for National Statistics (ONS)[21] and compared these to rates in men of equivalent age. [20 22]

Amongst women of CBP dispensed sodium valproate, we investigated the most common combinations of other ASMs dispensed in this population for the most recent calendar year of the study period. We calculated the percentage dispensed more than one ASM as a potential proxy of severity and/or control of epilepsy, as well as reporting the percentage taking sodium valproate alone.

Geographical variation in dispensings of sodium valproate
Drawing on geographical information at the point of dispense (lower-layer Super Output Area (LSOA) mapped to Local Authority District (LAD) which overlaps better with the newly formed Integrated Care Boards (ICB), we analysed variation in the rates of use of sodium valproate by women of CBP and men of the same age across England. We used the 2019 indicies of deprivation associated with each LSOA to report the deprivation decile profile of each ASM.[22]

Disease indications in women of CBP dispensed sodium valproate:
In women of CBP, we investigated the main disease indications (epilepsy, bipolar affective disorder, both or neither) associated with a dispensation of sodium valproate using HDRUK phenotypes[23] (**Appendix B;** codes clinically reviewed for relevance by CT and TW). In Wales, validated pre-existing study disease definitions were utilised.[24] GDPPR and Hospital Event Statistics (HES) records were linked to the dispensed medications records using the pseudo-identifier ID (a non-identifying unique master key that replaces the NHS number across all datasets) and screened for disease codes recorded in the women's EHR at any point up to the time of sodium valproate dispense. Results for Wales are presented separately as it was not possible to exactly map codes across countries. Prevalence of disease indication estimates at the time of dispensation are presented by age band expressed per 1000 women dispensed sodium valproate in each calendar year. We also evaluated evidence recorded within the general practice EHR (GDPPR) of implementation of the pregnancy prevention programme (PPP) amongst women of CBP by calendar year using codes detailed in **Appendix C**, and assessed whether this differed by disease indication.
Pregnancy rates in women of CBP dispensed sodium valproate and other ASMs:
Dispensings of ASMs during pregnancy were investigated by identifying instances where an ASM dispense occurred in a woman within an estimated pregnancy episode. Pregnancy episode was defined through linkage to Hospital Event Statistics (HES) maternity records where possible or otherwise via pregnancy code recorded in the GDPPR (**Appendix D**). HES maternity records enabled the pregnancy period to be estimated based on a known date of delivery, miscarriage or abortion. Please see **Supplementary Methods** for further detail on the identification of the pregnancy episode. Using this, we identified annual trends in the age-specific rates of pregnancy per 1000 women of CBP dispensed a ASM during the period 2019 to 2022, stratified by ASM.

We recorded evidence for dispense during the first trimester (days 1-90 of the pregnancy episode) and calculated the average quantity (in grams per day) of sodium valproate dispensed during the entire 40 weeks of pregnancy and by trimester. Within the NHSBSA data each dispensing event is accompanied by information about the quantity (number of items e.g. tablets) and medicine strength (concentration in mg or mg/ml). Dose was calculated by multiplying the quantity of items at each event by the concentration after converting to grams. The total number of grams dispensed was summed over the total pregnancy episode and during each trimester. This was divided by the corresponding number of days to calculate average grams per day (280 for the whole pregnancy episode; 90 for the first trimester).

Trends in epilepsy & recurrent seizures mortality by sex:
We examined English mortality data from the ONS available in the SDE. We extracted deaths by month from January 2015 to December 2022 including for ICD-10 codes G40 (Epilepsy & recurrent seizures) & G41 (Status epilepticus) where these codes appeared anywhere on the death certificate. Stratifying by sex, we fitted linear regression models to these data for the periods before and after the MHRA advice in March 2018 recording the slope and 95% confidence intervals from each model. In addition, time-series analysis was undertaken using autoregressive integrated moving average (ARIMA) models fitted to the earlier period January 2015 to March 2018 and used to predict the expected trend in epilepsy-related deaths from April 2018 onwards. This analysis was undertaken using the auto.arima function from the forecast package in R (version 4.2.2). Stationarity was tested using the Augmented Dickey–Fuller (ADF) and Kwiatkowski–Phillips–Schmidt–Shin (KPSS) tests.

Patient and Public Involvement statement:

Our protocol and manuscript were reviewed by patient and public participants from the BHF Data Science Centre.

Results

Data included and linkage between datasets are illustrated in **Figure 1** (England) and **Supplementary Figure 1** (Wales).

Prevalent and incident dispensings of sodium valproate & other ASMs over time and variation by sex
Monthly dispensings of sodium valproate to women aged 15-49 fell before, during and after the pandemic while dispensings to men were constant across the study period in England and Wales (**Figure 2 & Supplementary Figure 2)**. Prevalent rates of sodium valproate dispensed to women of CBP declined in all age bands in England between 2019 and 2022, contrasting with rates in men of similar age which were more stable and at a higher level (**Table 1**). Volumes of other anti-seizure medications in women of CBP such as lamotrigine, levetiracetam and topiramate increased over the study period (**Figure 2**). Prevalent rates of sodium valproate use were approximately four times higher amongst women aged 40-49 compared to women aged 20-29 (**Table 1**).

Incident rates of sodium valproate in women of CBP in England fell between 2019 and 2022 (**Table 1 & Figure 2**), from 7 to 5 in women aged 15-19, 11 to 7 in women aged 20-29, 14 to 7 in women aged 30-39 and 23 to 12 in women aged 40-49 (rates per 100,000 women of given age band). Incident use also declined in men of the same ages but remained at much higher levels at 53 to 43 in men aged 15-19, 59 to 47 in men aged 20-29, 57 to 42 in men aged 30-39 and 53 to 35 in men aged 40-49 (rates per 100,000 men of given age band). (**Table 1 & Figure 2**). In 2023, fewer than 400 women across all those in England aged 15-49 years were dispensed sodium valproate without first trying another ASM from those selected for inclusion in this analysis (**Supplementary Figure 3**).

Distribution of dispense of sodium valproate differed markedly by sex and, in comparison to other ASMs, were much lower in women of CBP compared to men in the same age bands (**Supplementary Figure 3**). Mirroring this, the uptake of the alternative ASMs, particularly lamotrigine and topiramate, was higher in women of CBP compared to men of the same age (**Supplementary Figure 3**). Dispense of sodium valproate after age 60 was much more balanced across genders.

In 2023, 64% of all women of CBP dispensed sodium valproate were using this medication exclusively in that calendar year, while 30% were dispensed two anti-seizure medications, with levetiracetam and lamotrigine being the most commonly dispensed in combination with sodium valproate (**Supplementary Figure 4)**.

Geographical variation in dispensings of sodium valproate
Geographical differences in the rates of dispense of sodium valproate to women of CBP were observed, with LADs in the Northwest, Eastern coastal and bordering Scotland having some of the highest rates (**Figure 3 & Supplementary Figure 5**).

Disease indications in women of CBP dispensed sodium valproate:
We found that for women of CBP dispensed sodium valproate, the most common indication was epilepsy (~751 per 1000 women in 2023), then bipolar affective disorder (~193 per 1000 women), and this trend was becoming more pronounced over time **(Figure 4)**. However, approximately 10% of women of CBP were being dispensed sodium valproate without evidence of either of these indications available in the electronic health record (**Figure 4 & Supplementary Figure 6)**. Indication patterns were similar in Wales, but an even higher proportion without evidence was observed, possibly reflecting incomplete mapping of codelists (**Supplementary Figure 6**). Bipolar affective disorder was a more common indication in the older groups of women of CBP (30-39, 40-49), with the younger CBP groups (15-19, 20-29) dominated by the epilepsy indication (**Supplementary Figure 7)**.

Pregnancy rates in women of CBP dispensed sodium valproate and other ASMs
The number of women of CBP who had any evidence of sodium valproate dispensed during pregnancy fell from 6.0 women per 1000 women of CBP taking sodium valproate in 2019 to 5.2 per 1000 women of CBP taking sodium valproate in 2022 in England (**Figure 5**). These rates were lower than for other ASMs with the highest rates observed for levetiracetam and lamotrigine. Lower pregnancy rates were also observed for women of CBP dispensed topiramate at 12.1 women per 1000 in 2019, although rates increased slightly in 2022 to 12.9. Absolute numbers of women dispensed sodium valproate during a pregnancy episode fell from 140 in 2019 to 85 in 2022 **(Figure 5**). Assigning each pregnancy to the year in which the pregnancy episode commenced to allow for pregnancies that cross two calendar years results in lower numbers (112 in 2019 and 62 in 2022 respectively) (**Table 2**). The majority of women dispensed sodium valproate during the pregnancy episode received some during the first trimester. Most women received an average dose of <1g sodium valproate per

day over the course of the pregnancy episode. Only 11 women were dispensed more than an average of 1g per day during pregnancies commenced in 2022; 15 received >1g per day on average in the first trimester.

Whilst some evidence of counselling according to the pregnancy prevention plan (PPP) was recorded in the GDPPR, we found no evidence of PPP counselling using the available codes for the majority of women dispensed sodium valproate, a pattern that was consistent across disease indications, although there is some evidence for increased recording of these codes over time (**Supplementary Figure 8**).

Trends in epilepsy related mortality by sex

Linear regression of counts of epilepsy-related deaths for the period January 2015 to March 2018 revealed no evidence for a change in death rates over time for either men or women of CBP age (**Figure 6)**. The ARIMA model fitted to the period January 2015 to March 2018 predicted constant death counts for the period after March 2018: 28 (95% CI 26.7-29.3) epilepsy related deaths per month for men; and 18 (95% CI 16.2-19.0) for women. Beta co-efficients from the linear models were positive during the subsequent period April 2018 to December 2022 for both sexes, with stronger evidence for change in men (beta=0.0039, P-value=0.034) than in women (beta=0.0019, P-value=0.066).

Discussion

We leveraged the scale of data that links dispensed medications to disease indications and demographic characteristics across the whole population of England and Wales to comprehensively describe the epidemiology of use of sodium valproate. This overcomes limitations of sampling found in epidemiological studies carried out to date. Such an approach can provide a mechanism for regulators and those responsible for health care delivery to track changes in dispensing of medicines and how this varies by characteristics including age, sex, geography, indication, pregnancy and presence of other comorbidities in near real time. Using these data, we have quantified the rates of use of sodium valproate, comparing use in women and men, and with other ASMs during the study period, which included the Covid-19 pandemic, the Cumberlege report and followed policy recommendations by the MHRA. We were able to investigate the indications for which sodium valproate was dispensed for the whole population, and describe geographical variation in its use. We have defined a systematic approach to dispensing of sodium valproate to women of CBP, including during pregnancy and dosage during different developmental periods of pregnancy.

Our findings demonstrate prevalent sodium valproate dispensing during the period 2019-2023 fell in women of CBP, although no changes were seen in men of equivalent age. However, geographical differences in the rate of dispense of sodium valproate to women of CBP by local authority district remain. For incident dispenses, declines were seen in both women of CBP and men. The rate of pregnancy amongst those taking sodium valproate fell from 6.0 to 5.2 pregnancies per 1,000 women aged 15-49 dispensed sodium valproate in England. These findings expand previous work and demonstrate that whole population linked records are useful to track and implement medicines safety.[25,26,27,28 29] Overall, these data demonstrate that there is evidence of harm reduction (meaningful reduction in sodium valproate-exposed pregnancies which have a high risk of serious lifelong harms) without increase in the most serious epilepsy-related harm of deaths in women during the study period.

There are some particular points worth of highlighting that this data science approach can be helpful for, but also where more research is needed taking into account the limitations of these analyses which could be supplemented by further investigation.

First, off-label use of sodium valproate could be a useful first target. Sodium valproate is the first-choice antiepileptic for newly diagnosed IGE based on evidence from the SANAD trials.[1,2] However, sodium valproate is also used in other forms of epilepsy and in bipolar affective disorder, where the evidence base is poor and other drugs are similarly effective. The data are able to reveal epilepsy codes broadly although granularity of subtype of epilepsy is not available, and therefore identifying non-IGE use of sodium valproate is not possible. However, in 10% of those with a sodium valproate dispense, we were unable to identify a previous indication for epilepsy or bipolar affective disorder in the EHR suggesting potential off-label use. It should be noted that incomplete recording or the availability of codes meanroutine data lack sensitivity to capture epilepsy or bipolar affective disorder in totality.[30] Codes for migraine were not available in the General Practice Extraction Service (GPES) Data for pandemic planning and research.

Second, our results demonstrate that the number of pregnant women in whom a sodium valproate dispense was detected fell during the study period. This could be attributed to implementation of MHRA guidance, although other factors such as reduced contact with the health care system, and lower rates of birth were also a characteristic of the pandemic that may have contributed to these trends and therefore ongoing pharmacovigilance is essential. Our approach provides a comprehensive method to do that, but also demonstrates that with linked data, individual drug registries may not be required, rather pipelines within the linked data can be informative across a range of drugs. This is particularly highlighted here with other ASMs: while we used these to benchmark sodium valproate use, it also provided additional valuable information. For example, concern has been raised about the teratogenic effect of topiramate from the Nordic Registry,[29] although a US study did not find higher risk of autism following topiramate exposure.[31] This is classed as an ASM for this research as this is how it is catalogued in the BNF; however, topiramate is also used as a treatment for other conditions such as migraine. Our data demonstrate that prevalent use of topiramate has increased over the period that we have studied. We also observe rates of pregnancy are higher in women taking topiramate and may be increasing. The data science approach described here could be replicated for topiramate, without having to establish a registry, rather re-using code across medicines and other pertinent characteristics.

Third, like any chronic condition, a switch away from a drug that has provided good control may contribute to loss of control. This is true of epilepsy and loss of control may lead to increased seizures and as a result health care utilisation and in extreme cases, death including sudden unexpected death in epilepsy (SUDEP). Epilepsy, particularly when seizures are not controlled, is associated with an increased risk of psychiatric disorders, cognitive impairment, cardiovascular and bone disease, physical injuries and increased mortality.[32] The fact that use of sodium valproate use still occurs during pregnancy may be of concern, but it may also be explained by the desire to avoid such complications, including SUDEP. During the review of this manuscript the Patient Safety Commissioner (PSC) published the Hughes report, highlighting the importance of shared decision making between women of child bearing potential, pregnant women and those treating their epilepsy.[33] This needs to be in place despite pressures on the system, given the enduring effects of harms to either the mother or fetus, the latter of which has also been economically quantified. Our approach aims to enhance pharmacovigilance as it could be deployed within the health care system, but also enhance it by seeding further research. For example, we have quantified the dose of sodium valproate used during pregnancy, demonstrating this is <1g/ day for the majority. Such evidence can be useful to more precisely understand dose response relationships, facilitated by linked maternal and children records. Such research will also be able to place UK data in the context of international findings, allowing us to more fully understand benefit and risk profiles.[34]

Linked to this is the importance of being able to track any unintended effects when switching away from sodium valproate. The confidential enquiry investigating maternal deaths (MBRRACE-UK) is an important source of information that aims to improve maternal health care and well-being. They observed that SUDEP may be increasing in women who are pregnant and during the post-partum period: in 2013-2015 there were 8 SUDEP deaths, in 2016-2018 there were 18 SUDEP deaths and in 2019-2021 there were 14 SUDEP deaths. In our analyses we did not detect a clear signal of increasing epilepsy related mortality although the codes we used are broad and not confined to SUDEP. Neither our, nor the MBRRACE report, can causally link switching away from sodium valproate with mortality. However, our data, if brought together with the approach used by MBRRACE could begin to tease out such associations and also extend analyses to morbidity amongst women (e.g. seizure control, hospitalisation, epilepsy subtypes), as well as sequential and/or combined use of ASMs and their effects on epilepsy related outcomes.

We do observe an emerging mortality trend in men. The timing of this trend does not overlap with recent advice from the MHRA relating to men and more research is required to ascertain the reasons for this trend. However, it does demonstrate the utility of a national approach for regulators and those implementing health policy. This is particularly important at a time when further changes to MHRA advice are being implemented, restricting its use in men as well as women under the age of 55. Our data science and flexible pipeline approach can enable near real time tracking to enhance pharmacovigilance strategies extending the analysis presented here by incorporating other analyses, e.g. health care utilisation. However, it should also be noted that trends over time are required to reliably interpret impacts on outcomes such as death as variation in the population due to other reasons, here the Covid-19 pandemic being one factor, could be responsible for year-to-year variation.

Fourth, shared decision making was highlighted by The Cumberlege report, with many women taking sodium valproate remaining unaware of the harms that are associated with it. Again using a data science approach, we found no primary care evidence for PPP for the majority of women, but this may be explained by PPP activity mostly occurring in secondary care and this information may not always transfer to the primary care record in a timely fashion or at all. Futhermore, this information may be stored as free text rather than recorded codes and is therefore not captured here. An audit of specialists suggested that this is occurring but implementation is not universal despite the regulatory advice. Digitisation of the risk acknowledgement form across primary and secondary care may give greater visibility to healthcare professionals and facilitate monitoring of trends in counselling. Greater sharing of this information with primary care to help identify and monitor these individuals is important, as the MHRA guidance places the onus on GPs to ensure individuals are counselled despite this counselling occurring in secondary care. Another limitation is the General Practice Extraction Service (GPES) Data for pandemic planning and research does not include all SNOMED codes that may be relevant for PPP and the Annual Risk Acknowledgement Form (ARAF), and evidence may therefore be underestimated in these analyses.

Finally, there are limitations which are important to acknowledge and could be answered in further analyses. These include understanding outcomes and health trajectories in those individuals switched away from sodium valproate, using individual level data, to understand where seizure control has been achieved or not, how this may be linked to the medicines they are switched to, or if we can investigate other factors that contribute to poor control. We have focussed here on mortality to examine unintended effects; poor control can also be proxied by health care utilisation which we have not investigated here and could be an additional and useful analysis. Some limitations of the data themselves include the non-availability of dispensing data prior to April 2018 within NHS England's Secure Data Environment. Access to this data would have facilitated more formal modelling of the impact of the policy recommendations made by the MHRA in 2018. It is possible that at least some of the dispense of sodium valproate without an indication for epilepsy or bipolar affective disorder can be explained by incomplete data in the EHR including partial coverage of codes and/or incomplete mapping or linkage of medicines data to other datasets. Other limitations of this analysis include assessment of "real-life" adherence, as it remains unknown amongst women dispensed sodium valproate what proportion went on to actually take the drug during pregnancy. It is not possible to accurately discern whether the pregnancy episodes reported in this study were planned or unplanned due to recording and reporting biases. It would also have been informative to measure use of contraception. However, because not all forms of contraception are recorded in the EHR this was not possible. Further research to understand the context of the increasingly uncommon but continued dispense of sodium valproate to pregnant women is vital. Finally, we were unable to incorporate data from Wales in all analyses (e.g. pregnancy rates by ASM) because of the need to prevent potential identification of individuals, demonstrating the requirement for very large datasets to understand rare conditions and/or rare treatments.

Conclusions

We found continuing but slowly declining use of sodium valproate by women of CBP in England and Wales, including during pregnancy, across the study period 2019 to 2023 which included the Covid-19 pandemic. Incident use also declined in men of the same age but remained at much higher levels. Ongoing pharmacovigilance continues to be essential to track use of this teratogenic medicine and the impact of regulatory changes on it, and could be extended to epilepsy outcomes including outpatient and emergency attendance and SUDEP.

Funding:

The British Heart Foundation Data Science Centre (grant No SP/19/3/34678, awarded to Health Data Research (HDR) UK) funded co-development (with NHS ENGLAND) of the Secure Data Environment service for England, provision of linked datasets, data access, user software licences, computational usage, and data management and wrangling support, with additional contributions from the HDR UK Data and Connectivity component of the UK Government Chief Scientific Adviser's National Core Studies programme to coordinate national Covid-19 priority research. Consortium partner organisations funded the time of contributing data analysts, biostatisticians, epidemiologists, and clinicians.

This research is part of the Data and Connectivity National Core Study, led by Health Data Research UK in partnership with the Office for National Statistics and funded by UK Research and Innovation (grant ref MC_PC_20058). This work was also supported by The Alan Turing Institute via 'Towards Turing 2.0' EPSRC Grant Funding.

This work was supported by the Con-COV team funded by the Medical Research Council (grant number: MR/V028367/1). This work was supported by Health Data Research UK, which receives its funding from HDR UK Ltd (HDR-9006) funded by the UK Medical Research Council, Engineering and Physical Sciences Research Council, Economic and Social Research Council, Department of Health and Social Care (England), Chief Scientist Office of the Scottish Government Health and Social Care Directorates, Health and Social Care Research and Development Division (Welsh Government), Public Health Agency (Northern Ireland), British Heart Foundation (BHF) and the Wellcome Trust. This research has been supported by the ADR Wales programme of work. ADR Wales, part of the ADR UK investment, unites research expertise from Swansea University Medical School and WISERD (Wales Institute of Social and Economic Research and Data) at Cardiff University with analysts from Welsh Government. ADR UK is funded by the Economic and Social Research Council (ESRC), part of UK Research and Innovation. This research was supported by ESRC funding, including Administrative Data Research Wales (ES/W012227/1). This work was supported by the Wales Covid-19 Evidence Centre, funded by Health and Care Research Wales.

RS, Research Professorship, NIHR303160, is funded by the NIHR for this research project. The views expressed in this publication are those of the author(s) and not necessarily those of the NIHR, NHS or the UK Department of Health and Social Care.

DH is supported by the Wellcome Trust (215621/Z/19/Z) and the Medical Research Foundation.
AL holds an NIHR funded academic clinical fellowship.

FT is funded by HDR UK.

CT is supported by a UCL UKRI Centre for Doctoral Training in AI-enabled Healthcare studentship (EP/S021612/1), MRC Clinical Top-Up, and a studentship from the NIHR Biomedical Research Centre at University College London Hospital NHS Trust.

AGM is a NIHR Senior Investigator and also part funded by NIHR ARC North West Coast. The views expressed in this article are those of the author(s) and not necessarily those of the NIHR, or the Department of Health and Social Care.

DW is supported by the NIHR, University College London Hospitals Biomedical Research Centre.

KK is supported by the National Institute for Health Research (NIHR) Applied Research Collaboration East Midlands (ARC EM) and the NIHR Leicester Biomedical Research Centre (BRC).

Acknowledgements:

This work was carried out with the support of the BHF Data Science Centre led by HDR UK (BHF Grant no. SP/19/3/34678). This study makes use of de-identified data held in NHS England's Secure Data Environment service for England and made available via the BHF Data Science Centre's CVD-COVID-UK/COVID-IMPACT consortium. This work uses data provided by patients and collected by the NHS as part of their care and support. We would also like to acknowledge all data providers who make health relevant data available for research.

This work uses data provided by patients and collected by the NHS as part of their care and support. We would also like to acknowledge all data providers who make anonymised data available for research. We wish to acknowledge the collaborative partnership that enabled acquisition and access to the de-identified data in Wales, which led to this output. The collaboration was led by the Swansea University Health Data Research UK team under the direction of the Welsh Government Technical Advisory Cell and includes the following groups and organisations: the Secure Anonymised Information Linkage (SAIL) Databank, Administrative Data Research Wales, NHS Wales Informatics Service, Public Health Wales, NHS Shared Services Partnership and the Welsh Ambulance Service Trust. All research conducted has been completed under the permission and approval of the SAIL independent Information Governance Review Panel (project number: 0911).

Data availability:

The data used in this study are available in NHS England's Secure Data Environment (SDE) service for England, but as restrictions apply they are not publicly available (https://digital.nhs.uk/services/secure-data-environment-service). The CVD-COVID-UK/COVID-IMPACT programme led by the BHF Data Science Centre (https://bhfdatasciencecentre.org/) received approval to access data in NHS England's SDE service for England from the Independent Group Advising on the Release of Data (IGARD) (https://digital.nhs.uk/about-nhs-digital/corporate-information-and-documents/independent-group-advising-on-the-release-of-data) via an application made in the Data Access Request Service (DARS) Online system (ref. DARS-NIC-381078-Y9C5K) (https://digital.nhs.uk/services/data-access-request-service-dars/dars-products-and-services). The CVD-COVID-UK/COVID-IMPACT Approvals & Oversight Board (https://bhfdatasciencecentre.org/areas/cvd-covid-uk-covid-impact/) subsequently granted approval to this project to access the data within NHS England's SDE service for England. The de-identified data used in this study were made available to accredited researchers only. Those wishing to gain access to the data should contact bhfdsc@hdruk.ac.uk in the first instance.

The data from Wales used in this study are available in the SAIL Databank at Swansea University, Swansea, UK, but as restrictions apply they are not publicly available. All proposals to use SAIL data are subject to review by an independent Information Governance Review Panel (IGRP). Before any data can be accessed, approval must be given by the IGRP. The IGRP gives careful consideration to each project to ensure proper and appropriate use of SAIL data. When access has been granted, it is gained through a privacy protecting safe haven and remote access system referred to as the SAIL Gateway. SAIL has established an application process to be followed by anyone who would like to access data via SAIL at https://www.saildatabank.com/application-process

Contributors:

C.S. is the Director of the BHF DSC and coordinated approvals for and access to data within NHS England's SDE and the SAIL Databank for CVD-COVID-UK/COVID-IMPACT. C.D., R.T., F.T., M.K., T.M., A.K., M.A., M.A.M, K.K., A.A., A.D.M, M.P, A.G.M., D.W., D.H., C.S. and R.S. contributed to the design of the study and oversight. T.M., A.K., and A.A. contributed to data collection. C.D., R.T., Y.Y.F., F.T., M.K., S.K., A.L., C.T., T.W., A.G.M, D.W. and R.S contributed to data analysis and/or interpretation of the data. C.D., R.T., Y.Y.F., F.T., A.D.M., M.P, A.G.M., D.W., D.H., C.S. and R.S. contributed to drafting the manuscript. All authors critically reviewed and provided input to manuscript drafts and approved the final version for submission to the journal.

R.S. is responsible for the overall content as guarantor.

Competing interests statement:

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare:

MP declares support paid to the University of Liverpool from Health Data Research UK; grant funding from the MRC and 4 industry partners (Roche, UCB, Eli Lilly and Novartis) for the MRC Clinical Pharmacology Training Scheme; Grant funding from the MRC and 4 industry partners (Astra Zeneca, GSK, Hammersmith Medicines Research and Optum) for the MRC Medicines Development Fellowship; Developed an HLA genotyping panel with MC Diagnostics with funding from NIHR i4i (no financial benefit); IMI funding for the ARDAT Consortium (www.ardat.org). MP is Medical Trustee British Heart Foundation, Council member for the Medical Research Council, Chair of the Prix Galien Foundation UK and Chair of the Commission on Human Medicines (CHM).

DH is a member of CHM.

RS is a member of the Pharmacovigilance Expert Advisory Group, a sub-committee of the CHM.

CT has received funding paid to University College London (UCL-GSK Phenomics Hub) from GlaxoSmithKline (GSK), outside of the scope of the submitted work.

AGM has received funding paid to University of Liverpool from UCB Pharma, Sanofi, Eiasi and GSK. He is a member of the MHRA valproate implementation group, chief investigator of the SANAD trials and senior author of the Cochrane reviews assessing the teratogenic effects of anti-seizure medications.

FT declares support from UKRI-MRC - Dementias Platform UK 2 - Integrated Dementia Experimental Medicine (MR/T033371/1), UKRI-ESRC, Health and Care Research Wales.

All other authors declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethics approval and consent statement:

The North East - Newcastle and North Tyneside 2 research ethics committee provided ethical approval for the CVD-COVID-UK/COVID-IMPACT research programme (REC No 20/NE/0161) to access, within secure trusted research environments, unconsented, whole-population, de-identified data from electronic health records collected as part of patients' routine healthcare.

Provenance and peer review:

Not commissioned; externally peer reviewed.

References:

1. Marson AG, Al-Kharusi AM, Alwaidh M, et al. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. Lancet 2007;369:1016-26.
2. Marson A, Burnside G, Appleton R, et al. The SANAD II study of the effectiveness and cost-effectiveness of valproate versus levetiracetam for newly diagnosed generalised and unclassifiable epilepsy: an open-label, non-inferiority, multicentre, phase 4, randomised controlled trial. Lancet 2021;397:1375-86.
3. Glauser TA, Cnaan A, Shinnar S, et al. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy. N Engl J Med 2010;362:790-9.
4. Meador KJ, Baker GA, Browning N, et al. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. N Engl J Med 2009;360:1597-605.
5. Christensen J, Gronborg TK, Sorensen MJ, et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. JAMA 2013;309:1696-703.
6. Wlodarczyk BJ, Palacios AM, George TM, Finnell RH. Antiepileptic drugs and pregnancy outcomes. Am J Med Genet A 2012;158A:2071-90.
7. Bromley R, Weston J, Adab N, et al. Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child. Cochrane Database Syst Rev 2014;2014:CD010236.
8. Weston J, Bromley R, Jackson CF, et al. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Cochrane Database Syst Rev 2016;11:CD010224.
9. New measures to avoid valproate exposure in pregnancy, https://www.gov.uk/government/news/new-measures-to-avoid-valproate-exposure-in-pregnancy, .
10. Valproate use by women and girls, https://www.gov.uk/guidance/valproate-use-by-women-and-girls, .
11. The Independent Medicines and Medical Devices Safety Review, chaired by Baroness Julia Cumberlege. First Do No Harm- The report of the Independent Medicines and Medical Devices Safety Review, https://www.immdsreview.org.uk/downloads/IMMDSReview_Web.pdf,2020 8 July 2020.
12. News story: Update on MHRA review into safe use of valproate, https://www.gov.uk/government/news/update-on-mhra-review-into-safe-use-of-valproate,. 2022.
13. Information on Sodium Valproate, https://www.sanofi.com/en/our-company/social-impact/responsible-business-values/sodium-valproate. 2023.
14. Epilim® (Valproate) - Risk of neurodevelopmental disorders including autism spectrum disorders in children after paternal exposure, https://www.hsa.gov.sg/announcements/dear-healthcare-professional-letter/epilim-(valproate)---risk-of-neurodevelopmental-disorders-including-autism-spectrum-disorders-in-children-after-paternal-exposure. 21 March 2023,.
15. Wood A, Denholm R, Hollings S, et al. Linked electronic health records for research on a nationwide cohort of more than 54 million people in England: data resource. BMJ 2021;373:n826.
16. Lyons RA, Jones KH, John G, et al. The SAIL databank: linking multiple health and social care datasets. BMC Med Inform Decis Mak 2009;9:3.
17. NHS Business Services Authority. Dispensing Data, https://www.nhsbsa.nhs.uk/prescription-data/dispensing-data.
18. Welsh Dispensing Dataset (WDDS), https://web.www.healthdatagateway.org/dataset/50ef6443-ed4b-40f9-97fb-1cfd53be6579.
19. Torabi F, Akbari A, North L, et al. Evaluating the effect of COVID-19 on dispensing patterns: a national cohort analysis. https://www.medrxiv.org/content/10.1101/2021.02.15.21251552v12021.
20. CVD-COVID-UK/COVID-IMPACT TRE Dataset Provisioning Dashboard, https://www.hdruk.ac.uk/wp-content/uploads/2023/07/230713-CVD-COVID-UK-COVID-IMPACT-TRE-Dataset-Provisioning-Dashboard-1.pdf.
21. Estimates of the population for the UK, England, Wales, Scotland and Northern Ireland, https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesforukenglandandwalesscotlandandnorthernireland.
22. GOV.UK. English indices of deprivation 2019, https://www.gov.uk/government/statistics/english-indices-of-deprivation-2019,.
23. HDRUK Phenotype Library, https://phenotypes.healthdatagateway.org/,.
24. Fonferko-Shadrach B, Lacey AS, White CP, et al. Validating epilepsy diagnoses in routinely collected data. Seizure 2017;52:195-8.
25. Medicines and Pregnancy Registry: Valproate use in females aged 0 to 54 in England (April 2018 to March 2022), https://digital.nhs.uk/data-and-information/publications/statistical/mi-medicines-and-pregnancy-registry,.
26. McTaggart S, MacColl G, Gronkowski K, Wood R, Leach JP, Bennie M. Impact of regulatory safety notices on valproate prescribing and pregnancy outcome among women of child-bearing potential in Scotland: a population-based cohort study. BMJ Open 2022;12:e058312.

27. Medicines and Healthcare products Regulatory Agency. CPRD Study Monitoring the Use of Valproate in Girls and Women in the UK January 2010 to June 2019, https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/844070/CPRD_valproate_usage_report-3rd-revision-Nov-19.pdf, .
28. Abtahi S, Pajouheshnia R, Duran CE, et al. Impact of 2018 EU Risk Minimisation Measures and Revised Pregnancy Prevention Programme on Utilisation and Prescribing Trends of Medicinal Products Containing Valproate: An Interrupted Time Series Study. Drug Saf 2023;46:689-702.
29. Bjork MH, Zoega H, Leinonen MK, et al. Association of Prenatal Exposure to Antiseizure Medication With Risk of Autism and Intellectual Disability. JAMA Neurol 2022;79:672-81.
30. Mbizvo GK, Bennett KH, Schnier C, Simpson CR, Duncan SE, Chin RFM. The accuracy of using administrative healthcare data to identify epilepsy cases: A systematic review of validation studies. Epilepsia 2020;61:1319-35.
31. Hernandez-Diaz S, Straub L, Bateman BT, et al. Risk of Autism after Prenatal Topiramate, Valproate, or Lamotrigine Exposure. N Engl J Med 2024;390:1069-79.
32. Kodankandath TV, Theodore D, Samanta D. Generalized Tonic-Clonic Seizure. StatPearls. Treasure Island (FL)2023.
33. Patient Safety Commissioner. The Hughes Report: Options for redress for those harmed by valproate and pelvic mesh, https://www.patientsafetycommissioner.org.uk/our-reports/the-hughes-report/,2024.
34. Cohen JM, Alvestad S, Suarez EA, et al. Comparative Risk of Major Congenital Malformations With Antiseizure Medication Combinations vs Valproate Monotherapy in Pregnancy. Neurology 2024;102:e207996.

Table 1: Incident and prevalent rates of sodium valproate dispense in women and men aged 15-49 years by age-band in England 2019-2022; rate dispensed per 100,000.

	Women				Men			
	2019	**2020**	**2021**	**2022**	**2019**	**2020**	**2021**	**2022**
Age-specific rate of sodium valproate dispense per 100,000								
Prevalent								
15-19	729	636	602	595	2,787	2,934	2,801	2,871
20-29	1,110	1,069	968	892	4,426	4,646	4,720	4,634
30-39	2,172	1,915	1,714	1,549	6,029	6,222	6,302	6,307
40-49	5,013	4,590	4,100	3,709	8,151	8,361	8,364	8,313
Incident								
15-19	7	5	5	5	53	46	40	43
20-29	11	7	6	7	59	52	50	47
30-39	14	10	9	7	57	48	44	42
40-49	23	15	12	12	53	42	39	35
Total count of dispensings of sodium valproate								
Prevalent								
15-19	11,660	10,330	9,975	10,090	44,570	47,630	46,390	48,720
20-29	40,045	37,950	34,105	31,915	159,590	164,930	166,215	165,725
30-39	81,260	71,625	64,285	58,855	225,590	232,700	236,410	239,635
40-49	179,005	163,040	144,360	130,270	291,055	296,965	294,515	291,970
Incident								
15-19	105	85	80	90	845	745	665	735
20-29	380	245	230	235	2,130	1,835	1,755	1,670
30-39	505	385	325	260	2,140	1,805	1,665	1,610
40-49	805	525	435	420	1,885	1,500	1,370	1,230

Table 2: Summary of use of sodium valproate in women identified with dispense during pregnancy; N per year, N women dispensed during first trimester, total dose in grams dispensed during pregnancy; England 2019-2022. Each pregnancy is assigned only to the year in which it commenced; total N=325.

	Year pregnancy start			
N women	**2019**	**2020**	**2021**	**2022**
Total pregnant women	112	73	78	62
Dispensed during first trimester	102	69	72	57
Average grams per day dispensed during pregnancy				
<0.5g	73	48	41	34
0.5 - 1g	23	14	18	17
>1g	16	11	19	11
Average grams per day dispensed during first trimester				
<0.5g	48	28	33	17
0.5 - 1g	26	26	19	25
>1g	27	14	22	15
Average grams per day dispensed during second & third trimesters				
<0.5g	38	17	19	17
0.5 - 1g	17	14	11	19
>1g	16	10	25	<10

Figure 1: Flowchart to illustrate data sources and linkage between datasets included in analysis, England

Figure 2: Monthly counts of prevalent and incident ASMs dispensed in the community January 2019 to December2023; men and women aged 15-49 years, England. Vertical lines indicate dates of pandemic lockdowns for reference.

Figure 3: Geographical distribution of sodium valproate dispensed to women of CBP in England by Local Authority District, 2022; rate per 10,000 women aged 15-49 years

Figure 4: Women aged 15-49 years dispensed sodium valproate with evidence of epilepsy or bipolar affective disorder in the electronic health record by year 2019-2023 in England; rate per 1000

Figure 5: Rate of dispense during a pregnancy episode, 2019 to 2022 in England per 1000 women aged 15-49 dispensed ASM

	Pregnancy rate per 1000 women aged 15-49 dispensed ASM				Total count of pregnant women aged 15-49 dispensed ASM			
	2019	2020	2021	2022	2019	2020	2021	2022
Sodium Valproate	6.0	5.2	5.4	5.2	140	105	95	85
Topiramate	12.1	12.3	12.2	12.9	535	550	580	610
Carbamazepine	26.9	25.8	25.7	23.5	830	760	740	650
Lamotrigine	47.1	45.9	46.6	46.7	2900	2980	3210	3375
Levetiracetam	56.0	54.5	56.0	53.9	1960	2015	2175	2170

Figure 6: Epilepsy and recurrent seizures mortality (ICD-10 G40 & G41) over time; count of deaths in men and women of child-bearing age 15-49 years by year and month, 2015 to 2022; England. Solid black vertical lines indicate MHRA policy change; broken vertical lines indicate pandemic national lockdowns.

	Jan 2015 to March 2018			April 2018 to December 2022		
	Coefficient	SE	P-value	Coefficient	SE	P-value
Males	-0.0032	0.0021	0.134	0.0039	0.0018	0.034
Females	0.0004	0.0022	0.872	0.0019	0.0010	0.066