

## Quality Improvement Data Report: Prescription of valproate to patients of childbearing potential

### Introduction

Valproate is licensed for use in epilepsy and bipolar disorder. It is also sometimes used to prevent migraine headaches. Although it is a very effective and safe drug for some patients, there are **significant risks**<sup>1</sup> if valproate is taken during pregnancy. It can cause birth defects (including spina bifida and face and skull malformations) and problems with development.

This report has been produced as part of the programme of RCGP/CPRD Quality Improvement reports, which focus on prescribing and patient safety and is specific to your practice.

The table below shows patients who meet the following criteria:

- Anyone whose gender is not male
- Age 12-55 years in 2021
- Any valproate prescription (sodium valproate, valproic acid or valproate semisodium) issued in 2021

The code list used to identify valproate prescriptions is available on the [project page on the CPRD website](#)<sup>2</sup>.

The search included only currently registered patients that have not dissented from secondary use of their clinical data. The analysis is based on our latest database build, for which data were extracted from your practice on Tuesday 5<sup>th</sup> October, 2021.

### Patients identified at practice

Patient Identifier	Birth Year	Number of prescriptions issued in 2021	Date of last issue	Pregnancy Prevention Programme (PPP) recorded	Patient not capable of becoming pregnant
1234	1978	6	20/07/2021		
5678	1984	1	13/05/2021		Y
9010	1992	2 <sup>†</sup>	18/09/2021	Y	
9543	1986	3 <sup>†</sup>	12/06/2021	Y	

<sup>†</sup> - this patient was listed in your previous valproate report

<sup>1</sup> Sodium Valproate - NHS England  
<https://www.england.nhs.uk/patient-safety/sodium-valproate>

<sup>2</sup> Project page on CPRD website  
<https://www.cprd.com/generalpractitioner/QualityImprovementProject.asp>

## Recommended next steps

The MHRA has produced a template letter to invite patients for a treatment review, which can be accessed from the project page on the [RCGP website](#)<sup>3</sup>. A link to the letter is [here](#).

The MHRA also provides a [Guide for Healthcare Professionals](#)<sup>4</sup> which contains a comprehensive list of actions to follow when engaging with patients using valproate and how to implement a Pregnancy Prevention Plan (PPP, also known as PREVENT):

- Ensure continuous use of **highly effective** (implant or coil) contraception in all patients of childbearing potential (consider the need for pregnancy testing if not a highly effective method).
- Check that all patients have an up to date, signed, Annual Acknowledgment of Risk Form each time a repeat prescription is issued.
- Ensure the patient is referred back to the specialist for annual review.
- Refer to the specialist urgently (within days) in case of unplanned pregnancy or where a patient wants to plan a pregnancy

If a PPP is in place, please make this clear on the patient's electronic healthcare record, e.g. by using the appropriate SNOMED code. If they are not, please arrange an appropriate appointment with the patient.

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<sup>3</sup> Project webpage on RCGP website  
<https://www.rcgp.org.uk/clinical-and-research/our-programmes/quality-improvement/quality-improvement-prescribing-and-patient-safety-reports.aspx>

<sup>4</sup> Guide for Healthcare Professionals  
[https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/708850/123683\\_Valproate\\_HCP\\_Booklet\\_DR15.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/708850/123683_Valproate_HCP_Booklet_DR15.pdf)

## Rationale<sup>5</sup>

In patients who take valproate while pregnant, around 1 in 10 babies will have a birth defect. Birth defects include:

- spina bifida (where the bones of the spine do not develop properly);
- facial and skull malformations (including cleft lip and palate, where the upper lip or facial bones are split);
- malformations of the limbs, heart, kidney, urinary tract and sexual organs.

About 3 to 4 children in every 10 may have developmental problems where the long-term effects are not known. The effects on child development include:

- being late in learning to walk and talk;
- lower intelligence than other children of the same age;
- poor speech and language skills;
- memory problems.

Children exposed to valproate in the womb are three times more likely to have autism or autistic spectrum disorders. There is also some evidence children may be more likely to be at risk of developing symptoms of attention deficit hyperactivity disorder (ADHD).

In England, current [advice from the National Institute for Health and Care Excellence \(NICE\)](#)<sup>6</sup> states that valproate should not be prescribed for any condition in patients of childbearing potential. If other options are ineffective or not tolerated and a [pregnancy prevention programme \(PPP\)](#)<sup>7</sup>, also known as PREVENT, is in place then an exception can be made.

<sup>5</sup> Valproate use by women and girls, MHRA

<https://www.gov.uk/guidance/valproate-use-by-women-and-girls>

<sup>6</sup> Valproate in children, young people and adults: summary of NICE guidance and safety advice <https://www.nice.org.uk/guidance/cg137/resources/valproate-in-children-young-people-and-adults-summary-of-nice-guidance-and-safety-advice-pdf-6723784045>

<sup>7</sup> Valproate medicines (Epilim▼, Depakote▼): Pregnancy Prevention Programme materials online <https://www.gov.uk/drug-safety-update/valproate-medicines-epilim-depakote-pregnancy-prevention-programme-materials-online>

## Further information about valproate in pregnancy

After the first CPRD valproate report, sent in late 2019 and early 2020, valproate has been the centre of many initiatives aiming to reduce harmful prescriptions.

The Independent Medicines and Medical Devices Safety Review (IMMDS), which investigated the harmful effects of valproate on those who can become pregnant, was [published by Baroness Cumberlege in July 2020](#)<sup>8</sup>. In response to the Cumberlege Review, NHS England and NHS Improvement wrote to every patient of childbearing potential (aged 12-55) and a valproate prescription. The letter informed them of the risks of valproate use in pregnancy and asked patients to liaise with their GP or specialist for a treatment review, to ensure they are using appropriate pregnancy prevention methods. A copy of the letter has been [published](#)<sup>9</sup> and is available in other languages. There may have been an increase in engagement from those with a valproate prescription.

Baroness Cumberlege's review also recommended a valproate registry be implemented, which the MHRA have now launched in partnership with NHS Digital as the [Medicines and Pregnancy Registry](#)<sup>10</sup>. The registry contains data on all NHS prescriptions of valproate in patients of childbearing age in England and brings together data from the NHS Business Services Authority (BSA), Maternity Services Data Set (MSDS) and Hospital Episode Statistics (HES).

[Registry data](#)<sup>11</sup> collected in England between April 2018 and September 2020 shows that, within the reporting period:

- 47,532 females (ages 0-54) were prescribed one or more prescriptions for valproate in one or more months within the reporting period
- 180 females were prescribed valproate while pregnant
- 238 females stopped receiving prescriptions of valproate prior to their pregnancy

The [second Medicines and Pregnancy Registry report](#)<sup>12</sup> was published on September 30th 2021 and shows exposure to valproate during pregnancy is still occurring.

Work is underway to extend the valproate registry to include Scotland and Wales.

The NHS Business Services Authority (BSA) has developed a dashboard to track the use of valproate medicines and data will be produced every month, making it easier for healthcare professionals to monitor the issue. Data for each GP practice, primary care network or CCG can be accessed via the [valproate dashboard](#)<sup>13</sup> on the BSA website via the ePACT2 portal. For those not registered for ePACT2, data can also be viewed through the [Catalyst - public insight portal](#)<sup>14</sup>.

<sup>8</sup> First Do No Harm - The report of the Independent Medicines and Medical Devices Safety Review  
[https://www.immidsreview.org.uk/downloads/IMMDSReview\\_Web.pdf](https://www.immidsreview.org.uk/downloads/IMMDSReview_Web.pdf)

<sup>9</sup> Letter to women and girls taking sodium valproate from NHS England and NHS Improvement  
<https://www.england.nhs.uk/publication/letter-to-women-and-girls-taking-sodium-valproate/>

<sup>10</sup> Medicines and Pregnancy Registry  
<https://digital.nhs.uk/data-and-information/publications/statistical/mi-medicines-and-pregnancy-registry/>

<sup>11</sup> Medicines and Pregnancy Registry report on Valproate use in females aged 0 to 54 in England (April 2018 to September 2020)  
<https://digital.nhs.uk/data-and-information/publications/statistical/mi-medicines-and-pregnancy-registry/valproate-use-in-females-aged-0-to-54-in-england-april-2018-to-september-2020>

<sup>12</sup> Medicines and Pregnancy Registry report on Antiepileptic use in females aged 0 to 54 in England: April 2018 to March 2021  
<https://digital.nhs.uk/data-and-information/publications/statistical/mi-medicines-and-pregnancy-registry/valproate-use-in-females-aged-0-to-54-in-england-april-2018-to-march-2021>

<sup>13</sup> NHS Business Services Authority Valproate Safety dashboard  
<https://www.nhsbsa.nhs.uk/epact2/dashboards-and-specifications/valproate-safety-dashboard>

<sup>14</sup> Catalyst - public insight portal  
<https://www.nhsbsa.nhs.uk/access-our-data-products/catalyst>

The prescribing of valproate is a potential trigger for a Structured Medication Review which can generate a practice-focused prescribing safety report that will ensure that women and girls on valproate are made aware of the potential harm if used in pregnancy when they are not having annual specialist reviews. [SMR guidance](#)<sup>15</sup> has been published 31 March 2021 for practices in England.

The General Medical Council (GMC), Nursing and Midwifery Council (NMC), and the General Pharmaceutical Council (GPhC) have developed a case study which explores how to approach difficult conversations and highlights the important role all healthcare professionals have in prescribing and dispensing valproate safely. The [case studies](#)<sup>16</sup> are jointly published on the respective websites.

The RCGP and the Royal College of Physicians have published [guidelines for clinicians](#)<sup>17</sup>, which are endorsed by all the medical Royal Colleges. The guidance is intended to provide practical information and guidance for healthcare professionals when there may be problems or questions about following the MHRA regulations, and sources of further support, for clinicians involved with valproate: it gathers data, where available, on best practice and summarises consensus opinion from nineteen national bodies across the UK.

The MHRA has been monitoring trends in the prescribing of valproate to assess the impact of evolving regulatory recommendations and introduction of the pregnancy prevention programme using primary care data from the Clinical Practice Research Datalink GOLD database:

- [CPRD study monitoring the use of valproate in girls and women in the UK: report from January 2010 to December 2019](#)<sup>18</sup> (PDF, 277KB, 8 pages)

The regulatory position on valproate in pregnancy has been endorsed by the European Medicines Agency:

- <https://www.ema.europa.eu/en/medicines/human/referrals/valproate-related-substances-0>

The Summary of Product Characteristics (SPCs) for valproate includes advice for prescribers:

- <https://www.medicines.org.uk/emc/search?q=valproate>

<sup>15</sup> Structured Medication Review guidance  
<https://www.england.nhs.uk/wp-content/uploads/2021/03/B0431-network-contract-des-smr-and-mo-guidance-21-22.pdf>

<sup>16</sup> Case study on discussing the risks of sodium valproate  
<https://www.gmc-uk.org/ethical-guidance/learning-materials/risks-of-sodium-valproate>

<sup>17</sup> RCGP and the Royal College of Physicians guidelines for clinicians  
[https://www.rcpch.ac.uk/sites/default/files/2021-01/Pan\\_College\\_Guidance\\_Document\\_on\\_Valproate\\_UseV2.1.pdf](https://www.rcpch.ac.uk/sites/default/files/2021-01/Pan_College_Guidance_Document_on_Valproate_UseV2.1.pdf)

<sup>18</sup> CPRD study monitoring the use of valproate in girls and women in the UK: report from January 2010 to December 2019  
[https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/880614/CPRD\\_valproate\\_usage\\_report\\_DSU\\_Feb\\_2020\\_final.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/880614/CPRD_valproate_usage_report_DSU_Feb_2020_final.pdf)

## Further information about the QI report programme

This report has been produced as part of the Quality Improvement collaboration between RCGP and Clinical Practice Research Datalink (CPRD), which produces confidential data reports on prescribing and patient safety for all practices signed up to the CPRD data extract.

Along with this report on valproate, there are two other reports, covering:

- Heart and Circulatory System
- Patients with Learning Disabilities or Autism or both.

There is further detail about the reports on the RCGP and CPRD project webpages:

- <https://www.rcgp.org.uk/clinical-and-research/our-programmes/quality-improvement/quality-improvement-prescribing-and-patient-safety-reports.aspx>
- <https://www.cprd.com/generalpractitioner/QualityImprovementProject.asp>

Clinicians who have used these reports have told us that they use them in the following ways:

1. To review the care of individual patients highlighted in the reports – where necessary, patients have their treatment changed
2. As the starting-point for discussions involving all clinicians within the practice around safe prescribing
3. As evidence for annual appraisals and revalidation, under Domain 2 – Safety and Quality
4. To flag all patients with the identified conditions in order to ensure that they will not be prescribed potentially unsafe drugs in future
5. As part of locality or cluster quality improvement meetings
6. As part of the practice's work for the Quality and Outcomes Framework (QOF)

If you know of colleagues who would like to receive Quality Improvement reports for their practice, they can sign up via the [CPRD website](#)<sup>19</sup>.

Please help us to make the reports better by filling in our [short online survey](#)<sup>20</sup>. We are writing up case studies of how the reports are used by practices, so please get in touch if you'd like your work to be shared and help other practices across the UK.

A write-up of the pilot phase of this Project has been published in the [British Journal of General Practice](#)<sup>21</sup>. The paper describes the development of the reports and our success in using routine datasets to provide quality improvement resources that impact directly on patient care.

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<sup>19</sup> CPRD joining form  
<https://www.cprd.com/joiningform>

<sup>20</sup> Online Survey  
[https://www.surveymonkey.co.uk/r/QIReport\\_Valproate](https://www.surveymonkey.co.uk/r/QIReport_Valproate)

<sup>21</sup> Quality improvement of prescribing safety: a pilot study in primary care using UK electronic health records  
<https://doi.org/10.3399/bjgp19X704597>