

Valproate medicines safety in community pharmacy

Practice-based audit 2018-19: Summary report

November 2019

Executive Summary

- Valproate medicines are used in the treatment of epilepsy, bipolar disorder and occasionally to prevent migraine headaches. Since its introduction in 1974, the product information for prescribers has included warnings about the possible risks of birth defects. A 2016 survey¹ found that one in five women prescribed valproate were unaware of the risks of taking this medicine during pregnancy and in the same year it was recorded that 400 women taking valproate became pregnant². In March 2018 the Medicines and Healthcare products Regulatory Agency (MHRA) strengthened its position and stated that valproate must no longer be used in women and girls of childbearing age* unless a Pregnancy Prevention Programme (PPP) is in place. The PPP ensures that patients understand the risks of taking valproate during pregnancy and have signed a Risk Acknowledgment Form. Patients must also be on highly effective contraception and have annual appointments with a specialist.
- Over 170 million valproate medicines were dispensed in community pharmacies in England during the year ending August 2018³. Pharmacists are experts in medicines and as well as ensuring medicines are supplied correctly and safely, community pharmacies provide patients and the public with advice and information to support them to take their medicines safely and as intended. Community pharmacists and their teams are therefore well placed to support women and girls of childbearing potential who are prescribed valproate medicines by having discussions with them about the importance of being on highly effective contraception and signposting patients to their GP or specialist if they are not enrolled on a PPP.
- To evaluate and improve patient safety and care in community pharmacies, the Company Chemists' Association (CCA) designed an audit which sought to explore the contribution of community pharmacies in supporting girls and women of childbearing potential taking valproate medicines. The audit was conducted in two phases (in Autumn 2018 and Spring 2019) to allow comparison over time and to ascertain whether there have been improvements in awareness, understanding and pharmacy practice to support valproate patients.
- Through widespread dissemination and communication, the audit materials were made available to pharmacy teams across the community pharmacy network, including small independent pharmacies and large multiple chains, located on the high street, in supermarkets and in shopping centres. This was the first time that a two-part audit was conducted, demonstrating that community pharmacy went beyond what is required in the NHS Terms of Service, in the interest of improving patient safety and care.
- In total 6,761 pharmacies conducted phase one of the audit and 6,480 pharmacies took part in phase two. Key findings from the audit demonstrate the important role pharmacy teams currently play in supporting women and girls prescribed valproate, as well as highlighting where further safety improvements can be made:
 - Pharmacy dispensing teams were aware of the risks associated with valproate medicines and pregnancy (phase one = 81%, phase two = 94%).
 - Over 36,000 valproate prescriptions were dispensed during both phases of the audit, with the majority of these being for Epilim (phase one = 58%, phase two = 72%).
 - During phase one, a quarter of prescriptions included information from the prescriber about whether a PPP was in place (26%). The phase two audit showed an increase in instances where this information was included (37%).
- The findings in this audit demonstrate the substantial role of pharmacy teams in ensuring women and girls taking valproate medicines are aware of, and understand the risks associated with taking their medication during pregnancy. As part of the safe dispensing of these medicines, pharmacy teams can engage in conversations and provide essential resources, such as patient cards and leaflets, to ensure the necessary precautions are taken for each patient. Pharmacy teams can also identify patients who may need to begin a PPP or require an annual specialist review and can signpost or refer patients to their GP or specialist as appropriate.

* The audit paperwork defined women of childbearing potential as girls and women aged between 12 and 49. This age range was specified as this was the definition being used at the MHRA Valproate Stakeholder Network around the time of the audit design.

Introduction

Practice-based audits provide a valuable opportunity to evaluate and review the systems and procedures operating in a pharmacy and ascertain what changes could be made to drive continual improvements in patient care and safety. Considering the significant risks associated with taking valproate medicines during pregnancy and the multidisciplinary approach needed to support at-risk patients, this audit topic was chosen to establish the current role of community pharmacies in this critical patient safety issue, and to help identify any improvements that can be made.

This paper reports on the audit which was undertaken in the financial year 2018-19. The audit was conducted in two stages; for one week during July and October 2018 and again between February and the end of March 2019. The two data sets were compared to identify any improvements in understanding, knowledge and actions taken in community pharmacies to contribute to the safe use of valproate medicines.

The audit was split into four sections:

1. Section one gathered information about the pharmacy teams' understanding and awareness of the risks associated with valproate and pregnancy.
2. Section two supported pharmacy teams to proactively identify any patients who may be at risk, using their Patient Medication Record (PMR) system.
3. Section three gathered information on the patients identified during the audit period who were at risk, and what actions were taken in the pharmacy to support them. For the eligible patients identified, pharmacy teams were asked to record the following information:
 - Patient age
 - Name of valproate medicine prescribed
 - Modified release (yes or no)
 - Duration of treatment
 - Total daily dose
 - If there was an indication on the prescription that a PPP was in place for the patient
4. Section four provided pharmacy teams with the opportunity to record what they learnt and any reflections from carrying out the audit, as well as further actions that they would take.

Background & context

Valproate is used in the treatment of epilepsy and bipolar disorder and since its introduction, the product information for prescribers has included warnings about the potential risk of birth defects. Despite these risks being known, 400 women taking valproate became pregnant in 2016⁴ demonstrating the considerable improvements that still need to be made to ensure all at-risk patients are aware of, and understand the harm that valproate can cause to unborn babies.

In 2018, valproate medicines were dispensed over 170 million times to patients in England⁵. If valproate is taken during pregnancy, up to four in ten babies are at risk of developmental disorders, and approximately one in ten are at risk of birth defects⁶. There is also evidence that babies exposed to valproate during pregnancy are more likely to have autism and are at a higher risk of developing Attention Deficit Hyperactivity Disorder (ADHD).

In April 2018, the MHRA changed the licence for valproate medicines so that they must no longer be prescribed to women or girls of childbearing potential unless they are on a Pregnancy Prevention Programme (PPP). The PPP ensures that all female patients understand the risks of taking valproate medicines during pregnancy and have signed a [Risk Acknowledgement Form](#), are on highly effective contraception if necessary, and see their specialist at least every year. The conditions of the PPP for valproate are consistent with the programmes available for thalidomide, isotretinoin and other highly teratogenic drugs.

As well as the strengthened regulatory position requiring that all women and girls be placed on a PPP if they are prescribed valproate medicines, a recommendation was put in place, preventing the use of valproate for migraines or bipolar disorder during pregnancy and a ban preventing the use of valproate to treat epilepsy during pregnancy unless no other effective treatment is available. These regulatory changes are further supported by a warning image included on valproate medicines packaging as well as the implementation of smaller pack sizes to encourage monthly prescribing. The audit was designed to establish how well these regulatory requirements were understood in the community pharmacy sector.

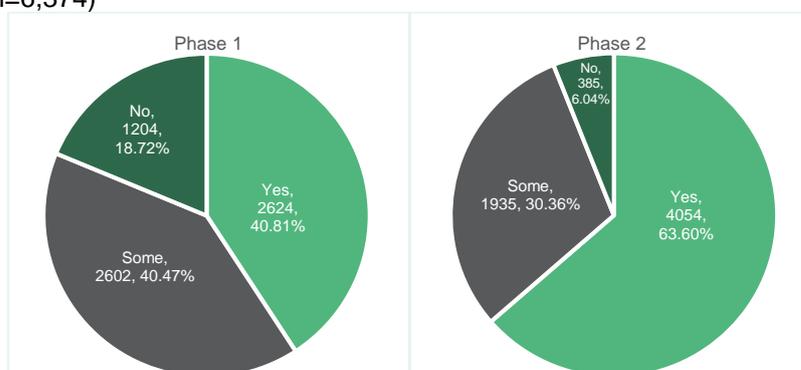
Results and discussion

1. Pharmacy teams' understanding and awareness of the risks associated with valproate and pregnancy

6,761 pharmacy teams completed phase one of the audit and 6,480 pharmacy teams conducted phase two. At the time of data analysis there were around 14,000 community pharmacies in the United Kingdom, meaning that around half of all community pharmacies conducted the audit (48.29% and 46.29% respectively).

For both phase one and phase two, 96% of respondents indicated that they were aware of the risks of abnormal pregnancy outcomes associated with the use of valproate medicines during pregnancy (96.17% and 96.03% respectively). The audit guidance materials specified that this section of the audit should be completed by the pharmacy professional leading the audit, therefore this is most likely a reflection of the awareness and understanding of pharmacists. Further questions sought to ascertain the level of awareness and understanding among other pharmacy team members (see figure one).

Figure 1: Were other members of your pharmacy dispensing team aware of the risks of abnormal pregnancy outcomes associated with the use of valproate medicines during pregnancy? (phase one: n=6,430, phase two: n=6,374)



Overall, awareness and understanding improved among team members. During phase two of the audit there were more community pharmacies in which the whole dispensary team were aware of the risks of abnormal pregnancy outcomes associated with the use of valproate medicines. This could be attributed to increased messaging and communications about the risks of valproate throughout health and care settings, from patient groups, and in the media, as well as the dissemination of information and materials from the MHRA.

Respondents were asked about the different actions that their pharmacy team take to support the safety of girls and women taking valproate. For both phases of the audit, the most common action that pharmacies took was to discuss the risks with the pharmacy team (79.90% and 78.29%).

Overall there was an increase in different actions undertaken by pharmacy teams in phase two compared to phase one. A total of 22,024 actions were noted for phase two respondents compared with 16,842 actions recorded during phase one. This may be indicative of an overall increase in the awareness and understanding among pharmacy teams and a more proactive attitude towards supporting and counselling patients who may be at risk.

MHRA guidance about the role of pharmacists in the safe supply of valproate medicines, states that the [patient card](#) should be provided every time valproate is dispensed⁷. This resource informs patients about the risks of valproate and pregnancy and gives advice about what patients should do if they are planning to have a baby or think they may be pregnant. It would be expected that all valproate patients in the audit were provided with a patient card. However, a minority of phase one and phase two respondents indicated that they handed out patient cards (21.43% and 40.09% respectively). Therefore, significant improvements are needed in this regard to ensure that all eligible patients receive the patient card every time their valproate medicine is dispensed.

Regulatory position on PPPs

In April 2018, the MHRA strengthened regulations around the provision of valproate, requiring that valproate medicines must no longer be used in women or girls of childbearing potential unless a PPP is in place. Around 85% of respondents were aware during phase one of the audit (84.38%) compared to almost 95% of participants in phase two (93.95%). This increased awareness among pharmacy teams may reflect enhanced understanding throughout other health and care settings about valproate medicines as well as information and resources being more widely available to clinicians.

Pharmacy teams were made aware of the strengthened regulatory position through a variety of ways. The most common way in which pharmacy teams were informed was via their superintendent's office or their Medication Safety Officer (MSO).

All the methods of communicating the strengthened regulatory position were more common among phase two respondents, suggesting that the dissemination was more widespread when the second phase of the audit was conducted. Cascading information through a variety of channels ensures that pharmacy teams are kept informed of critical patient safety information. Different team members may not have access to all forms of communication, or may prefer different methods, further highlighting the importance of communicating through a variety of channels to ensure all pharmacy staff are well informed.

2. Identifying patients who may be at risk using the PMR system

Recording information on the PMR

Comparing phase one and phase two, there was an increase in the recording of information on the PMR about interactions that occurred in the pharmacy with valproate patients. During phase two, information was added to the PMR for almost 80% of patients (78.37%), and the proportion of patients for whom no information was recorded reduced.

Recording information about actions that occurred in the pharmacy is essential to ensure continuity of care both between healthcare settings and in subsequent interactions in the same pharmacy. Keeping a record of this information can improve patient experience as well as enhance health outcomes and patient safety. Considering the use of locums in pharmacies, effective notetaking is even more critical.

3. Information gathered on patients encountered during the audit period who were at risk and actions taken in the pharmacy to support them

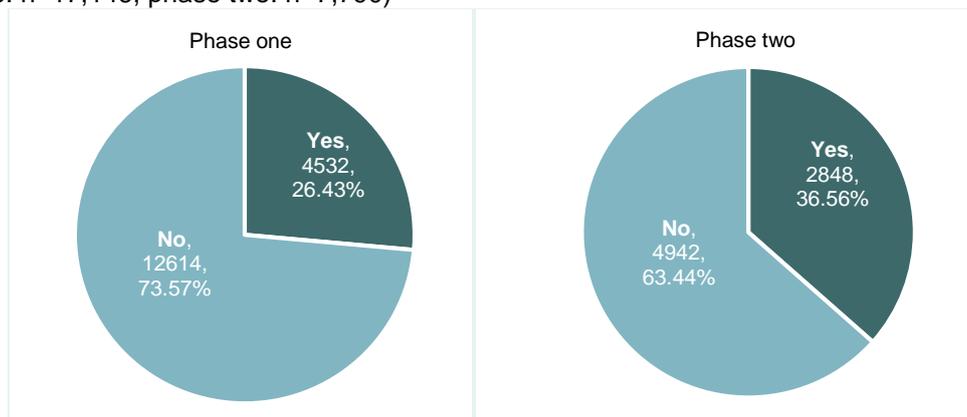
In total the ages of 25,932 patients were recorded during phase one compared to 9,898 patients encountered during phase two. Despite the large difference in the number of patient ages recorded, the proportion of each age category remained similar. For both phases, almost half of patients were aged between 40 and 49 (48.91% and 49.70% respectively). The proportion of patients encountered decreased with lowering age, with 12 to 18 year-olds being the age group least likely to be prescribed a valproate medicine. Despite being the least frequently encountered age group, effective communication with these young patients about the risks associated with valproate is crucial considering that the likelihood of them becoming pregnant may change over time. Guidance produced by the Royal College of General Practitioners, the Association of British Neurologists and the Royal College of Physicians states that, female patients aged between 13 and 15 should at least be under annual specialist review and females aged over 16 should be managed as adults and should therefore be put on a PPP⁸. Furthermore, younger patients may be more likely to be represented by a parent or carer and therefore it is essential that information about risks with future pregnancies are provided both verbally and via resources that can be passed onto the patient. Empowering patients to understand the risks and make informed reproductive choices is a key output of the work that community pharmacy teams undertake.

Duration of treatment

For both phase one and phase two, around half of all prescriptions were for 28 days, with a slight increase in 28-day prescriptions encountered during phase two (46.87% and 54.81% respectively). In Autumn 2018, smaller pack sizes were introduced to encourage monthly prescribing of valproate medicines. These were introduced to the market during the time of phase one data collation. It would therefore be expected that for phase two, 28-day prescribing would be more common.

Pregnancy Prevention Programme (PPP)

Figure 2: Proportion of valproate prescriptions that included an indication that a PPP was in place (phase one: n=17,146, phase two: n=7,790)



Overall, there was an increase in the proportion of prescriptions that included an indication about whether a PPP was in place. For phase one, about a quarter of prescriptions included PPP information (26.43%) compared to 37% of prescriptions encountered during phase two (36.56%). This suggests that between both audit phases there was improved awareness and implementation of PPPs for valproate patients.

Despite the increase, most prescriptions encountered still did not indicate whether a PPP was in place for the patient, therefore demonstrating that improvements still need to be made. Greater integration and collaboration between GPs, specialists, neurologists and community pharmacy teams will improve the safety outcomes for patients prescribed valproate medicines. If pharmacy teams are provided with information about whether a patient is enrolled on a PPP, they can then have the appropriate discussion with the patient and ensure that they are aware and understand all the relevant risks.

Was the patient physically present in the pharmacy?

Only around half of valproate patients were physically present in the pharmacy (48.55% for phase one and 53.88% for phase two). This small increase in the proportion of patients who were physically present in the pharmacy was accompanied by a reduction in the percentage of patients who had their medication delivered. This may be attributed to a reduction in delivery service options available to patients. For both phases of the audit, approximately one third of patients were represented by someone else going to the pharmacy on their behalf (29.89% and 29.58%).

The absence of the patient in the pharmacy when valproate is dispensed may provide a challenge to addressing the concerns and risks associated with taking the medicine during pregnancy. It is essential that the same advice and information is given to valproate patients who have their medicines delivered or those who are represented in the pharmacy by a family member or carer, without compromising confidentiality.

Referrals to GPs

Comparing phase one and phase two of the audit, there was a slight increase in the percentage of patients who were not referred to their GP (71.47% and 79.54% respectively). This may be due to more patients being aware of the risks and already being enrolled on a PPP. When dispensing valproate medicines, pharmacists must discuss the risks with female patients and ensure that they have seen their GP or specialist to discuss their treatment. During phase two, it is likely that a higher proportion of eligible patients encountered were already aware of the risks and had recently visited their GP or specialist, therefore removing the need for the pharmacy team member to refer the patient back to her GP. The reduction in GP referrals during phase two was accompanied by an increase in the proportion of valproate prescriptions that included an indication from the prescriber that a PPP was in place. If pharmacy teams are more aware about the patient's current treatment, this may reduce the need for referral onto the GP or specialist.

4. Pharmacy teams' reflections on carrying out the audit and further actions that they would take

Pharmacy teams were asked to detail the key learning points they made while conducting the audit. These included:

- Increased awareness of the requirement for a PPP to be in place
- Importance of engaging and educating the whole pharmacy team
- Importance of counselling patients every time a valproate prescription is presented in the pharmacy
- Increased awareness about signposting and referring patients onto other healthcare professionals, including for an annual specialist review
- Better understanding about the risks associated with other teratogenic drugs
- Importance of communicating with patient representatives and ensuring that both patients who have their medicines delivered and those who reside in care homes receive the essential information and advice about valproate medicines and pregnancy

Following completion of the audit, the most common action was to discuss the learning with the pharmacy team (68.25% and 70.83% of phase one and two respondents, respectively). Around half of respondents stated that they would share their learnings from the audit with locum pharmacists and about one in five participants indicated that they would appoint a valproate champion in their pharmacy.

Conclusions

The findings in this audit demonstrate the crucial role that pharmacy teams play in supporting women and girls who are prescribed valproate medicines. Providing effective care to these patients requires a joined-up approach from professionals across different health and care settings and this audit illustrates the substantial contribution of pharmacy teams. Through conversations about the requirement for a PPP, the provision of essential resources such as patient cards, or referring patients to their GP or a specialist, pharmacy teams are well-placed to provide critical advice and guidance to increase awareness and help prevent pregnancies in women taking valproate.

In the time period between the completion of phase one and two of the audit, key improvements were seen, for example in the awareness among the whole dispensary team about the risks associated with valproate medicines and pregnancy, and the strengthened regulatory position. However, the audit also illustrates areas where improvements are needed. For example, the responses suggest that pharmacy teams did not provide a patient card every time a valproate medicine was dispensed, as detailed in the MHRA guidance. Furthermore, not all valproate prescriptions dispensed during the audit included an indication from the prescriber that a PPP was in place for the patient. This crucial information is essential to facilitate joined-up and safe care for patients.

There were certain limitations with the data collation and audit design which could be addressed to inform potential future iterations of the audit. For example, it could be helpful to ascertain whether there are differing levels of awareness and understanding among pharmacy staff with different roles or experience. This information may help in communications planning to ensure that all healthcare professionals are well-informed. Future iterations of this audit may also focus on specific groups of valproate patients, for example, those with a lack of mental capacity and/or learning difficulties and who are particularly vulnerable. By targeting specific groups in this way, the audit may provide insight into how pharmacy teams can better support vulnerable patients by making reasonable adjustments. Furthermore, learnings from the data and the audit process could be used to support future audits reviewing other teratogenic drugs or those posing similar patient safety risks.

We welcome the inclusion of a valproate audit as part of the latest Pharmacy Quality Scheme (PQS) in England. The PQS is a component of the Community Pharmacy Contractual Framework and helps pharmacies to support the wider NHS system through delivering consistently high-quality patient care. Including an audit on valproate as part of the PQS demonstrates the commitment from NHS England and Improvement to better support women and girls taking valproate medicines and recognises the key role that community pharmacy teams play in tackling this patient safety issue. It is expected that most community pharmacies in England will participate in this PQS valproate audit, thereby ensuring sector-wide awareness and understanding continues to improve as well as compliance with the MHRA regulatory requirements.

Next steps & recommendations

Recommendations for community pharmacies

- Pharmacy organisations and pharmacy teams should continue work to **increase awareness and understanding** about the risks associated with taking valproate medicines during pregnancy. Through collaboration, such as via the MHRA Valproate Stakeholder Network and with patient groups, the pharmacy sector can help to ensure patient safety messages and updates are effectively communicated across health and care settings. Improving the level of engagement within the pharmacy workforce will enable pharmacy teams to better support patients.
- As per the MHRA guidance, all patients presenting in community pharmacy with a prescription for valproate should be **counselled** on the risks and the requirement for a PPP to be in place. A **patient card** should be given out **every time** valproate medicines are dispensed.
- Accurate and regular **PMR annotations** should be made of all interactions and relevant conversations with girls and women of childbearing age (or their patient representative) who are prescribed valproate, especially considering the use of locums in community pharmacies.
- The MHRA guide for healthcare professionals on the risks of valproate use in girls and women of childbearing potential should be included as part of the **induction process** for any new pharmacy team members to ensure that all pharmacy professionals are made aware of the risks at the start of their career in pharmacy.

For community pharmacies to be successful in delivering the actions above and to strive for continual patient safety improvements, the sector will also benefit from clear guidance and support from the government, the regulator and manufacturers. Some examples of actions to be taken by these different stakeholders are listed below:

Recommendations for the regulator

- The General Pharmaceutical Council could ensure that, as part of its **inspections** of pharmacy premises, systematic checking of compliance with the MHRA's guidelines for valproate is maintained and the output of this is recorded in the inspection outcome report. Continued analysis and reporting of this area of compliance will support in driving up best practice across the sector.

Recommendations for the professional body

- As the organisation responsible for the leadership and support of the pharmacy profession, the Royal Pharmaceutical Society could support all pharmacy teams by providing **guidance** and advice for the sector as well as promoting **training**. For example, community pharmacy teams could be better supported in how to provide advice to patients lacking mental capacity, including those represented by a parent or carer.

Recommendations for the government and the MHRA

- The audit results demonstrate that information is not always provided on valproate prescriptions about whether a **PPP** is in place for the patient. This information is critical to inform discussions in the pharmacy and therefore, further improvements are needed to ensure that all prescribers are including this information on prescriptions.
- We welcome the current work of the MHRA to create a **registry** of women and girls of childbearing age who are taking valproate. This will help to track PPP compliance and we would recommend enabling access to this registry in community pharmacy to facilitate improved patient care and safety.
- Special consideration should be made to the **'off label'** use of valproate-containing medicines. It is important that all health professionals are aware that a PPP must be in place for patients prescribed these valproate products. The MHRA should continue its work in monitoring adverse reactions to off-label valproate medicines and communicate any safety issues.

Recommendations for valproate manufacturers

- Manufacturers must ensure that supplies of small valproate packs are maintained to continue to **encourage 28-day prescribing** and ensure that valproate materials, such as the patient card are supplied with every order placed.
- Manufacturers should consider providing financial support to research new forms of access to information including access to training materials.
- As an essential medicine, as defined by The World Health Organisation, there should be no interruption to UK supply of valproate containing medicines.

¹ <https://www.epilepsysociety.org.uk/worrying-lack-knowledge-over-epilepsy-medicine-risks-pregnancy#:~:text=The%20MHRA%20has%20issued%20guidance%20on%20the%20safe%20supply%20of%20valproate%20to%20community%20pharmacy%20FINAL.PDF>

² <https://www.rpharms.com/Portals/0/RPS%20document%20library/Open%20access/Support/Valproate%20safe%20supply%20-%20community%20pharmacy%20FINAL.PDF>

³ n=170,687,305 <https://digital.nhs.uk/data-and-information/publications/statistical/prescription-cost-analysis>

⁴ <https://www.rpharms.com/Portals/0/RPS%20document%20library/Open%20access/Support/Valproate%20safe%20supply%20-%20community%20pharmacy%20FINAL.PDF#page=2&zoom=100,0,0>

⁵ <https://digital.nhs.uk/data-and-information/publications/statistical/prescription-cost-analysis/2018>

⁶ <https://www.gov.uk/guidance/valproate-use-by-women-and-girls>

⁷ https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/708850/123683_Valproate_HCP_Booklet_DR15.pdf

⁸ <https://www.rcog.org.uk/globalassets/documents/guidelines/valproate-guidance-march-2019.pdf>