Use of prescribing indicators as a means of identifying variation in the prevalence of valproate prescribing between health communities: a cross-sectional study

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ABSTRACT

Objective To determine the appropriateness of valproate prescribing indicators in England and Wales as a means of identifying variation in the prevalence of valproate use among women and girls of childbearing potential between health communities.

Methods and analysis Cross-sectional study using an ecological design using routinely published, publicly available valproate prescribing data for the period January to March 2019 and 2018 mid-year population estimates.

Results In England and Wales, 87.7 people in every 1000 people prescribed valproate were women or girls aged 14–45 years (range 60.4–133.2). The prevalence of valproate use among all women and girls of childbearing age was 1.49 cases per 1000 women and girls aged 14–45 years (range 0.47–3.13). Considerable variation in prevalence was observed depending on which of two measures was used. The relative risk of exposure between health communities increased from 2.2 to 6.6 depending on the measure used, leading to the identification of different health communities being a priority for action.

Wide variation was observed in the prevalence of valproate use among individuals other than women and girls aged 14–45 years (mean prevalence 3.89 cases per 1000 population, range 2.42–7.78). The prevalence of valproate use in all Clinical CommissioningGroups and Local Health Boards was lower in the at-risk population than in the rest of the population (p=0.046) with a strong positive correlation observed between the prevalence of valproate use in these two groups (p<0.001).

Conclusion Current indicators may lead to a failure to systematically review women and girls of childbearing age prescribed valproate. Urgent consideration should be given to changing the indicators used in England and Wales.

INTRODUCTION

The harmful effects of prenatal exposure to sodium valproate (valproate) are well established. Valproate’s teratogenic effects were first identified in the early 1980s¹ with major congenital malformations known to occur in as many as 1 in 10 children exposed to it during pregnancy.² Subsequently, exposure...
in utero has been found to be associated with increased risk of autism spectrum disorder, attention-deficit hyperactivity disorder and a 30%–40% risk of developmental disorder.\(^3\) With increasing recognition of these risks, patient support groups have argued strongly for government and medicines regulatory agencies to take decisive action to reduce the risk of valproate exposure during pregnancy.\(^5\)

Product information for medicines containing valproate has carried warnings about the possible risk of birth defects since the medicine was first licensed in 1974, and warnings have been progressively strengthened over time as new risks were identified.\(^6\) However, it was not until 2015 that the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK issued guidance that valproate use should be restricted not only during pregnancy but also in all women of childbearing potential ‘unless clearly necessary’.\(^5\) Further measures, including updating product information, the production of educational materials and placing warnings on the packaging of valproate medicines, were taken between 2015 and 2018 to first ensure women were better informed about the risks of taking valproate during pregnancy, and latterly to contraindicate its use in women and girls at-risk unless they were enrolled in a pregnancy prevention programme (PPP) (Box 1).

Since the introduction of additional regulatory measures, the number of women and girls aged 14–45 years receiving prescriptions for valproate in the UK has declined from approximately 35 000 per year between 2010 and 2012\(^7\) to 20 000 in 2018.\(^8\) However, the reduction in use among at-risk individuals has been slower than might have been anticipated given the nature of the regulatory response and consideration is now being given to further action to restrict use.\(^8\)

The importance of making resources available to identify patients exposed to valproate in primary care has been argued by others\(^9\) and in 2018, the National Health Service Business Services Authority (NHSBSA) began publishing quarterly data on the number of women and girls of childbearing age who have received prescriptions for valproate. These measures are intended to contribute to the monitoring of the effectiveness of the MHRA’s regulatory measures and support the safe and appropriate use of valproate. The objective of this study was to determine the appropriateness of the valproate prescribing indicators in England and Wales as a means of identifying Clinical Commissioning Groups (CCGs) in England and Local Health Boards (LHBs) in Wales, with above-average rates of prescribing of valproate among women and girls of childbearing potential.

**MATERIALS AND METHODS**

This was a retrospective observational study using an ecological and cross-sectional design using routinely published valproate prescribing (for Wales) and dispensing (for England) data for the period January to March 2019 (‘the study period’) and population data for all CCGs and LHBs in England and Wales. Data for analysis were obtained in October 2019 from websites maintained by the NHSBSA, All Wales Medicines Strategy Group (AWMSG), Office of National Statistics (ONS) and StatsWales.

**Data sources**

The number of patients dispensed a prescription for valproate, derived from prescriptions submitted to the NHSBSA for payment by pharmacies and dispensing doctors in England, for the period January to March 2019, were taken from the NHSBSA’s website. Data were available aggregated by CCG.\(^6\) Similar data for Wales, providing the total number of patients prescribed valproate extracted from general practice (GP) clinical systems and aggregated by LHB, were available from the

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**Box 1 Chronological order of MHRA regulatory action taken against valproate since 2015**

- **January 2015**
  - Product information updated to reflect current understanding of available evidence.
  - Educational materials made available to inform about risks associated with valproate.
  - Valproate made a black triangle medicine subject to additional monitoring.

- **February 2016**
  - Updated educational materials disseminated to specialist prescribers, general practitioners and pharmacists.
  - Confirmation that from later in 2016 outer packaging for medicines containing valproate will include a warning for women on the risk of adverse pregnancy outcomes.

- **April 2017**
  - Patient safety alert issued highlighting risks of valproate exposure to the unborn child.
  - Organisations directed to undertake systematic identification of women and girls taking valproate and to use the MHRA resources to support them to make informed choices.

- **April 2018**
  - Notification that valproate medicines must no longer be used in women and girls of childbearing potential unless a pregnancy prevention programme (PPP) is in place.
  - Confirmation that visual warning symbol will be added to the carton of valproate medicines by September 2018 with advice to pharmacists to dispense in original containers.
  - Introduction of new absolute contraindication for use of valproate medicines in pregnancy for the treatment of the bipolar disorder.

- **July 2019**
  - MHRA Board considers further regulatory measures as recommended by the Commission on Human Medicines:
    - Directly recalling women of childbearing age on valproate for specialist review.
    - A move towards close specialist supervision of prescribing of valproate to women of childbearing age.
    - Confirmation of continuing work to establish a registry to track all women and girls taking valproate to measure compliance with the PPP.

MHRA, Medicines and Healthcare Products Regulatory Agency.
AWMSG.\textsuperscript{11} 12 Data for the number of women and girls aged 14–45 years who dispensed or prescribed valproate were also obtained for each CCG and LHB, respectively. A patient is included in the number of patients prescribed valproate, reported by the NHBSA and AWMSG, if they had one or more prescriptions for valproate dispensed (England)/issued (Wales) during the study period. Patients who had multiple valproate prescriptions dispensed/issued are counted only once.

We used ONS mid-year population estimates for 2018,\textsuperscript{13} for all CCGs in England and from the Statswales website for all LHBs in Wales,\textsuperscript{14} to estimate the population in each CCG and LHB during the study period.

Analysis

Our outcome was the prevalence of valproate use in each CCG and LHB. For CCGs, the prevalence of valproate use was calculated using the number of unique valproate users who had one or more prescriptions for valproate dispensed during the study period. For LHBs, where GP prescribing data were available but dispensing data were not, the prevalence was calculated using the number of unique valproate users who had one or more prescriptions issued by a GP during the study period. We were aware that differences in the method of calculating prevalence between CCGs and LHBs could lead to an overestimate of prevalence among LHBs (because some valproate users may not have their prescription dispensed) however, we considered that this would not impact on our analysis. This was because in order to be in the study cohort, a valproate user only needed to have one prescription dispensed during the study period and we assumed the number of users not having any prescription dispensed would be low. We were also mindful that the purpose of the study was to compare different measures of the prevalence of valproate use and any differences in our data would affect the different measures equally.

We calculated two alternative measures of the prevalence of valproate use among women and girls of childbearing potential. First, we reproduced the NHBSA and AMWSG prescribing measures by calculating the number of women and girls aged 14–45 years receiving a prescription for valproate as a proportion of all patients receiving valproate for each CCG and LHB. Second, we calculated an alternative measure, the prevalence of valproate prescribing among all women and girls aged 14–45 years (who we considered to be the ‘population at risk’ from exposure to valproate), for each health community using the ONS mid-year population estimates. CCGs and LHBs were ranked and allocated to deciles for each measure. For both measures, we used the calculated prevalence rate for each CCG and LHB to calculate the relative risk (RR) between the organisations with the highest and lowest prescribing prevalence. We also calculated the RR of receiving valproate between women and girls aged 14–45 years and the rest of the population in each CCG and LHB (calculated by subtracting the number of women and girls aged 14–45 years from the total population). Differences in the RR and the ranking of individual CCGs and LHBs arising from the alternative methods for calculating the prevalence of valproate prescribing were described. We used z tests to calculate differences in the proportion of populations using valproate. Finally, we used linear regression to examine the association (Pearson’s Correlation Coefficient) between the prevalence of valproate prescribing in women and girls aged 14–45 years, and the total population excluding women and girls aged 14–45 years. Microsoft Excel (Microsoft Corporation 2016) was used to calculate simple descriptive statistics and Stata Statistical Software release V.16 (StataCorp. 2019) to calculate appropriate inferential statistics.

RESULTS

The total population of all CCGs and LHBs in England and Wales in the study period was 59.1 million. Of these, 11.8 million (20.0%) were women and girls aged between 14 and 45 years. A total of 201 415 unique valproate users were identified between January and March 2019 giving rise to an overall prevalence of 3.41 cases per 1000 population (range 1.94–6.93 cases per 1000 population). Valproate prescribing was less frequent among women and girls aged 14–45 years than among the total population representing only 8.8% of all valproate users (17667/201415).

The proportion of valproate users at risk of prenatal exposure

Between January and March 2019, the mean prevalence of exposure to valproate among women and girls aged 14–45 years was 87.7 cases per 1000 patients prescribed valproate (range 60.4–133.2). The RR in the highest prevalence CCG or LHB was approximately double that of the CCG or LHB with the lowest prevalence (RR=2.2).

The prevalence of valproate use among women and children of childbearing potential

Between January and March 2019, the mean prevalence of exposure to valproate among women and girls aged between 14 and 45 years (the population at risk) was 1.49 cases per 1000 women and girls aged 14–45 years (range 0.47–3.13). The RR between the CCGs and LHBs with the highest and lowest prevalence increased to 6.6, three times the variation observed when measuring prevalence as the proportion of all valproate users and with fewer CCGs and LHBs falling within two standard errors of the England and Wales prevalence rate (97/198 vs 167/198) (figure 1).

When we looked at the CCGs and LHBs in the highest prevalence decile (decile one) for each measure (n=20) (table 1), where we postulate action to reduce prevalence would be focused, we found little overlap between the health communities identified. Only six CCGs and LHBs (30%) appeared in the highest decile for both measures. The CCG that had the highest prevalence of all CCGs or LHBs using population at risk (all women aged 14–45 years) as the denominator, was in fact below the mean...
prescribing rate when measured using the approach adopted by the NHSBSA and AWMSG. We identified 1808 women and girls at risk in decile one using proportion of all patients prescribed valproate as the measure.
the prevalence of valproate use among all women and girls of childbearing potential. The prevalence of valproate prescribing in decile one was significantly higher in the CCGs and LHBs in decile one derived from the second measure (2.57 cases vs 1.94 cases, difference 0.63 cases per 1000 women and girls at risk, 95% CI 0.01–1.25, p=0.046).

The prevalence of valproate use excluding women and children of childbearing potential

Between January and March 2019, the mean prevalence of exposure to valproate among the population excluding women and girls of childbearing age was 3.89 cases per 1000 population (range 2.42–7.78). The RR between the CCGs and LHBs with the highest and lowest rate of exposure was 3.21.

The association between the rate of valproate prescribing in women and girls aged 14–45 years and the total population excluding women and girls aged 14–45 years

Positively we found the mean rate of valproate prescribing in England and Wales was lower in women and girls aged 14–45 years than in the rest of the population (ie, when women and girls aged 14–45 years were excluded) (1.62 vs 3.92 cases per 1000 population, difference −2.31, 95% CI −2.50 to −2.11, p<0.001). This was the case in all CCGs and LHBs (figure 2). However, we found a wide difference in the RR of being prescribed valproate among women and girls aged 14–45 years and the rest of the population, when we compared the CCGs or LHBs with the smallest and widest variations between the two groups. Overall, women and girls aged 14–45 years were 62% less likely to be prescribed valproate than the rest of the population (RR=0.38), however, this ranged from a reduced likelihood of 82% to just 35% (RR range 0.18–0.65) in the CCG with the smallest difference in prevalence between the two groups. A strong positive correlation was observed

| CCG/LHB                              | All people prescribed valproate | Women and girls aged 14–45 years prescribed valproate | Women and girls per 1000 people prescribed valproate | All women and girls aged 14–45 years | Women and girls aged 14–45 years per 1000 population at risk |
|--------------------------------------|---------------------------------|-----------------------------------------------------|-----------------------------------------------------|--------------------------------------|-------------------------------------------------------------|
| NHS Blackpool CCG                    | 966                             | 79                                                  | 81.78                                                | 25 243                               | 3.13                                                        |
| NHS North East Lincolnshire CCG      | 792                             | 88                                                  | 111.11                                               | 29 347                               | 3.00                                                        |
| NHS Great Yarmouth and Waveney CCG   | 1026                            | 107                                                 | 104.29                                               | 36 176                               | 2.96                                                        |
| NHS Hastings and Rother CCG          | 906                             | 85                                                  | 93.82                                                | 30 691                               | 2.77                                                        |
| NHS St Helens CCG                    | 902                             | 92                                                  | 102.00                                               | 33 672                               | 2.73                                                        |
| NHS North Cumbria CCG                | 1467                            | 147                                                 | 100.20                                               | 53 954                               | 2.72                                                        |
| NHS Southport and Formby CCG         | 501                             | 49                                                  | 97.80                                                | 18 575                               | 2.64                                                        |
| Abertawe Bro Morgannwg University Health Board | 2624                           | 265                                                 | 100.99                                               | 102 342                              | 2.59                                                        |
| NHS Wyre Forest CCG                  | 453                             | 44                                                  | 97.13                                                | 17 028                               | 2.58                                                        |
| NHS Knowsley CCG                     | 764                             | 78                                                  | 102.09                                               | 30 322                               | 2.57                                                        |
| NHS South Kent Coast CCG             | 816                             | 91                                                  | 111.52                                               | 35 957                               | 2.53                                                        |
| NHS Newark and Sherwood CCG          | 533                             | 54                                                  | 101.31                                               | 21 578                               | 2.50                                                        |
| NHS Durham Dales, Easington and Sedgefield CCG | 1324                           | 121                                                 | 91.39                                                | 48 792                               | 2.48                                                        |
| NHS South West Lincolnshire CCG      | 445                             | 51                                                  | 114.61                                               | 21 688                               | 2.35                                                        |
| NHS Bradford City CCG                | 456                             | 50                                                  | 109.65                                               | 21 416                               | 2.33                                                        |
| NHS South Tees CCG                   | 1247                            | 124                                                 | 99.44                                                | 53 162                               | 2.33                                                        |
| NHS Hull CCG                         | 1208                            | 131                                                 | 108.44                                               | 56 415                               | 2.32                                                        |
| NHS Halton CCG                       | 550                             | 58                                                  | 105.45                                               | 25 170                               | 2.30                                                        |
| Cwm Taf University Health Board      | 1640                            | 136                                                 | 82.93                                                | 59 839                               | 2.27                                                        |
| NHS Isle of Wight CCG                | 547                             | 48                                                  | 87.75                                                | 21 464                               | 2.24                                                        |
| England and Wales total              | 201 415                         | 17 667                                              | 87.71                                                | 11 828 753                           | 1.49                                                        |

CCG, Clinical Commissioning Group; LHB, Local Health Board; NHS, National Health Service.
between the prevalence of valproate prescribing to women and girls aged 14–45 years and the prevalence of valproate prescribing in the rest of the population in the respective CCG or LHB (Pearson’s correlation $r=0.4738$, $n=198$, $p<0.001$) (Figure 2). We found that higher rates of valproate prescribing among women and girls aged 14–45 years are a consequence of higher rates of valproate prescribing in general.

Discussion

This study examined the appropriateness of valproate prescribing indicators in England and Wales as a means of identifying variation in the prevalence of valproate use among women and girls of childbearing potential between health communities.

Our findings demonstrate the importance of appropriate indicator selection to support reducing variation in valproate use between CCGs and LHBs. We found that current prescribing indicators do not adequately support identifying those CCGs and LHBs in which there is a high prevalence of valproate use among women and girls of childbearing age when differences in the population structure of individual health communities are accounted for using accepted epidemiological techniques.

The concept of the population at risk is an important one in epidemiology because it accounts for absolute differences in the prevalence of a disease that arise between study populations as a result of demographic differences in the make-up of those populations. This is fundamental to making meaningful comparisons. By definition, the ‘population at risk’ can only include those people who are potentially susceptible to the disease being studied. Given in this study, we are concerned with the harms associated with exposure in utero, the population at risk cannot include men, or women and girls who are not of childbearing age. This problem has been referred to previously as the ‘floating numerator’. Our findings add weight to previous studies demonstrating how the omission or use of inappropriate denominators leads to fallacious conclusions being inferred from research.

In this study, we have been able to demonstrate that in areas where absolute numbers of women and girls prescribed valproate are higher; this in the vast majority of CCGs and LHBs simply reflects higher rates of valproate prescribing among the general population. It is important to point out that we do not believe that there is anything particularly remarkable about this finding, indeed we believe that it is entirely intuitive because we are not aware of any compelling reason for valproate to...
be prescribed more frequently in, for example, women than men.

Given this is the case, we find the choice of the denominator in the existing NHSBSA and AWMSG indicators somewhat surprising. Not only does it differ from that used by the MHRA to measure the reduction in valproate use over time, but it also misapplies the generally accepted principles of measuring disease frequency with worrying results. Continued use of the existing NHSBSA and AWMSG indicators may mean some health communities, which we consider should be a priority for intervention, may not be identified because the high prevalence of valproate prescribing among women and girls of childbearing age is masked by a high prevalence among men and women not in the population at risk. Given this is the case, we believe that the indicator chosen by the NHSBSA and AWMSG while able to identify health communities with wide differences in the prevalence of valproate use between the at-risk and the rest of the population is unlikely to identify any notable differences in prescribing rates in the population at risk between health communities. We argue that the most appropriate denominator would not be all persons prescribed valproate, but all women and girls aged 14–45 years; a similar measure has been adopted for use in Scotland.18

Data sharing and benchmarking against key indicators is an effective tool to support quality improvement and is widely used in the NHS. Prescribing indicators have been used in the NHS for over 30 years to measure the quality and effectiveness of prescribing in GP.19 20 Although there is some evidence of the effectiveness of the role of prescribing indicators in supporting improving quality in prescribing21 particularly where they form part of multifaceted interventions22 23 they have been most commonly used to monitor changes in prescribing behaviour and cost over time.24 Being shown to be an outlier can be an ‘eye opener’ and highlight priority areas for local action to change prescribing behaviour and improve quality. Conversely, clinicians may be falsely reassured where their performance appears better than or similar to their peers and this may lead to the continuation of current (unsafe) practice. It is therefore paramount that data and analyses are robust in order to identify areas for review and to motivate organisations and prescribers where change is needed.

We found wide differences between CCGs and LHBs in the rate of valproate use among the overall population suggesting some health communities have been more successful than others in reducing valproate use. Understanding the reasons for the relative success of these organisations may provide useful insight for those apparently not addressing the issue at hand. Although it was not within the scope of this study to explore the reasons for this finding, we suggest it is one that would benefit from further research because such wide variation cannot be explained easily. This might examine, for example, whether differences can be attributed to differing population structures or whether they are associated with local commissioning arrangements for or availability of neurology services.

We believe the main strength of this study is that it combines routinely published valproate prescribing and dispensing data with population data to draw attention to the importance of applying epidemiological principles to the development of prescribing indicators. However, the study is not without limitations. The ecological design means that although we found a significant positive association between the prevalence of valproate use among women and girls of childbearing age and the prevalence among the total population excluding women and girls aged 14–45 years, in each health community, this will not necessarily be true in individual GPs in those communities. We cannot therefore rule out the effect of chance on variation between health communities. We recommend future work should use GP in addition to aggregated data in an appropriate mixed-effects model to address this. The treatment of epilepsy, for which valproate is most commonly prescribed, is likely to be led and strongly influenced by the availability (or lack of availability) of hospital neurology services. The use of GP data to produce prescribing indicators assumes that GPs are responsible for and willing to act on unwarranted variation; in this therapeutic area, we think this is unlikely without additional specialist input. A final limitation is that the publicly available data used to estimate the number of women and girls of childbearing age exposed to valproate will both include individuals who are part of the valproate PPP25 and exclude those prescribed valproate by their hospital specialist rather than their GP. This means the number of women and girls at risk in our analysis is likely to overstate the actual number at risk.

A targeted universalism26 approach is necessary to minimise fetal exposure to valproate and reduce the risk of congenital malformation, developmental and behavioural disorders. The statements issued by MHRA insisting that valproate medicines are only prescribed if other treatments are ineffective or not tolerated and only then if the conditions of the PPP are met, apply to all clinicians. Ranking CCGs and LHBs using relative differences in prevalence draws attention to a minority of outliers when in reality there will be women and girls exposed unnecessarily to valproate in every health community. All those at risk require urgent review.

There are, however, challenges to compliance with the requirements and a commitment to their implementation is required. Given limited specialist capacity to oversee changes to prescribing, prioritisation will be necessary along with wider consideration of how to develop and enhance skills among the wider team to support this work. The Clinical Practice Research Datalink, a real-world research service supporting retrospective and prospective public health and clinical studies sponsored by the MHRA and the National Institute for Health Research, and Royal College of General Practitioners have recently produced resources to support individual GPs to audit their valproate prescribing. This is a positive step that
it is hoped will support efforts to reduce the number of women and girls exposed to valproate.27

Despite a concerted effort on the part of regulators, the NHS and patient groups, many women are simply unaware of the risks of valproate in pregnancy. Taking further regulatory action, perhaps even going so far as to revoke valproate’s license, would deny some women the informed choice between continuing to use it and switching to a potentially less effective alternative. The preferred solution must be for individualised review and discussions between patients and their clinicians.

Although not without their limitations, prescribing indicators have an important role in helping prioritise where to place more intensive efforts to reduce risk, we are concerned that the current indicator may be giving false reassurance to clinicians failing to systematically review and where appropriate change treatment for women and girls of childbearing age. We recommend urgent consideration be given to changing the indicator used in England and Wales as we describe.

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Contributors AE and AH conceptualised the study. AE collected the data. AH and AE undertook the analysis. AE, AH, KH and ACS were involved in the data interpretation, manuscript preparation and final submission. All authors were involved in reviewing versions of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval All data used in this study were freely available in the public domain.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. Data are available upon reasonable request. Original data can be shared upon reasonable request. The source data used in this study are publicly available from the following sources: patients prescribed valproate in England (https://www.nhsbsa.nhs.uk/prescription-data/prescribing-data/sodium-valproate); patients prescribed valproate in Wales (http://www.awmsg.org/docs/awmsg/medman); clinical commissioning group population estimates (https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/cleancollectioncommissioninggroupbyyearpopulationestimates); estimates by local health boards and age (https://statswales.gov.wales/Catalogue/Population-And-Migration/Population/Estimates/Local-Health-Boards/populationestimates-by-ihb-age).

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