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Impact of regulatory safety notices on valproate prescribing and pregnancy outcome among women of child-bearing potential in Scotland: a population-based cohort study

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ABSTRACT

Objective To examine the impact of Medicines and Healthcare products Regulatory Agency (MHRA) safety alerts on valproate prescribing among women aged 14–45 years in Scotland and examine trends in pregnancies exposed to valproate.

Design Population-based cohort study.

Participants 21 983 women of all ages who received valproate between January 2011 and December 2019.

Methods All valproate prescriptions issued to women in Scotland between January 2011 and December 2019 were identified and prevalence/incidence rates per 10 000 population derived. The impact of regulatory safety alerts on prescribing was analysed using Joinpoint models. Linked pregnancy records for January 2011 to September 2019 were identified and annual rates of pregnancy per 1000 valproate-treated women aged 14–45 years were calculated for each pregnancy outcome: live birth, stillbirth, miscarriage and termination.

Results Annual prevalent and incident rates of valproate prescribing declined in women aged 14–45 years between 2011 and 2019 from 40.5 to 18.3 per 10 000 population (54.8% reduction) and 7.9 to 1.3 per 10 000 population (83.5% reduction), respectively. Statistically significant changes occurred around the times of the MHRA safety alerts. The number of valproate-exposed pregnancies conceived each year fell from 70 in 2011 to 20 in 2018, a 71.4% reduction, and the number of live births fell from 52 to 14, a 73.0% reduction. Expressed as a rate this was a 46.4% decrease from 15.3 to 8.2 per 1000 valproate-treated women aged 14–45 years in 2011 and 2018, respectively. Live birth was the most common pregnancy outcome.

Conclusion This study demonstrates, for the first time, the capabilities of national data sets to identify drug exposure and derive pregnancy outcome at scale across Scotland. Building on this as part of an evolving national/UK surveillance capability will continue efforts to minimise in-utero exposure to valproate; enabling ongoing surveillance to understand better long-term outcomes, and to inform better provision of health and wider support services.

Strengths and limitations of this study

► This is the first comprehensive national analysis in Scotland, using routine health system administrative data, to quantify pregnancy outcomes arising from valproate prescribing in pregnancy.

► The study considers all pregnancy outcomes: live birth, stillbirth, miscarriage (excluding early miscarriage not requiring obstetrical care) or termination.

► The study has not investigated the long-term outcomes of children exposed in utero which would require linkage to educational data sets and much longer follow-up.

► Building on these national capabilities, as part of an evolving UK landscape, will support continuing efforts to minimise in-utero exposure of potentially teratogenic medicines.

INTRODUCTION

Valproate (valproic acid and its sodium salts) is a well-established medicine licenced for use in the treatment of epilepsy, bipolar disorder and to prevent migraine headache.[1] Valproate is generally considered an effective and safe medicine and is included in the WHO List of Essential Medicines.[2]

Importantly, valproate is known to be teratogenic causing serious harm to babies exposed in utero during pregnancy. Major congenital anomalies, particularly spina bifida, occur approximately three times more frequently than expected and are associated with increasing dose and the use of multiple antiepileptic drugs. A specific 'valproate-syndrome' also exists, characterised by dysmorphic features and developmental delay. Children exposed to valproate during pregnancy are at risk of lowered IQ and a higher risk of autism. It has been estimated that congenital anomalies affect up to

1 in 10 valproate-exposed pregnancies and that developmental and cognitive impairment affects 4 in 10 children exposed to valproate in utero.[3 4]

Because of these substantial risks, and following a Europe wide review completed in 2014, regulators including the European Medicines Agency and, in the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) issued strengthened guidance to prescribers on use of valproate in pregnancy. This included the avoidance of use in pregnancy unless other treatments are ineffective or not tolerated and recommended that women of childbearing potential requiring valproate treatments should use adequate forms of contraception.[5 6] Regulators continued to issue a series of safety notices (2015–2018) concerning the use of valproate in women of childbearing potential.[6–10] This has included direct communications to clinicians and the creation of a number of support tools.[9 10] The most recent of these notices in the UK (April 2018) placed valproate within a *Pregnancy Prevention Programme* whereby a number of conditions must be met including explicitly recorded patient consent for valproate to be used in women of childbearing potential.[9 10]

The impact of these safety notices has been monitored by the MHRA through a series of analyses of valproate use in girls and women in the UK using the Clinical Practice Research Datalink (CPRD), the most recent of which reported a 50%–54% reduction in valproate prescribing among women aged 14–45 years and a 84%–87% reduction in new initiations of treatment in 2019 compared with 2010.[11] An estimated 78% decline in valproate-exposed pregnancies during this period was also reported.

Specifically within Scotland and following the latest MHRA safety notice in 2018,[10] a prescribing National Therapeutic Indicator measuring variation and change in the number of 13–45 year-old women treated with valproate as a proportion of all women treated has been in use. While this has shown a reduction by this measure, there was an approximately twofold variation across NHS Boards.[12]

This study presents the findings of a programme of work, commissioned in 2018 by the Chief Medical and Pharmaceutical Officers of the Scottish Government and the MHRA to: examine the impacts of the MHRA safety alerts on trends in the prevalence and incidence of prescribing of valproate in girls and women aged 14–45 years in Scotland and; to examine trends in the exposure and outcome of pregnancies to valproate.

METHODS
Data sources
The National Health Service (NHS) in Scotland is a publicly funded health system that provides universal healthcare coverage to a population of approximately 5.4 million. Public Health Scotland (PHS) hosts a variety of national data sets including prescribed/dispensed medicines,[13] and obstetric/maternity care.[14–17] Record linkage is enabled through a unique NHS patient identifier, the Community Health Index (CHI) number, assigned to every resident at birth or entry into the NHS system.[18] Data linkage was performed by PHS, as data controller with approvals secured through the Caldicott Guardian.

Valproate prescribing
Data for reimbursed prescriptions for valproate issued to women between January 2010 and December 2019 were retrieved from the National Prescribing Information System (PIS), which records all NHS prescriptions dispensed in the community.[13] Prescriptions for valproate were identified by approved name, which encompassed valproic acid and its sodium and semisodium salts.

Subjects were stratified into age bands based on their age on 31 December of the year of prescribing: 0–13 years; 14–45 years; and 46 years and older, and the numbers of individuals receiving a prescription in each year were identified as prevalent prescribing. The numbers of new patients, defined as receiving a prescription for the first time within the data set, was identified as incident prescribing. Results are reported from 2011 as 2010 was used to exclude prior prescribing and identify incident prescribing from 2011. National Records of Scotland mid-year population estimates were then used to calculate prescribing prevalence and incidence rates per 10 000 population.[19]

Impact of regulatory safety notices
Analysis of the impact of regulatory safety notices on prevalent and incident prescribing of valproate was conducted using Joinpoint models[20] applied to prevalent and incident prescribing rates for each calendar quarter (January–March (Q1), April–June (Q2), July–September (Q3), October–December (Q4)). Joinpoint is a regression software program that allows the user to specify a minimum and maximum number of Joinpoints to model against a trend series.[21 22] The programme uses permutation tests with Monte-Carlo sampling when the number of possible permutations is large.

We used a Monte-Carlo sample size of 4999 and a minimum of zero (a straight line) and a maximum of five Joinpoints for prevalence and incidence data to test if the numbers of patients receiving valproate had changed at or around the times when MHRA drug safety alerts were issued between 2015 and 2018.[5–8 10] Joinpoint can indicate both statistically significant and no-significant changes in trend, up to the maximum set, if the latter improves the statistical significance of the other trend changes.[23]

For both prevalent and incident prescribing, this gave 36 quarterly observations from Q1 2011 to Q4 2019 including an approximate 4-year period prior to the first MHRA drug safety updates in December 2014,[5] and seven quarters following the introduction of the Valproate Pregnancy Prevention Programme in April 2018.[10]

Valproate exposure during pregnancy

End of pregnancy records for the period January 2011–September 2019 were identified for any woman aged 14–45 years prescribed valproate between January 2010 and December 2019 from the:

SMR02 Maternity Inpatient and Day Case data set for end of pregnancy records relating to live births, stillbirths, miscarriages and terminations managed in a maternity setting.[14]

SMR01 General Acute Inpatient and Day Case data set for miscarriages managed in a gynaecology setting.[15]

AAS Notification of Abortion Statistics for terminations of pregnancy performed under the Abortion Act Scotland (AAS).[16]

National Records of Scotland register of stillbirths at >24 weeks gestation.[17]

For each pregnancy the outcome was recorded, that is, live birth; stillbirth; miscarriage; or termination, and date of conception was imputed based on gestational age in completed weeks recorded on the end of pregnancy record (with date of conception assumed to be at 2^{+0} (ie, 2 weeks and 0 completed days) gestation. Where gestational age was missing, date of conception was calculated as follows:

► Live births: assume delivery at 40 weeks, impute date of conception as date of birth minus 38 weeks.

► Stillbirths: assume delivery at 32 weeks, impute date of conception as date of delivery minus 30 weeks.

► Terminations of pregnancy: SMR02 records with no matching AAS record, assume termination of pregnancy at 16 weeks as these are likely to be later terminations performed in fetal medicine settings, impute date of conception as date of termination minus 14 weeks. Gestation is universally present for AAS records.

► Miscarriages: assume miscarriage at 12 weeks, impute date of conception as date of miscarriage minus 10 weeks.

For all pregnancies with an imputed conception date between 1 January 2011 and 31 December 2018, the pregnancy data were then linked to the valproate prescribing history from PIS and the pregnancy was considered valproate-exposed if there existed a prescription record between the imputed date of conception and the end date of the pregnancy.[11 24]

Annual rates of pregnancy per 1000 valproate-treated women aged 14–45 years were calculated for each pregnancy outcome: live birth, stillbirth, miscarriage and termination. For direct comparison with MHRA analysis,[11] the annual rate of valproate exposed pregnancies per 10 000 completed pregnancies was also calculated for pregnancies ending in 2011–2019.

Sensitivity analyses were performed on the numbers of pregnancies considered exposed if prescriptions up to 30 and 60 days prior to conception date were included.

Patient and public involvement

Patients and the public were not involved in the design, data provision, analysis or publication of the study.

RESULTS

We identified 21 983 women of all ages who received valproate between January 2011 and December 2019. The proportion of prescriptions with a valid CHI increased over time from 95.73% in 2010 to 99.05% in 2019. Table 1 presents the annual absolute numbers and rate per 10 000 population for both prevalent and incident prescribing by age groups 0–13 years; 14–45 years and 46+ years.

The annual prevalent rate of valproate prescribing declined in all female age groups between 2011 and 2019: from 40.5 to 18.3 per 10 000 population (54.8% reduction) in women aged 14–45 years; from 14.4 to 6.7 per 10 000 population (53.5% reduction) among those aged <14 years, and from 60.0 to 50.1 per 10 000 population (16.5% reduction) in women aged 46 years and over.

The annual incident rate of valproate prescribing saw a marked decline across all age groups over the same period from 7.9 to 1.3 per 10 000 population (83.5% reduction) in women aged 14–45 years; from 3.4 to 1.5 per 10 000 population (55.9% reduction) among those aged <14 years, and from 7.8 to 2.7 per 10 000 population (65.4% reduction) in women aged 46 years and over.

These changes in annual prevalent and incident prescribing rates by age group are presented graphically in online supplemental figures S1, S2.

Impact of regulatory safety notices

Figures 1 and 2 present the Joinpoint analysis for prevalent and incident valproate prescribing, expressed as a quarterly rate per 10 000 population, for the 14–45 years age group over the study period, respectively. For prevalent valproate prescribing there was a general decline in the quarterly prescribing rate and we identified five Joinpoints, four of which were statistically significant trend changes: at 2012 Q1 (steepening); at 2014 Q4 (steepening); at 2015 Q3 (flattening) and at 2017 Q4 (steepening). The latter three of these changes occur at, or within one-quarter of the publication of regulatory safety notices (figure 1).

As for prevalent prescribing, the quarterly incident valproate prescribing rate showed a general decline and Joinpoint analysis identified two Joinpoints, both of which were statistically significant changes in trend. One of these, 2015 Q1, occurred around the time of the earliest regulatory safety notices in December 2014/January 2015 (figure 2).

Valproate exposure during pregnancy

A total of 8108 women aged 14–45 years were identified who had been treated with valproate at any time between 2011 and 2018. There was a total of 2215 conceived pregnancies among those women during that time period and

Table 1 Number of female patients prescribed valproate and rate per 10000 population by age group 2011–2019

Age group	Year								
	2011	2012	2013	2014	2015	2016	2017	2018	2019
Prevalent prescribing n (rate per 10000 population)									
13 years and under	558 (14.4)	530 (13.6)	513 (13.2)	479 (12.3)	444 (11.3)	391 (9.9)	345 (8.7)	284 (7.2)	263 (6.7)
14–45 years	4573 (40.5)	4418 (39.3)	4182 (37.5)	3953 (35.7)	3565 (32.3)	3170 (28.8)	2875 (26.3)	2423 (22.3)	1996 (18.3)
46 years and over	7274 (60.0)	7335 (59.8)	7397 (59.7)	7405 (59.0)	7351 (57.9)	7282 (56.8)	7078 (54.7)	6887 (52.9)	6584 (50.1)
Total	**12 405 (45.5)**	**12 283 (44.9)**	**12 092 (44.1)**	**11 837 (43.0)**	**11 360 (41.1)**	**10 843 (39.0)**	**10 298 (37.0)**	**9594 (34.5)**	**8843 (31.6)**
Incident prescribing n (rate per 10000 population)									
13 years and under	133 (3.4)	115 (3.0)	117 (3.0)	96 (2.5)	74 (1.9)	58 (1.5)	52 (1.3)	35 (0.9)	60 (1.5)
14–45 years	891 (7.9)	807 (7.1)	741 (6.6)	651 (5.8)	460 (4.2)	367 (3.3)	339 (3.1)	171 (1.6)	144 (1.3)
46 years and over	934 (7.8)	940 (7.8)	887 (7.2)	770 (6.2)	679 (5.4)	653 (5.1)	527 (4.1)	477 (3.7)	358 (2.7)
Total	**1958 (7.2)**	**1862 (6.8)**	**1745 (6.4)**	**1517 (5.5)**	**1213 (4.4)**	**1078 (3.9)**	**918 (3.3)**	**683 (2.4)**	**562 (2.0)**

365 of these were considered to have been exposed to valproate during the pregnancy.

Table 2 shows conceptions and their outcomes expressed per 1000 women aged 14–45 years treated with valproate by year of conception. Valproate-exposed conceptions dropped from 15.3 per 1000 women treated with valproate in 2011 to 8.2 per 1000 women treated with valproate in 2019, a reduction of 46.4%.
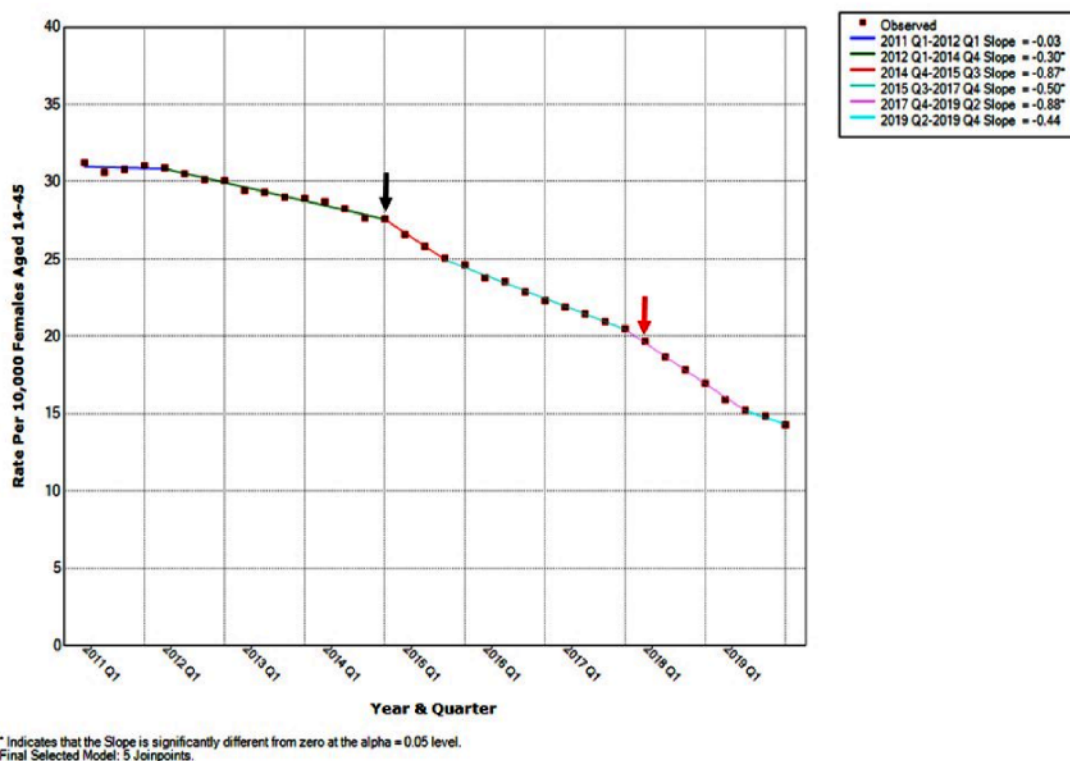

* Indicates that the Slope is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 5 Joinpoints.

Figure 1 Joinpoint analysis of quarterly valproate prevalent prescribing rates per 10000 population in women 14–45 years, 2011–2019 (↓=first MHRA safety notice; ↓=latest MHRA safety notice including Pregnancy Prevention Programme). MHRA, Medicines and Healthcare products Regulatory Agency.
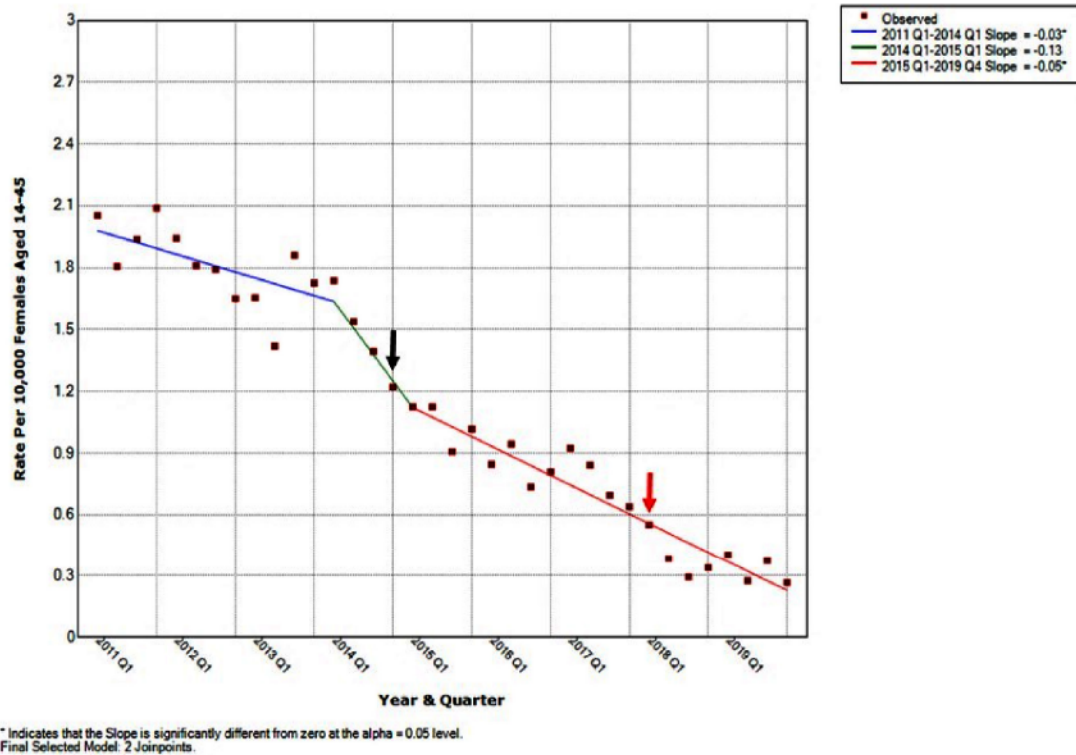
Figure 2 Joinpoint analysis of quarterly valproate incident prescribing rates per 10 000 population in women 14–45 years, 2011–2019 (↓=first MHRA safety notice; ↓=latest MHRA safety notice including Pregnancy Prevention Programme). MHRA, Medicines and Healthcare products Regulatory Agency.

In absolute terms, the number of valproate-exposed pregnancies fell from 70 in 2011 to 20 in 2018 and the number of babies born who had been exposed to valproate in utero reduced from 52 to 14.

Figure 3 presents valproate-exposed pregnancies expressed as a rate per 10 000 total completed pregnancies, the measure reported by the MHRA in their monitoring reports.[25–27] This fell from 12.1 per 10 000 for pregnancies

Table 2 Total pregnancies and their outcomes in valproate-treated women aged 14–45 years by conception year 2011–2018

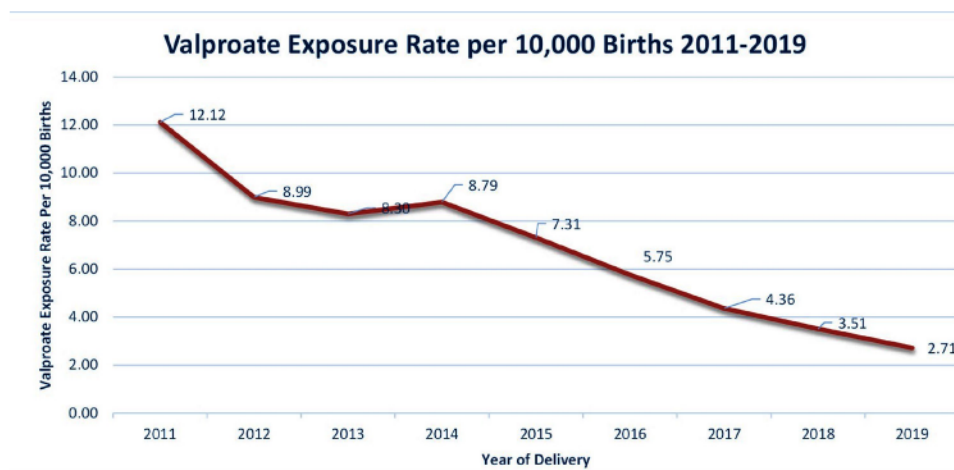| Year	Women aged 14–45 prescribed valproate during year (N)	Valproate-exposed pregnancies conceived during year (N)	Valproate-exposed pregnancy rate (per 1000 treated women)		
2011	4572	70	15.3		
2012	4415	63	14.3		
2013	4179	59	14.1		
2014	3952	48	12.1		
2015	3565	50	14.0		
2016	3170	34	10.7		
2017	2875	21	7.3		
2018	2430	20	8.2		
Year	**Outcome of valproate-exposed pregnancies (N, %)**				
	Live birth		**Miscarriage**	**Stillbirth**	**Termination of pregnancy**
2011	52	(74)	7 (10)	0 (0)	11 (16)
2012	52	(83)	3 (5)	0 (0)	8 (13)
2013	40	(68)	7 (12)	0 (0)	12 (20)
2014	33	(69)	2 (4)	0 (0)	13 (27)
2015	38	(76)	6 (12)	0 (0)	6 (12)
2016	26	(76)	0 (0)	0 (0)	8 (24)
2017	19	(90)	1 (5)	0 (0)	1 (5)
2018	14	(70)	1 (5)	0 (0)	5 (25)

Figure 3 Valproate-exposed pregnancies per 10000 completed pregnancies in Scotland, 2011–2019.

that completed in 2011 to 2.7 per 10000 pregnancies for those that completed in 2019, a 77.7% reduction.

Sensitivity analysis

Extending the criteria for identifying pregnancies as valproate exposed by including prescriptions within 30 or 60 days prior to conception increased the number of pregnancies considered as valproate exposed by 14.8% and 24.7%, respectively. The effect varied by pregnancy outcome and was greatest for pregnancies that ended in termination (46.9% and 67.2% increase, respectively). These data are presented in the online supplemental file 1.

DISCUSSION

Our analysis is based on linking, for the first time, comprehensive prescribing data and pregnancy-related events from several large national administrative data sets covering the Scottish population. Between 2011 and 2019 the number of girls and women aged 14–45 years being treated with valproate for all indications fell from 4573 in 2011 to 1996 in 2019 (table 1). As a rate per 10000 population, which adjusts for changes in the size of the population age group, this represents a 54.8% decrease from 40.5 to 18.3 per 10000 population. There was an even more marked 83.5% reduction in the incident prescribing of valproate from 7.9 to 1.3 per 10000 population in this age group. Joinpoint analysis showed that significant changes in the trends for treatment with valproate occurred around the times of the MHRA Drug Safety Notices.

For pregnancies conceived between 2011 and 2018, pregnancies where valproate was prescribed during the pregnancy fell by 46.4% from 15.3 to 8.2 pregnancies per 1000 valproate-treated women aged 14–45 years. Much of this change occurred from 2015, suggesting that the MHRA safety alerts have had an effect. In absolute terms, the number of valproate-exposed pregnancies fell from 70 pregnancies conceived in 2011 to 20 conceived in 2018.

In common with others,[11 24] we considered a pregnancy as valproate-exposed if there was a prescribing event between the imputed date of conception and the end of the pregnancy. Sensitivity analysis found that including prescriptions issued within 30 or 60 days prior to conception had an overall modest effect on increasing the number of pregnancies identified as valproate-exposed but there was a more marked effect for pregnancies that ended in termination (online supplemental file). This is possibly a consequence of termination generally occurring early in pregnancy and there being only a short window for prescribing to occur during pregnancy. However, and more worryingly, this differential increase in terminated pregnancies being identified as potentially valproate-exposed may indicate that extending the prescription to the pre-conception period is capturing genuinely exposed pregnancies and that a relatively high proportion of these were unplanned. Between 2011 and 2018 there were 442759 live births in Scotland[28] and 99002 terminations of pregnancy[29] giving a live birth to termination ratio of 4.5. For valproate-exposed pregnancies, with exposure between conception and pregnancy end, the corresponding figures are 274 live births and 64 terminations giving a ratio of 4.3. However, extending the definition of exposure to having received a prescription in the preconception period reduces this ration to 3.2 for prescriptions within 30 days of conception and to 3.0 for having received a prescription up to 60 days prior to conception. This is an area that warrants further investigation and might be a valuable measure in assessing the impact and success of the Pregnancy Prevention Programme and an important consideration if attempting to examine or interpret whether the risks for valproate-exposed babies affect maternal decisions when pregnancy occurs.

Regularly updated estimates of the number of pregnancies in the UK that have been exposed to valproate have been published by the MHRA.[11 25–27] These use the CPRD Gold database, which holds patient records from a representative sample (8%) of general practices. CPRD uses a pregnancy identification algorithm developed and validated by the London School of Hygiene and Tropical

Medicine to identify pregnancies, including start and end dates.[30] The latest of these reports that prescribing of valproate in pregnancy declined by 77.8% (from 11.09 per 10 000 pregnancies (95% CI 9.12 to 13.48) to 2.46 per 10 000 pregnancies (95% CI 1.25 to 4.86)) between 2010 and 2019.[11] By this measure, we observed a 77.7% reduction from 12.1 to 2.7 per 10 000 pregnancies between 2011 and 2019 (figure 2).

A cross national study examined antiepileptic prescribing during pregnancy in the UK, France and two regions in Italy.[24] The UK data were obtained from the CPRD and the authors reported a decline in valproate-exposed pregnancies from 1.4 to 0.6 per 1000 pregnancies between 2007 and 2015. In France, valproate prescribing during pregnancy declined from approximately 1.9 to 0.7 per 1000 pregnancies over the same period, with much of that decrease occurring between 2009 and 2011. In the Emilia Romana region of Italy there was a decline from 0.6 to 0.3 per 1000 pregnancies whereas in Tuscany valproate prescribing during pregnancy remained flat throughout the study period at 1.6–1.7 per 1000 pregnancies.

Our results are very similar to these two studies[11 24] and show a reduction in valproate-exposed pregnancies from 12.1 per 10 000 pregnancies that completed in 2011 to 2.7 per 10 000 pregnancies that completed in 2019: a reduction of 77.7% (figure 2).

Strengths and limitations

Ours is the first study, to our knowledge, that is based on comprehensive data for a whole population rather than a sample, as observed in other publications to date.[12 24–27] We have used data from multiple national data sets relating to pregnancy and birth and have been able to report on all types of pregnancy outcomes. While, taken together, the data sets used identify the vast majority of pregnancies in Scotland, some early miscarriages that do not require hospital inpatient or day-case care will not have been captured. It is therefore not currently possible to assess the extent to which these early pregnancies have been exposed to valproate.

The observed decline in the conception rate among valproate-treated women might be explained by improved pregnancy planning and better use of contraception. Because of how contraceptive services are delivered, and particularly for long-acting reversible contraception, which is the method favoured by the Pregnancy Prevention Programme but is often delivered through sexual health services, we were unable to reliably link contraceptive use to valproate prescribing to examine whether any changes had occurred.

While we have identified significant changes in conception rate over time, we have not been able to fully explore, for example, whether the increased awareness of the potential harms of valproate exposure during pregnancy affected the proportion of exposed pregnancies ending in termination. This would be challenging given the increasingly small numbers of valproate-exposed pregnancies. We have also not examined the frequency of congenital

anomalies or the long-term cognitive outcomes for those exposed to valproate in utero. The latter would require linkage to Scotland's national congenital anomaly data set and other databases of educational outcomes[31] and should be considered a part of building a comprehensive surveillance system for in utero exposures moving forward. National capabilities at this scale could enable more systematic examination of medicines to support earlier recognition of teratogenic risks, avoiding unnecessary exposure.[32]

This study has demonstrated the current capabilities of Scottish national data sets to identify drug exposure and derive pregnancy outcome at scale. Building on this as part of an evolving national/UK registry and surveillance capability will be an important step in: augmenting current harm minimisation systems within routine clinical care; responding to the independent safety review and recommendations by Baroness Cumberlege report—First Do No Harm,[33] and; delivery of the Scottish and UK government responses to the Cumberlege Report.[34 35]

CONCLUSION

The rate of valproate treatment in women of reproductive age has reduced substantially in recent years which, combined with a halving of the pregnancy rate in valproate-treated women, has resulted in a major reduction in the numbers of pregnancies and babies exposed to valproate in utero.

Some women may choose to become pregnant while taking valproate, particularly if it is for them the only effective epilepsy medicine. We should, however, continue to ensure that we avoid unintentional, unplanned and uninformed pregnancies in women, exposed to valproate.

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Supplemental material
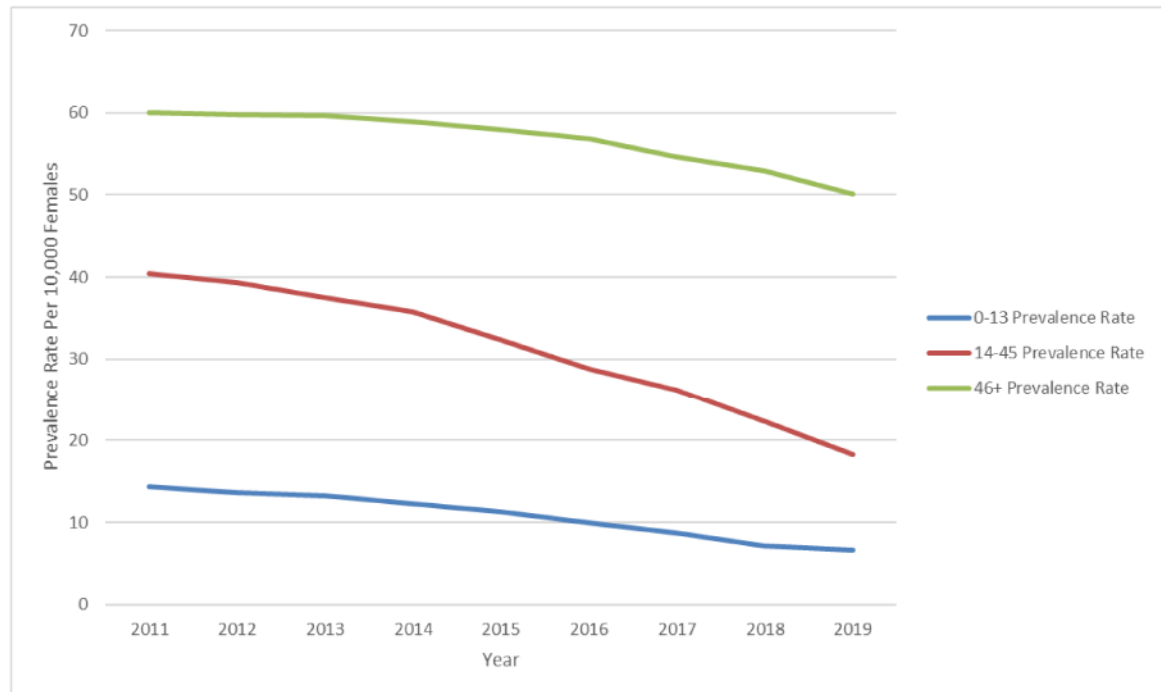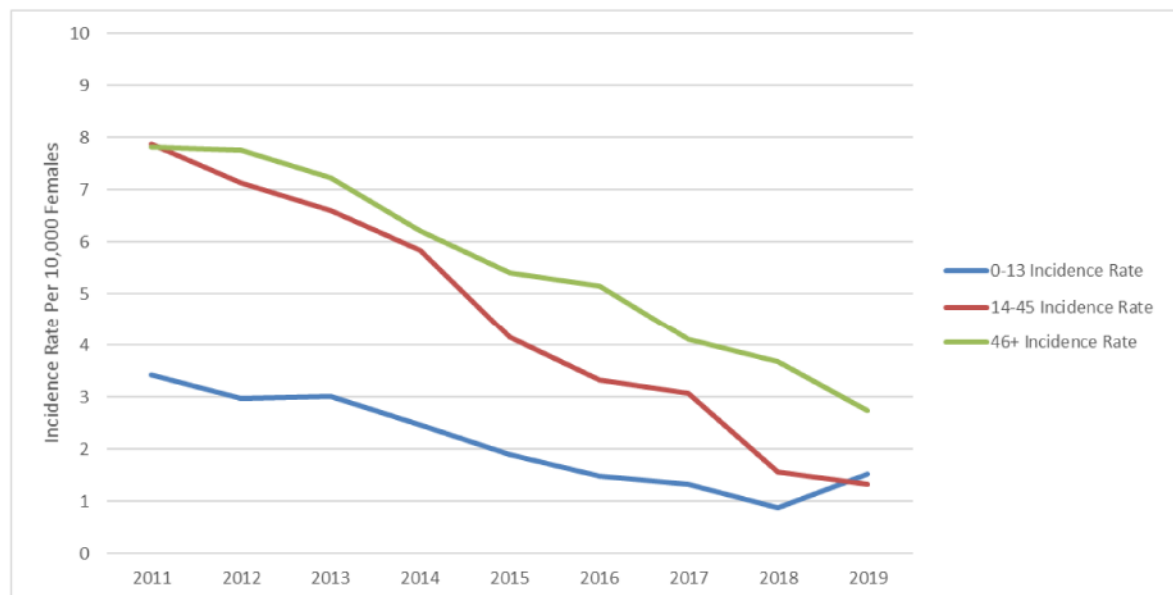
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Supplementary file

Figure S1: Annual valproate prevalent prescribing rates per 10,000 population in females by age group 2011-2019

Figure S2: Annual valproate incident prescribing rates per 10,000 population in females by age group 2011-2019

Supplemental material

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Table S1: Sensitivity analysis for valproate exposed pregnancies by pregnancy outcome

Valproate exposure criteria	Total	Live Birth	Stillbirth	Miscarriage	Termination
During pregnancy	365	274	0	27	64
During pregnancy or 30 days prior	419 (+14.8%)	297 (+8.4%)	0 (+0%)	28 (+3.7%)	94 (+46.9%)
During pregnancy or 60 days prior	455 (+24.7%)	319 (+16.4%)	0 (+0%)	29 (+7.4%)	107 (+67.2%)