Rapid assessment of the number of women and children exposed to sodium valproate in Ireland

1975-2015

August 2018

Contents

Summary

There is evidence that some anti-epileptic drugs (AEDs) are teratogenic - they are associated with an increased risk of foetal anti-convulsant syndrome (FACS), an umbrella name for a group of conditions that can affect some babies exposed to AEDs while in utero.

Valproate medicines are one group of anti-epileptic drugs (AEDs). One of these, sodium valproate, has been licensed for use in Ireland for epilepsy since 1975 and for bipolar disorder since 2008.

This analysis aimed to provide an estimate of the likely prevalence of specific major congenital abnormalities and neuro-developmental disorders arising from exposure of children to sodium valproate in the womb, between 1975 and 2015, in Ireland.

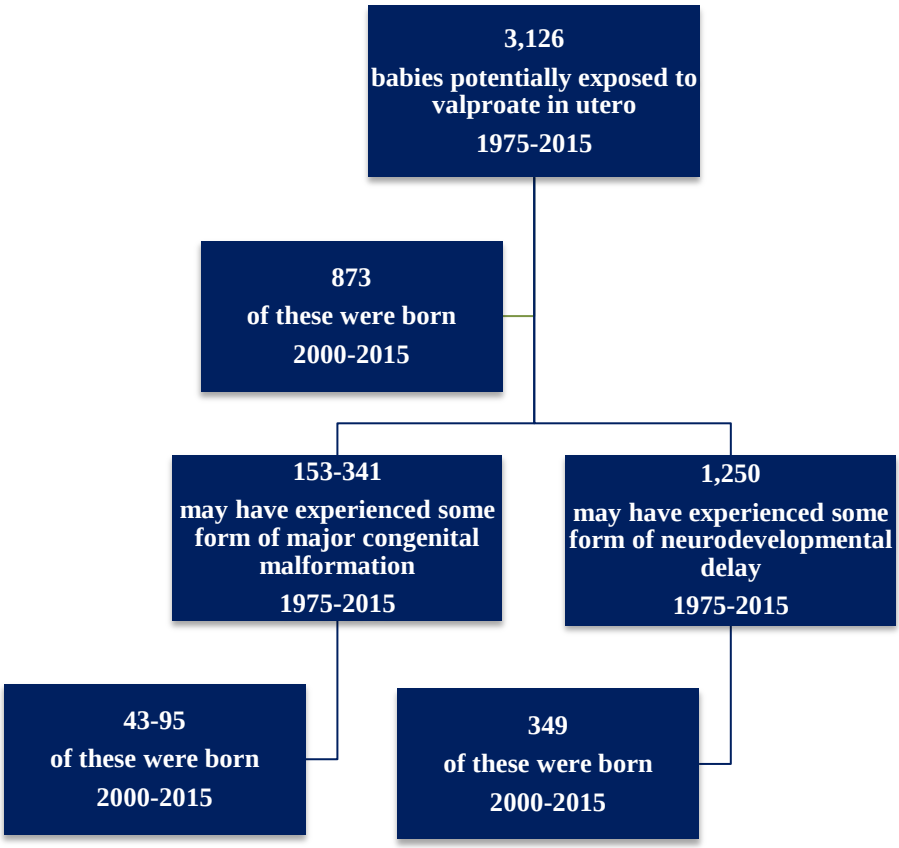
It is estimated that, between 1975 and 2015, inclusive, approximately 3,083 (3,058 epilepsy; 25 other indications) maternities were in women who were taking valproate when becoming pregnant.

It is estimated that, between 1975 and 2015, inclusive, approximately 3,126 (3,100 epilepsy; 26 other indications) babies were potentially exposed to valproate in utero. Of these, it is estimated that 873 were born between 2000 and 2015, inclusive. These will now be aged 2-18 years. A similar number of children, currently aged 0-16, were potentially exposed in the years from 2002-2017, inclusive.

On the basis of the above estimations and on emerging international data regarding rates of major congenital malformation and neurodevelopmental delay following exposure to valproate in utero, it is estimated that between 1975 and 2015, between 153 and 341 children will have experienced a major congenital malformation and up to 1,250 children will have experienced some form of neurodevelopmental delay. Of children born since 2000, it is estimated that between 43 and 95 will have experienced a major congenital malformation and 349 will have experienced some form of neurodevelopmental delay; a similar number of children, born between 2002 and 2017 and currently aged 0-16, are likely to have experienced such a malformation and/or delay.

It should be emphasised that there is no single source of data relating to the use of valproate in pregnancy in Ireland. Furthermore, while some individual datasets might have held useful information, the inability to link these datasets meant that they were of little value. The analysis therefore relied to a large extent on international data, is subject to a large range of assumptions and limitations (as detailed herein) and the resulting estimates should be viewed as a broad guide for those tasked with planning diagnostic and management services for people affected by this issue; the true impact of valproate on women and children will only become apparent as data is collected prospectively over the coming weeks and months.

Figure 1 Summary overview of estimated numbers exposed and affected



1.0 Background

1.1 Anti-epileptic drugs (AEDs)

There is evidence that certain antiepileptic drugs (AEDs) are teratogenic - they are associated with an increased risk of congenital malformation (birth defects). In addition to epilepsy, AEDs are also frequently used for other indications, such as migraine, pain syndromes, and psychiatric disorders including bipolar disorder.[1]

1.2 Foetal anti-convulsant syndrome (FACS)

Foetal anti-convulsant syndrome (FACS) is an umbrella name for a group of conditions that can affect some babies if they are exposed to AEDs while in the womb. These include major congenital malformations and problems with cognitive development.

Major congenital malformations are generally defined as structural abnormalities of surgical, medical, functional, or cosmetic importance. Such structural abnormalities are established during organogenesis, within the first 8–10 weeks of gestation, often before the woman is aware that she is pregnant.

In women with epilepsy who are not exposed to AEDs, the incidence of major congenital malformations is similar to the background risk for the general population (2-3%).

For women with epilepsy who are exposed to AEDs, the risk is dependent on the type, number and dose of AED. Data from six international registries demonstrate that the risks are highest with valproate medicines.

Table 1.1 Rates of major congenital malformations in six different studies[2]

	Valproate	Carbamazepine	Lamotrigine	Phenobarbital	Phenytoin
International Lamotrigine Pregnancy Registry[27]	..	..	35/1558 (2%)	..	..
Finnish Medical Birth Registry and drug prescription databases[25]	28/263 (11%)	22/805 (3%)	..	..	1/38 (3%)
Swedish Medical Birth Registry*	29/619 (5%)	35/1318 (3%)	26/867 (3%)	..	8/119 (7%)
UK Epilepsy and Pregnancy Register[28]	44/715 (6%)	20/900 (2%)	21/647 (3%)	..	3/82 (4%)
North American AED Pregnancy Registry[29]	30/323 (9%)	31/1033 (3%)	31/1562 (2%)	11/199 (6%)	12/416 (3%)
International Registry of Antiepileptic Drugs and Pregnancy (EURAP)[30]	98/1010 (10%)	79/1402 (6%)	37/1280 (3%)	16/217 (7%)	6/103 (6%)

Data are number with major congenital malformations/number exposed to antiepileptic drug monotherapy (%). AED=antiepileptic drug. *Källén K, University of Lund, Sweden, personal communication.

[1] Teratogenic effects of antiepileptic drugs. Tomson, T. & Battino, D.. Lancet Neurology, 2012
[2] Teratogenic effects of antiepileptic drugs. Tomson, T. & Battino, D.. Lancet Neurology, 2012

Valproate medicines are one group of AEDs. These include sodium valproate, valproic acid and valproate semi-sodium. They can be used to treat epilepsy and bipolar disorder, and to prevent migraines. They have been licensed for use in Ireland since the 1970s. The subject of this assessment, sodium valproate, has been licensed for use in Ireland under the brand name Epilim since 1975.

In women who take sodium valproate the risk of a major congenital malformation appears to be up to 11%.[3,4] Birth defects can include spina bifida, malformation of the limbs, and facial and skull malformations. An evidence review in 2010 suggested that, compared with no use of an AED, use of valproate monotherapy was associated with increased risks for spina bifida (OR12·7), atrial septal defect (2·5), cleft palate (5·2, 2·8–9·9), hypospadias (4·8, 2·9–8·1), polydactyly (2·2), and craniosynostosis (6·8).[5]

Importantly, this review went on to emphasise that, while the relative risks are high, the absolute risks of a specific malformation are low and the majority of children born to women who take valproate in pregnancy will not have a malformation. The authors estimated that the absolute risk of having a child with spina bifida is approximately 0.6% in cases of exposure to valproate monotherapy during the first trimester. The estimated absolute risks for the other five malformations after exposure were as follows: atrial septal defect, 0.5%; cleft palate, 0.3%; hypospadias, 0.7%; polydactyly, 0.2%; and craniosynostosis, 0.1%.

Studies since 2009 have demonstrated that the use of sodium valproate (at any stage) in pregnancy can also affect a child's cognitive development; problems (including delays in learning to walk and talk, lower intelligence than children of the same age and poor speech and language skills) occur in up to 40% of preschool children exposed to valproate in the womb and the risk of autism is up to five times higher than base level. [6]

In one study, a group of children living in Northern Ireland who had been exposed to monotherapy with AEDs were assessed at ages ranging from 9 to 60 months.[7] Children born to healthy mothers served as control children. A significant developmental delay was noted in 9% (5/58) of children exposed to valproate; mild delay was reported in 31% (18/58). Of the control children, 2% had significant delay and 2% had mild delay.

A 2014 Cochrane review reported that children exposed to sodium valproate in utero had a significantly lower developmental quotient including intelligence quotient (IQ), verbal IQ and

[3] Valproate and Fetal AntiConvulsant Syndrome. House of Commons. Debate Pack. 2017

[4] http://www.ema.europa.eu/ema/index.jsp%3Fcurl%3Dpages/medicines/human/referrals/Valproate_and_related_substances/human_referral_prac_000032.jsp%26mid%3DWC0b01ac05805c516f

[5] Valproic Acid Monotherapy in Pregnancy and Major Congenital Malformations. Jentink, J et al. NEJM, 2010

[6] http://www.ema.europa.eu/ema/index.jsp%3Fcurl%3Dpages/medicines/human/referrals/Valproate_and_related_substances/human_referral_prac_000032.jsp%26mid%3DWC0b01ac05805c516f

[7] Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. Cummings et al. Arch Dis Child 2011

performance IQ when compared with those born to women with epilepsy but who were not taking AEDs, and to those born to women without epilepsy.[8]

Increasing evidence suggests a dose–dependent relationship with developmental outcome and the risks also appear to be greater when sodium valproate is taken with other AEDs as combination therapy.

There is limited evidence regarding the rate of spontaneous abortion in women receiving sodium valproate or other AEDs, although a 2017 report from the EURAP registry reported that 5.8% (760/13,100[12,952 on AEDs]) of pregnancies in WEE taking AED(s) registered prospectively (before seventeen weeks gestation) with it since 1999 had ended in spontaneous abortion.[9,10]

[8] Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child. Cochrane Database Syst Rev. 2014

[9] Teratogenic effects of antiepileptic drugs. Tomson, T. & Battino, D.. Lancet Neurology, 2012

[10] EURAP. An International Antiepileptic Drugs and Pregnancy Registry. Interim Report - November 2017. Battino D., Tomson T

2.0 Current Guidance

In 2014, the European Medicines Agency (EMA) stated that

> *Valproate should not be used to treat epilepsy or bipolar disorder in girls and in women who are pregnant or who can become pregnant unless other treatments are ineffective or not tolerated. Women for whom valproate is the only option after trying other treatments, should use effective contraception and treatment should be started and supervised by a doctor experienced in treating these conditions*.[11]

A concern raised by epilepsy charities and patient groups was that there had been a lack of information for women about the risks associated with sodium valproate; surveys in the UK in 2016 and 2017 suggested that approximately 20% of women taking sodium valproate were unaware of the risks in pregnancy. In Ireland, a small 2016 survey (n=29) reported that almost half of women/ parents of girls taking valproate had not had conversations with their medical team about the dangers associated with the drug.

In March 2018, based on an assessment that their 2014 recommendations had not been effectively communicated to women, the EMA stated that valproate medicines are now contraindicated in girls and women able to have children unless the terms of a special pregnancy prevention programme are followed.[12] These include:

- an assessment of each patient's potential for becoming pregnant,
- pregnancy tests before starting and during treatment as needed,
- counselling about the risks of valproate treatment and the need for effective contraception throughout treatment,
- a review of ongoing treatment by a specialist at least annually,
- introduction of a new risk acknowledgement form that patients and prescribers will go through at each such annual review to confirm that appropriate advice has been given and understood.

As before, valproate treatment should never be started unless alternative treatments are not suitable, including in young girls below the age of puberty.

In pregnancy, valproate is contraindicated and an alternative treatment should be decided on, with appropriate specialist consultation, for women planning pregnancy. While valproate is absolutely contra-indication for women with bipolar disorder or migraine, there may be a small number of women with epilepsy for whom there is no suitable alternative treatment to valproate and who should be appropriately supported and counselled.

[11] PRAC recommends strengthening the restrictions on the use of valproate in women and girls, EMA 2014

[12] New measures to avoid valproate exposure in pregnancy endorsed. EMA, March 2018

3.0 Number of People Affected

France

A study published in April 2017 estimated that valproate drugs taken by pregnant women in France caused at least one major congenital malformation in 2150–4100 children between 1967 (when the drug was launched) and 2016.[13]

The French Government estimates that approximately 14,322 pregnant women were exposed to valproate between 2006 and 2014, affecting approximately 450 children. [14]

Belgium

Approximately 12,295 women aged 19-49 were taking sodium valproate in Belgium in 2015.[15]

United Kingdom

A 2017 report from NHS England estimated that, of 173,787 patients taking sodium valproate in England, around 10% of these were women aged 14-45 (17,848).

Multiple UK sources quote a figure of 20,000 children affected since 1973. However, this appears to be based simply on an assumption that 40% (19,200) of all women who received sodium valproate while pregnant in the UK (estimated 48,000) will have given birth to a baby with FACS.

United States

In the United States in 2012, about 1.5 million outpatients received valproate, and roughly 22% (341,000) of these were women of 'reproductive potential' (13-45 years); 67% of the total took the drug for mood and psychiatric disorders, 9% for migraine, and 9% for epilepsy.[16]

Ireland

Prevalence of Epilepsy

In 2009, a study by UCD on behalf of Epilepsy Ireland (formerly Brainwave) reported that:[17]

- Self Report Data (QNHS, 2007) – based on the data, is was estimated that 31,000 adults in Ireland were living with a diagnosis of epilepsy
- Drug Data (PCRS, 2002-2005) - Overall prevalence rates of treated epilepsy, ranged from 8.3 per 1,000 people in 2002 to 9.0 per 1,000 in 2005. Increases were noted each year from 2002

[13] France bans sodium valproate use in case of pregnancy. Casassus, B. Lancet, 2017
[14] France bans sodium valproate use in case of pregnancy. Casassus, B. Lancet, 2017
[15] EMA Public Hearing on Valproate, page 15 file:///C:/Users/ronanglynn/Desktop/SV_publichearing_EMA.pdf
[16] FDA. Drug Safety Communication: valproate anti-seizure products contraindicated for migraine prevention in pregnant women due to decreased IQ scores in exposed children. 2013. https://www.fda.gov/Drugs/DrugSafety/ucm350684.htm
[17] The prevalence of epilepsy in Ireland. Linehan C, et al. 2009.

to 2005. Extrapolated to Ireland's total population of those aged over 5 years of age at that time, between 33,000 and 36,000 people were being treated for epilepsy.

- Primary Care (GP survey) – Estimated that 35,880 persons with epilepsy attended primary care in Ireland

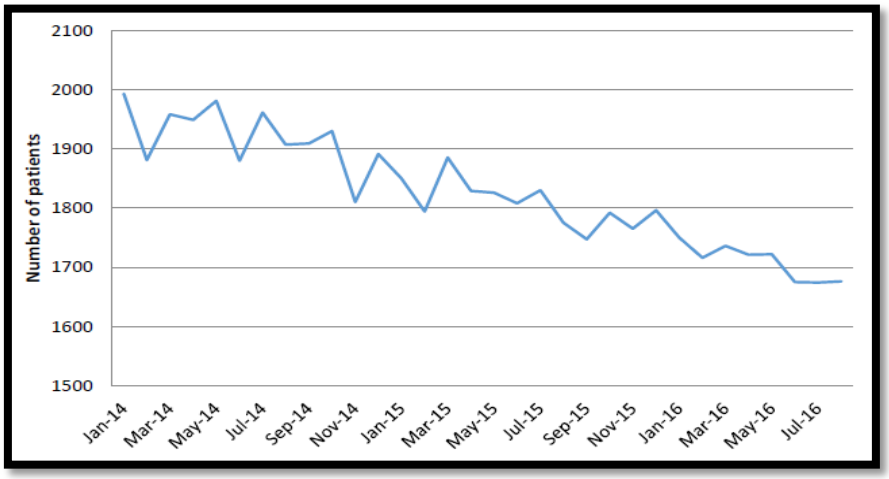
Prescribing trends of AEDs

Analysis of PCRS data (GMS, LTI, DPS) for women aged 16-44 years between 2008 and 2013 revealed that

- The rate of prescribing decreased from 3.5/1000 to 3.14/1000 over the study period
- This decrease was confined to those on the LTI; prescribing rates increased for GMS & DPS
- Prescribing rates were higher in rural versus urban locations[18]

An updated analysis of this data reported that approximately 300 fewer women were in receipt of sodium valproate in August 2016 compared to January 2014 (figure 3.1).[19]

Figure 3.1 Total number of women (16-44 years) in receipt of sodium valproate (GMS, DP & LTI schemes combined)



Prevalence of FACS

The FACS Forum has estimated that approximately 400 children may be affected by FACS in Ireland. This appears to be based on an extrapolation of UK figures above.

A 2018 research paper from the Department of Clinical Genetics at Our Lady's Children's Hospital, Crumlin reported diagnosing 29 cases in the 21 year period from 1995 to 2016.[20] Separately, it has been reported that that Department has diagnosed a total of 43 cases of FACS.

[18] Prescribing trends for sodium valproate in Ireland. Murphy et al. Eur J Epilepsy, 2016
[19] Update report on the utilisation of sodium valproate in women (16-44 years) Medicines Management Programme , HSE, March 2017
[20] Fetal valproate syndrome. The Irish experience. Mohd Yunos H & Green A. 2018. IJMS

4.0 Objectives

- Provide an estimate of the number of women who were taking sodium valproate when becoming pregnant, between 1975 and 2015
- Provide an estimate of the number of children who may have been exposed to sodium valproate in the womb, between 1975 and 2015
- Provide an estimate of the likely prevalence of major congenital abnormalities and neuro-developmental disorders arising from exposure of children to sodium valproate in the womb, between 1975 and 2015

5.0 Methodology

- The annual number of maternities resulting in a live birth was obtained from the Central Statistics Office (CSO)
- The internationally accepted rate of epilepsy in pregnancy was applied to this data in order to estimate the number of women with epilepsy who gave birth annually
- Data from the Irish component of the UK and Ireland Epilepsy in Pregnancy Register was then used to provide an estimate of the proportion and number of maternities in women with epilepsy (WEE) who were taking sodium valproate when becoming pregnant
- Data from the CSO (live births; singleton and twin births) was used to estimate the number of babies born to WWE who had potentially been exposed to valproate in utero
- UK data was used to estimate the number of women affected and children potentially exposed to valproate in utero as a consequence of valproate prescribing for conditions other than epilepsy
- The number of children who may have experienced a major congenital malformation or neurodevelopmental delay as a consequence of exposure to sodium valproate in utero was calculated using data from the UK and Ireland Epilepsy in Pregnancy Register and the Cochrane Collaboration.

6.0 Results

6.1 Number and proportion of pregnancies in women with epilepsy

Although it is generally accepted that approximately 1 in 200 (5/1000) pregnancies occur in women with epilepsy (WWE), rates vary across studies (Table 6.1). This variation is due to differences in how studies defined their 'study population', in the types of studies undertaken and where they were performed. For example, while an analysis of women attending the specialist service at the Rotunda from 2004-13 suggested that 8.6/1000 pregnancies occur in WWE, it is unlikely that this is representative of the Irish population as a whole due to the specialist nature of the services provided there (i.e. it is likely that a greater proportion of pregnancies at the Rotunda are in WWE as it is likely that a greater number of WWE choose to attend the Rotunda because of the availability of the specialist service there).

Table 6.1 Variation in reported prevalence of epilepsy in pregnancy

Reference	Type of Study	Proportion
Angus-Leppan et al., 2018[21]	Review	5/1000
Fairgrieve, 2000[22]	Analysis of 1997/98 UK data. All births (live births, stillbirths and medical terminations)	6.1/1000
Holohan et al., 2016[23]	Analysis of attendances at Epilepsy Clinic, Rotunda Hospital, 2004-2013	8.6/1000
Olaffson et al., 1998[24]	Population based study, live births, 1972-1990, Iceland	3.3/1000
Vajda et al., 2014[25]	Australian Data, all pregnancies	5.3/1000
Borthen et al, 2010	Norwegian Medical Births Registry (mandatory), 1999-2005	7.7/1000
Daniellson et al, 2018[26]	Norwegian Medical Births Registry (mandatory), First time pregnancies, 23 weeks +, 2004-2012	8.0/1000

From 1975 to 2015, inclusive, 2,531,769 maternities resulting in a live birth were recorded in the Republic of Ireland. This varied from 47,670 (1994) to 74,335 (2009) maternities annually. Taking the internationally accepted figure of 5/1,000 maternities, it is estimated that over the 40 years approximately 12,658 maternities occurred in WWE which resulted in a live birth (Table 6.2). Estimates are also provided on the basis that the rate of epilepsy in pregnancy may vary, from 3.3/1000 (total number maternities resulting in live birth in Ireland = 8,357) to 8.0/1,000 live births (n=20,252).

[21] Weighing the risks of valproate in women who could become pregnant. Angus-Leppan, H. and Liu, R.. BMJ, 2018
[22] Population based, prospective study of the care of women with epilepsy in pregnancy. Fairgrieve, SD. BMJ, 2000
[23] Maternal Mortality in Women with Epilepsy. Holohan et al., IMJ, 2016
[24] Pregnancies of women with epilepsy: a population-based study in Iceland. Olaffson et al. Epilepsia, 1998
[25] The Australian Register of Antiepileptic Drugs in Pregnancy: Changes over time in the epileptic population. Vajda et al. J Clin Neurosci, 2014
[26] Hypertensive pregnancy complications in women with epilepsy and antiepileptic drugs: a population-based cohort study of first pregnancies in Norway. Daniellson et al. Obsterics and Gynaecology, 2018

Table 6.2 Number of maternities resulting in live births per year in Ireland and estimates of the number of these in WWE, 1975-2015

Year	Number of maternities resulting in a live birth	Rate of epilepsy in pregnancy		
		5.0/1,000	3.3/1,000	8.0/1,000
		Number of maternities in women with epilepsy resulting in a live birth		
1975	66,379	332	219	531
1976	66,933	335	221	535
1977	68,072	340	225	545
1978	69,450	347	229	556
1979	71,793	359	237	574
1980	73,271	366	242	586
1981	71,425	357	236	571
1982	70,055	350	231	560
1983	66,352	332	219	531
1984	63364	317	209	507
1985	61,736	309	204	494
1986	60,993	305	201	488
1987	57,818	289	191	463
1988	53,981	270	178	432
1989	51,398	257	170	411
1990	52,425	262	173	419
1991	52,142	261	172	417
1992	50,505	253	167	404
1993	48,748	244	161	390
1994	47,670	238	157	381
1995	48,138	241	159	385
1996	49,996	250	165	400
1997	52,071	260	172	417
1998	53,262	266	176	426
1999	53,191	266	176	426
2000	54,084	270	178	433
2001	56,962	285	188	456
2002	59,620	298	197	477
2003	60,645	303	200	485
2004	61,007	305	201	488
2005	60,456	302	200	484
2006	64,427	322	213	515
2007	70,287	351	232	562
2008	73,807	369	244	590
2009	74,335	372	245	595
2010	73,906	370	244	591
2011	72,669	363	240	581
2012	70,415	352	232	563
2013	67646	338	223	541
2014	66028	330	218	528
2015	64307	322	212	514
Total	**2,531,769**	**12,658**	**8,357**	**20,252**

6.2 Number and proportion of women with epilepsy who became pregnant whilst taking valproate

Studies suggest that the use of valproate in women has declined over time. In Norway, the number of women using valproate for epilepsy declined by 26% from 2008 to 2012.[27] Data from the UK General Practice Research Database (GPRD), meanwhile, suggests that valproate prescribing in WWE aged 15-44 years declined substantially, from a peak use of 40.5% in 1999 to 29.5% in 2008.[28] As noted above, a recent analysis of valproate prescribing trends in Ireland, in women aged 16-44 with epilepsy (as identified through their participation in the Long Term Illness scheme), revealed that prescribing rates decreased from 3.5/1000 to 3.14/1000 from 2008 to 2013.

These declines are likely due to a) increasing awareness of the risks associated with the use of valproate in pregnancy and b) the increasing availability of alternative medications; between 1990 and 2011, fifteen new AEDs were approved by the US Food and Drug Administration and/or European Medicines Agency and introduced to the market.[29]

Few studies have examined prescribing trends for valproate in WWE while pregnant (Table 6.3). However, data from the Australian Register of Antiepileptic Drugs in Pregnancy suggests that the proportion of WWE who became pregnant whilst taking valproate declined from approximately 31% in the period 1999-2005 to 24% in the period 2006-2012. Similarly, while an analysis of data in the UK suggested that approximately one third of WWE who became pregnant had been taking valproate

Table 6.3 Sample of studies reporting the proportion of women with epilepsy who were prescribed valproate while pregnant

Reference	Type of Study	Proportion
Fairgrieve, 2000[30]	Analysis of 1997/98 UK data. All births (live births, stillbirths and medical terminations)	29.4% (88/300)(monotherapy)
Campbell et al, 2014[31]	UK and Ireland Register (voluntary), 1996-2012	16.1% (monotherapy) (1290/8,000*)
Vajda et al., 2014[32]	Australian Registry (voluntary), 1999-2012	31.3% (1999-2005) 24.4% (2006-2012)
Borthen et al, 2010[33]	Norwegian Medical Births Registry (mandatory), 1999-2005, all pregnancies delivered	7.7% (monotherapy) & 1.4% (polytherapy)
Daniellson et al, 2018[34]	Norwegian Medical Births Registry (mandatory), First time pregnancies, 23 weeks +, 2004-2012	2.9% (51/1,778)(monotherapy)

*This is an approximate number and needs to be verified

[27] Changes in utilisation of antiepileptic drugs in epilepsy and non-epilepsy disorders – a pharmacoepidemiological study and clinical implications. Baftiu et al. Eur J Clin Pharmacol 2016

[28] Trends in antiepileptic drug utilisation in UK primary care 1993–2008: Cohort study using the General Practice Research Database. Nicholas et al, Seizure, 2012

[29] Chemical properties of anti-epileptic drugs (AEDs). Bialer et al, Adv Drug Del Res, 2012

[30] Population based, prospective study of the care of women with epilepsy in pregnancy. Fairgrieve, SD. BMJ, 2000

[31] Malformation risks of antiepileptic drug monotherapies in pregnancy: updated results from the UK and Ireland Epilepsy and Pregnancy Registers. Campbell et al. Epiepsy, 2014

[32] Australian Register of Antiepileptic Drugs in Pregnancy: Changes over time in the epileptic population. Vajda et al. J Clin Neurosci, 2014

[33] Delivery outcome of women with epilepsy: a population-based cohort study. Borthen et al. BJOG, 2010

[34] Hypertensive pregnancy complications in women with epilepsy and antiepileptic drugs: a population-based cohort study of first pregnancies in Norway. Daniellson et al. Obsterics and Gynaecology, 2018

when becoming pregnant in 1997/98, more recent data from the UK and Ireland Register suggests that, over the entire period from 1996-2012, the proportion taking valproate when becoming pregnant was 16%.

As part of this current analysis, data from the Irish component of the UK and Ireland Epilepsy in Pregnancy Register, from its inception in 2001 to 2015, inclusive, was accessed (Table 6.4). Over this period, 1,017 maternities were registered; taking the rate of epilepsy in pregnancy at 5/1000 (see section 6.1 above), this suggests that the registry captured approximately 20% of all maternities in WWE over this time period.

The Irish data closely mirrors that of the full UK and Irish Register in that, over the entire period, 16.62% of all maternities registered were in women who had been prescribed valproate when becoming pregnant. This varied from a high of 34% in 2002 to less than or equal to 5% in 2011, 2012, 2014 and 2015.

Table 6.4 Total number of maternities and total number and proportion of those maternities in WWE prescribed valproate, Irish Epilepsy in Pregnancy Register, 2001-2015

Year	Total number maternities in WWE*	Total number maternities in WWE registered	Total number maternities in WWE registered with valproate	Proportion of maternities in WWE registered with valproate (%)	Estimated total number of maternities in WWE who were taking valproate when becoming pregnant
2001	285	48	13	27	77
2002	298	68	23	34	101
2003	303	86	28	33	99
2004	305	95	28	29	90
2005	302	101	23	23	69
2006	322	64	11	17	55
2007	351	69	8	12	41
2008	369	46	6	13	48
2009	372	77	12	16	58
2010	370	80	≤5	6	23
2011	363	80	≤5	≤5	18
2012	352	7	≤5	≤5	18
2013	338	54	≤5	6	19
2014	330	79	≤5	≤5	8
2015	322	63	≤5	≤5	15
Total	**4,982**	**1,017**	**169**	**16.62**	**739**

WWE, women with epilepsy

*This assumes that approximately 1 in 200 (5/1000) pregnancies occur in women with epilepsy (see section 6.1 above).

Note: In years where the number or proportion of women who were prescribed valproate while pregnant was ≤5, the data has been censored for confidentiality.

No data is available regarding prescribing rates of valproate in WWE in Ireland prior to 2001. However, based on the UK data outlined in Table 6.3 and professional opinion in Ireland, it is assumed that the prescribing rates seen in the Irish Registry in the early part of the millennium (27-34%, 2001-2003) are likely to reflect prescribing rates throughout the 1990s. Similarly, is has been

assumed that similar rates would have been seen in the late 1970's (following a ramp-up in prescribing in the early years) and 1980s. These assumptions have been included in Table 6.5 below.

Table 6.5 Estimated total number of maternities and proportion of those maternities in WWE who were taking valproate when becoming pregnant, 1975-2000

Year	Total number maternities in WWE*	Estimated proportion of maternities in WWE who were taking valproate when becoming pregnant (%)	Estimated total number of maternities in WWE who were taking valproate when becoming pregnant
1975	332	5	17
1976	335	10	34
1977	340	15	51
1978	347	20	69
1979	359	34	122
1980	366	34	124
1981	357	34	121
1982	350	34	119
1983	332	34	113
1984	317	34	108
1985	309	34	105
1986	305	34	104
1987	289	34	98
1988	270	34	92
1989	257	34	87
1990	262	34	89
1991	261	34	89
1992	253	34	86
1993	244	34	83
1994	238	34	81
1995	241	34	82
1996	250	34	85
1997	260	34	88
1998	266	34	90
1999	266	34	90
2000	270	34	92
Total	**7,676**	-	**2,319**

WWE, women with epilepsy
*This assumes that approximately 1 in 200 (5/1000) pregnancies occur in women with epilepsy (see section 6.1 above).

Therefore, based on available data and the assumptions outlined above, it is estimated that, between 1975 and 2015, inclusive, approximately 3,058 maternities were in WWE who were taking valproate when becoming pregnant.

6.3 Number of children of women with epilepsy who may have been exposed to sodium valproate in utero, 1975-2015

The above analysis is based on maternities – as opposed to babies born. A number of these maternities will have resulted in twins, triplets and other multiple births. Appendix 1 separates out the estimated number of maternities resulting in singleton and twin births in WWE who were taking valproate, when becoming pregnant. **In total, it is estimated that, between 1975 and 2015, inclusive, approximately 3,100 babies were born to WWE and who had potentially been exposed to valproate in utero.**

6.4 Number and proportion of women who were prescribed sodium valproate for reasons other than epilepsy, while pregnant

The proportion of women in Ireland and, specifically the proportion of pregnant women, who take or have taken sodium valproate for reasons other than epilepsy is very difficult to assess. There is no Registry for women who take valproate for these other indications, and no previous analysis has been undertaken at either local or national level. While valproate has been licensed for use in epilepsy since 1975, it has only been licensed for use in bipolar disorder since 2008 and is not currently licensed for any other condition.

Internationally, an analysis of the Australian Register of Antiepileptic Drugs in Pregnancy reported that, between 1999 and 2016, just 2% of women who registered and were taking sodium valproate were doing so for an indication other than epilepsy. [35]

An assessment of psychotropic medication (including valproate) use in pregnancy in the UK between 1995 and 2012 noted that, of 495,624 pregnant women analysed, 607 (0.12%) were prescribed valproate in the 1-3 months before pregnancy. Of these, 66 (10.9%) had a record of psychosis or depression; the remainder (n=541) had a diagnosis of epilepsy or some other condition. It is not clear when valproate was licensed for use in bipolar disorder in the UK.

This data will need to be captured prospectively as part of the data collection exercise which takes place over the coming weeks and months.

In the absence of any other method of calculating the likely number of women and children affected as result of prescription of valproate for reasons other than epilepsy, the UK figure above of 10.9% has been extrapolated to the Irish epilepsy data; it has been assumed that the latter represents 89.1% of

[35] Outcomes of pregnancies in women taking antiepileptic drugs for non-epilepsy indications Jazyeri et al, Seizure:Euro J Epilepsy, 2014

all valproate prescriptions in women who became pregnant in Ireland between 2008 and 2015, inclusive. Similarly, it has been assumed that the 213 babies who were born to WWE and who had potentially been exposed to valproate in utero between 2008 and 2015, inclusive, represent 89.1% of all babies potentially exposed over that time period.

Table 6.6 Estimated additional number of maternities and babies potentially exposed to valproate as a result of prescribing for conditions other than epilepsy, 2008-2015, inclusive

Estimated total number of maternities in WWE who were taking valproate when becoming pregnant	207
Estimated total number of maternities in women without epilepsy who were taking valproate when becoming pregnant	25
Total maternities	**233**
Estimated total number of babies born to WWE who had potentially been exposed to valproate in utero	213
Estimated total number of babies born to women without epilepsy who had potentially been exposed to valproate in utero	26
Total babies potentially exposed	**239**

6.5 Total number of women and children who may have been exposed to sodium valproate (regardless of indication), 1975-2015

In total, it is estimated that, between 1975 and 2015, inclusive, approximately 3,083 (3,058 WEE; 25 for other indications) maternities were in women who were taking valproate when becoming pregnant.

In total, it is estimated that, between 1975 and 2015, inclusive, approximately 3,126 (3,100 WEE; 26 for other indications) babies were potentially exposed to valproate in utero. Of these, it is estimated that 873 (847 WWE; 26 for other conditions) babies born between 2000 and 2015, inclusive, were potentially exposed to valproate in utero. These will now be aged 2-18 years. It is reasonable to assume that a similar number of children, currently aged 0-16, were potentially exposed in the years from 2002-2017, inclusive.

6.6 Total number of children who may have experienced a major congenital malformation or neurodevelopmental delay as a result of exposure to sodium valproate in utero, 1975-2015

Data from the UK and Ireland Epilepsy in Pregnancy Register and the Cochrane Collaboration suggest that between 4.9% and 10.3% of children experience a major congenital malformation following exposure to valproate in utero. Based on these figures, it is estimated that between 1975 and

2015, inclusive, between 153 and 341 children will have experienced a major congenital malformation as a result of exposure to valproate in utero in Ireland. Of these, between 43 and 95 children born since 2000 will have experienced such a malformation. It is reasonable to assume that a similar number (43-95) of children, born between 2002 and 2017 and currently aged 0-16, have experienced such a malformation.

Table 6.7 Estimated number of children who have experienced a major congenital malformation as a result of exposure to valproate in utero

	Irish Register 2001-2016	Campbell et al, UK & Irish Register 1996-2012[36]	Weston et al, Cochrane 2016 (monotherapy)[37]	Number of children potentially affected (n=3,126) 1975-2015	Number of children potentially affected (n=873) 2000-2015
Any major malformation	**4.9%**	**6.7%***	**10.9%****	**153-341**	**43-95**
Cardiac	**-**	**1.1%**	**-**	**34**	**10**
Cleft Palate or Facial Cleft	**-**	**1.1%**	**-**	**34**	**10**
Hypospadias	**-**	**1.2%**	**-**	**38**	**11**
Neural Tube Defects	**-**	**1.1%**	**-**	**34**	**10**
Gastrointestinal	**-**	**0.6%**	**-**	**19**	**5**
Skeletal	**-**	**0.8%**	**-**	**25**	**7**
Other	**-**	**0.8%**	**-**	**25**	**7**

* Defined as any abnormality of an essential embryonic structure requiring significant treatment and present at birth or discovered in the first 6 weeks of life.

**This included neural tube, cardiac malformations, orofacial cleft/craniofacial and skeletal or limb malformations.

The true overall risk for neurodevelopmental disability is unknown for valproate, a situation mirrored for all antiepileptic drugs.[38] However, some reports claim that up to 40% of children exposed to valproate in utero experience some form of neurodevelopmental delay.[39] On this basis, it is possible that up to 1,250 children, born between 1975 and 2015, inclusive, experienced this outcome as a result of exposure to valproate in utero in Ireland. Of these, approximately 349 children born since 2000 will have experienced some form of delay. It is reasonable to assume that a similar number (~349) of children, born between 2002 and 2017 and currently aged 0-16, have experienced some form of delay.

[36] Malformation risks of antiepileptic drug monotherapies in pregnancy: updated results from the UK and Ireland Epilepsy and Pregnancy Registers. Campbell et al. Epiepsy, 2014

[37] Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Weston et al. Coch Data Sys Reviews, 2016

[38] Women and valproate: what should neurologists do? Craig. BMJ, 2018

[39] Sodium valproate in pregnancy: what are the risks and should we use a shared decision-making approach? Macfarlane, A. and Greenhalgh, T. BMC Pregnancy Childbirth 2018

7.0 Limitations

This analysis has been subject to a large range of assumptions (as detailed above) and limitations and should be interpreted with these in mind.

It was not possible to take account of variation in the duration of valproate use during pregnancy, dosage of valproate prescribed to individual women, nor whether valproate was used as monotherapy or as part of polytherapy. It seems clear that the association between valproate and congenital malformations is dose-related (in the treatment of epilepsy at least); analysis of data from the EURAP registry, for example, revealed that the rate of congenital malformations identified by 1 year of age was 5.6% when the daily dose of valproate was less than 700 mg at conception, 10.4% when the dose was between 700 and 1499 mg, and 24.2% when the dose was 1500 mg or higher.[40]

No account has been taken of differences in socio-economic status or urban-rural area of residence. It is known that women from more deprived areas have higher rates of valproate use in pregnancy in Scotland (although this did not affect rates of major congenital malformation), while a recent analysis of valproate prescribing in women aged 16-44 in Ireland reported that rates of valproate use were higher in rural compared to urban areas.[41,42] It is possible, therefore, that use of valproate and subsequent development of malformation or neurodevelopmental delay will not have been distributed evenly across communities in Ireland.

The estimates refer to the potential number of maternities and live births exposed and affected; it was not possible to retrospectively estimate the number of maternities associated with valproate which did not result in a live birth.

The analysis is premised on the licensed prescribing of valproate for epilepsy and bipolar disorder. It was not possible to estimate likely exposure of women and children to valproate as a result of off-licence prescribing.

It should be reiterated that there is no single source of data relating to the use of valproate in pregnancy in Ireland. Furthermore, while some individual datasets might have held useful information, the inability to link these datasets meant that they were of little value. The analysis has therefore relied to a large extent on international data and **the resulting estimates should be viewed as a broad guide for those tasked with planning diagnostic and management services for people affected by this issue; the true impact of valproate on women and children will only become apparent as data is collected prospectively over the coming weeks and months.**

[40] Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. Tomson et al, Lancet Neurol 2011

[41] The effect of socioeconomic status on treatment and pregnancy outcomes in women with epilepsy in Scotland. Campbell et al, Epilepsy Behav, 2013

[42] Prescribing trends for sodium valproate in Ireland. Murphy et al. Eur J Epilepsy, 2016

Appendix 1 Number of maternities in WWE and estimated number of babies potentially exposed to valproate in utero, separated out into singleton and twin births, 1975-2015

	Maternities resulting in a singleton birth				Maternities resulting in twin birth	
Year	**Number of maternities**	**Total number maternities in WWE**	**Proportion maternities in WWE who were taking valproate when becoming pregnant (%)**	**No. babies potentially exposed**	**Total number maternities in WWE**	**No. babies potentially exposed**
1975	65,587	328	5	16	4	0
1976	66,152	331	10	33	4	1
1977	67,262	336	15	50	4	1
1978	68,618	343	20	69	4	2
1979	71,053	355	34	121	4	2
1980	72,490	362	34	123	4	3
1981	70,699	353	34	120	4	2
1982	69,276	346	34	118	4	3
1983	65,599	328	34	112	4	3
1984	62,628	313	34	106	4	2
1985	61,079	305	34	104	3	2
1986	60,343	302	34	103	3	2
1987	57,181	286	34	97	3	2
1988	53,337	267	34	91	3	2
1989	50,765	254	34	86	3	2
1990	51,767	259	34	88	3	2
1991	51,524	258	34	88	3	2
1992	49,892	249	34	85	3	2
1993	48,161	241	34	82	3	2
1994	47,053	235	34	80	3	2
1995	47,448	237	34	81	3	2
1996	49,299	246	34	84	3	2
1997	51,307	257	34	87	4	3
1998	52,497	262	34	89	4	3
1999	52,434	262	34	89	4	2
2000	53,341	267	34	91	4	2
2001	56,044	280	27	76	4	2
2002	58,709	294	34	100	4	3
2003	59,723	299	33	99	4	3
2004	60,011	300	29	87	5	3
2005	59,505	298	23	68	5	2
2006	63,419	317	17	54	5	2
2007	69,155	346	12	41	6	1
2008	72,455	362	13	47	7	2
2009	73,114	366	16	58	6	2
2010	72,640	363	6	23	6	1
2011	71,334	357	≤5	18	7	1
2012	69,164	346	≤5	17	6	1
2013	66,346	332	6	18	6	1
2014	64,771	324	≤5	8	6	0
2015	63,079	315	≤5	15	6	1
Total	-	-	-	3,022	-	78