Sodium valproate: who knew what and when? Cumulative meta-analysis gives extra insights

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Sodium valproate is licensed in the EU for treating generalised, partial or other forms of epilepsy. It has also been used to treat bipolar disorder and to prevent migraine. In February of this year, the European Medicines Agency recommended that sodium valproate should not be used during pregnancy unless no other *effective* treatment is available, and that it must not be used in women able to have children, unless the conditions of a pregnancy prevention programme are met.[1] These measures to protect women and their children are welcome, but we argue that they should have been instituted several years ago, as the evidence was clear as far back as 1990 that there were risks of congenital malformations in women exposed to valproate.

In 1992, Antman and colleagues used cumulative meta-analysis to show that expert recommendations often lagged behind pooled estimates of clinical trials.[2] In a cumulative meta-analysis, the combined result is summarised by adding each new clinical trial result to the previous. This can be a useful technique for assessing both benefits and harms, allowing interpretation of what was known and when it emerged.

In 2015, Tanoshima *et al* performed a systematic review of 59 cohort studies published between 1983 and 2014, using cumulative meta-analysis. We used their analysis (see figure 1 to interpret signals of valproate-associated major congenital malformations and to determine when they emerged.[3] In 1990, Hunter and Allen published an assessment of the risk of congenital malformations among 88 women with epilepsy using valproate.[4] The results were not significant. However, when they were added to the cumulative meta-analysis of the previous seven studies (bringing the number of women studied to 846), a statistically significant effect for an increased risk of major congenital malformations emerged, with a cumulative risk ratio (RR) of 2.60 (95% CI 1.24 to 5.44; p=0.01).

A doubling of risk is an important measure, as it provides sufficient certainty in law to establish causation.[5] In US and UK courts of law, a doubling of risk is accepted as a minimum threshold for determining specific causation.

With the addition of more studies between 1990 and 2014, the summary RR varied between 1.79 and 2.60. However, the signal that the risk with valproate doubled was clearly established in 2004 when the results from Wide *et al* (the 25th study to be analysed) were added. The cumulative meta-analysis now included 4538 patients, and the result showed a permanent cumulative doubling of

risk (RR 2.06; 95% CI 1.53 to 2.77; p<0.0001). An even more convincing estimate was reached in the following year when even the lower bound of the CI was greater than 2 (see figure 1).

Despite these results, sodium valproate continued to be used widely. The signal of congenital malformations provided by the cumulative evidence in 1990 showed that there were problems, and by 2005 there could be no doubts whatsoever about the association. Many individual studies provided uncertain effects, which will have led to delays and misunderstandings over the interpretation of the harms. However, there was also evidence of lower risks with other antiepileptic drugs.

Furthermore, the risk of neural tube defects was already apparent in 1992, when 954 women were included in the cumulative meta-analysis (RR 4.62; 95% CI 1.46 to 14.62; p<0.005).[3] From that time, women taking valproate should have been given routine folic acid supplements, despite conflicting reports of the effect of valproate on folic acid concentrations.[6] The lower boundary of the CI exceeded 2.0, with the publication of the eighth study in 1992 (cumulative rate ratio 6.99; 95% CI 2.68 to 18.20; p<0.001).

Teratogenicity of valproate in animals was first reported in the 1970s, significant signals in humans were present from 1990 onwards and by 2005 the evidence for major congenital malformations was overwhelming. Since then, the estimated RR and its CIs have remained stable. The latest estimate shows a more than doubling of the risk (RR 2.24, 95% CI 2.13 to 2.80) for congenital malformations, based on an analysis of over 20 000 subjects.

A prospective study, published in 2018, based on data from the international registry of antiepileptic drugs (EURAP), in women exposed to antiepileptic drug monotherapy at conception, highlighted the smaller risks with other drugs available at the time compared with valproate. The study showed that different antiepileptic drugs and dosages have different teratogenic risks. Among 7555 prospective pregnancies, the prevalence of major congenital malformations for valproate (10.3%) was nearly double those of phenobarbital (6.5%), phenytoin (6.4%) and carbamazepine (5.5%). The prevalence of major congenital malformations also increased significantly with dose for those three comparators.[7]

Our analysis shows the value of cumulative meta-analysis, which, in our view, should be performed as standard in systematic reviews when any concerns about harms arise during the use of medications. The move towards living systematic reviews could help facilitate this process, although the number of these in production remains small.[8]

Study ID	Cumulative participants	Favors VPA / Favors Non-VPA	Risk ratio (95% CI)	Z
1. Koch S (1983)	46		2.40 (0.46 to 12.45)	1.04
2. Markestad T (1984)	87		1.77 (0.37 to 8.40)	0.72
3. Kelly TE (1984)	150		1.66 (0.36 to 7.65)	0.65
4. Robert E (1985)	210		1.80 (0.58 to 5.59)	1.02
5. Lazzaroni Fossati F (1986)	230		1.68 (0.63 to 4.50)	1.04
6. Bertollini R (1987)	746		2.01 (0.90 to 4.39)	1.69
7. Kaneko S (1988)	777		1.92 (0.87 to 4.26)	1.60
8. Hunter RW (1990)	846		2.60 (1.24 to 5.44)	2.53
9. Tanaka H (1991)	929		2.76 (1.41 to 5.42)	2.95
10. D'Souza SW (1991)	964		2.50 (1.29 to 4.85)	2.71
11. Froscher W (1991)	1016		2.32 (1.24 to 4.35)	2.62
12. Battino D (1992)	1222		2.18 (1.23 to 3.87)	2.66
13. Koch S (1992)	1250		2.29 (1.28 to 4.08)	2.80
14. Omtzigt J (1992)	1476		2.39 (1.43 to 3.98)	3.33
15. Tanganelli P (1992)	1554		2.31 (1.39 to 3.83)	3.22
16. Kaneko S (1993)	1592		2.23 (1.36 to 3.66)	3.17
17. Steegers-Theunissen RPM (1994)	1677		2.47 (1.54 to 3.98)	3.73
18. Samren EB (1997)	2090		1.79 (1.19 to 2.68)	2.80
19. Kaneko S (1999)	2232		1.70 (1.16 to 2.49)	2.74
20. Canger R (1999)	2232		1.70 (1.16 to 2.49)	2.74
21. Al Bunyan M (1999)	2280		1.69 (1.15 to 2.46)	2.70
22. Samren EB (1999)	2455		1.91 (1.27 to 2.89)	3.08
23. Holmes LB (2001)	2678		1.88 (1.24 to 2.84)	3.00
24. Kaaja E (2003)	3272		1.93 (1.31 to 2.83)	3.34
25. Wide K (2004)	4528		2.06 (1.53 to 2.77)	4.76
26. Meischenguiser R (2004)	4611		2.09 (1.56 to 2.80)	4.94
27. Wyszynski DF (2005)	5808		2.24 (1.72 to 2.91)	6.00
28. Artama M (2005)	6445		2.56 (2.02 to 3.25)	7.72
29. Morrow J (2005)	8905		2.48 (2.02 to 3.04)	8.65
30. Kini U (2005)	9103		2.45 (2.01 to 2.99)	8.87
31. Viinikainen K (2006)	9103		2.45 (2.01 to 2.99)	8.87
32. Burja S (2006)	9127		2.44 (2.00 to 2.98)	8.84
33. Vajda FJE (2006)	9472		2.60 (2.14 to 3.15)	9.73
34. Meador KJ (2006)	9472		2.60 (2.14 to 3.15)	9.73
35. Vajda FJE (2007)	9596		2.47 (2.04 to 2.98)	9.40
36. Dean J (2007)	9815		2.38 (1.98 to 2.86)	9.27
37. Kini U (2007)	9931		2.38 (1.99 to 2.86)	9.34
38. Vajda FJE (2007)	10091		2.53 (2.10 to 3.04)	9.91
39. Eroglu E (2008)	10171		2.52 (2.10 to 3.03)	9.95
40. Morrow J (2008)	10859		2.47 (2.05 to 2.96)	9.66
41. Martinez Ferri M (2009)	11128		2.49 (2.08 to 2.99)	9.91
42. Mawer G (2009)	11180		2.50 (2.09 to 3.00)	10.02
43. Vajda FJE (2010)	11467		2.47 (2.08 to 2.94)	10.24
44. Miskov S (2010)	11526		2.46 (2.07 to 2.93)	10.22
45. Tomson T (2011)	14881		2.28 (1.96 to 2.64)	10.78
46. Vajda FJE (2011)	14881		2.28 (1.96 to 2.64)	10.78
47. Kochen S (2011)	14881		2.28 (1.96 to 2.64)	10.78
48. Vajda FJE (2011)	14881		2.28 (1.96 to 2.64)	10.78
49. Hernandez-Diaz S (2012)	18507		2.35 (2.03 to 2.71)	11.55
50. Cassina M (2013)	18766		2.33 (2.01 to 2.69)	11.51
51. Kabbi W (2013)	18782		2.33 (2.02 to 2.69)	11.54
52. Veiby G (2014)	18782		2.33 (2.02 to 2.69)	11.54
53. Campnell E (2014)	20609		2.46 (2.14 to 2.81)	13.01
54. Abe K (2014)	20677		2.34 (2.13 to 2.80)	12.97

Risk ratio (95% CI): 0.1, 0.5, 1, 5, 10

Annotations:
- 1983: Koch's study shows no significant effect of valproate on congenital malformations
- 1990: The cumulative risk ratio reaches statistical significance after eight studies have been combined
- 2004: The cumulative risk ratio shows double the risk (P<0.0001)
- 2005: The lower bound of the 95% confidence interval shows that the risk is more than doubled
- 2014: The latest estimate in more than 20,000 individuals confirms that the risk is more than doubled
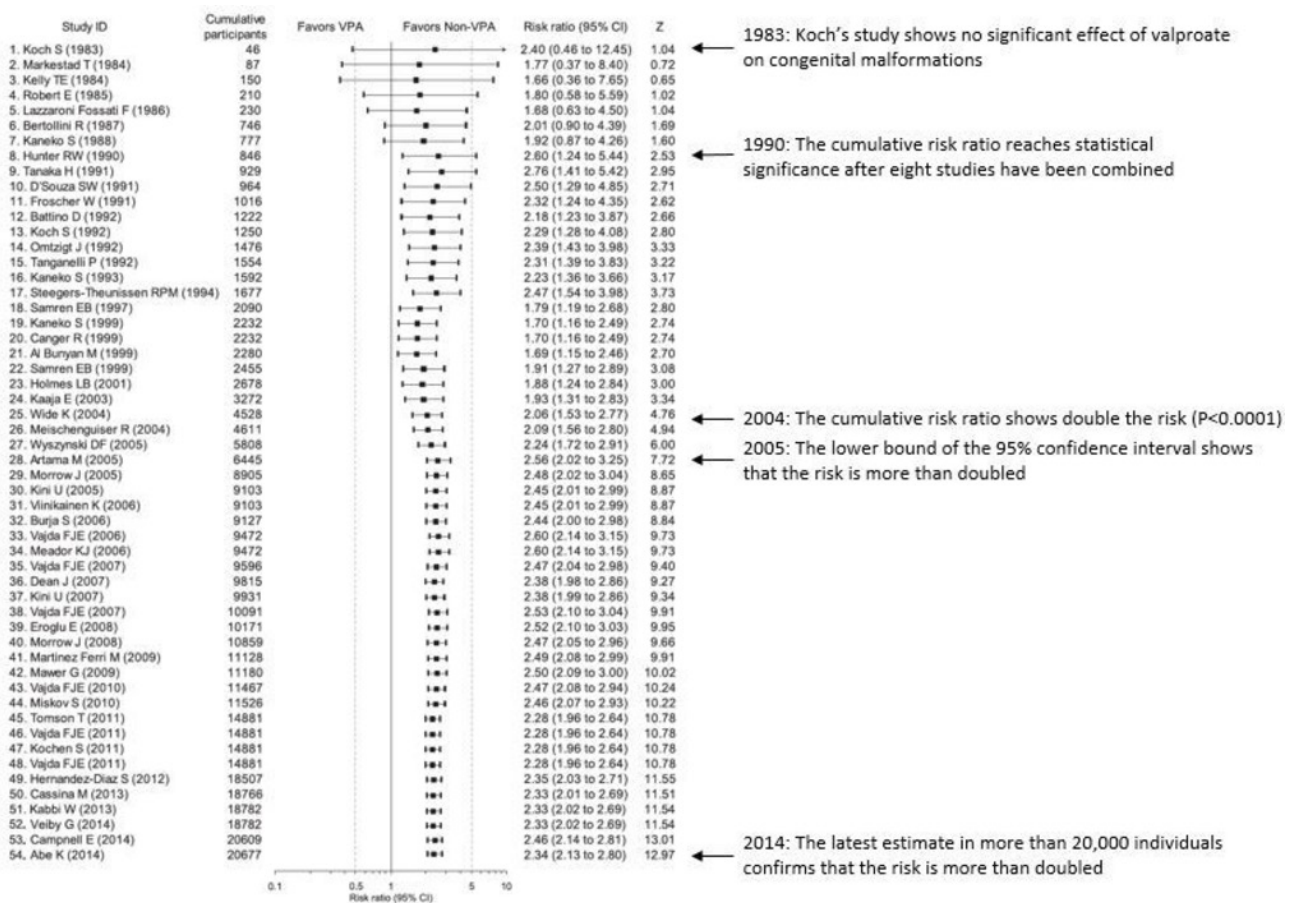
Figure 1 Cumulative risk ratios of congenital malformations between valproate (VPA) and non-valproate groups for combined major congenital malformations. [High resolution version of this image is available as Supplementary file 1]

In 2014, the European Medicines Agency recommended strengthening the restrictions on the use of valproate in pregnancy and women of childbearing potential,[9] and in 2018 further measures were required to avoid unnecessary valproate exposure.[10] However, we consider that regulators, governments, drug companies, journal editors, prescribers and systematic reviewers have all acted too late. We, therefore, consider that from 1990 individuals should have been offered the opportunity to switch to treatments with lower risks, where they existed, and given minimum effective doses of valproate if alternative treatments were not available or advisable. In the intervening years, many women's children will have been harmed. Manufacturers and regulators should be responsible for ensuring that cumulative analyses are carried out as part of postmarketing risk management plans.

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