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## Original article

## Economic evaluation of anti-epileptic drug therapies with specific focus on teratogenic outcomes

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**Abstract****Background:**

Anti-epileptic drugs are known to be teratogenic, yet many women do need to continue the anti-epileptic drug use during pregnancy.

**Objectives:**

To perform an economic evaluation of the anti-epileptic drug choice in young women who potentially wish to become pregnant. In particular, to estimate the impact of teratogenicity on the costs per quality adjusted life year (QALY).

**Methods:**

A decision-tree model is used to calculate the costs per QALY, taking into account the malformation risk in offspring due to the exposure to carbamazepine, lamotrigine or valproic acid, based on the European birth cohort of 2007. Probabilistic sensitivity analyses were performed using Monte Carlo simulation.

**Results:**

Valproic acid is dominated by carbamazepine after rank ordering on costs. The incremental cost-effectiveness of lamotrigine vs carbamazepine was estimated at €175,534 per QALY. Although valproic acid was dominated by carbamazepine in terms of costs and related effects, it is clinically relevant to compare lamotrigine with valproic acid. In particular, treatment options are dependent on several individual and clinical characteristics and these agents are therefore not always considered as interchangeable for all specified populations. The incremental cost-effectiveness for lamotrigine vs valproic acid was estimated at €13,370 per QALY. With assuming a willingness to pay threshold of €50,000 per QALY, results from the probabilistic analysis resulted in an acceptance level for lamotrigine vs carbamazepine and lamotrigine vs valproic acid of 4% and 99%, respectively.

**Conclusion:**

Based on epidemiological data it is advised to whenever possible avoid valproic acid during pregnancy. Both carbamazepine and lamotrigine are estimated to be cost-effective treatment options vs valproic acid if focused on teratogenicity.

**Introduction**

Epilepsy is a chronic disease with an age-dependent increase in prevalence. About 0.5% of all teenage girls are using anti-epileptic drugs<sup>1,2</sup>. A considerable part of these girls are still using the same anti-epileptic drug when they wish to become pregnant, as switching is not considered to be easy and stopping often not an option. In pregnancy, ~3.3 per 1000 women are using anti-epileptic drugs

in the first trimester, the period in which risks for congenital malformations occur<sup>3,4</sup>. Teratogenicity differs between specific anti-epileptic drugs. Therefore, it is important for the prescribers to already keep in mind potential future wishes to become pregnant when choosing between anti-epileptic therapies in younger girls.

Carbamazepine, valproic acid and lamotrigine are the most used anti-epileptic drugs, both among pregnant and non-pregnant women<sup>5,6</sup>. All three agents are first choice options for partial epilepsy. However, in the case of generalized epilepsy only valproic acid presents as the drug of first choice and both carbamazepine and lamotrigine are second choice therapies<sup>7,8</sup>. This is despite the fact that a recent Cochrane review could not find evidence to support the belief that valproic acid is superior to carbamazepine in preventing generalized tonic-clonic seizures<sup>9</sup>.

Valproic acid is a relatively cheap and very effective anti-epileptic drug, which is already a successful treatment option in epilepsy for over 40 years. However, it is associated with an increased risk for major congenital malformations compared to other anti-epileptic drugs<sup>10</sup>. Maternal use increases the risk for spina bifida, cleft palate, hypospadias, atrial septal defect, polydactyly and craniosynostosis in the newborns. In contrast, carbamazepine has been shown to be only associated with an increased risk for spina bifida, with a risk even significantly lower than for valproic acid<sup>11</sup>. Lamotrigine on the other hand is more expensive, but up to now not associated to any specific malformations<sup>5,12,13</sup>.

No information is yet available on the cost-effectiveness of these safety issues in anti-epileptic treatments. In society the willingness to pay for a healthy child is often high and potentially difficult to compare to the willingness to pay for an intervention which will add an extra year to individuals' life expectancies. 'Interventions' with a higher willingness to pay are certainly not uncommon for economic analyses considering safety risks (e.g., blood products)<sup>14</sup>. Also, the general willingness to pay to avoid health losses is greater than the willingness to pay for health gains<sup>15</sup>.

The aim of this study is to perform an economic evaluation for anti-epileptic drugs initiated in young women with a potential wish to become, applying the societal perspective and focusing on safety in the offspring rather than efficacy. Notably, efficacies of the drugs will be assumed similar.

## Methods

### Data and assumptions

Based on the EUROCAT *Antiepileptic Study Database* the prevalence for major congenital malformations in the general population is ~2.8%<sup>12</sup>. This prevalence increases

in the case of maternal carbamazepine (3.3%)<sup>11</sup>, lamotrigine (3.2%)<sup>5</sup> or valproic acid (7.5%)<sup>10</sup> exposures. The decision tree for specific malformations associated with choices in anti-epileptic drug use is presented in Figure 1. Some specific malformations are known to be increased by these anti-epileptic drugs, however it does not fully explain the total prevalence<sup>5,10-13</sup>. The unexplained part is defined as 'not otherwise specified' (NOS).

### Health gains

For all associated malformation sub-groups we estimated the quality-of-life and the life expectancy of the offspring based on the published literature (Table 1)<sup>16-31</sup>. For our 'rest group' of NOS malformations it was not possible to find any reference. Therefore, we took the quality-of-life of pregnancy outcomes with an extreme low birthweight as a proxy (0.97) in the base case analysis<sup>23</sup>. This assumption was varied in both univariate (to see how sensitive the analysis is for this parameter) and probabilistic sensitivity analysis.

### Costs

We assumed lifetime use of anti-epileptic drugs starting at age 15. Based on European life tables, we estimated the lifetime costs for the three anti-epileptic drugs in 2010 Euros: carbamazepine (dose 1000 mg/day) at €2707, lamotrigine (dose 300 mg/day) at €11,329 and valproic acid (dose 1500 mg/day) at €3694<sup>8,32</sup>. These values were based on Dutch prices.

Lifetime costs for each of the specific malformations were estimated based on published literature. All costs are presented for 2010 Euros. If costs were originally calculated in another currency or from another year we used the historical exchange rate and deflator<sup>33,34</sup>. Table 1 gives an overview of all lifetime costs per malformation subgroup.

### Incremental cost-effectiveness and cost-utility analysis

In the incremental cost-effectiveness analysis the net costs per quality adjusted life year (QALY) were calculated comparing the three anti-epileptic drugs, by dividing the difference in the 'total net lifetime costs' by the sum of the differences in, respectively, the life years lost and the quality-of-life lost (presented in Table 2). All costs and health gains were discounted following the Dutch guidelines for conducting pharmacoeconomic studies with 4% and 1.5%, respectively<sup>35</sup>.

The analysis is performed based on the European Union (27 countries) birth cohort of 2007 which consist of 5,285,057 live births (49% male) and the average life

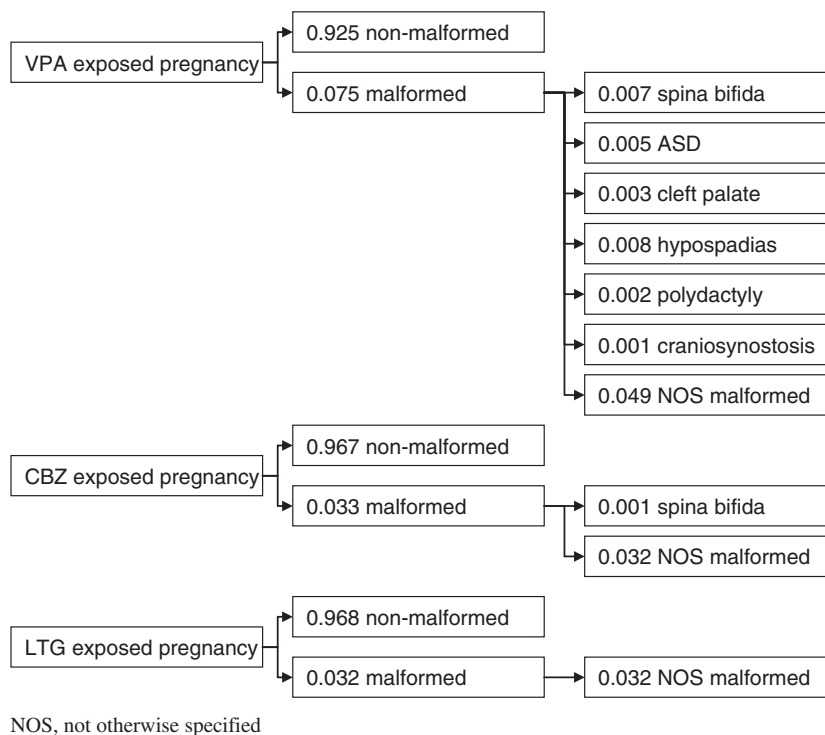


Figure 1. Decision tree showing the prevalence per specific malformation associated with valproic acid (VPA), carbamazepine (CBZ) and lamotrigine (LTG)<sup>5,10,11</sup>.

Table 1. Discounted losses in quality-of-life and life years and the lifetime costs per case for the associated malformation sub-groups for the base case<sup>16-31</sup>.

Malformation	Lifetime loss in quality	Life years lost	Lifetime costs per case
Spina bifida	20.3	15.1	€138,964
Atrial Septal Defect	0.4	0	€6591
Cleft palate	1.3	0	€13,345
Hypospadias	0.8	0	€5890
Polydactyly	0	0	€893
Craniosynostosis	5.0	0	€14,990
NOS malformation	1.2	4.9	€94,052

expectancy at birth of this cohort at 79.2 years<sup>32</sup>. As the prevalence of first trimester exposure to anti-epileptic drugs is ~3.3 per 1000, 17,441 pregnancies of the EU 2007 birth cohort would be expected to be first trimester exposed<sup>3,4</sup>. We calculated the total costs and effects based on assuming that all 17,441 women used carbamazepine, lamotrigine or valproic acid. For our model, we assumed equal effectiveness of the three drugs in all women. We know that in practice this is not the case due to differences in severity, type of epilepsy and interpersonal differences. However, it is difficult to account for such heterogeneity and all three drugs have proven to be effective in the most common types of epilepsy<sup>7,9</sup>. Therefore, incremental cost-effectiveness results were solely driven by safety differences.

Probabilistic analysis was conducted to account for uncertainty around the lifetime costs of the malformations, the prevalence of the specific malformations and the QALYs per treatment option. Cost-effectiveness planes were constructed based on Monte Carlo simulation (10,000 replicates) to test the robustness of the health economic outcomes. Additionally, cost-effectiveness acceptability curves were derived to estimate the probability of acceptance with varying willingness-to-pay thresholds.

## Results

The total number of malformed pregnancy outcomes, life years and quality-of-life lost estimated for the 17,441 pregnancies analyzed are shown in Table 2. The general risk for malformations is 2.8%, which would result in 493 malformed pregnancy outcomes. This background risk is presented in the first column. The subsequent analyses are based on the incremental estimates compared to the background risk.

If the three drugs are rank ordered on costs, one can directly see that valproic acid is dominated (higher costs and more quality-of-life losses than carbamazepine). From an economic point of view, due to the dominance, valproic acid would not be considered as a first choice treatment option. However, as the indications for the three drugs are not exactly the same and, therefore, not 100%

Table 2. Total net costs (4% discount rate) and health effects (1.5% discount rate) for carbamazepine, lamotrigine and valproic acid for the European birth cohort of 2007 (17,441 exposed births).

	Background risk	Carbamazepine	Lamotrigine	Valproic acid
Malformations	493	579	566	1247
Total costs malformations	€46,393,507	€55,642,951	€53,241,218	€100,702,189
Lifetime drug costs	€0	€47,206,615	€197,583,337	€64,418,409
Total lifetime costs	€46,393,507	€102,849,566	€250,824,555	€165,120,598
Life years lost	2417	3104	2774	6110
Quality of life lost	591	1192	679	3752
QALYs lost	3008	4296	3453	9862

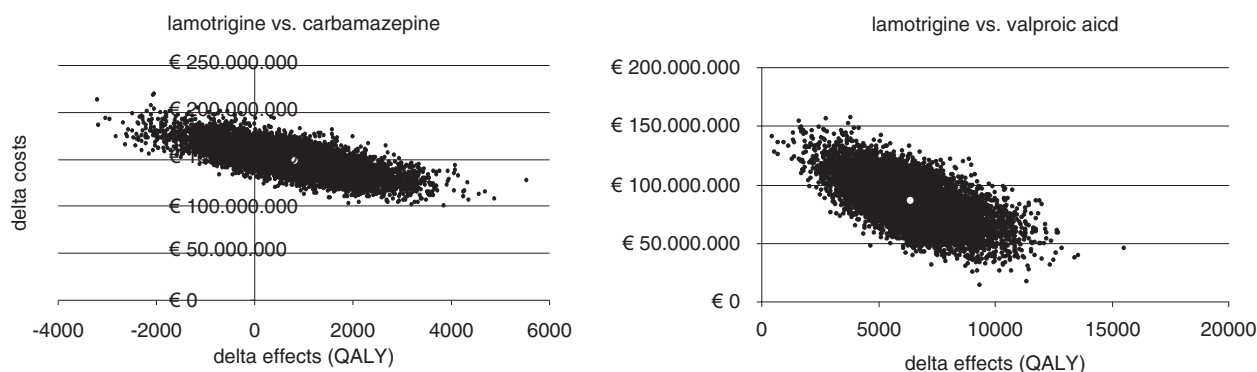


Figure 2. Incremental cost-effectiveness planes for lamotrigine vs carbamazepine and vs valproic acid: comparing differences (delta) in costs and effects.

interchangeable, the incremental cost-effectiveness is calculated for both lamotrigine vs carbamazepine and lamotrigine vs valproic acid. The incremental cost-effectiveness of lamotrigine vs carbamazepine and lamotrigine vs valproic acid were estimated at €175,534 and €13,370 per QALY, respectively.

Table 2 shows that the anti-epileptic drug price is the main driver of the incremental cost-effectiveness. In particular, this is related to the nature of use of these agents, which is basically lifetime. The prices of carbamazepine and valproic acid are quite stable over recent years.

With only limited sources for quality-of-life data on specified and NOS malformations, sensitivity analysis was directed at this. Notably, the outcomes were quite robust. In particular, results remained essentially unchanged with increasing or decreasing the estimated losses in quality-of-life and life years with 50% (€170,168–184,074 per QALY for lamotrigine vs carbamazepine and €11,685–14,793 per QALY for lamotrigine vs valproic acid).

In Figure 2 the incremental cost-effectiveness planes are presented for both lamotrigine vs carbamazepine and lamotrigine vs valproic acid. All estimates for the comparison of lamotrigine vs carbamazepine are located in the northern quadrants, with the highest density in the northeast. For the comparison of lamotrigine vs valproic acid all

estimates are located in the northeast quadrant, indicating a better quality-of-life for additional costs.

As there is no formal willingness-to-pay threshold in the Netherlands, cost-effectiveness acceptability curves are calculated to estimate the probability of acceptance for different willingness-to-pay thresholds in Figure 3<sup>36</sup>. Arbitrarily considering a willingness-to-pay threshold of €50,000 per QALY, the probability of the acceptance for lamotrigine vs carbamazepine and lamotrigine vs valproic acid were estimated at 4% and 99%, respectively. The median incremental cost-effectiveness is estimated at €173,353 per QALY for lamotrigine vs carbamazepine and at €13,548 per QALY for lamotrigine vs valproic acid.

## Discussion

Carbamazepine, lamotrigine and valproic acid are all first-choice therapy options in the treatment of partial epilepsy. In general, valproic acid is widely used, but from a health economic point of view it would not be a first-choice therapy option for women with a potential wish to become pregnant with partial epilepsy as it is dominated by carbamazepine. Lamotrigine results in better quality-of-life outcomes in the offspring at higher costs of €175,534 per QALY. This could be interpreted as unfavorable.

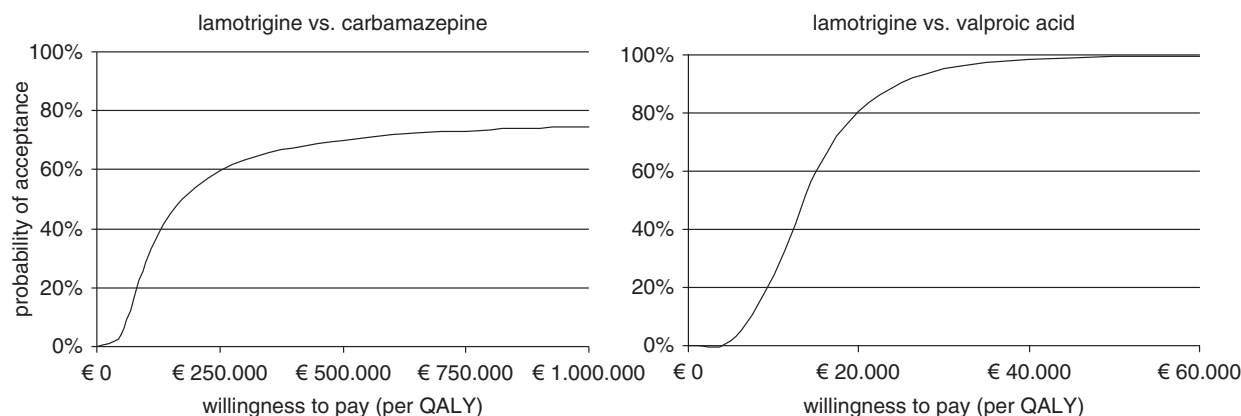


Figure 3. Cost-effectiveness acceptability curves for lamotrigine vs carbamazepine and lamotrigine vs valproic acid.

However, we should keep in mind that economic evaluations based on solely safety outcomes of drugs for the next generation could be comparable to other economic evaluations in which safety is important, for example, blood transfusions. In this field, interventions are still implemented with a net cost of several millions per QALY<sup>14</sup>.

Our results are conservative. For example, we do not take into account that these drug costs cover all costs for the mother, independent of the number of children. If a woman delivers two children, the drug costs can crudely be divided by two and cost-effectiveness improves drastically. Additionally, we took into account the lifetime drug costs starting at the age of 15; cost-effectiveness would improve if only drug costs during fertile years would be counted.

In the analyses, we assumed that the three drugs are equally effective in all women who require these anti-epileptic drugs. This does not necessarily correspond with the daily practice situation as, for example, not all women will receive the standard dose. Therefore, in daily practice the therapy choice should be made on an individual level based on effectiveness which is dependent on several factors, with a pharmacologically uncontrolled woman probably being the most expensive. Therefore, despite the dominance, valproic acid is not to be ruled out as an alternative treatment option in clinical practice as it reflects a very effective drug with a lot of treatment experience. In particular, it is known that there is a subgroup of women that only successfully respond to valproic acid and, for some specific types of epilepsy, valproic acid might be considered as the best or even the only treatment option. Considering the exact indications, lamotrigine may be considered more comparable to valproic acid than to carbamazepine for some specific types of epilepsy. Therefore, we also calculated the incremental cost-effectiveness ratio for lamotrigine vs valproic acid, resulting in €13,370 per QALY, which can be conceived as a favorable cost-effectiveness ratio.

We did not include effects on the cognitive development of the children. Valproic acid exposure during

pregnancy has been associated with a lower IQ in the child<sup>37</sup>. No evidence exists for a comparable cognitive effect for carbamazepine or lamotrigine. Notably, as lamotrigine is a newer drug there is no data yet available on the school performance of children exposed to lamotrigine. Obviously, lower IQ could possibly result in less contribution to society over lifetime (e.g., production losses). The same holds true for some of the malformations (e.g., spina bifida). Potential production losses and related losses in tax contribution in the next generation are nicely described in the field of assisted reproduction<sup>38</sup>. Further work could be directed to formally include these aspects in our model design.

Notably, only limited evidence exists on the parameter assumptions for the economic evaluation. The available studies presenting quality-of-life and life expectancy data applied various methods, which are sometimes difficult to compare. Also, cost data were derived from several studies performed all over the world. Apart from acknowledging this limitation and justifying these assumptions as the best there are, we feel that this analysis also nicely illustrates one of the major problems in performing economic evaluations in the field of teratology research. For example, the estimates for the lifetime costs for any malformation are based on a study which took into account only 16 different malformations (accounting for 33% of the prevalence of all major malformations)<sup>12,31</sup>.

Ideally most assumptions are derived from clinical trial data, however these study designs are unethical to use for estimating teratogenicity of drugs. Therefore, information has to be derived from observational studies. For economic evaluations information is required on the association between a specific drug and a specific malformation. Cohort studies often do not have enough power to provide a precise estimate. Case-control studies do provide such information but are generally more difficult to integrate in the economic analyses.

Pharmacoeconomic analyses are not common in the field of teratology, but could help to make initial therapy

choices, taking into account potential safety risks for the offspring. From the current analysis, it becomes clear that there are still a lot of important methodological issues left that need to be discussed further. In this paper the analysis is performed for a specific birth cohort. Analyses taking into account the risk for malformations need to be based on large numbers as the prevalence of major malformations is only ~3% of all births, which correspondingly could require economic analysis based on multiple cohorts. Furthermore, an imminent question relates to the willingness to pay threshold for avoiding teratogenic risks in offspring; in particular, is this comparable to that for drugs improving the quality-of-life of the actual consumer?

## Conclusions

In short, based on epidemiological data it is recommended to avoid valproic acid exposure during pregnancy due to a higher risk of teratogenicity<sup>39</sup>. Also from a health economic point of view, the use of the teratogenic anti-epileptic drugs carbamazepine and lamotrigine is estimated to be cost-saving and cost-effective, respectively, if compared to valproic acid. This definitely holds true if analyses investigating teratogenicity are interpreted as interventions to enhance safety<sup>14</sup>. The cost-effectiveness of such interventions directed at safety and averting losses in quality-of-life are generally interpreted differently with much higher willingness to pay being documented as for interventions with superior effectiveness. Yet, the best treatment option should in the end be made on an individual tailor-made basis and would not only rely on health-economic outcomes. The latter merely serve to provide general guidance on the overall level.

## Transparency

### Declaration of interest

This study was not funded.

### Declaration of financial/other interest

JJ and LTWdJvdB are involved in a study about lamotrigine, which is partly funded by GSK. CB currently works for GSK and MJP served in several scientific advisory boards for GSK. JJ's husband works for GSK. CB and MJP received grants from Sanofi-Aventis. LTWdJvdB served in a scientific advisory board for Novartis.

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