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Teratogenic effects of antiepileptic drugs

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Abstract

Many antiepileptic drugs (AEDs) have therapeutic applications that extend beyond epilepsy to include neuropathic pain, migraine headaches and psychiatric disorders. The risk of some AEDs has been clearly established, but for newer drugs, small sample sizes and polytherapy exposures preclude a conclusive determination of their teratogenic potential. Most women with epilepsy will require AED therapy throughout their entire pregnancy to control seizures; the vast majority of pregnancies in women with epilepsy have positive outcomes. A conservative estimate suggests that AED monotherapy doubles, and polytherapy triples, the risk for major congenital malformations. Furthermore, while evidence is still accruing, recent investigations suggest that exposure to select AEDs results in altered cognitive function later in development. There is no evidence to suggest that additional folic acid supplementation ameliorates the increased risk of congenital malformations conferred by *in utero* AED exposure.

Keywords

AED; birth defects; carbamazepine; epilepsy; lamotrigine; levetiracetam; phenobarbital; phenytoin; teratogen; topiramate; valproate

The risks associated with *in utero* antiepileptic drug (AED) exposure are of considerable importance to the estimated 30,000 children born to epileptic mothers each year in the USA alone [1]. Pregnancies involving maternal health issues other than epilepsy are also at risk for teratogenic AED exposure, as many of these medications have found additional utility in the treatment of neuropathic pain and migraine headaches, as well as in psychiatric disorders. This expansion of the clinical application of these compounds has significantly increased the exposure of potentially pregnant women to AEDs.

Although one must not lose sight of the fact that the risk of some AEDs has been clearly established, but remains unclear for newer drugs due to small sample sizes and polytherapy exposures, most women with epilepsy (WWE) will require AED therapy throughout their entire pregnancy to control seizures. Of particular concern is the potential for the mother to develop tonic–clonic seizures, which can result in significant adverse health outcomes for the fetus, including, but not limited to, intracranial hemorrhage, transient bradycardia and heartbeat

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abnormalities (summarized in [1]). The European and International Registry of Antiepileptic Drugs in Pregnancy (EURAP) has recently reported more favorable outcomes with regards to status epilepticus than the 30% maternal mortality and 50% pregnancy mortality reported in older studies [2,3]; however, discontinuing AED therapy during pregnancy is still discouraged by most practitioners.

For the most part, the clinical course of pregnancies in WWE is uneventful, with most children born free from either structural or behavioral abnormalities. However, given the *in utero* exposure to AEDs, these children are at a greater risk of being born with birth defects. Available data strongly suggest that this increased risk for adverse outcomes observed in WWE is not a sequelae of epilepsy or seizures *per se*, but is instead directly due to the teratogenic effects of AEDs. While figures are quite variable based on the study design and their inherent limitations, Tomson and Battino found that pooled data from 26 studies revealed a major congenital malformation (MCM) rate of 6.1% in offspring of women with epilepsy who were treated with AEDs, 2.8% among children of women with untreated epilepsy and 2.2% in the healthy control group, which we refer to throughout this article [4]. In other work, the observed frequency of MCMs was 3.7% in pregnancies complicated by AED monotherapy and 6.0% observed in AED polytherapy [5]. The most common malformations observed secondary to *in utero* AED exposure are cardiac malformations, followed by hypospadias and facial clefts, which echoes the pattern of malformations seen in the general population. Treatment with certain AEDs is associated with a greater risk of specific malformations. The strongest data indicates that valproate exposure is associated with a 1–2% risk of neural tube defects (NTDs), a 10- to 20-fold increase over the general population (EURAP) and an increased risk of neurodevelopmental deficits [6,7].

The astute clinician has always been credited with being the primary means of identifying potential human teratogens [8,9], and this has been the case for AEDs as well. Now that the teratogenicity of these compounds has been established for over 40 years, refining risk assessments depends on the quality of the epidemiological data that can be acquired. One of the greatest difficulties in evaluating early literature concerning birth defects is the divergent methodologies used; in particular, the inclusion of cases into various groupings, which makes comparisons between studies difficult or impossible and clouds etiology. After the definition of the term MCM by Holmes *et al.* in 2001 [10], inclusion criteria of subjects were more homogenous. Unfortunately, before this date, and even after, the categories of major and minor malformations, as reported in the literature, were often variable and not described clearly, or not described at all. Owing to the limited number of reports, the data published is valuable, even if it presents an undesirable methodology [5].

Unfortunately, most studies on the teratogenic effects of AEDs are too small and underpowered to draw significant conclusions. This is not unexpected, given the relatively few pregnancies complicated each year by AEDs, such that multicenter design studies are the only feasible approach to gather unbiased data on a significant number of pregnancy outcomes. Data that is collected by highly specialized epilepsy centers are more likely to reflect that from the more intractable patients, which involves a more aggressive treatment regimen and potentially skews the data. Registry data is one way to circumvent the relative scarcity of AED-exposed pregnancies, but it is most often data that is voluntarily reported and subject to significant bias. Conclusions drawn largely from registry data must be carefully considered in the context of what we know about other AEDs, and what is understood about the pharmacology and physiology of the compound in question. Tomson and Battino provide an excellent overview of the difficulties inherent in study design [11].

Teratogenicity of AEDs

Carbamazepine

Carbamazepine (CBZ) is an iminostilbene derivative used primarily in the management of epilepsy and trigeminal neuralgia. Observational studies have shown that the use of CBZ in pregnancy is associated with a higher risk of MCMs in the exposed offspring [12,13]. Other investigations using different methodologies have failed to find an increased statistical risk of MCMs due to CBZ exposure [5,14]. Morrow *et al.* reported 20 MCMs among 900 CBZ-exposed pregnancies, which is a prevalence rate of 2.2% with 95% CI: 1.4–3.4 [5]. This is the lowest risk for MCMs amongst all AED monotherapy exposures reported in the literature (Table 1). When dosage was compared between healthy and malformed infants, there was no statistical significance ($p = 0.56$), suggesting that genetic factors are interacting with the CBZ exposure contributing disproportionately to the risk for MCMs.

Meador *et al*. reported a MCM rate of 4.6% (95% CI: 3.48–5.76) in a meta-analysis including 4411 woman taking CBZ throughout their pregnancies [15]. When compared with the other frontline AEDs, the teratogenic potential of CBZ was significantly lower. Association between CBZ exposure and specific MCMs has also been considered. Two studies have found *in utero* CBZ exposure to be associated with an increased risk of orofacial clefts [16,17]. Hernandez-Diaz *et al*. reported a 24-fold increase of isolated oral clefts following exposure to CBZ during pregnancy, compared with the prevalence in the general population (frequency of 0.19 out of 1000) [16]. Thomas *et al.* reported that in an Indian population, 6.3% of infants born to women maintained on CBZ monotherapy had cardiac malformations [18]; other studies have reported a frequency of 0.7% [5], similar to what is expected in the general population [19]. Nevertheless, the reported prevalence of cardiac malformations is difficult to compare, due to differences in diagnosis and inclusion criteria in the published literature. Hernandez-Diaz *et al.*, in an effort to evaluate the effect of folic acid antagonists, compared 1242 cases of NTDs with a control group of children with malformations whose etiology is thought to be independent of folic acid status [20]. Six cases of CBZ exposure with NTDs were identified, the adjusted OR was 6.9 (95% CI: 1.9–25.7). This study clearly suggests an increased risk for NTDs secondary to *in utero* CBZ exposure.

Gabapentin

Gabapentin (GBP) is water-soluble and structurally similar to the neurotransmitter GABA [21]. Recently, it has also been used in the control of neuropathic pain. Unfortunately, studies with reliable *in utero* GBP exposure levels are limited and universally inconclusive (Table 1) [5,22,23]. Montouris *et al.* evaluated 44 pregnancies with exposure to GBP as monotherapy, as well as polytherapy. Two MCMs were found for a response rate of 4.5%. Only 17 cases were exclusively on monotherapy, of which, only one baby was found to have a MCM (unilateral renal agenesis). In this particular case, GBP was altered at 16 weeks of gestation to phenobarbital (PB). The other MCM, hypospadias, was detected in a baby exposed *in utero* to valproate and GBP [21]. Morrow *et al.* reported 31 patients receiving GBP as monotherapy, finding only one MCM, a ventricular septal defect. The rate was 3.2%, 95% CI: 0.6–16.2, which was not statistically significant ($p = 0.782$) [5].

Lamotrigine

Lamotrigine (LMT) is a phenyltriazine compound thought to act by inhibiting the release of glutamate acting in the voltage-dependent sodium channels [24]. The use of LMT as an AED, and also as a neuromodulator, in mood disorders has been increasing worldwide over the past few years. Evidence of LMT's teratogenicity remains uncertain, but the limited existing data suggest that LMT is less teratogenic than either valproic acid (VPA) or phenytoin (PHT), with respect to inducing structural abnormalities (Table 1) [1,25]. Interpretation of the teratological

data is compromised by methodological difficulties, such as small study sample sizes and uncontrolled clinical trials, as previously described for AEDs in general. For a review of LMT, see Prakash *et al.* [26]. Morrow *et al.* reported 647 LMT-complicated pregnancies, and found that prenatal exposure to this drug produced fewer MCMs than observed with VPA [5]. The MCM rate for LMT exposures was 3.2% (95% CI: 2.1–4.9). However, the study was insufficiently sensitive to exclude a substantially increased risk of MCM (risk ratio [RR]: 0.92; 95% CI: 0.41–2.05) [14]. The same authors found that LMT doses were significantly higher in the cases of MCM than that observed in the controls [5].

There is evidence suggesting that prenatal LMT exposure may increase the risk of craniofacial defects. Holmes *et al.* showed that LMT exposure was associated with a higher prevalence of cleft lip, cleft palate and cleft lip and palate; 7.3 out of 1000 in both monotherapy and polytherapy exposures (all defects combined), a 10.4-fold increase (95% CI: 4.3–24.9) compared with controls (predominantly a higher RR of cleft palate alone, 4.4 out of 1000) [27]. Hunt and coworkers observed only a single case of isolated cleft palate in 1151 LMT monotherapy-exposed pregnancies reported in a UK pregnancy registry (Table 1) [28]. In spite of the limitations concerning such data and other methodological problems, the use of LMT in pregnancy has generally been reported to be safer than other anticonvulsants. Due to the inherent difficulty in the interpretation of data in observational uncontrolled studies, it is not yet possible to conclude that LMT exposure is associated with an increased risk for oral clefts, especially cleft palate.

Levetiracetam

The use of levetiracetam (LEV) as a broad-spectrum AED has been increasing of late. In a recent survey, Meador *et al.* observed that the most frequently prescribed monotherapies in WWE were either LMT or LEV, probably owing to its high level of tolerability coupled with good efficacy, and the general belief that these drugs may be safer than the older, frontline AEDs [15]. Teratogenic effects are virtually unknown (Table 1). Data from the UK epilepsy and pregnancy registry published in 2006 failed to find MCMs in 39 patients receiving LEV monotherapy [28]. Holmes *et al.* reported data from the North American AED epilepsy registry that revealed a MCM rate of 2.03% in 197 LEV monotherapy exposures during pregnancy [29].

Phenobarbital

Phenobarbital is a barbiturate compound with sedative and hypnotic properties. PB is no longer generally regarded as a first-line drug for epilepsy in the USA and Europe, having been replaced by newer drugs. Owing to its low cost and effectiveness, it remains a front-line treatment for partial and general tonic–clonic seizures in many other countries. With respect to teratogenicity, Holmes *et al.* found an increased risk of MCM in the offspring of 77 WWE using PB as monotherapy for seizure control [30]; Meador *et al.* reported a rate of 4.9%, higher than CBZ but lower than that reported for PHT and VPA [1]. Previous studies did not find a significant risk for MCMs [12], but did report that cardiac-related malformations are present at a higher frequency when compared with other malformations in PB-exposed infants (see Table 1). Table 2 shows the number of malformations of cardiac origin associated with PB monotherapy, as well as the prevalence rate of total MCMs. Thomas *et al.* found that the risk of congenital heart defects as not significantly higher for PB or any specific AED [18].

Phenytoin

Phenytoin is a hydantoin derivative component whose structure is similar to barbiturates, but it has minimal sedative effects. Fetal hydantoin syndrome (FHS) was initially described, in part, by Loughnan *et al.* [31] and expanded upon by Hanson and Smith, when they formally named the syndrome [32]. Among the many dysmorphic findings associated with this

syndrome, hypoplasia and irregular ossification of the distal phalanges was originally believed to be the single most characteristic feature. These infants displayed facial dysmorphism including: epicanthal folds, hypertelorism, broad flat nasal bridges, an upturned nasal tip, wide prominent lips and, in addition, distal digital hypoplasia, intrauterine growth retardation and mental retardation. Subsequently, Hanson *et al.* reported a prevalence of FHS of 11%, with an additional 30% of the *in utero*-exposed children expressing some of the syndrome's features [33]. It is now common nomenclature to consider children presenting with a more limited pattern of dysmorphic characteristics secondary to *in utero* hydantoin exposure to be expressing fetal hydantoin effects [34]. Thus, the teratogenicity of PHT has been established amongst clinicians and basic scientists for almost 40 years. As is often the case, some studies found significant associations between *in utero* PHT exposure and MCMs [1,25,35,36], and others failed to find such associations (see Table 1) [5,37,38].

Topiramate

Topiramate (TPM) is a broad-spectrum sulfamate-substituted monosaccharide compound used mainly in the treatment of epilepsy and, more recently, as a prophylactic agent in migraine therapy. It has been reported that during pregnancy, TPM plasma concentrations vary considerably, most likely due to an enhanced elimination [39]. The drug's pharmacokinetic behavior cannot be predicted in all patients, making it necessary to carefully monitor plasma levels of TPM when utilized during pregnancy.

Exposure data during pregnancy are astonishingly limited (see Table 1). Some studies failed to find any risk of MCM with the use of TPM as a monotherapy in pregnancy [5,40]. However, Hunt *et al.* reported 70 monotherapy exposures of TPM and observed a rate of MCM of 4.8% (95% CI: 1.7–13.3), which almost tripled to 11.2% (95% CI: 6.7–18.2) in polytherapy [41]. Four out of the total MCMs in both groups were oral clefts (two patients on monotherapy). The prevalence rates of oral clefts (2.2%) and hypospadias (5.1%) were 11- and 14-times higher with TPM exposure than the background rates for these malformations in the UK (one in 500 and one in 300 live births, respectively). In this study, the confidence intervals are wide and the number of cases is insufficient to be able to draw strong conclusions about the effects of prenatal exposure to TPM. Still, the trend is difficult to ignore [42]. Holmes *et al.* showed a statistically significant increased rate of MCM in 197 enrolled TPM-complicated pregnancies, 4.1% with a 95% CI: 1.9–7.6% and a RR of 2.5. Cases included a range of common birth defects, including two infants affected with cleft lip [29].

While Ornoy *et al.* found that birth weight of term infants was significantly lower in his cohort of patients exposed *in utero* to TPM [40], this has not yet been validated in other studies [23, 41]. The mean birth weights for live infants exposed to TPM monotherapy were well within normal values; however, there was a clear trend toward lower birth weights amongst infants receiving TPM as part of AED polytherapy regimens and in patients that received higher doses of TPM monotherapy. Some lingering concern exists that TPM may increase the risk of oral clefts and hypospadias. Since low birth weight is one of the principal causes of morbidity and mortality among infants, this potential risk needs to be analyzed more carefully.

Valproic acid

Valproic acid is used primarily as an anticonvulsant and mood-stabilizing drug, but it is also now widely used in the treatment of migraine headaches and schizophrenia. A consistent finding that has emerged in multiple pregnancy registries and prospective pregnancy studies indicates that VPA causes a significant dose-dependent increased risk to the developing infant of both anatomical and behavioral teratogenic effects. Most recently, Meador *et al.* published a meta-analysis that revealed that gestational VPA is associated with a 10.7% (95% CI: 8.16–13.29) risk of MCMs, which occurred in multiple body/organ systems [1]. The data obtained

from pregnancy registries demonstrates an increased risk of MCMs associated with VPA exposure relative to the other AEDs. In a Finnish cohort of 7500 births, VPA monotherapy resulted in a MCM prevalence of 5.4 versus 2.8% for untreated mothers, with an odds ratio (OR) of 1.98 (95% CI: 1.53–2.55) [43]. In the North American Pregnancy Registry, Wyszynski and colleagues observed MCMs in 10.7% of VPA-exposed infants versus 2.9% from the other AEDs when their exposure was from monotherapy. Data from the Australian Pregnancy Registry described MCMs from VPA exposure in 17.1% of the infants versus 2.4% MCMs from the other AEDs [44]. The UK Pregnancy Registry had three-times as many MCM cases from VPA exposures than from CBZ (6.2 vs 2.2%) [5], and the International Lamotrigine Pregnancy Registry reported 12.5% MCMs when the mother received LMT polytherapy with valproate versus 2.7% MCMs from other LMT polytherapy regimens without valproate [45]. Most recently, the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) Study Group confirmed both the increased risk of poor fetal outcome (MCM or death) and the dose-dependent effect of VPA in a prospective study (20.3% with VPA vs 10.7% with PHT, 8.2% with CBZ and 1% with LMT) [46]. It is suggested that the risk of MCMs increases significantly at 600 mg/day, with the largest attributable risk observed at doses exceeding 1000 mg/day, although as is the case with all AEDs, individual susceptibility is genetically determined and even very low daily dosages can be teratogenic in some individual mother–infant pairs.

Vigabatrin

Vigabatrin (VGB) is an irreversible inhibitor of GABA-transaminase. Very little data concerning its teratogenicity have been reported. Exposure during adulthood produces an irreversible visual field loss in 30–40% of users [47], thus it is generally only used in patients with specific refractory epilepsy. Reported teratogentic outcomes from monotherapy exposures to VGB have been inconsistent. The European Agency for the Evaluation of Medicinal Products reported that 14.5% of 192 VGB-exposed pregnancies had congenital malformations, of which 64.3% were MCMs; however, women evaluated in this study were also exposed to other AEDs [48]. Sorri *et al.* reported two cases of children with VGB exposure with malformations, but both mothers were also receiving other AEDs during pregnancy (CMZ and VPA) [49]. Lawthom *et al.* reported no visual implications in four children with *in utero* exposure to VGB [50].

Risk of MCMs due to polytherapy

Several meta-analyses of pregnancy outcomes subsequent to AED polytherapy have revealed that the use of multiple AEDs is associated with higher rates of MCMs, ranging from 16.8 [6] to 6.0% (vs 3.7% for monotherapy) [5]. This is especially apparent when VPA is utilized in the polytherapy treatment regimen, as 12.5% of pregnancies were affected with a MCM when the AED polytherapy involved VPA versus 2.7% in polytherapy without VPA [45], and the risk of MCM in polytherapy without VPA (OR: 1.97; CI: 0.58–6.66) was increased (OR: 2.49; CI: 1.31–4.70) in VPA polytherapy [37]. While these have been consistent findings in current meta-studies, it is important to remember that these results often reflect outdated treatment paradigms, as drug selection, dose, monitoring and management philosophies have changed considerably.

Neurobehavioral end points of AEDs

It has long been established that most CNS teratogens produce functional deficits in individuals who may or may not have structural abnormalities [51,52]. Accumulating evidence, reviewed by Bromley *et al.* [7], suggests that *in utero* exposure to AEDs confers a risk of cognitive and behavioral problems. In a study conducted by the Kerala Registry of Epilepsy and Pregnancy, Thomas reported that children under the age of 2 years gestationally exposed to AEDs possessed the lowest mental development mean scores. AED-exposed infants had the highest

number of children in the impaired range when exposed to VPA (40.8%), PHT (37.9%), CBZ (29.7%) or PB (26.8%) [53]. In a large multicenter, NEAD study, Meador showed that 3-year-old children gestationally exposed to VPA had significantly lower IQ scores than those children exposed to other AEDs, and that this effect was dose-dependent [54]. On average, VPA-exposed children had an IQ of 92, which was 9 points lower than those exposed to LMT (95% CI: 3.1–14.6) and 7 points lower than those exposed to CBZ (95% CI: 0.6–12.0). Furthermore, maternal and offspring IQs were significantly correlated in all AED treatment groups, with the exception of VPA. Notably, more children had IQs that fell into the impaired range when exposed to VPA (13%) versus PHT (5%), CBZ (3%) or LMT (2%). A substudy of the NEAD investigation evaluated the ability to generate ideas in terms of quantity (fluency/flexibility) and quality (originality) in 54 children (mean age: 4.2 years) exposed to AED monotherapy (CBZ, LMT and VPA). The results revealed that fluency and originality were lower in the VPA group than the LMT and CBZ groups [55].

While evidence is still accruing, recent work does suggest that AED exposure results in altered cognitive function later in development. Kantola-Sorza reported that older children exposed to AED monotherapy performed poorer on attentional tasks, while children exposed to AED polytherapy performed poorer on auditory attention, sentence repetition and the fine motor task [56]. While too small to allow drug comparisons, a follow-up study of older AED-exposed children (aged 10–20 years) revealed that, with the exception of CBZ, all AEDs had a negative impact on intellectual functioning [57].

Other compounds

The reader should be aware that compounds, including, but not limited to, felbamate, primidone, succinimides, tiagabine and zonisamide, have been excluded from this review due to their poor representation in the published literature [58–61]. In regards to the teratogenic potential of oxcarbazepine, several studies [29,37,62] have not been able to demonstrate a direct association with birth defects in monotherapy exposures, owing to the small amount of data available in literature.

With respect to benzodiazepines, early studies have associated the consumption of diazepam during pregnancy with orofacial clefts [63,64], but these studies have several methodological problems: the information was collected retrospectively and not controlled for multiple drug use. More recent studies have not found any particular association between orofacial clefts [65] or other MCMs [38,66]. Gidai *et al.* documented 112 live-born pregnancies with a history of prenatal exposure to extremely high doses of diazepam without a higher risk of developing congenital abnormalities, including orofacial clefts [63]. Winker *et al.* observed 1979 infants whose mothers consumed benzodiazepines and/or benzodiazepine receptor agonists, finding an increased risk for preterm birth and low birth weight [67]. The OR for MCM without concomitant anticonvulsant therapy was 1.22 (95% CI: 0.97–1.52). When malformations were analyzed as a group, a higher frequency of pylorostenosis or alimentary tract atresia (especially small gut) was found, showing a RR of 4.9 (95% CI: 1.3–12.5).

Treatment guidelines

The authors refer you to several recent and comprehensive guidelines concerning the use of AEDS in the gravid epileptic patient representing the position of the American Academy of Neurology [68–70]. Keep in mind that no other class of widely used pharmaceutical compounds has the potential to inflict comparable harm to the developing infant. In summary, the risk for malformations must be analyzed in terms of each specific patient, their clinical and familial history and the risk–benefit ratio for the patient of child-bearing years. The ideal situation is to achieve optimal seizure control, while using the lowest doses possible and avoiding polytherapy. Close monitoring of serum levels in pregnancy may be advisable with some

AEDs. In particular, the use of VPA as a monotherapy or polytherapy should be avoided in women of child-bearing years whenever possible. Please refer to Box 1 for a summary of the literature concerning folate and birth defect risk associated with AED exposure.

Box 1

Prophylactic folic acid supplementation

Based on significant evidence [151], the US Public Health Service recommends that all women of childbearing potential consume 0.4 mg/day of folic acid (commonly available in over-the-counter multivitamin supplements) to reduce their risk of having a child with a neural tube defect (NTD) [149]. Furthermore, it is recommended that high-risk women take 4 mg/day [152–154]. Additionally, it must be noted that folic acid must be present within the first 25 days post-conception to protect against NTDs.

Since the most-studied antiepileptic drug (AED), valproic acid (VPA), is an established disruptor of folate metabolism, it was expected that folic acid supplementation would ameliorate its teratogenicity. On the contrary, there is a growing literature of case reports concerning the lack of any benefit derived from folic acid supplementation in women receiving VPA therapy during pregnancy [155–157]. As recently reviewed by Ornoy, there is no evidence to demonstrate that the risk of NTDs can be reduced further by folic acid supplementation in women taking VPA [158], a position previously articulated by Yerby [159]. For example, it was found that folic acid intake of approximately 0.4 mg daily did not reduce the risk of fetal malformations in subjects using AEDs known to disrupt folate metabolism in early pregnancy (carbamazepine, phenobarbital, phenytoin and primidone), even if it did so in subjects using other folic acid antagonists [20]. Investigators from The North American AED Pregnancy Registry recently report similar findings. They observed that 6.7% of the over 500 registry-enrolled infants had a major congenital malformation; maternal periconceptional use of folic acid was not associated with a statistically significant reduction in the risk of having an infant who had a major malformation, including NTDs. The investigators take care to note that the dosage of folic acid was not considered in these analyses, and it is possible that folic acid supplementation at higher dosages may be more preventive in women with epilepsy who are taking AEDs, although this has not been experimentally established [160]. Therefore, it remains unclear whether a periconceptional dose of folic acid greater than 0.4 mg daily would be beneficial in women using AEDs. Morrell states that as there is no direct positive evidence that folic acid supplementation provides protection against the increased risk of birth defects conferred by VPA treatment; recommendations that folic acid be given at higher, pharmacologic, doses in this population is not supported by ‘evidence-based medicine’ [161]. In summary, while low folate levels have been associated with an increased risk of major congenital malformations and NTDs in women taking AEDs [159], the majority of studies examining folic acid supplementation have found no decrease in risk, particularly for VPA [59,162,163].

Mechanisms of AED teratogenicity

Given the limitations inherent in human epidemiological and clinical studies of AED-complicated pregnancies, there is a great deal to be learned from fundamental reproductive and molecular studies using model organisms. The following section is devoted to a comprehensive review of the literature of just a few of the frontline AEDs, as teratogenic studies of the newer AEDs are not well reported in public scientific literature.

Carbamazepine

Carbamazepine has not been studied as extensively as VPA or PHT. The first study by Fritz and colleagues failed to observe any increase in fetal abnormalities when pregnant mice were treated with up to 250 mg/kg/day orally on gestational days 6–16 [71]. Small increases in the rate of cleft palate, dilated cerebral ventricles and growth retardation were observed in mouse fetuses that were similarly treated during the period of organogenesis [72–75]. In mice chronically exposed to CBZ in their diet prior to and throughout gestation, a significant number of fetuses were observed with congenital defects of the CNS or urogenital system [76]. In experiments comparing teratogenicity of CBZ with other anticonvulsant drugs, it was consistently less teratogenic than PHT or primidone [72,74,77]. In rats, CBZ had a limited teratogenic and embryotoxic effect [78]. Of the few abnormalities that were induced by gastric intubation throughout the period of organogenesis, edema was the most commonly observed, although fetuses with gastroschisis, omphaloceles, hydronephrosis, ventricular septal defects, hydrocephaly and skeletal defects were also reported.

The mechanism by which CBZ exerts its teratogenicity is largely unknown. The study on Swiss-Webster Vancouver (SWV) mice indicated that similar to PHT, CBZ could be biotransformed to a reactive teratogenic metabolite that might be responsible for the observed fetotoxicity [79]. The primary pathway of metabolism for CBZ involves the oxidative formation of carbamazepine-10,11-epoxide, which is thought to be responsible for the teratogenicity of the parent drug [80]. This was confirmed in a study on pregnant mice where carbamazepine-10,11-epoxide treatment significantly increased the incidence of malformations in fetuses [81,82].

Gabapetin

Experimental studies in rodents show that GBP exposure during pregnancy causes delayed ossification of bones in the skull, vertebrae, forelimbs and hindlimbs. Also, higher frequencies of hydroureter and/or hydronephrosis were identified; on the contrary, there was no evidence suggesting an increase in the rate of MCM in these experimental models. Prakash *et al.* reported a statistically significant increase in the resorption of fetuses exposed to GBP following early (E1–6) and midgestation (E7–12) exposure, directly proportional to GBP dosage [83]. In addition, the length and weight of mouse fetuses decreased significantly with the administration of GBP during mid- and late-gestation (E13–17). Malformations most commonly observed in the exposed fetuses were craniofacial defects, including brachygnathia, pointed snouts, open eyes, cataracts and thickened short necks, as well as limb defects, including rudimentary and malrotated limbs.

Lamotrigine

When pregnant rats were treated with LMT from E14 to E19 (the neuronal migration stage), pathological studies of the pups reported dose-dependent alterations in the neocortex and hippocampus. High doses of LMT (20 mg/kg/day) reduced maternal weight gain by approximately 20% and significantly reduced litter size. Treatment of pregnant rats with lower doses of LMT (5, 10 and 15 mg/kg) failed to affect either maternal weight gain or litter size. Prenatal exposure to LMT induced hippocampal and cortical malformations in a dose-dependent manner. Moreover, these effects were found at plasma LMT concentrations that are within the human therapeutic range for the drug [84]. In two studies on pregnant OT mice administered with LMT (Lamictal, Wellcome Co., UK) via either a single intraperitoneal treatment (50–300 mg/kg) or three doses (25–75 mg/kg) on E7 or E8, a high incidence of abortions and a significant decrease in maternal body weight were recorded. The LMT exposure resulted in a significant increase of resorptions and craniofacial malformations (exencephaly, cleft palate, arched palate and midfacial hypoplasia), urogenital abnormalities and varying degrees of caudal regression and skeletal defects were also noted. These observed effects were

most likely secondary to the severe maternal toxicity observed in the treated dams [85,86]. One study has reported a folate-mediated rescue of LMT-induced cleft palate [87].

Levetiracetam

Levetiracetam is the ethyl analog of the nootropic drug, piracetam. On E8–12, pregnant SWV mice were injected intraperitoneally, once daily with the dose of 600, 1200 and 2000 mg/kg of LEV or 600 and 1200 mg/kg of 2-pyrrolidone-*N*-butyric acid (PBA), the main metabolite of LEV in humans. No significant gross external malformations were observed in any of the treatment groups; however, fetal weights were significantly reduced and resorption rates were significantly increased, but only at the highest LEV dosages. The incidence of skeletal abnormalities, specifically hypoplastic phalanges, was significantly increased in both PBA treatments and in the intermediate 1200-mg/kg/day LEV group. Results of this study demonstrate that both LEV, and its major human metabolite, PBA, do not induce major structural malformations in developing SWV embryos [88]. Similar results were observed in experiments on rats and rabbits [89]. Fetal skeletal abnormalities were increased in rats treated with at least 350 mg/kg/day throughout gestation, as well as in those that were exposed to 3600 mg/kg/day given only during organogenesis. Similarly, rabbits treated with at least 600 mg/kg/day during organogenesis had an increased frequency of skeletal defects. *In utero* growth retardation was observed under conditions similar to those that induce skeletal abnormalities, whereas fetal mortality was increased in rats exposed to 1800 mg/kg/day throughout pregnancy.

Phenobarbital

While it is the oldest AED (almost 100 years in use), PB was not broadly tested for teratogenicity until the mid-1970s. The first study on mice demonstrated that PB, administered orally during the period of organogenesis in subtoxic doses to pregnant dams, induced only a modest 4.3% incidence of cleft palates among exposed fetuses [71]. In neurobehavioral experiments on rats, PB exposure increased offspring mortality, impaired growth and delayed some aspects of postnatal motor development [78]. In a study designed to examine the role of the genotype on sensitivity to PB-induced malformations, three highly inbred mouse strains (SWV, C57BL/6J and LM/Bc) received the drug via chronic oral administration. PB was found to have a significant teratogenic potential in mice, resulting in skeletal, cardiac, renal, neural and urogenital defects in a dose-related fashion. The LM/Bc strain was most sensitive to PB, with 46.7% of the fetuses exposed to the highest maternal plasma concentrations having malformations. C57BL/6J fetuses were the most resistant strain, with only 28.6% abnormalities [90]. In a subsequent study on the same mouse strains, the pattern of malformations induced by PB was compared with teratogenic effects of PHT treatment. Results of this study showed that PB induced a higher frequency of malformations (urogenital, cleft palate and cardiac), while the effect of PHT was related to an increased impairment of growth, leading to incomplete development, such as hydronephrosis, skeletal ossification delays or dilated cerebral ventricles [90]. The mechanism of PB teratogenicity is largely unknown. It was demonstrated that PB upregulates cytochrome P450s of the 2B family [91], and produces oxidative stress through the generation of superoxide radicals. These, in turn, led to the production of hydroxyl radicals, resulting in the formation of 8-oxodeoxyguanine that results in GC to TA transversions. Chronic feeding of oxazepam and PB upregulates CYP2B [92]. These findings suggest that PB-induced oxidative stress may be responsible for the observed developmental defects.

Phenytoin

Phenytoin has been one of the most widely studied of all the AEDs, starting with Massey's initial investigation [93]. Regardless of the route of administration, orally or via injection, PHT disrupts normal embryonic development in a number of different species, including the mouse,

rat, rabbit, cat and monkey [94–98]. The vast majority of experimental studies on the teratogenicity of PHT have focused on the ability of this compound to induce orofacial clefts, reflecting the early human clinical reports of an increase in the incidence of cleft lip and/or cleft palate among the offspring of epileptic patients [99–102]. These studies demonstrated that cleft palate can be induced in susceptible mouse strains when doses as low as 12.5 mg/kg/day are administered to the pregnant dam during the sensitive period for palate closure. Malformations other than cleft lip and/or cleft palate were observed in a number of the experimental studies. Harbison and Becker were the first to describe a variety of defects in mouse fetuses exposed to PHT during gestational days 8–15 [94]. The abnormal fetuses were growth retarded, with shortened long bones, and had hydronephrosis and renal hemorrhage; there were also fetuses that had defective ossification of the sternebrae, open eyes, ectrodactyly and internal hydrocephalus. A similar pattern of defects was reported by the same investigators in rat fetuses [96]. This basic spectrum of birth defects was confirmed, and expanded upon, by subsequent investigations into the teratogenicity of PHT to include tracheoesophageal fistulas, cutaneous hemorrhages and NTDs. The differences in the pattern of malformations observed were generally attributable to the differences in species or strain of the experimental animals, route of administration and dosages used in the various studies [71,73,103,104].

Finnell described a pattern of congenital defects in the offspring of pregnant mice that were chronically treated prior to and throughout pregnancy with PHT added to their drinking water [105], which was comparable to that observed in the human FHS [32]. This pattern of malformations included ossification delays of the distal phalanges, occiput, sternebrae, vertebral centra and the bones of the midfacial region. The most consistently observed visceral malformations included dilated or immaturely developed cerebral ventricles, renal agenesis, hydronephrosis, cutaneous and renal hemorrhage, and cardiac, digital and ocular abnormalities [105]. Using this animal model, it was possible to recreate the structural defects observed in the human prenatal hydantoin syndrome in mice.

In spite of considerable effort on the part of several groups of investigators, the mechanism by which PHT exerts its teratogenic effect remains unclear. Of the many different hypotheses that have been set forth, one of the favored theories proposes that PHT is metabolized to a toxic reactive intermediate that is responsible for the observed teratogenic effects. Specifically, an arene oxide metabolite produced enzymatically during the bioactivation of PHT by the cytochromes P450 may be the actual teratogenic molecule [106–108]. Such oxidative metabolites are thought to occur prior to the formation of the dihydrodiol metabolite 5-(3,4-dihydroxy-l,5cyclohexadien-l-yl-5-phenylhydantoin) from PHT in a reaction catalyzed by the enzyme epoxide hydrolase [109]. Arene oxides, in general, are highly reactive, and when the rate of their bioactivation exceeds the detoxification capacity of the organism, the electrophilic center of the molecule is capable of binding covalently to nucleophilic sites found in fetal macromolecules, such as nucleic acids [106,107,110,111]. It is possible that the arene oxide intermediate produced during the bioactivation of PHT in the maternal liver may be sufficiently stable to cross the placenta and bind to fetal tissues. The other possibilities for this molecule to be the primary teratogenic agent involve it being tautomerized to a more stable oxepin, which can then cross the placenta and isomerize back to a reactive arene oxide intermediate [107] or the arene oxide could actually be bioactivated in the fetal liver [106,112,113]. An alternative bioactivating pathway for the induction of PHT-induced congenital defects involves the co-oxidation of the drug to free radical intermediates centered in the hydantoin nucleus by prostaglandin synthetase [114]. As a result of such bioactivation, free radical intermediates may result in oxidant stress, initiate lipid peroxidation reactions and/or bind covalently to essential nucleic acids. This hypothesis is based on both *in vivo* [114] and *in vitro* [115] studies.

It was also suggested that PHT can act through Ras-dependent signal transduction. In experiments on mouse embryos cultured *in vitro*, it was demonstrated that inhibition of the *K*-

ras oncogene protected the embryos from PHT-induced structural defects [116]. Finally, it is possible that the oxidative intermediate of interest is one that is not sufficiently detoxified by enzymatic conjugation with reduced glutathione [117,118]. While a glutathione conjugate of PHT has not as yet been demonstrated, PHT is capable of producing a slight, yet significant, depletion of hepatic glutathione synthetase in pregnant mice [108]. When mice are pretreated with compounds that deplete natural stores of glutathione, such as diethyl male-ate [119] or acetaminophen [108], there is a marked increase in the covalent binding of PHT and a subsequent increase in the teratogenic response frequency. In a murine whole-embryo culture study, it was demonstrated that PHT-induced reactive oxygen species cause DNA oxidation, which results in embryo dysmorphogenesis. The addition of superoxide dismutase or catalase to a culture medium significantly reduced or completely eliminated all PHT-initiated dysmorphological disturbances [120]. In another *in vivo* and *in vitro* study, pregnant mice were treated simultaneously with PHT and stiripentol (a cytochrome P450 inhibitor) and PHT was incubated with hepatic microsomes in the presence of stiripentol. This compound significantly decreased the frequency of PHT-induced malformations, as well as inhibited covalent binding of PHT to NADPH *in vitro*. These results suggest that oxidative biotransformation of PHT by cytochrome P450 resulting in reactive oxidation species can be responsible for the teratogenicity of this AED [121,122].

Topiramate

Limited scientific information on the teratogenicity of this second-generation AED is only available from the online TOXNET database for the healthcare professional [201]. Fetuses from pregnant mice treated orally during the period of organogenesis with TPM doses of 20, 100 and 500 mg/kg presented with an increased incidence of fetal malformations (primarily craniofacial defects). Fetal body weights and skeletal ossification were reduced at doses of 500 mg/kg; decreased maternal body weight gain also occurred at this dose. In studies on rats, the frequency of limb malformations (ectrodactyly, micromelia and amelia) was increased among the offspring of dams treated with TPM 400 mg/kg or more during the period of organogenesis. Clinical signs of maternal toxicity were seen at doses of 400 mg/kg and above, and maternal body weight gain was reduced during treatment with doses of 100 mg/kg or more. Fetal toxicity (reduced fetal body weights and increased incidence of structural variations) was observed at doses as low as 20 mg/kg. In studies on rabbits receiving TPM, embryo/fetal mortality was increased at doses of 35 mg/kg and greater, and teratogenic effects (primarily rib and vertebral malformations) were observed at doses of 120 mg/kg. Evidence of maternal toxicity (decreased body weight gain, clinical signs and/or mortality) was seen at doses of 35 mg/kg and above [123].

Valproic acid

Valproic acid (2-propylvaleric acid) and its toxic/teratogenic properties have been described in several animal model systems (zebrafish, *Xenopus*, mouse, rat, hamster, gerbil, rabbit, dog and rhesus monkey) *in vivo* and *in vitro* for over 40 years [124,125]. When administered in sufficiently high doses (e.g., 200–800 mg/kg/day in a mouse or rat) to pregnant dams, depending on the route (orally, subcutaneously, intraperitoneally or intravenously), gestational stage, species and strain, VPA invariably produces a range of developmental defects that increase in a dose-dependent manner. The most commonly observed adverse developmental effects were skeletal defects in the ribs, vertebrae, digits and craniofacial bones. These adverse effects were reflected in ossification defects, abnormal numbers and shapes. Similar results were obtained in the rabbit, with an increased frequency of axial and appendicular skeletal abnormalities observed following administration of 350 mg/kg/day doses of either calcium or sodium valproate [126]. High doses of VPA also produced intra-uterine growth retardation, craniofacial, skeletal and cardiac defects in rhesus monkeys [127]. As is the case in human studies, laboratory rodents exposed to VPA present with NTDs. VPA treatment during early

neural tube formation (E8 in the mouse) results in exencephaly, which is the rodent equivalent of human anencephaly. There were also posterior NTDs produced In some mouse strains when injected three times at 6-h intervals on E9 [128–131]. NTDs can be induced by VPA in exposed mouse embryos when the maternal plasma VPA concentration is in excess of 225 μg/ml, irrespective of the route of administration [132]. This drug concentration is between two- and five-times the desired human therapeutic level [133]. Finnell and colleagues have demonstrated that both VPA and its 4-propyl-4-pentenoic acid metabolite (4-en-VPA) are capable of producing exencephaly in mouse embryos exposed to a single intraperitoneal injection on E8.5 [134]. The different strains of mice used in this study displayed a widely differing sensitivity to the induction of NTDs, suggesting that susceptibility to VPA-induced exencephaly has a strong genetic component [128,135]. Morphological observation of mouse embryos exposed to VPA at E8.5 revealed their altered pattern of neurulation, due to the interaction of as yet unknown genetic factors and VPA.

Nau and colleagues have examined various analogs and metabolites of VPA and have determined that strict structural requirements must be met for the compound to exert a teratogenic effect [124]. To be teratogenic, the compound must have the following: a free carboxyl group, an α-hydrogen atom, branching of carbon chains, no double bonds on C-2 or C-3 and an alkyl substituent on C-2 that is larger than the methyl groups. Homologous compounds containing shorter or longer alkyl chains are less teratogenic than the parent VPA molecule. If there are substitutions of the α-hydrogen atom or double bonds in the 2 or 3 carbon positions (2-en or 3-en VPA), the teratogenic activity of the compound is diminished or abolished entirely [136]. The addition of a double bond in the 4 position (4-en-VPA) does not seem to interfere with the teratogenic potential of the compound [128]. This high specificity of the teratogenic response of VPA differs from the broad, generalized specificity of its anti-epileptic activity, suggesting that the two mechanisms of action are unrelated [136]. Bialer and colleagues utilized pharmaco- and toxico-kinetic considerations in designing various derivatives of VPA that are more potent as anticonvulsants and have the potential to be nonteratogenic and nonhepatotoxic [137].

Several hypotheses have been set forward in an attempt to elucidate the mechanism by which VPA disrupts embryonic development. Wegner and Nau suggested that teratogenic doses of VPA alter folate metabolism in the embryo via increasing the level of tetrahydrofolate and decreasing levels of 5-formyl- and 10-formyltetrahydrofolates. These changes could be induced by VPA-mediated inhibition of transfer of the formyl group via glutamate formyltransferase. A closely related structural analog of VPA (2-en-VPA), which exhibits antiepileptic activity but not teratogenicity, did not adversely impact embryonic folate metabolism [138]. It has been shown in rats that VPA provoked hepatic DNA hypomethylation, suggesting that VPA affects methionine synthesis through an altered methionine synthase activity, an effect that impairs methionine availability and disrupts the methylation cycle, inducing DNA hypomethylation [139]. More recently, it has been proposed that histone deacetylases (HDACs) are direct targets for VPA [140,141]. HDACs deacetylate lysine residues on histone tails, and induce transcriptional repression through chromatin condensation. Drugs modulating the acetylation status of histones, such as HDAC inhibitors, can inhibit cell growth and induce terminal differentiation, which can adversely alter the normal pattern of embryonic development. Menegola and colleagues showed a direct correlation between somite hyperacetylation and axial abnormalities, which further support HDAC inhibition as the mechanism by which the drug exerts its teratogenic effects [142]. Researchers using teratocarcinoma F9 cells tested a large, structurally diverse set of VPA derivatives and found that only VPA derivatives with a teratogenic potential in mice were able to induce a hyperacetylation in core histone H_4 in cultured cells. They also demonstrated that this marker of functional HDAC inhibition occurs almost immediately (15 min) after exposure to VPA, whereas there were no changes in HDAC protein levels (HDAC 2 and 3) as long as 24 h post-

treatment. The quantitative correlation between the IC_{50} (HDAC) and the teratogenic potential of VPA derivatives demonstrated in this study, clearly points toward HDACs as the teratogenic receptors of VPA-induced NTDs [143]. Other *in vitro* studies showed that HDAC inhibitors alter *Wnt* signaling, inducing *Wnt*-dependent gene expression at doses that cause developmental effects. Interestingly, structural VPA analogs that do not interact with *Wnt* do not show teratogenic effects. These observed effects support the view that altered *Wnt* signaling is an important mechanism underlying VPA-induced teratogenesis [144].

Vigabatrin

Vigabatrin is an enzyme-activated, irreversible inhibitor of GABA-transaminase that enhances brain GABA levels. To evaluate its teratogenic potential, VGB was tested on OT mice. Pregnant mice were injected intraperitoneally with 300, 450 or 600 mg of VGB per kilogram of body weight, once on one of the gestation days 7–12. The highest dose (600 mg/kg) was lethal to all injected mice but the lower doses did not induce any maternal toxicity. Growth retardation, as well as mandibular and maxillary hypoplasia and exomphalos, were observed in the malformed fetuses from the VGB-treated groups. Analysis of stained skeletons revealed hypoplasia of midfacial bones, stage-dependent increase in the frequency of cervical and lumbar ribs and rib fusion, as well as sternal and vertebral malformations in the drug-treated fetuses. A homeotic shift in terms of presacral vertebral number and decreased ossification of the phalanges and tarsal were observed in a significant number of VGB-treated fetuses [145]. When the pregnant dams were injected intraperitoneally with 450 mg/kg of VGB in early gestation (E1–5), similar results were observed [146]. These results indicate that prenatal exposure to VGB and VPA generates cortical and hippocampal malformations linked to cell migration defects, indicating that this may be a common mechanism for the deleterious effects of AEDs on fetal brain development [147].

Expert commentary

The issue at hand is how to manage pregnancies in women who must be therapeutically maintained on AEDs, irrespective of the indication, for the duration of their pregnancies. While it is not possible to provide general guidelines that are applicable to all women taking these medications during pregnancy, there are a few important principles that the primary caretakers managing the health of the prospective mother should try to follow. The first principle is that as long as any AED must be taken during pregnancy, there is no absolutely safe dose that will provide therapeutic efficacy without the potential risk of inducing developmental or structural defects in the exposed infant. While it is true that higher drug dosages pose a greater risk than lower doses of the same therapeutic agents, it is well understood that teratogens work on susceptible genotypes, additionally interacting with other environmental variables, to induce their damage to the unborn. Every pregnancy represents a unique occurrence of genetic variables and environmental factors with which any of the available AEDs must interact. We currently lack the means to identify those high-risk mother–infant pairs that are exceedingly sensitive to specific AED-induced teratogenesis, which would guide the selection of the most appropriate therapy. Hopefully such preconceptional tests will be available in the near future. For the present time, for those women whose healthcare needs require daily administration of these compounds, the prevailing wisdom holds that the lowest efficacious dosage is most desirable to minimize the risk for dysmorphic events, major malformations or developmental delays in the exposed embryo. This is especially true for VPA, but it applies to all of the other major AEDs.

The second principle is to try to avoid polytherapy whenever possible in the management of pregnant patients. Although the latest results from registry data are not as dire as they were in the past, polytherapy with two or more AEDs presents a greater risk to the developing embryo.

Finally, with respect to providing supplemental folic acid (principle three) to mitigate the risks associated with AEDs for inducing complex structural malformations, such as NTDs or craniofacial malformations, there is no consistent evidence in the scientific literature to suggest that it is effective in reducing the risks associated with the concomitant AED exposure. However, since it is possible for an infant to have one of the folic acid-responsive birth defects coincidentally and not directly related to the AED therapy, it is highly advisable that the standard of care for all women be equally applied to those maintained on AEDs prior to and throughout their pregnancies.

Five-year view

Being able to use biomarkers to properly match the AED with the lowest teratogenic potential for any given mother–infant pair, while providing adequate protection from seizures, has been a long sought after goal. Advanced DNA sequencing technology, where more thorough investigations can be conducted at increasingly higher resolution and steadily decreasing costs, has brought the field to the point where in the next 5 years, genetic biomarkers of teratogenic risk are expected to be available. It is incumbent upon national funding agencies to embrace the existing large cohorts, such as NEAD, and provide the resources to couple the neurodevelopmental testing of *in utero* AED-exposed infants with rigorous investigations of maternal and infant genotypes. It is also expected that within the next 5 years there will be a push towards more high-throughput methods, using cell-based assay systems, to discover and test new AEDs. The potential is greatest in the use of embryonic stem cell collections, which are exposed to thousands of compounds from existing small molecule libraries and allowed to differentiate; this testing is expected to reveal the relevant biological pathways altered by library compounds and involved in AED activity, production of malformations and thereby lead to the development of new AEDs that are more specific and better matched clinically to individuals with specific seizure disorders. In addition to developing new AEDs, these experiments can also focus on refining the predictive value of biomarkers, where specific genotypes or resulting transcript levels would be used to derive an algorithm that provides predictive information on increases in MCM risk due to specific AEDs. With this information available, the following generation of AEDs may also be selected to circumvent the teratogenic targets of existing AEDs, and ultimately eliminate the increased risk for MCMs due to AED exposure.

Key issues

- Women with epilepsy are not the only ones for whom antiepileptic drugs (AEDs) pose a teratogenic threat, as many AEDs have therapeutic applications in neuropathic pain, migraine headaches and psychiatric disorders.
- The vast majority of pregnancies in women with epilepsy are uneventful, with most AED-exposed children born free from either structural or behavioral abnormalities.
- While there is a great deal of variability between studies, the prevalence of major congenital malformations is elevated from a general population frequency of 2.2% in all pregnancies, to 3.7% observed in pregnancies complicated by AED monotherapy and 6.0% observed in AED polytherapy.
- The risk of some AEDs has been clearly established, but for newer drugs, small sample sizes and polytherapy exposures preclude a conclusive determination of their teratogenic potential. Most women with epilepsy will require AED therapy throughout their entire pregnancy to control seizures.

- The most common malformations observed secondary to *in utero* AED exposure are cardiac malformations, followed by hypospadias and facial clefts, which echoes the pattern of malformations seen in the general population.
- Treatment with certain AEDs is associated with a greater risk of specific malformations. These include neural tube defects in valproic acid- and carbamazepine-complicated pregnancies.
- Recent investigations suggest that exposure to certain AEDs, most notably valproic acid, results in altered cognitive function later in life.
- There is no evidence that additional folic acid supplementation ameliorates the increased risk of congenital malformations resulting from *in utero* AED exposure.

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Table 1

Reports of teratogenicity associated with various antiepileptic drug monotherapy.

Authors (year)	Study methodology	N	Rate of MCM (%)(95% CI)	Risk (95% CI)	Ref.
Carbamazepine					
Samrén (1999)	Retrospective cohort	376	3.7	RR: 2.6 (1.4–5.0)	[12]
Kaneko (1999)	Prospective	158	5.7	OR: 1.9	[35]
Holmes (2001)	Prospective	58	5.2	OR: 3.0 (0.6–16)	[10]
Matalon (2002)	Meta-analysis	795	5.5	OR: 2.36 (1.62–3.43)	[13]
Wide (2004)	Retrospective	703	4.0	NA	[36]
Artama (2005)	Retrospective	805	4.0	OR: 1.27 (0.7–2.23)	[37]
Vajda (2006)	Prospective and retrospective	155	3.8	p = 1.0000	[38]
Morrow (2006)	Prospective	900	2.2	OR: 1.0	[5]
Hernandez-Diaz (2007)	Prospective	873	2.5 (1.6–3.7)	OR: 1.6 (0.9–2.8)	[16]
Vajda (2007)	Prospective	234	3.0	OR: 0.82 (0.21–3.26)	[38]
Meador (2008)	Systematic review and meta-analysis	4411	4.6	NA	[6]
Gabapentin					
Montouris (2003)	Prospective and retrospective	17	5.9	NA	[23]
Morrow (2006)	Prospective	31	3.2 (0.6–16.2)	OR: 1.33 (0.17–10.20)	[5]
Vajda (2007)	Prospective	11	0	NA	[38]
Holmes (2008)	Prospective	127	0.8 (0.039– 3.8)†	NA	[27]
Lamotrigine					
Morrow (2006)	Prospective	647	3.2 (2.1–4.9)	OR: 1.44 (0.77–2.67) RR: 0.92 (0.41–2.05)	[5]
Vajda (2006)	Prospective and retrospective	61	0	p = 0.3960	[25]
Vajda (2007)	Prospective	146	1.4	OR: 0.37 (0.06–2.26)	[38]
Meador (2008)	Systematic review and meta-analysis	1337	2.9 (2.00–3.82)	NA	[6]
Holmes (2008)	Prospective	684	2.80 (1.7–4.3)	RR: 1.4 (0.9 –2.3)	[27]
Hunt (2009)	Prospective	1151	2.4 (1.7– 3.5)	NA	[28]
Levetiracetam					
Long (2003)	Case series	3	0	NA	[148]

Authors (year)	Study methodology	N	Rate of MCM (%)(95% CI)	Risk (95% CI)	Ref.
Ten Berg (2005)	Prospective	2	0	NA	[149]
Morrow (2006)	Prospective	22	0	NA	[5]
Levetiracetam					
Hunt (2006)	Prospective	39	0	NA	[150]
Holmes (2008)	Prospective	197	2.0 (0.65–4.8)†	NA	[27]
Phenobarbital					
Samrén (1999)	Retrospective	172	2.9	RR: 2.0 (0.8–5.3)	[12]
Holmes (2001)	Prospective	64	4.7	OR: 2.7 (0.6–16.4)	[10]
Holmes (2004)	Prospective	77	6.5 (2.1–14.5)	RR: 4.2 (1.5–9.4)	[29]
Meador (2008)	Systematic review and meta-analysis	945	4.9 (3.22–6.59)	NA	[6]
Phenytoin					
Samrén (1999)	Retrospective	151	0.7	RR: 0.5 (0.1–3.4)	[12]
Holmes (2001)	Prospective	87	3.4	OR: 1.9 (0.3–9.2)	[10]
Artama (2005)	Retrospective	38	2.6	OR: 0.95 (0.02–6.11)	[37]
Morrow (2006)	Prospective	82	3.7 (1.3–10.2)	OR: 1.64 (0.48–5.62)	[5]
Vajda (2006)	Prospective and retrospective	17	5.9	p = 0.5113	[25]
Vajda (2007)	Prospective	31	3.2	OR: 0.90 (0.09–8.88)	[38]
Meador (2008)	Systematic review and meta-analysis	1198	7.4 (3.60–11.11)	NA	[6]
Holmes (2008)	Prospective	390	2.6 (1.2–4.5)†	NA	[27]
Topiramate					
Morrow (2006)	Prospective	28	2.0	OR: 7.1 (2.0–22.6)	[5]
Vajda (2007)	Prospective	15	0	NA	[38]
Ornoy (2008)‡	Prospective	29	3.5	NA	[40]
Hunt (2008)	Prospective UK Epilepsy and Pregnancy Register	70	4.8 (1.7–13.3)	NA	[41]
Holmes (2008)	Prospective	197	4. (1.9–7.6)†	NA	[27]
Valproate					
Kaneko (1999)	Prospective	81	11.1	OR: 4	[35]
Samrén (1999)	Retrospective	158	5.7	RR: 4.1 (1.9–8.8)	[12]

Authors (year)	Study methodology	N	Rate of MCM (%)(95% CI)	Risk (95% CI)	Ref.
Wide (2004)	Retrospective	268	9.7	NA	[36]
Valproate					
Artama (2005)	Retrospective	263	10.7	OR: 4.18 (2.31–7.57)	[37]
Morrow (2006)	Prospective	715	6.2 (4.6–8.2)	OR: 2.78 (1.62–4.76) RR: 2.52 (1.17–5.44)	[5]
Vajda (2006)	Prospective and retrospective	113	16.8	p = 0.0262	[25]
Vajda (2007)	Prospective	166	13.3	OR: 4.07 (1.18–14.0)	[38]
Meador (2008)	Systematic review and meta-analysis	2097	10.7 (8.16–13.29)	NA	[6]

†CI for the prevalence of malformations is reported only in the North American Antiepileptic Drug Pregnancy Registry Winter Report [201].

‡The original rate in Ornoy 2008 is 9.8% including syndromic and polytherapy exposures. The rate that appears in the table is adjusted to monotherapy exposures and isolated malformations.

MCM: Major congenital malformation; NA: Not available; OR: Odds ratio; RR: Relative risk.

Table 2

Risk of major congenital malformation and congenital heart defects associated with phenobarbital monotherapy.

Study	CM (n)	Cardiac malformations	% of cardiac malformations (cases/n)	Ref.
Samrén (1999)†	3	2	66.67	[12]
Holmes (2001)	3	2	66.67	[10]
Holmes (2004)	5	3	60.00	[29]
Thomas (2008)	NA	Three out of 43 monotherapy exposures		[18]

†One cardiac defect was associated with an aberrant chromosome.

CM: Congenital malformation; NA: Not available.