Antiepileptic Drugs and Pregnancy Outcomes

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Abstract

The treatment of epilepsy in women of reproductive age remains a clinical challenge. While most women with epilepsy require anticonvulsant drugs for adequate control of their seizures, the teratogenicity associated with some antiepileptic drugs is a risk that needs to be carefully addressed. Antiepileptic medications are also used to treat an ever broadening range of medical conditions such as bipolar disorder, migraine prophylaxis, cancer and neuropathic pain. Despite the fact that the majority of pregnancies of women with epilepsy who are receiving pharmacological treatment are normal, studies have demonstrated that the risk of having a pregnancy complicated by a major congenital malformation is doubled when comparing the risk of untreated pregnancies. Furthermore, when antiepileptic drugs (AEDs) are used in polytherapy regimens, the risk is tripled, especially when valproic acid (VPA) is included. However, it should be noted that the risks are specific for each anticonvulsant drug. Some investigations have suggested that the risk of teratogenicity is increased in a dose-dependent manner. More recent studies have reported that *in utero* exposure to AEDs can have detrimental effects on the cognitive functions and language skills in later stages of life. In fact, the FDA just issued a safety announcement on the impact of VPA on cognition (Safety Announcement 6-30-2011). The purpose of this document is to review the most commonly used compounds in the treatment of women with epilepsy, and to provide information on the latest experimental and human epidemiological studies of the effects of antiepileptic drugs in the exposed embryos.

Keywords

antiepileptic drugs; teratogenicity; pregnancy; birth defects; epilepsy

INTRODUCTION

During pregnancy, women experience a series of physiological changes that have consequences for the pharmacokinetics and pharmacodynamics of the drugs and medications they take. Monitoring epilepsy in pregnancy is very challenging despite the narrowly focused goal of establishing an optimal seizure control regimen with the lowest possible dose of antiepileptic drug(s). To accomplish this, it is of particular importance to understand the physiological changes that the human body undergoes during pregnancy.

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During the course of pregnancy, the plasma volume progressively increases and affects the drug disposition within the body. The volume of the drug distribution, its elimination, and its half-life; all will change considerably over time. The total drug plasma concentration declines, and in some cases, this can adversely affect seizure control. Additionally, the storage of fat increases and fat-soluble drug elimination slows down. Conversely, cardiac output and renal blood flow increase, influencing the renal elimination of the medications [Pennel, 2003]. The activities of the cytochrome P450 superfamilies that are essential for drug metabolism in the liver are induced during pregnancy [Sabers et al., 2009]. Plasma protein concentration is lower, in particular, albumin and α1-acid glycoproteins, which are essential antiepileptic drugs (AEDs) transporters in the blood stream. This will be manifested as lower total drug level, but in most cases, the unbound concentration of the drug will not change so that their efficacy may remain unaffected. As a reminder, the therapeutic and toxic effects of AEDs are caused by the fraction of the drug in plasma that is not bound to the transport proteins, in other words, the unbound form of the drug. This unbound fraction also directly determines the transplacental crossing of the active compound and thus the exposure of the embryo and/or foetus.

Epilepsy is a brain disorder involving repeated, spontaneous seizures of any type. Seizures (convulsions) are episodes of disturbed brain function that cause changes in attention or behavior. They are caused by abnormally excited electrical signals in the brain [Vorvick et al., 2010]. Epilepsy can be caused by variety of etiologic factors known or idiopathic, directly or indirectly affecting central nervous system e.g. stroke, ischemia, traumatic brain injury, infectious encephalitis, congenital brain defects, phenylketonuria, brain tumors, liver and kidney failure, to name just a few. The most characteristic symptoms of epilepsy are seizures, which vary greatly in severity from petit mal, absence seizures, to grand mal, generalized violent tonic-clonic convulsions. Treatment of this condition is difficult and in most cases, one seeks control, but no cure. Symptoms (seizures), however, can be successfully reduced or eliminated with the proper anticonvulsant medication treatment regimen. Based on severity and etiology, mono- or polytherapy is recommended for this lifelong disease.

The vast majority of patients suffering from seizures require daily AED therapy, and in most instances, this is a lifelong treatment. This is also true for epileptic women during their reproductive years. Approximately 25,000 children are born to mothers with epilepsy each year in USA alone [Meador et al., 2008]. Although the majority of these children are normal, the risks associated with *in utero* AED exposure are of considerable importance. These infants have significantly higher risks of having one of the features of the embryopathy (i.e., major malformations, microcephaly, growth retardation, and hypoplasia of the midface and fingers) associated with *in utero* exposure to AEDs, than do control infants. While figures are quite variable based on the study design and their inherent limitations, Holmes and co-workers found that approximately 20.6% of children exposed to one AED, and 28% of those exposed to two or more drugs, had at least one feature characteristic of the fetal antiepileptic drug embryopathy [Holmes et al., 2001]. Major malformations affected 4.5% and 8.6% of these infants, respectively. Other authors observed major birth defects in 3.2 – 7.8% of pregnancies complicated by AED monotherapy, and 6.0 – 9.3% in AED polytherapy [Artama et al., Canger et al., 1999; Cunnington et al., 2005; Kaaja et al., 2003; Kaneko et al., 1999; Mawer et al., 2010; Morrow et al., 2006; Samren et al. 1999; Wide et al., 2004; Wyszynski et al., 2004; 2005]. The meta analysis of 26 studies compiled by Tomson and Battino 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 [Tomson and Battino, 2009]. Available data strongly suggest that this increased risk for adverse outcomes observed in *women with epilepsy* (WWE) is not a consequence of epilepsy or

seizures *per se*, but is instead directly due to the teratogenic effects of AEDs. Studies showed that offspring born to epileptic women who did not take anticonvulsant drugs had the same risk of birth defects as the infants born to control, seizure free women [Holmes et al., 2001].

In the past 20 years 15 new AEDs has been approved by the US Food and Drug Administration and/or European Medicines Agency and introduced to the market [Bialer, 2011]. Individuals with seizures comprise the largest group of patients treated with AEDs; however, these agents are also widely used for treatment of other neurological disorders. From over 30 medications used primarily to control seizures, several such as clonazepam, lamotrigine, divalproex are frequently used by psychiatrist to treat bipolar disorder and anxiety. Neurologists often use topiramate, gabapentin, and levetiracetam in patients suffering migraine headaches and other pain. Other seizure medication like clonazepam are used for controlling panic disorder and social phobia, pregabalin is used in the treatment of fibromyalgia, lamotrigine for severe unremitting depression and maniac symptoms [Cascade et al., 2008]. 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 while the risk of some AEDs has been clearly established, there are unknown risks associated with exposure to the newer drugs, due to small sample sizes and polytherapy exposures. Still, most 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 abnormalities [Meador et al., 2008]. The European and International Registry of Antiepileptic Drugs in Pregnancy (EURAP) has recently reported more favourable outcomes with regards to status epilepticus than the 30% maternal mortality and 50% pregnancy mortality reported in older studies [Pennell, 2006; Tomson et al., 2011]; nevertheless, discontinuing AED therapy during pregnancy is still discouraged by most practitioners.

The most common malformations observed secondary to *in utero* AED exposure are cardiac malformations, followed by hypospadias and facial clefts, which follows the pattern of the most common malformations seen in the general population. Treatment with certain AEDs is associated with a greater risk of specific malformations. The strongest data indicate 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), an increased risk of neurodevelopmental deficits, reduced verbal abilities, and poorer attentional tasks [Bromley et al. 2009; Kantola-Sorza et al., 2007; McVearry et al., 2009; Meador et al., 2008, 2011; Nadebaum, 2011; Thomas et al., 2008]. The astute clinician has always been credited with being the primary means of identifying potential human teratogens [Crombie, 1984; Carey et al., 2009], 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 the 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 if not impossible, and clouds the etiology of the observed malformations. After the definition of the term MCM by Holmes et al. in 2001, inclusion criteria of subjects into epidemiological studies were more homogenous. Unfortunately, prior to this date and even for some years after, the categories of major and minor malformations as reported in the literature were often variable and were poorly described, if they were described at all. Owing to the limited number of reports, the data published are valuable, even if compromised by less than desirable methodology [Morrow et al., 2006]. 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. As a result, multicenter design studies are the only feasible approach to gather unbiased data on a significant number of pregnancy outcomes. Data that are 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 towards more abnormal outcomes. Registry data are one way to circumvent the relative scarcity of AED-exposed pregnancies, but it is most often data that are voluntarily reported that are 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 [2009] provide an excellent overview of the difficulties inherent to the study design for the teratogenicity of AEDs.

This review is a new, updated and extended version of our previous paper published in the "Expert Review of Neurotherapeutics" [Hill et al., 2010]. The field is moving rapidly in order to provide new data on the potential teratogenicity of the latest generation of AEDs. In this latest revision of this timely review of the teratogenicity of AEDs, we added two new sections to the Introduction, briefly describing the neurological disorder-epilepsy and providing brief but fundamental information on metabolism and pharmacodynamics of drugs during pregnancy. The core part of the manuscript, discussing each consecutive AEDs was extended by supplying information concerning the drug's chemical structure, mechanism of action and pharmacokinetics. The subparagraph on AEDs and folate supplementation was substantially expanded and new information on VPA impairing children cognitive development was included.

ANTIEPILEPTIC DRUGS

Carbamazepine (Carbatrol, Epitol, Equetro, Tegretol)

Definition and Common Uses—Carbamazepine (CBZ), IUPAC name 5H-dibenzo(b,f)azepine-5-carboxamide, $C_{15}H_{12}N_2O$ is an iminostilbene derivative with a carbamyl group at the fifth position. This moiety is vital for the anti-seizure functioning. It is primarily used clinically in the management of epilepsy and trigeminal neuralgia, and also in bipolar disorders. Previous research suggests that the anti-seizure activity of CBZ relies on its ability to limit the action potentials evoked by slowing the rate of recovery of the voltage activated sodium channels [Goodman and Gilman, 2004; McLean and McDonald, 1986]. Carbamazepine is erratically absorbed after oral administration. About 70% of the drug is bound to plasma proteins, and concentrations in the cerebrospinal fluid correspond to the unbound concentration of CBZ in plasma. Metabolism of this compound occurs predominantly in the liver by CYP3A4; its metabolite 10, 11 epoxide is also active. CBZ induces other subtypes of CYP450 and UDP-glucuronosyl transferase, enhancing the metabolism of other compounds.

During pregnancy, total concentration of CBZ levels have been shown to decrease approximately 25% and the decline of unbound levels is even more pronounced in the last trimester. In the first trimester, changes are not significant, but total plasma concentration and free plasma concentrations decrease slightly. The free fraction has been found to increase in a non-significant manner [Sabers et al., 2009; Tompson et al., 1994]

Animal Studies/Mechanism of Teratogenesis—Carbamazepine is one of the first generation antiepileptic drugs. The first study on the teratogenicity of carbamazepine failed to demonstrate any increase in fetal abnormalities when pregnant mice were treated with up to 250 mg/kg/day orally on gestational days 6-16 [Fritz et al., 1976]. Further studies showed

small increases in the rate of cleft palate, dilated cerebral ventricles and growth retardation in mouse foetuses that were similarly treated during the period of organogenesis [Eluma et al., 1981; Eluma, 1984; Paulson et al., 1979; Sullivan et al., 1977]. When mice were chronically exposed to CBZ in their diet prior to and throughout gestation, a significant number of fetuses with congenital defects of the central nervous system or urogenital system were observed [Finnell et al., 1986a]. In experiments comparing teratogenicity of CBZ with other anticonvulsant drugs, it was consistently less teratogenic than phenytoin or primidone [El-Sayed et al. 1983; Eluma et al., 1984; Sullivan et al., 1977]. In rats, CBZ was embryotoxic and teratogenic at doses of 400 and 600mg/kg [Vorhees et al., 1990]. Among the 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 lowest dose of 200 mg/kg did not induce any birth defects but reduced significantly the foetal body weight. The most recent study on mice injected intraperitonealy with low doses of CBZ (clinically relevant to a human dosage) during organogenesis produced fetuses with brachygnathia, calvarial deformity, vertebral deformity, short tail, and brachydactyly, as has been observed in previous studies. Additionally, significant numbers of foetuses presented with mild to severe exophthalmos [Afshar et al., 2010].

The mechanism by which CBZ exerts its teratogenicity remains largely unknown. The results of the study on Swiss-Vancouver (SWV) mice indicated that similar to phenytoin, CBZ could be biotransformed to a reactive teratogenic metabolite that might be responsible for the observed fetotoxicity [Finnell et al., 1995]. 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 [Lindhout et al., 1984]. This was confirmed in a study on pregnant mice where carbamazepine-10, 11-epoxide treatment significantly increased the incidence of malformations in foetuses [Bennett et al., 1996; Tecoma, 1999].

Human Epidemiological Studies—Observational studies have not been conclusive with respect to the teratogenicity of CBZ in pregnancy (Table I). Some epidemiological studies have found an increased risk of MCMs in the exposed offspring [Matalon et al. 2002; Tomson and Battino, 2009], while other have failed to find any statistically increased risk of malformations due to CBZ exposure [Harden et al., 2009]. The lowest risk for MCMs amongst all AED monotherapy exposures was reported in the study by Morrow and collaborators [2006], who examined 900 CBZ-exposed pregnancies, and reported 20 cases with MCMs, which is a prevalence rate of 2.2% (95%CI: 1.4-3.4). When dosage was compared between healthy and malformed infants, there was no statistically significant difference (p = 0.56), suggesting that genetic factors might be interacting with the CBZ exposure contributing to the risk of birth defects. In a meta-analysis including 4411 woman taking CBZ throughout their pregnancies, Meador and colleagues [2008] reported a MCM rate of 4.6% with a 95% CI of 3.48-5.76. When compared with the other frontline AEDs, the teratogenic potential of CBZ was significantly lower. Association between CBZ exposure and specific malformations has also been considered. Two studies have found *in utero* CBZ exposure to be associated with an increased risk of orofacial clefts. Hernandez-Diaz et al. [2007] reported a 24-fold increase of isolated oral clefts following exposure to CBZ during pregnancy, when compared with the prevalence in the control population (frequency of 0.19 out of 1000). Thomas and co-workers [2008] performed a study in an Indian population, finding that 6.3% of infants born to women maintained on CBZ monotherapy had cardiac malformations. Other studies have reported a frequency of MCM of 0.7% following CBZ exposure [Morrow et al., 2006], similar to what is expected in the general population [Hoffman and Kaplan, 2002]. The reader must be careful with the interpretation of these

data, as the reported prevalence of cardiac malformations is difficult to compare, due to differences in diagnosis and inclusion criteria in the published literature.

Phenytoin (Di-Phen, Dilantin, Phenytek)

Definition and Common Uses—Phenytoin (PHT), IUPAC name 5,5-diphenylimidazolidine-2,4-dione, $C_{15}H_{12}N_2O_2$ is a hydantoin derivative component which structure is similar to barbiturates, but it has minimal sedative effects. It has been used primarily to treat epilepsy. It is effective in partial and tonic-clonic seizures. PHT inhibits the repetitive firing of action potentials, by slowing the rate of recovery of the sodium channels. [Hardman et al., 2001]

About 90% of phenytoin is bound to plasma proteins, principally albumin. Minimal variations in the PHT that is bound to proteins change dramatically the absolute amount of the active –unbound- fraction of the drug, particularly in neonates. About 95% of the drug is metabolized in the liver by the CYP450 enzyme; and the principal product is a non-active metabolite, paraydroxyphenyl. The metabolism of PHT is saturable, because the rate of elimination is non-linear; it varies as a function of its concentration.

Studies show that during pregnancy, total PHT plasma concentration is significantly lowered in the first trimester, and continue decreasing as the pregnancy proceeds towards parturition. The free fraction of PHT maintains the same level during the first trimester, but varied significantly in both second and third trimesters, when compared to baseline concentrations [Tomson et al., 1994]. Early studies have shown that PHT can cross the placenta, and accumulates in placental tissue. [Kluck et al., 1988]

Animal Studies/Mechanism of Teratogenesis—Starting with Massey's initial investigation, phenytoin's teratogenic potential has been amongst the most widely studied of all of the AEDs [Massey, 1966]. Regardless of the route of administration, orally or parenterally, PHT adversely affects the process of embryogenesis in a number of different species, including the mouse, rat, rabbit, cat and monkey [Harbison and Becker, 1969, 1972; Khera, 1979; McClain and Langhoff, 1980; Mercier-Parot and Tuchmann-Duplessis, 1974]. Since the early human clinical studies reported an increase in the incidence of cleft lip and/or cleft palate among the offspring of epileptic patients, the vast majority of experimental studies on the teratogenicity of PHT have focused on the ability of this compound to induce orofacial clefts [Abela et al., 2005; Elshove, 1969; Finnell and Chernoff, 1984; Sulik et al., 1979]. Results of these studies showed that the lowest dose of PHT able to induce cleft palate in susceptible mouse strains was 12.5 mg/kg/day administered to the pregnant dam during the period of palate formation. In several experimental studies, birth defects other than cleft lip and/or cleft palate were observed. Harbison and Becker were the first to describe a variety of defects in mouse fetuses exposed to PHT during gestational days 8-15 [Harbison and Becker, 1969]. The exposed, affected fetuses were growth retarded, with shortened long bones and defective ossification of the sternebrae, some had kidney defects (hydronephrosis and renal hemorrhage); while others had, open eyes, ectrodactyly and internal hydrocephalus. A similar pattern of defects was reported by the same investigators in rat fetuses [Harbison and Becker, 1972]. 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 observed pattern of malformations were generally attributable to the differences in species or strain of the experimental animals, route of administration and dosages used in the various studies [Finnell et al., 1993; Fritz et al., 1976; McDevitt et al., 1981; Paulson et al., 1979].

In a chronic mouse exposure study, PHT added to drinking water prior to and throughout pregnancy resulted in a pattern of congenital defects in the offspring that was comparable to those observed in the human FHS [Finnell, 1981, Hanson and Smith, 1975]. 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. This pattern of malformations also included ossification delays of the distal phalanges, occiput, sternebrae, vertebral centrae and the bones of the midfacial region [Finnell, 1981]. 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 undertaken by 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. More specifically, an arene oxide metabolite produced enzymatically during the bioactivation of PHT by the cytochromes P450 may be the actual teratogenic molecule [Lum and Wells 1986; Martz et al., 1977; Wells and Harbison, 1980,]. Such oxidative metabolites are thought to occur prior to the formation of the dihydrodiol metabolite 5-(3,4-dihydroxyl, 5cyclohexadien- l-yl-5-phenylhydantoin) from PHT in a reaction catalyzed by the enzyme epoxide hydrolase [Chang et al., 1970]. Arene oxides are highly reactive compounds, and when the rate of their bioactivation exceeds the detoxification capacity of the organism, the electrophilic center of this molecule is capable of binding covalently to nucleophilic sites found in fetal macromolecules, such as nucleic acids [Jerina and Daly, 1974; Strickler et al., 1985]. These intermediate compounds produced in the maternal liver during the bioactivation of PHT may be sufficiently stable to cross the placenta and bind to fetal tissues. It is also possible that this molecule is being tautomerized to form a more stable oxepin, able to cross the placenta and then it isomerizes back to a reactive arene oxide intermediate [Wells and Harbison, 1980]. The arene oxide could actually also be bioactivated in the fetal liver [Blake and Martz 1980; Martz et al., 1977; Strickler et al., 1985]. An alternative mechanism for the PHT-induced congenital defects involves the co-oxidation of the drug to free radical intermediates centered in the hydantoin nucleus by prostaglandin synthetase [Wells and Vo, 1989]. As a result of such bioactivation, free radical intermediates may result in oxidative stress, initiate lipid peroxidation reactions and/or bind covalently to essential nucleic acids and proteins. This hypothesis is based on both *in vivo* [Wells and Vo, 1989] and *in vitro* [Kubow and Wells, 1989] studies. One study suggested that PHT can act through Ras-dependent signal transduction. In the whole embryo culture experiment with mouse embryos, it was demonstrated that inhibition of the K-ras oncogene protected the embryos from PHT-induced structural defects [Winn and Wells, 2002]. Lastly, it has been suggested that the oxidative intermediate of interest is one that is not sufficiently detoxified by enzymatic conjugation with reduced glutathione [Diepold et al., 1982, Moldeus and Jemstrom, 1983]. 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 [Lum and Wells, 1986]. When mice are pretreated with compounds that deplete natural stores of glutathione, such as diethyl maleate [Harbison, 1978] or acetaminophen [Lum and Wells, 1986], 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 [Winn and Wells, 1995]. In order to ameliorate the teratogenic effect of PHT in the *in vivo* and *in vitro* study, pregnant mice were treated simultaneously with PHT and stiripentol (a cytochrome P450 inhibitor) or 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 [Finnell et al., 1994, 1999].

Human Epidemiological Studies—The Fetal hydantoin syndrome (FHS) was initially described, in part, by Loughnan and colleagues in 1973 and expanded upon by Hanson and Smith, when they formally named the syndrome in 1975. 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 of the syndrome. Infants with FHS displayed facial dysmorphism including epicanthal folds, hypertelorism, broad depressed nasal bridge, an upturned nasal tip, wide prominent vermilion of the lips and additionally, digital hypoplasia, intrauterine growth restriction and intellectual disability. Subsequently, Hanson et al. 1976 reported a prevalence of FHS in 11% of exposed infants, with an additional 30% of the *in utero*-exposed children expressing some of the syndrome's features. It is now common to consider children presenting with a more limited pattern of dysmorphic characteristics secondary to *in utero* hydantoin exposure to be expressing fetal hydantoin effects [Hanson and Smith, 1986]. 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 [Kaneko et al., 1999; Meador et al., 2008; Vajda et al., 2006; Wide et al., 2004], while others failed to find such associations [Artama et al., 2005; Morrow et al., 2006; Vajda et al., 2007, 2012] (Table II).

Phenobarbital (Solfoton)

Definition and Common Uses—Phenobarbital (PB), IUPAC name 5-Ethyl-5-(1-methylbutyl)-2,4,6(1H,3H,5H)-pyrimidinetrione, $C_{11}H_{18}N_2O_3$ 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. However, owing to its low cost and effectiveness, it remains a front-line treatment for partial and general tonic-clonic seizures in many parts of the world. It is usually not very well tolerated, one of the reasons why other AEDs are usually preferred over this drug. PB is known of the sedative side effects and substantial slowing of cognitive functions. Absorption after oral administration is complete but slow in the gastrointestinal tract. Approximately 50% of the drug is bound to plasma proteins and tissues. The metabolism of PB is principally performed by the CYP2C9 (about 75%), which belongs to the P450 family of enzymes. The unmetabolized portion is eliminated through the kidneys. Phenobarbital induces hepatic metabolism, so other drugs can be more rapidly degraded when co-administered with PB [Hardman et al., 2001]. During pregnancy, total and unbound plasma concentrations of PB can decline 25 to 50% compared to baseline [Sabers and Tomson, 2009]. Phenobarbital is known to cross the placenta [Kluck et al., 1988].

Animal Studies/Mechanism of Teratogenesis—PB is the oldest AED (almost 100 years) in use; however, it was not broadly tested for its teratogenic potential until the mid-1970s. The initial study on mice demonstrated that orally administered PB during the period of organogenesis in subtoxic doses to pregnant dams induced cleft palates in a modest 4.3% of exposed fetuses [Fritz et al., 1976]. 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 be significantly teratogenic in all tested mice strains, resulting in skeletal, cardiac, renal, neural and urogenital defects in a dose-related fashion. The LM/Bc strain was the most sensitive to PB, with 46.7% of the fetuses exposed to the highest maternal plasma concentrations having malformations and C57BL/6J was the most resistant strain, with only

28.6% fetuses with abnormalities [Finnell et al., 1987a]. When the pattern of malformations induced by PB was compared with the teratogenic effects of PHT treatment on the same mouse strains, the results 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 [Finnell et al., 1987a, 1987b]. In neurobehavioral experiments on rats, PB exposure caused increased offspring mortality, impaired growth and delayed some aspects of postnatal motor development [Vorhees, 1983]. The mechanism of PB teratogenicity remains largely unknown. It was demonstrated that PB upregulates cytochrome P450s of the 2B family and produces oxidative stress through the generation of superoxide radicals [Waxman and Azaroff, 1992]. These, in turn, led to the production of hydroxyl radicals, resulting in the formation of 8-oxodeoxyguanine that results in GC to TA transversions. Results of another study confirmed that chronic feeding of oxazepam and PB upregulates CYP2B [Griffin et al., 1996]. These findings suggest that PB-induced oxidative stress may be responsible for the observed developmental defects.

Human Epidemiological Studies—The rate of MCM induced by PB monotherapy exposure during pregnancy is shown in Table III. In 2004, Holmes and colleagues found an increased risk for MCM in the offspring of 77 WWE maintained on PB monotherapy for seizure control. Meador et al. [2008] reported a MCM rate of 4.9%, which was found to be higher than the MCM rate in women treated with CBZ, but lower than those found in groups exposed to PHT and VPA. Earlier studies did not find a significant risk for MCMs [Samren et al., 1999].

Three different studies have reported that the number of malformations of cardiac origin associated with PB monotherapy constitute between 60 to 66% of the total of MCM that have been found to be associated with *in utero* exposure to this drug [Holmes et al., 2001, 2008; Samren et al., 1999]. Thomas et al. [2008] documented that in 43 monotherapy exposures to PB during pregnancy; only three infants had a congenital heart defect. No statistical significance was found between healthy PB-exposed infants versus PB-exposed infants that had a congenital heart defect. Results of the studies mentioned above indicate that the association between cardiac defects and PB, if any, appears to be weak and further studies with larger sample sizes are needed to evaluate the teratogenicity of PB.

Valproic Acid (Depakene, Depakote, Epilim, Stavzor)

Definition and Common Uses—Valproic acid (VPA), IUPAC name 2-propylpentanoic acid, $C_8H_{16}O_2$ also known as 2-propylvaleric acid, has been used primarily as a wide-spectrum anticonvulsant and mood stabilizing drug, but recently its use has been expanded as a prophylactic agent in the control of migraine headaches, and as a first line drug in certain types of schizophrenia. Valproate's mechanism of action is believed to be mediated by its ability to inhibit sustained repetitive firing induced by depolarization, by increasing the recovery of voltage-activated sodium channels. It also reduces the low-threshold calcium current (T), making it effective in tonic-clonic, partial, myoclonic, and absence seizures. VPA is rapidly absorbed in the gastrointestinal tract, and is highly bound to plasma proteins (90%). While most of the drug undergoes hepatic metabolism through the uridine diphosphate glucurunosyltransferase enzyme, and β-oxidation, it also induces, at a lesser extent, the CYP2C9 and CYP2C19 enzymes. Less than 5% of VPA is excreted unchanged [Hardman et al., 2001]. During pregnancy, total plasma concentration of VPA can decrease from 25 to 50%, but the concentration of the unbound, active drug tends to remain unchanged [Sabers and Tomson, 2009].

Animal Studies/Mechanism of Teratogenesis—The embryotoxic/teratogenic properties of Valproic acid (2-propylvaleric acid) have been studied in several animal model systems (zebrafish, *Xenopus*, chicken, mouse, rat, hamster, gerbil, rabbit, dog and rhesus monkey) *in vivo* and *in vitro* (mouse ES cells) for over 40 years [Gurvich et al., 2005; Hsieh et al., 2012; Nau and Hendrickx, 1987; Riebeling et al., 2011]. 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 abnormalities in the skeletal system. Abnormal number or shape of ribs, vertebrae, number of ossification points in the digits or abnormal ossification of craniofacial bones were the most frequently reported. 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 [Petrere et al., 1986]. Beside skeletal defects, high doses of VPA also induced craniofacial, skeletal and cardiac defects as well as intrauterine growth retardation in rhesus monkeys [Hendrickx et al., 1988]. Laboratory rodents exposed to VPA often present with defects of the central nervous system that are also observed in human studies. VPA treatment during early neural tube formation (E8 in the mouse) results in exencephaly, which is the rodent equivalent of human anencephaly. Others reported that spina bifida can be induced in some mouse strains when injected three times at 6-h intervals on E9 [Ehlers et al., 1992; Emmanouil-Nikoloussi et al., 2004; Finnell et al., 1988; Menegola et al., 1996]. Pharmacokinetic study showed that VPA can induce neural tube defects in exposed mouse embryos when this drug reaches maternal plasma concentrations of 225 μg/ml, irrespectively of the route of administration [Nau, 1985]. This drug concentration is between two- and five-times the desired human therapeutic level [Niedermeyer, 1983]. In a study demonstrating differential mouse strain sensitivity to VPA induced birth defects, Finnell and colleagues found that both VPA and its 4-propyl-4-pentenoic acid metabolite (4-en-VPA) are capable of producing exencephaly in mouse embryos when the dam was exposed to a single intraperitoneal injection on E8.5 [Finnell et al., 1988]. These different strains of mice displayed a widely differing sensitivity to the induction of NTDs, suggesting that the induced malformation has a strong genetic component [Finnell et al., 1986b, 1988]. Morphological observation of mouse embryos exposed to VPA at E8.5 revealed an altered pattern of neurulation that is due to the interaction of as yet unknown genetic factors and VPA. Nau and Hendrickx [1987] examined various analogs and metabolites of VPA and determined that strict structural requirements must be met for the compound to exert a teratogenic effect. To be teratogenic, the compound must have the following: a free carboxyl group, an a-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 [Nau and Loscher, 1986]. 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 [Finnell et al., 1988]. This high specificity of the teratogenic response of VPA differs from the broad, generalized specificity of its antiepileptic activity, suggesting that the two mechanisms of action are unrelated [Nau and Loscher, 1986]. 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 non-teratogenic and non-hepatotoxic [Bialer, 1999]. In a comparative teratogenicity studies several VPA analogs and stereoisomers were tested on mice showing variable teratogenic potential dependent on the chemical structure [Kaufmann et al., 2010; Pessah et al., 2010; Shimshoni et al., 2008; Sobol

et al., 2006]. A number of 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-formyl-tetrahydrofolates. 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 [Wegner and Nau 1992]. 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 [Alonso-Aperte, 1999]. More recently, it has been proposed that histone deacetylases (HDACs) are direct targets for VPA [Gottlicher et al., 2001; Phiel et al., 2001]. HDACs induce transcriptional repression by deacetylating lysine residues on histone tails which leads to chromatin condensation. Several studies showed that 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 et al., 2006; Di Renzo et al., 2007]. 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 [Menegola et al., 2005]. 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 H4 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 IC50 (HDAC) and the teratogenic potential of VPA derivatives demonstrated in this study, clearly points toward HDACs as the teratogenic receptors of VPA-induced NTDs [Eikel et al., 2006]. 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 [Wiltse, 2005].

Recently, the HDAC activities of VPA derivatives were investigated by estimating histone H3 acetylation in L-cells by immunoblotting. Changes in histone H3 acetylation levels induced by exposure to VPA and several VPA derivatives of varying teratogenic potential were performed after 24-hr incubations with 1 mM of the test compounds. It was found the three strongest teratogens (i.e. butyl-, pentyl- and hexyl-4-yn-VPA) significantly increased the degree of histone H3 acetylation [Gotfryd et al., 2011]. These investigators observed a highly significant linear correlation between the teratogenic potencies of the test compounds and their effects on histone H3 acetylation (n = 42, R^2 = 0. 5080, $p < 0.0001$) [Gotfryd et al., 2011].

Human Epidemiological Studies—Data from pregnancy registries and prospective studies revealed an increased risk of MCMs in the offspring of pregnant women with exposure to VPA during the first trimester of pregnancy. The types of birth defects most often reported in valproate exposure during pregnancy are: neural tube defects, orofacial clefts, congenital heart defects, hypospadias, and skeletal abnormalities [Werler et al., 2011]. Morrow reported that for 715 valproate monotherapy exposures, 1% of the pregnancy outcomes were NTDs, 1.5% orofacial clefts, 0.7% congenital heart defects, 0.9% hypospadias and/or genitourinary tract defects, 0.5% gastrointestinal tract defects and 1.1% skeletal defects [Morrow et al., 2006]. In a Finnish cohort of 7500 births, monotherapy with

VPA had a prevalence of MCM of 5.4% as opposed to 2.8% for untreated mothers, with an odds ratio (OR) of 1.98 (95% CI: 1.53-2.55) [Artama et al., 2006]. In the North American Pregnancy Registry, Wyszynski and colleagues [2005] reported major malformations in 10.7% of VPA-monotherapy exposed infants versus 2.9% from monotherapy exposures to other AEDs different than VPA. Data from the Australian Pregnancy Registry described MCMs following VPA exposure in 17.1% of the infants versus 2.4% MCMs presumably caused by exposure to other AEDs [Vajda and Eadie, 2005]. Meador and collaborators published a meta-analysis that revealed that gestational valproate was associated with a 10.7% (95%CI: 8.16–13.29) risk of MCMs. The UK Pregnancy Registry had three-times as many MCM cases from VPA exposure as from CBZ (6.2 versus 2.2%) [Morrow et al., 2006], and the International Lamotrigine (LMT) Pregnancy Registry found 12.5% MCMs when mothers received LMT polytherapy with valproate versus 2.7% MCMs from other LMT polytherapy regimens without valproate [Cunnington and Tennis, 2005]. Most recently, the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) Study Group confirmed both an increased risk of adverse fetal outcomes (MCM or death) and the dose-dependent effect of VPA in a prospective study (20.3% with VPA as opposed to 10.7% with PHT, 8.2% with CBZ and 1% with LMT) [Meador et al., 2006].

In addition to those previously well documented congenital malformations, more recently VPA has been also shown to impair the cognitive development of *in utero* exposed children [FDA safety announcement 2011]. In a retrospective study of children aged 6 or greater born to epileptic mothers in the United Kingdom, it was shown that prenatal exposure to VPA was associated with a lower verbal intelligence quotient (IQ). This study failed to find such an association with *in utero* phenytoin or carbamazepine exposure [Adab et al., 2004]. The follow up study of the same cohort of children confirmed that exposure to VPA *in utero* was associated with poorer adaptive behavior and a higher rate of maladaptive behaviors. These children were compromised with respect to daily living skills and skills relating to socialization [Vinten et al., 2009]. Similar results published by Meador and colleagues from prospective, international study on three year old children, showed that *in utero* exposure to valproate was associated with an increased risk of impaired cognitive function relative to other frontline AEDs [Meador et al., 2009 and 2011]. In an observational study of children less than two years of age, it was demonstrated that children prenatally exposed to VPA were at an increased risk of delayed early cognitive development when compared to control non-VPA exposed children, or children exposed to LEV [Shallcross et al., 2011]. Even though all of the epidemiological behavioral studies had several limitations (e.g., small number of children in each group, confounding factors, subjective rating scale, and involvement of parents susceptible to bias) that limit generalization of the results, they all clearly indicated that VPA was a behavioral teratogen.

In summary, studies have consistently observed that *in utero* exposure to VPA causes a significant dose-dependent increased risk of both anatomical and behavioral teratogenic effects (Table IV). It is suggested that the risk of MCMs significantly increases at 600 mg/day, with the largest attributable risk observed at doses that exceeded 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 highly sensitive individuals [Diav-Citrin et al., 2008].

Lamotrigine (Lamictal)

Definition and Common Uses—Lamotrigine (LMT), IUPAC name: 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine, $C_9H_7C_{12}N_5$ is a phenyltriazine compound thought to act by inhibiting the release of glutamate acting in the voltage dependent sodium channels [Leach et al., 1986]. It was initially developed as an antifolate agent under the

erroneous hypothesis that antagonizing folate would effectively inhibit seizures. The use of LMT as an AED, and also as a neuromodulator in mood disorders has been increasing worldwide over the past few years. LMT is a wide-spectrum AED; its mechanisms of action include blocking the sustained and repetitive firing of mouse spinal neurons, and the delay of recovery from inactivation of recombinant sodium channels. Recent studies demonstrated that LMT increased significantly the voltage threshold and increased the action potential attenuation during repetitive firing in CA1 rat brain slices, suggesting that the molecule might as well be acting as a sodium channel blocker [Englund et al., 2011; Hardman et al., 2001].

After oral administration, LMT is absorbed completely in the gastrointestinal tract and metabolized through glucuronidation in the liver. The kinetics of this drug is highly unstable in pregnant women, and can be easily influenced by the co-administration of other drugs. Enzymatic induction of the N-2 glucuronide pathway has been found to be significantly increased during pregnancy [Ohman et al., 2008], and after the 32nd week of gestation, clearance of LMT can be even three times higher than it was before pregnancy. The total plasma concentration of LMT during pregnancy can decrease more than 50% [Sabers and Tomson, 2009].

Animal Studies/Mechanism of Teratogenesis—When pregnant rats were treated with LMT from gestational day 14 to 19 (the neuronal migration stage), the pathological evaluation of 30-day postnatal pups revealed dose-dependent alterations in the neocortex and hippocampus. High doses of LMT (20 mg/kg/day) were maternally toxic, reducing maternal weight gain by approximately 20% and embryotoxic significantly reducing 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. The observed hippocampal and cortical malformations induced by prenatal exposure to LMT were dose-dependent. Moreover, these effects were found at plasma LMT concentrations that are within the human therapeutic range for this drug [Manent et al., 2008]. In two studies on pregnant TO mice administered with LMT (Lamictal, Wellcome Co., UK) via either a single intraperitoneal injection (50-300 mg/kg) or three doses (25-75 mg/kg) on gestation day 7 or 8, a high incidence of abortions and a significant decrease in maternal body weight as well as maternal mortality 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. It should be noted that the observed effects were most likely secondary to the severe maternal toxicity observed in the treated dams [Bastaki et al., 2001; Padmanabhan et al., 2003]. One study has reported a folate-mediated rescue of LMT-induced cleft palate [Prakash et al., 2007].

Human Epidemiological Studies—Some recently available evidence suggests that exposure to LMT could be increasing the risk of orofacial clefts in the offspring of women exposed to this drug in the first trimester of pregnancy. Holmes and colleagues [2008] found that prenatal LMT exposure in both monotherapy and polytherapy regimens produced a 10.4-fold increased risk when compared to controls. Findings suggested that there was a particular high risk of having an infant with an isolated cleft palate. Careful interpretation of this data is important, as outcomes reported can be biased when the analyses include polytherapy regimens as well as monotherapy exposures. Clearly, the polytherapy regimens are more likely to be associated with a higher prevalence rate of birth defects when compared to the prevalence of monotherapy exposures in AEDs other than VPA. On the contrary, Hunt and coworkers analyzed the effect of LMT monotherapy in 1151 exposed pregnancies in the United Kingdom, finding only a single case of isolated cleft palate [Hunt et al., 2009].

Morrow and collaborators [2006] analyzed 647 LMT-exposed pregnancies and found that prenatal exposure to this drug produced fewer MCMs than what was observed with monotherapy exposure to VPA. The MCM rate for LMT exposures was 3.2%, with an OR of 1.44 (95%CI 0.77-2.67) vs. 3.5% of the control unexposed reference group, and the rate of VPA-induced MCMs was 6.2%, with an OR of 2.78 (95%CI 1.62-4.76). The same authors found that LMT doses were remarkably higher in the cases of pregnancies complicated with major birth defects, than that observed in the non-birth defect affected pregnancies [Morrow et al., 2006]. However, the study was insufficiently sensitive to exclude a substantially increased risk of MCM, RR of 0.9 (95%CI: 0.41-2.05) [Harden et al., 2009].

The extent of LMT's teratogenicity remains inconclusive, but some of the limited existing data suggest that LMT is less teratogenic than either valproic acid or phenytoin [Meador et al., 2008; Vajda et al., 2006, 2010]. Interpretation of this data is compromised by methodological difficulties, such as small study sample sizes and uncontrolled clinical trials, as it is for AEDs in general (Table V). 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 VPA and no more hazardous than other commonly used anticonvulsants (Vajda et al., 2010). 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. Also, changes in the use of AEDs in women of reproductive age, where LMT use has been slowly increasing over the use of valproate, will help us clarify the risk-benefit of this drug in the context of maternal and fetal health.

Levetiracetam (Keppra)

Definition and Common Uses—Levetiracetam (LEV), IUPAC name (S)-2-(2-oxopyrrolidin-1-yl)butanamide, $C_8H_{14}N_2O_2$ is a pyrrolidine, the racemically pure S-enantiomer of α-ethyl-2-oxo-1-pyrrolidineacetamide [Hardman et al., 2001]. The use of LEV as a broad-spectrum AED has been increasing of late. The mechanism of action of this drug is not fully understood. Several studies have identified a binding site in the central nervous system, the synaptic vesicle protein 2A, which seems to boost neurotransmission by increasing the number of secretory vesicles [Gillard et al., 2003; Lynch et al., 2004]. Unfortunately, the role of LEV as an antiepileptic agent is unclear. In rat hippocampal tissue, LEV has been found to induce significant expression of proteins that were involved in cytoskeleton, energy metabolism, neurotransmission, signal transduction, myelinization, and stress response.

LEV is absorbed in the gastrointestinal tract, and primarily excreted through the urine. One-fourth of the dose is metabolized by hydrolysis of the acetamide group. The majority is eliminated unchanged through the kidney. LEV does not appear to have pharmacokinetic interactions with other AEDs. In the third trimester of pregnancy, total plasma levels of LEV can be significantly reduced up to 50%. Studies have demonstrated that LEV crosses the placenta in a considerable manner, and has a slow elimination in the neonate. Despite these facts, the LEV concentration declines effectively after birth with no evidence of accumulation in the exposed newborns [Tomson et al., 2007].

Animal Studies/Mechanism of Teratogenesis—Levetiracetam and its main metabolite in humans, 2-pyrrolidone-N-butyric acid (PBA) were tested on pregnant SWV mice. The dams were injected daily on gestation days 8-12 intraperitoneally, with the dose of 600, 1200 and 2000 mg/kg of LEV or 600 and 1200 mg/kg of PBA. The highest LEV doses significantly increased the resorption rate and reduced the fetal weight; however, no

significant gross external malformations were observed in any of the treatment groups. In both PBA treated groups and in the intermediate 1200mg LEV group, the incidence of skeletal abnormalities, specifically hypoplastic phalanges, was significantly increased. Results of this study demonstrate that both LEV, and its major human metabolite, PBA, do not induce major structural malformations in developing SWV embryos [Isoherranen et al., 2003]. Similar results were observed in experiments on rats and rabbits [Thomson/ Micromedex, 2007]. Increased skeletal abnormalities were observed in rats treated with at least 350 mg/kg/day throughout gestation, as well as in fetuses from dams that were exposed to 3600 mg/kg/day only during organogenesis. In the LEV study on rabbits, only in the group treated with at least 600 mg/kg/day during organogenesis an increased frequency of skeletal defects was detected. *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.

Human Epidemiological Studies—The use of LEV and LMT are substantially increasing in WWE of reproductive age, probably owing to their good efficacy coupled with a high level of tolerability, and the general belief that these drugs may be safer than the older AEDs. However, the teratogenic effects of LEV are virtually unknown [Hunt et al., 2009; Meador et al., 2009] (Table VI). The largest study to date of pregnancy outcomes of women receiving LEV monotherapy treatment in pregnancy was performed by Holmes and collaborators [2008] using data from the North American Epilepsy Registry. Analysis of 197 women reported a rate of MCM of 2.03% in pregnancies exposed to this compound in the first trimester [Holmes et al., 2008].

Topiramate (Topamax, Topiragen)

Definition and Common Uses—Topiramate (TPM), IUPAC name 2,3:4,5-Bis-O-(1-methylethylidene)-beta-D-fructopyranose sulfamate, $C_{12}H_{21}NO_8S$ 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 [Öhman et al., 2009]. The pharmacokinetics of this drug cannot be predicted in all patients, making it necessary to carefully monitor plasma levels of TPM when utilized during pregnancy. Following oral administration, TPM is absorbed rapidly. In blood, this compound is highly bound to erythrocytes and not plasma proteins. Despite the identification of six metabolites that resulted from hydroxylation, hydrolysis, and glucuronidation, this compound mostly undergoes renal elimination in the form of the unchanged molecule [Lyseng-Williamson and Yang, 2007]. A recent study demonstrated that in pregnant New Zealand white rabbits, TPM half-life was significantly increased, and clearance was significantly decreased, both measured in late stages of pregnancy [Matar and Marafie, 2011]. Öhman and colleagues [2009] found significant changes in TPM kinetics during pregnancy, reporting an increased dose/concentration ratio in the two last trimesters of pregnancy (80%), which corresponds to a decrease in TPM concentration of approximately 40%. Despite these changes, investigators could not establish a correlation between decreased TPM concentration and deterioration of seizure control.

Animal Studies/Mechanism of Teratogenesis—Very limited scientific information on the teratogenicity of TPM is available from the online sources or scientific literature. According to the TOXNET database for the healthcare professional (toxnet.nlm.nih.gov), TPM induced an increased incidence of malformations (primarily craniofacial defects) in fetuses from pregnant mice treated orally during the period of organogenesis with TPM doses of 20, 100 and 500 mg/kg. The highest dose of 500mg/kg was associated with a slight degree of maternal toxicity, which may have contributed to the decrease body weight gain.

This dose of TPM also induced a reduction of fetal body weights and delayed the process of skeletal ossification. The results from the studies on rats were to some extent similar to those reported on mice. 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. In the offspring of dams treated with TPM 400 mg/kg or more during the period of organogenesis, the frequency of limb malformations (ectrodactyly, micromelia and amelia) was increased. Fetal toxicity (reduced fetal body weights and increased incidence of structural variations) was observed at doses as low as 20 mg/kg. Rabbits were more sensitive to TPM treatment than were rodents. The dose of 35mg/kg induced embryonic and fetal mortality. Rib and vertebral malformations were observed at the dose of 120mg/kg. Evidence of maternal toxicity (decreased body weight gain, clinical signs and/or mortality) was seen at doses of 35 mg/kg and above [Thomson/Micromedex, 2007]. In the most recent study of TPM on rats treated with 40, 100 and 200mg/kg orally on gestational days 8-12, limb malformations similar to those reported in previous studies were observed. Specifically, flexion deformities, syndactyly, ectrodactyly, and brachydactyly, as well as missing carpal and metacarpal bones were reported. Additionally, pathological changes were observed in the placentas such as extensive hemorrhages and deposition of the fibrinoid, which increased the thickness of the placental barrier [Mishara and Singh, 2008].

Human Epidemiological Studies—Data of TPM teratogenicity are remarkably limited (Table VII). Two studies have reported an increased risk for specific birth defects in association with TPM exposure during pregnancy. Firstly, Hunt et al. [2008] reported 70 TPM monotherapy exposures 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) if TPM was used in a polytherapy regimen. Four of the total MCMs observed in both monotherapy and polytherapy regimens were oral clefts (two on monotherapy). The prevalence rates of oral clefts (2.2%) and hypospadias (5.1%) were respectively 11 and 14 times higher with TPM exposure than the background rates for these malformations in the United Kingdom (1 in 500 and 1 in 300 live births, respectively). The confidence intervals in this study are wide and the number of cases at this time is insufficient to draw strong conclusions of the effects of prenatal exposure to TPM. Nevertheless, the trend is difficult to ignore. The second study was published by Holmes and collaborators in 2008, where a statistically significant increased rate of MCM was present in 197 enrolled TPM-exposed pregnancies, (4.1%: 95%CI: 1.9-7.6) and a RR of 2.5 when compared to controls (Rate of 1.62%). Cases included a range of common birth defects, including two infants affected with cleft lip.

Recent data from the North American AED pregnancy registry reported a prevalence of MCM of 3.8% in 289 women exposed to TPM in the first trimester of pregnancy, versus 1.3% in the unexposed reference group. The authors also reported an increased risk of TPM exposed infants to have cleft lip, with a prevalence of 0.65% when compared with the expected prevalence for isolated cleft lip of 0.07%. [Hernandez-Diaz et al., 2010]. There were a number of studies that failed to find a risk of MCM in monotherapy exposures to TPM in pregnancies, and other unbalanced risk factors might as well be influencing these outcomes. [Morrow et al., 2006; Ornoy et al., 2008]. Nonetheless, as of March, 2011, the FDA considers TPM to be a Category D drug, based upon new data demonstrating an increased risk for cleft lip and cleft palate in babies born to women who use the medication during pregnancy.

It has been suggested that gestational exposure to AEDs might influence birth weight [Ornoy et al., 2008] for live born infants exposed to TPM in monotherapy. While the mean birth weights were within normal limits; 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. This observation has not yet been

validated in other studies [Montouris et al., 2003; Hunt et al., 2008]. A more recent study also reported that TPM-exposed neonates presented a higher prevalence of low birth weight in non-malformed liveborn singletons (9.8%), than controls (3.6%), evidencing a RR of 2.7 (95%CI: 1.4-5.1). In the same study, reports of LMT and CBZ fail to demonstrate an increased risk for either MCM or low birth weight (<2500gm) compared to the control unexposed reference group [Hernandez-Diaz, 2010].

Remaining concern exists over the possibility that TPM may increase the risk of oral clefts and hypospadias. Further, 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, and if possible, use of safer AED in women of reproductive age should be addressed.

Gabapentin (Fanatrex, Gabarone, Gralise, Horizant, Neurontin)

Definition and Common Uses—Gabapentin (GBP), IUPAC name 2-[1-(aminomethyl)cyclohexyl]acetic acid, C9H17NO2 is a water-soluble molecule that is structurally similar to the neurotransmitter gamma amino butyric acid (GABA), but covalently bound to a lipophilic cyclohexane ring. It is indicated for post-herpetic neuralgia and partial seizures with or without generalization in adults, and commonly used in partial seizures in children. The anti-seizure mechanisms of action are not well understood. It has been described that GBP increased the non-activating cation current (IH) in the pyramidal neurons in the hippocampal area CA1, through a cAMP-independent mechanism, producing a decreased dendritic excitability of the neurons, and interneurons It also inhibits high-voltage calcium channels in central neurons in the rat brain. [Peng et al., 2011; Stefani et al., 1998; Surges et al., 2003].

GBP is almost completely absorbed after oral administration, and undergoes renal excretion in the form of the unchanged metabolite. It does not alter other drug concentrations. Unfortunately there is no data available that describe accurately the pharmacokinetics of GBP during pregnancy.

Animal Studies/Mechanism of Teratogenesis—Study on IRC mice treated with GBP during pregnancy demonstrated a statistically significant increase in the resorption of fetuses in groups of mice exposed to GBP during early pregnancy (gestation days 1-6) and mid-gestation (gestation days 7-12). This embryotoxic effect was observed in mice treated with all tested GBP doses (113, 226, and 452 mg/kg body weight per day). In addition, the length and weight of mouse fetuses decreased significantly with the administration of GBP during mid- and late-gestation (gestational days 13-17). Various gross malformations were observed with all the three doses when gabapentin was administered at mid-gestation (7-12). The 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. The mid-gestation exposure significantly affected the developing brain. The highest dose of GBP caused reduced brain weight with vacuolization of the brain cortex [Prakash et al., 2008]. In another study on Balb/C mice treated with lower doses of GBP (25 and 50 mg/kg/day intraperitoneally) throughout the pregnancy (gestational days 1-15), growth retardation and increased resorption rates in fetuses from treated groups was recorded. Gabapentin also induced gross malformations including: exencephaly, limbs defects, brachygnathia and vertebral column deformity. Skeletal malformations included delayed ossification, scoliosis, calvaria deformity, and mandibular hypoplasia [Afshar et al., 2009].

Human Epidemiological Studies—Human studies with reliable GBP exposure levels are limited and universally inconclusive (Table VIII) [Harden et al., 2009; Morrow et al.,

2006]. Montouris et al. evaluated 44 pregnancies with exposure to GBP in both, monotherapy and polytherapy regimens. Two MCMs were found for a rate of 4.5%. In this study, only 17 cases were exclusively on monotherapy, and of those, only one infant was found to have a MCM (unilateral renal agenesis). In this particular case, GBP was changed at 16 weeks of gestation to phenobarbital (PB), which makes it difficult to associate GPB exposure as the unique compound potentially involved in the etiology of the unilateral renal agenesis. The other case consisted of an infant with hypospadias, but the patient was exposed to both valproate and GBP, and polytherapy itself, particularly with valproate has been associated with an increased risk of teratogenic potential. [Montouris, 2003].

Morrow et al. [2006] 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 significantly different when compared to the expected rate in the general population. ($p = 0.782$). Further research is needed to understand the physiology of this compound during pregnancy, and its potential teratogenicity in humans –if any.

Vigabatrin (Sabril)

Definition and Common Uses—Vigabatrin (VGB), IUPAC name (RS)-4-aminohex-5-enoic acid, $C_6H_{11}NO_2$ is an enzyme-activated, irreversible inhibitor of GABA transaminase that enhances brain GABA neurotransmitter levels. It is one of the most recent FDA approved drugs for the treatment in epilepsy [French, 1999] Careful and specific uses must be taken into consideration due to the documented visual loss resulted from the transport of this drug to the retina. Approximately 30% of adults that have received this medication suffer from concentric bilateral visual loss. VGB has been shown to be effective in the treatment of infantile spasms, and as a coadjuvant medication in refractory epilepsy [Chong and Bazil, 2010]. Vigabatrin is not known to significantly interact with other drugs. It is rapidly absorbed after oral ingestion, and in plasma it is usually not bound to proteins. Cerebrospinal fluid levels of this drug are 10% of plasma levels after 6 hours of ingestion, and the elimination of VGB is mainly through the kidney [Rey et al., 1992].

Animal Studies/Mechanism of Teratogenesis—The teratogenic potential of 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 treated mice but no signs of maternal toxicity were observed with the lower doses. 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 [Abdulrazzaq et al., 1997]. When the pregnant mouse dams were injected intraperitoneally with 450 mg/kg of VGB in early gestation (gestation days 1, 3 or 5), similar results were observed. Growth retardation, presence of cervical ribs and sternum abnormalities as well as general delayed skeletal system ossification process were reported [Padmanabhan et al., 2008]. Reproductive toxicity studies with Vigabatrin were also conducted on rats. Pregnant dams were treated with 200mg VGB/kg/day on gestational days 14-19. In the brain of exposed fetuses, VGB induced hippocampal and cortical dysplasia, which was likely to result from a neuronal migration defect and neuronal death. Similar brain pathologies were observed in rat fetuses exposed to VPA, suggesting that this may be a common mechanism for the deleterious effects of AEDs that act on GABA signaling with respect to fetal brain development [Manant et al., 2007]. In a more recent, extensive study in mice, it was shown that VGB

administered at a relatively low non-toxic dose to dams (350 mg/kg) resulted in an increased fetal loss and intrauterine growth retardation when exposure occurred during late gestation [Padmanabhan et al., 2010].

Human Epidemiological Studies—Exposure to VGB during adulthood produces an irreversible visual field loss in 30-40% of users [Eke et al., 1997], thus it is generally only used in patients with refractory epilepsy. Very little data concerning teratogenicity of this drug have been published, and reported teratogenic outcomes from monotherapy exposures to VGB have been inconsistent. Sorri et al. [2005] reported two cases of children with VGB exposure with malformations, but both mothers were also receiving other AEDs during pregnancy (CMZ and VPA). Lawthom et al., 2009 reported no visual implications in four children with in utero exposure to VGB. 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.

ANTIEPILEPTIC DRUGS and FOLIC ACID SUPPLEMENTATION

Treatment with most commonly used AEDs is associated with reduced serum folate levels and the individual may be at risk for hyperhomocysteinemia [Hiilesmaa et al., 1983 Lewis et al., 1995; Linnebank et al., 2011]. Since maternal folate level normally decline during pregnancy, use of AEDs may further increase the risk of folate deficiency. Multiple studies indicated that there is a link between the use of AEDs and serum folate level in pregnant women [Dansky et al., 1987; Munoz-Garcia et al., 1983; Ogawa et al., 1991]. Such studies revealed that there is an inverse correlation between folate and several AEDs blood levels. Significant groups of patients receiving AEDs had serum folate level below the normal physiologic range (4-15ng/ml), and pregnant women taking multiple anticonvulsants tended to have an increased risk for folate deficiency compared with those receiving monotherapy [Dansky et al., 1987]. These studies also demonstrated that folic acid supplementation enabled women taking AEDs to regain normal serum folate concentration.

Since it remains one of the most often prescribed of all AED, and given that valproic acid (VPA) is known to disrupt folate metabolism, it was logical to expect that supplementation with folic acid would ameliorate the teratogenic effects of this drug in the prenatally exposed infants. However, a growing literature has consistently been reporting the lack of any benefit in terms of protection from NTDs derived from folic acid supplementation in women receiving VPA therapy during pregnancy [Candito et al., 2007; Craig et al., 1999; Pittschieler et al., 2008]. As recently reviewed by Ornoy and colleagues [2009], there is no evidence to demonstrate that the risk of NTDs can be further reduced by folic acid supplementation in women taking VPA, a position previously articulated by Yerby and co-workers [2003]. Similar findings, concerning other AEDs known to disrupt folate metabolism has been also reported [Hernandez-Diaz et al., 2000]. In that study, daily folic acid supplementation of approximately 0.4 mg failed to reduce the risk of fetal malformations in women taking: carbamazepine, phenobarbital, phenytoin or primidone, even though it was beneficial in women taking other folic acid inhibitors. 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 [Nambisan et al., 2003]. Therefore, it

remains unclear whether a periconceptional dose of folic acid greater than 0.4 mg daily might be beneficial for women that are using AEDs. Morrell states that as there is no direct evidence that folic acid supplementation protects 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' [Morrell, 1998]. In summary, while low folate levels have been associated with an increased risk of major congenital malformations in women taking AEDs [Yerby et al., 2003], the majority of studies examining folic acid supplementation have found no decrease in risk, particularly for VPA [Jentink et al., 2010; Kaaja et al., 2003, Kjaer et al., 2008; Morrow et al., 2009].

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, all women of reproductive age should be recommended to take daily 0.4 mg of folic acid supplementation.

Unlike the human situation, in experimental animal models there does appear to be some beneficial influence of folate supplementation in mitigating the teratogenic effects of select AEDs. In a recent study, mice treated with relatively high doses of VGB (350 - 450 mg/kg) during late gestation demonstrated not only substantially reduced serum folate level, but also significant increases in fetal death and intrauterine growth retardation (IUGR) as well as abortions of fetuses [Padmanabhan et. al., 2010]. However, when the VGB treated dams were supplemented with folinic acid, their folate concentrations returned to normal levels and there were no abortions and the incidence of IUGR was significantly decreased. Although these results are very encouraging, one must remember that direct extrapolation between species is very complex and difficult. Mouse and human does share some anatomical and physiological features but they also differ greatly in e.g.: absorption, metabolism, pharmacokinetics, excretion, placenta structure and many other aspects. Further research is clearly needed to understand if supplementation with folic acid or other forms of folate may be effective in the prevention of antiepileptic drug-induced teratogenesis.

CONCLUSIONS

The principal issue is how to effectively manage pregnancies in women who must be maintained on AEDs, irrespective of the indication, during the entire length of their pregnancy. It is of considerable difficulty to provide general guidelines that can be applied to all women taking these medications, due to the varied clinical manifestations of epilepsy and differences among individual patients. There are a few important principles that the primary caretakers managing the health of the prospective mothers should try to follow, based on the premise that seizures should be adequately controlled during pregnancy.

The first principle is to try to avoid polytherapy whenever possible in the management of women of reproductive age that are at risk of getting pregnant. Although the latest results from registry data are not as dire as they were in the past, polytherapy, meaning two or more AEDs, pose a greater risk to the developing embryo.

The second principle is that as long as any AED must be taken during pregnancy, there is *no absolute safe dose* that will provide therapeutic efficacy without the potential risk of inducing developmental or structural defects in the exposed infant. While evidence suggests that higher drug dosages and polytherapy regimens generally pose a greater risk than do lower doses of the same therapeutic agents, it is well known that teratogens work on susceptible genotypes, such that interacting with multiple environmental variables increase the possibility of damage to the developing embryo. Every pregnancy represents a singular occurrence of genetic variables and environmental factors with which any of the available

AEDs must interact. Under ideal circumstances, identification of those mother-infant pairs that are exceedingly sensitive to specific AEDs, would help in the decision-making process of which therapeutic agent to be used. Hopefully such preconceptional tests will be available in the near future. For the present time, for those women whose healthcare necessities require daily administration of these compounds, the prevailing knowledge holds that the lowest efficacious dosage is most desirable to minimize the risk for dysmorphic events, major malformations or developmental delay in the exposed embryo. This is especially true for valproic acid, but it also applies to all of the other AEDs.

Finally, 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 folic acid supplementation is effective in reducing the risks associated with the concomitant AED exposure.

Acknowledgments

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Table I

Epidemiological studies concerning Carbamazepine monotherapy during pregnancy and the risk of birth defects

Author *	Study methodology	n	Rate of MCM	OR/RR (95% CI)
Samrén 1999	Retrospective cohort	376	3.7%	RR 2.6 (1.4–5.0)
Kaneko 1999	Prospective	158	5.7%	OR 1.9
Holmes 2001	Prospective	58	5.2%	OR 3.0 (0.6–16)
Matalon 2002	Meta-analysis	795	5.5%	OR 2.36 (1.62–3.43)
Wide 2004	Retrospective	703	4.0%	NA
Artama 2005	Retrospective	805	4.0%	OR 1.27 (0.7- 2.23)
Vajda 2006	Prospective and retrospective	155	3.8%	NA
Morrow 2006	Prospective	900	2.2%	OR 1.0
Hernandez-Diaz 2007	Prospective	873	2.5%	OR 1.6(0.9–2.8)
Vajda 2007	Prospective	234	3.0%	OR 0.82 (0.21-3.26)
Meador 2008	Systematic review and meta-analysis	4,411	4.6%	NA
Mawer 2010	Controlled, observational	74	3.0%	OR 1.45 (0.23-7.37)
Vajda 2012	Retrospective	301	6.3%	NA

RR- risk ratio, OR- odds ratio, CI- confidence interval, NA- data not available Updated from [Hill et al., 2010. Teratogenic effects of antiepileptic drugs. Expert Rev Neurother 10(6):943-59.]

*
First author of listed paper

Table II

Epidemiological studies concerning Phenytoin monotherapy during pregnancy and the risk of birth defects

Authors	Study methodology	n	Rate of MCM	OR/RR (95% CI)
Samrén 1999	Retrospective	151	0.7%	RR 0.5 (0.1–3.4)
Holmes 2001	Prospective	87	3.4%	OR 1.9 (0.3-9.2)
Artama 2005	Retrospective	38	2.6%	OR 0.95 (0.02- 6.11)
Morrow 2006	Prospective	82	3.7%	OR 1.64 (0.48 - 5.62)
Vajda 2006	Prospective and retrospective	17	5.9%	NA
Vajda 2007	Prospective	31	3.2%	OR 0.90 (0.09-8.88)
Meador 2008	Systematic review and meta-analysis	1,198	7.4%	NA
Holmes 2008	Prospective	390	2.6%	NA
Vajda 2012	Retrospective	35	2.9%	NA

RR- risk ratio, OR- odds ratio, CI- confidence interval, NA- data not available Updated from [Hill et al., 2010. Teratogenic effects of antiepileptic drugs. Expert Rev Neurother 10(6):943-59.]

Table III

Epidemiological studies concerning Phenobarbital monotherapy during pregnancy and the risk of birth defects

Authors	Study methodology	n	Rate of MCM	OR/RR (95% CI)
Samrén 1999	Retrospective	172	2.9%	RR 2.0 (0.8–5.3)
Holmes 2001	Prospective	64	4.7%	OR 2.7 (0.6-16.4)
Holmes 2004	Prospective	77	6.5%	RR. 4.2 (1.5-9.4)
Meador 2008	Systematic review and meta-analysis	945	4.9%	NA

RR- risk ratio, OR- odds ratio, CI- confidence interval, NA- data not available From [Hill et al., 2010. Teratogenic effects of antiepileptic drugs. Expert Rev Neurother 10(6):943-59.]

Table IV

Epidemiological studies concerning Valproic Acid monotherapy during pregnancy and the risk of birth defects

Authors	Study methodology	n	Rate of MCM	OR/RR (95% CI)
Kaneko 1999	Prospective	81	11.1%	OR 4.0
Samren 1999	Retrospective	158	5.7%	RR 4.1 (1.9–8.8)
Wide 2004	Retrospective	268	9.7%	NA
Artama 2005	Retrospective	263	10.7%	OR 4.18 (2.31-7.57)
Morrow 2006	Prospective	715	6.2%	OR 2.78 (1.62-4.76) RR 2.52 (1.17-5.44)
Vajda 2006	Prospective and retrospective	113	16.8%	NA
Vajda 2007	Prospective	166	13.3%	OR 4.07 (1.18-14.0)
Meador 2008	Systematic review and meta-analysis	2097	10.7%	NA
Mawer 2010	Controlled, observational	57	11.3%	OR 5.94 (1.84-19.19)
Vajda 2012	Retrospective	215	16.3%	NA

RR—relative risk, OR—odds ratio, CI—confidence interval, NA—data not available Updated from [Hill et al., 2010. Teratogenic effects of antiepileptic drugs. Expert Rev Neurother 10(6):943-59.]

Table V

Epidemiological studies concerning Lamotrigine monotherapy during pregnancy and the risk of birth defects

Authors	Study methodology	n	Rate of MCM	OR/RR (95% CI)
Morrow 2006	Prospective	647	3.2%	OR 1.44 (0.77 - 2.67) RR 0.92 (0.41-2.05)
Vajda 2006	Prospective and retrospective	61	0	NA
Vajda 2007	Prospective	146	1.4%	OR 0.37 (0.06-2.26)
Meador 2008	Systematic review and meta-analysis	1337	2.9%	NA
Holmes 2008a	Prospective	684	2.80%	RR 1.4 (0.9 –2.3)
Hunt 2009	Prospective	1,151	2.4%	NA
Mawer 2010	Controlled, observational	40	5.4%	OR 2.66 (0.52-13.68)
Vajda 2012	Retrospective	231	5.2%	NA

RR–relative risk, OR–odds ratio, CI–confidence interval, NA–data not available Updated from [Hill et al., 2010. Teratogenic effects of antiepileptic drugs. Expert Rev Neurother 10(6):943-59.]

Table VI

Epidemiological studies concerning Levetiracetam monotherapy during pregnancy and the risk of birth defects

Authors	Study Methodology	n	Rate of MCM	OR/RR (95% CI)
Long 2003	Case series	3	0%	NA
Ten Berg 2005	Prospective	2	0%	NA
Morrow 2006	Prospective	22	0%	NA
Hunt 2006	Prospective	39	0%	NA
Holmes 2008	Prospective	197	2.0%	NA
Vajda 2012	Retrospective	22	0	NA

RR—relative risk, OR—odds ratio, CI-Confidence Interval, NA- data not available Updated from [Hill et al., 2010. Teratogenic effects of antiepileptic drugs. Expert Rev Neurother 10(6):943-59.]

Table VII

Epidemiological studies concerning Topiramate monotherapy during pregnancy and the risk of birth defects

Authors	Study Methodology	n	Rate of MCM	OR/RR (95% CI)
Morrow 2006	Prospective	28	2.0%	OR 7.1 (2.0 - 22.6)
Vajda 2007	Prospective	15	0%	NA
Ornoy 2008	Prospective	29	3.5%	NA
Hunt 2008	Prospective	70	4.8%	NA
Holmes 2008	Prospective	197	4.1%	NA
Hernandez-Diaz 2010	Prospective	289	3.8%	2.8 (1.0-8.1)
Vajda 2012	Retrospective	31	3.2%	NA

RR- Relative Risk, OR- Odds Ratio, CI-Confidence Interval, NA- data not available Updated from [Hill et al., 2010. Teratogenic effects of antiepileptic drugs. Expert Rev Neurother 10(6):943-59.]

Table VIII

Epidemiological studies concerning Gabapentin monotherapy during pregnancy and the risk of birth defects

Authors	Study Methodology	n	Rate of MCM	OR/RR (95% CI)
Montouris 2003	Prospective and Retrospective	17	5.9%	NA
Morrow 2006	Prospective	31	3.2%	OR 1.33 (0.17 - 10.20)
Vajda 2007	Prospective	11	0%	NA
Holmes 2008	Prospective	127	0.8%	NA
Vajda 2010	Retrospective	14	0%	NA

RR—relative risk, OR—odds ratio, CI-Confidence Interval, NA—data not available Updated from [Hill et al., 2010. Teratogenic effects of antiepileptic drugs. Expert Rev Neurother 10(6):943-59.]