



# Outcomes of pregnancies in women taking antiepileptic drugs for non-epilepsy indications

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## ABSTRACT

**Purpose:** Antiepileptic drugs (AEDs), particularly valproate (VPA), are known to be teratogens when taken by women with epilepsy (WWE), but the risk in women who take these drugs for indications other than epilepsy have been little studied. This study aims to investigate the incidence of birth defects in children born to mothers taking AEDs for non-epilepsy indications.

**Methods:** The Australian Pregnancy Register (APR), established in 1998, is a prospective observational study operating with ethical approval and informed written consent for participation. Of the 2066 pregnancies enrolled in the Register, 98% are WWE and the remainder received AEDs for other indications. Data from this Register was analysed to study the rates of congenital malformations (CM) in infants exposed to AEDs in utero in WWE compared to those women taking AEDs for other indications. **Results:** The malformation rates in pregnancies of WWE taking AEDs (5%), is higher than the rates of infants born to untreated WWE (2%). There were 32 pregnancies enrolled from 29 mothers taking AEDs for indications other than epilepsy (2 women/2 pregnancies were lost to follow up). Out of 30 pregnancies, 9 of which were exposed to VPA, 1 resulted in a child with a malformation (3%) (cleft palate) on 1700 mg/day of valproate.

**Conclusions:** This is the first attempt to assess the use of AEDs in a prospective study of women who are pregnant but do not have active epilepsy. Although underpowered, this study suggests that women taking AEDs for non-epilepsy indications have a similar risk of having a child with a CM as compared with women taking AEDs for epilepsy. Larger numbers are required to investigate the risk of AED-associated malformations in this important group.

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## 1. Introduction

Antiepileptic drugs (AEDs) have been used to treat indications other than epilepsy for over 50 years, but this usage has increased over recent years [1]. Non-epileptic conditions include both mood disorders and neurological conditions. The following are the main non-epilepsy indications treated by AEDs and the drugs used to treat them (drugs used to treat are in parenthesis, for abbreviations see below\*): bipolar disorder (VPA, CBZ, LTG), anxiety (VPA, LTG, TPM, benzodiazepines), migraine (VPA, TPM), neuropathic pain

(VPA, CBZ, TPM, PHT), trigeminal neuralgia (VPA, LTG, TPM), schizophrenia (VPA, CBZ, LTG) and multiple sclerosis (CBZ, LTG, GBP). AEDs have been particularly effective in treating bipolar disorder, and some AEDs such as VPA and LTG are now first line treatments [2,3]. Bipolar disorder typically manifests during reproductive years [4], and pregnant women with bipolar disorder who are not medicated have an increased risk of a recurrence of symptoms as well unfavorable pregnancy outcomes, making it difficult for women to safely cease the drug [5]. Similarly, women are 2–3 times more likely to develop multiple sclerosis (MS) than men and over 50% of patients with MS develop their symptoms during their childbearing years [6].

Exposure to AEDs during the first trimester of pregnancy in women with epilepsy is established for most AEDs to increase the risk threefold of having a child with a birth defect. This risk is increased up to 17-fold for VPA [7–9]. However, whether AED teratogenicity is specific to patients with epilepsy, or whether it affects all indications has not yet been well studied. This paper reports the incidence of birth defects for a cohort of women taking

*Abbreviations:* AED, antiepileptic drug; APR, Australian Pregnancy Register; AZ, acetazolamide; CBZ, carbamazepine; CLZ, clonazepam; CM, congenital malformation; GBP, gabapentin; LTG, lamotrigine; MS, multiple sclerosis; PGB, pregabalin; TPM, topiramate; VPA, valproate; WWE, women with epilepsy.

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AEDs for non-epilepsy indications from the Australian Pregnancy Register of Anti-epileptic Drugs.

- Abbreviations: CBZ: carbamazepine, GBP: gabapentin, LTG: lamotrigine, TPM: topiramate, VPA: valproate

## 2. Participants and methods

### 2.1. The Australian pregnancy register

The Australian Pregnancy Register (APR) is a national, prospective, observational, telephone interview-based register recruiting three groups of women:

1. WWE taking AEDs during the first trimester of pregnancy
2. WWE not taking AEDs during the first trimester of pregnancy
3. Women without epilepsy taking AEDs during the first trimester of pregnancy

Details of the register have been reported elsewhere [10]. Women were recruited nationwide on a voluntary basis. Eligible women were made aware of the Register through their medical practitioners, health professionals and other relevant sources such as the website and social media. All communication with women was on the telephone. Four interviews were conducted: in the first or second trimester of pregnancy, at 7 months of pregnancy, within the first month of birth and at the end of the first or second year. Details of the pregnancy and birth such as birth defects were recorded into the confidential database and each mother was given an individual identification number.

### 2.2. Data analysis

All data for this analysis was collected from the APR between mid-1999 and August 2016. Relevant data was found by filtering the database for case subjects without epilepsy and AED exposed controls without epilepsy. Details of each subject's AEDs and birth outcomes were recorded and assessed for any birth defects. Statistical analysis was not conducted due to the small numbers but comparisons were made between the different groups defined above. Ethical approval was obtained from The Melbourne Health Human Research Ethics Committee (HREC).

## 3. Results

At the time of this analysis there were 2066 pregnancies enrolled in the APR, including 38 twin pregnancies. Of these pregnancies, 32 were from women taking AEDs for a non-epilepsy

indication, 2 of which were lost to follow up. 27/30 pregnancies were from unique women, while 3 women had 2 pregnancies each. For 17/30 pregnancies the women were taking folate before conception. All but three pregnancies involved folate supplementation in the first trimester. The indications as listed in Table 1 are: bipolar disorder (n = 16), pain (n = 6), multiple sclerosis (n = 2) anxiety (n = 1), depression (n = 1), hyperekplexia (n = 2), periodic ataxia (n = 1) and sleep disorder (n = 1). Of these 30 pregnancies, 1 resulted in a child with a major congenital malformation (cleft palate) in 2002. The mother of this child was taking VPA 1700 mg for bipolar disorder. She was taking folate before conception and also in the first trimester at a dose of 1 mg. Her pregnancy was registered in the Australian Pregnancy Register before the child with the malformation had been born. She had one induced abortion (maternal choice) earlier in 1993 while not on AEDs, prior to her VPA exposed pregnancy.

Table 1 shows the total number of non-epileptic women in the Australian Pregnancy Register suffering from each non-epileptic indication followed by which AED was taken during pregnancy. There were 32 women taking AEDs for indications other than epilepsy however 2/32 were lost to follow up and are therefore not included. Two of the women with bipolar disorder were on AED polytherapy, both of which included VPA in the combination. The two polytherapy combinations were: VPA + LTG and VPA + LTG + GBP + TPM.

\*\*Hyperekplexia: a neurological condition in which sufferers experience exaggerated reactions to noise, movement or touch.

Table 2 shows the dose ranges of VPA. All patients suffered a bipolar disorder. The most common doses were above 300 mg and up to 2000 mg which is above the upper limit of permissible doses for pregnant WWE [7,9,11].

Table 3 shows the number of birth defects in all categories of women enrolled in the Australian Pregnancy Register. Those lost to follow up have been excluded (20 pregnancies in total). It should be noted that of the 94 pregnancies resulting in a defect in WWE taking AEDs in the first trimester 5 were twin pregnancies. 2/5 twin pregnancies resulted in both twins having defects while in 3/5 only one of the twins had a defect. There were no twin pregnancies with defects in the other patient groups.

**Table 2**

VPA doses taken for APR non-epilepsy indications.

VPA doses (mg)	Bipolar Disorder
0–300	1
301–600	2
601–1000	2
1001–1500	2
1501–2000	2

**Table 1**

Exposure to AEDs during pregnancy according to non-epilepsy indication.

Indication	No of pregnancies	VPA	LTG	GBP	CLZ	PGB	CBZ	AZ	TPM	Polytherapy
Bipolar Disorder	16	9*	9*	1*					1*	2*
Pain	6			3	2	1				
MS	2			1			1			
Depression	1						1			
Sleep Disorder	1				1					
Anxiety	1				1					
Hyperekplexia**	2				2					
Periodic Ataxia	1							1		
Total	30	9	9	5	6	1	2	1	1	2

Abbreviations AZ: acetazolamide, CBZ: carbamazepine, CLZ: clonazepam, GBP: gabapentin, LTG: lamotrigine, PGB: pregabalin, TPM: topiramate, VPA: valproate, MS: multiple sclerosis.

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