Psychiatr. Pol. 2019; 53(2): 223–244
PL ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE)
www.psychiatriapolska.pl
DOI: https://doi.org/10.12740/PP/105906

Adverse outcomes during pregnancy and major congenital malformations in infants of patients with bipolar and schizoaffective disorders treated with antiepileptic drugs: A systematic review

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Summary

Background. Antiepileptic drugs (AEDs), which are commonly used as a treatment for acute phases and prevention of relapses in bipolar disorder (BD) and schizoaffective disorder (SAD), have been often associated to adverse outcomes in pregnancy and major congenital malformations (MCM). We aimed to summarize available evidence assessing these outcomes when AEDs are used in pregnant women with BD and/or SAD.

Methods. We searched four databases from inception to 18 January, 2019. We included peer-reviewed observational studies on the use of AEDs in pregnant women with BD or SAD. We excluded studies not reporting data on BD or SAD, not specifying the AED or not assessing pregnancy outcomes or MCM.

Results. The pooled records amounted to 2,861. After duplicate removal and inclusion/exclusion criteria application, we included 9 observational studies assessing patients with BD and SAD. The AEDs evaluated were lamotrigine (LTG), valproate (VPA), carbamazepine (CBZ), oxcarbazepine (OXC), topiramate (TPR), and gabapentin (GBP). VPA and CBZ were the AED most commonly associated to MCM. LTG showed the best safety profile. Higher rates of complications during pregnancy were observed in treated and untreated women with BD compared to healthy controls.

Conclusions. AEDs may produce adverse outcomes in pregnancy and MCM in children of pregnant women with BD or SAD, showing higher risks at higher doses. LTG could be

considered in this type of patients, given the low rate of adverse events. VPA and CBZ use should be avoided during pregnancy.

Key words: affective disorders, antiepileptic drugs, teratogenicity

1. Introduction

Bipolar Disorder (BD) is a chronic affective disorder characterized by manic, hypomanic, depressive or mixed episodes. In general population, lifetime prevalence of bipolar spectrum disorders has been estimated at 2.4% [1].

The few available studies focusing on pregnant patients with BD have reported that they are more likely to have low birthweight infants (9.8% vs. 5.7%), preterm births (14.2% vs. 6.9%) and small for gestational age (SGA) children (22.3% vs.15.7%) compared with pregnant women with no history of mental illness [2]. BD patients have also shown significantly higher risk of pre-eclampsia and gestational diabetes [3–6]. Some researchers have assessed the influence on these outcomes of modifiable variables such as smoking, which has found to double the risk of delivering a preterm infant, and illicit drug use, which increases the risk by almost one and half times [7]. The relationship between adverse outcomes in pregnancy and pharmacotherapy has also been evaluated [8].

Mood stabilizers are considered among the most effective drugs for acute phases and prevention of relapses in BD and schizoaffective disorder (SAD), representing first – or second-line treatments in clinical guidelines [9, 10]. AEDs are typically used for their mood-stabilizing properties in BD and SAD and an increasing number of indications other than epilepsy, including migraines, anxiety, BD, SAD, and neuropathic pain, raise the issue of their exposure to a greater number of women of childbearing age [11, 12]. Currently, the prevalence of AEDs use in pregnancy is between 0.2% and 0.5% [13]. AEDs have been reported to increase the risk for obstetric complications or major birth defects in infants of women treated during pregnancy. This is associated with higher maternal serum AEDs levels and exposure to multiple anticonvulsants at the same time. Actually, VPA and CBZ are classified as category 'D' drugs by the US Food and Drug Administration (FDA) and are contraindicated during pregnancy [14]. The most common malformations caused by *in utero* AED exposure are cardiac malformations, followed by hypospadias and facial clefts. Neural tube defects have been reported in 1% to 2% of infants who were exposed to AEDs during the first trimester [8, 15].

Almost all drugs commonly used for treating BD are also excreted into breast milk and the risk of toxicity for breast-fed infants from them is significant. These risks should be carefully balanced against the increased risk of recurrence if a patient's medication is changed or discontinued [16].

VPA is considered the most teratogenic drug in the neuropsychiatric pharmacopeia, since it has a 1–5% rate of fetal abnormalities, particularly neural tube defects [17], but also cardiovascular malformations, cleft palate, intrauterine growth retardation, hypospadias, hydrocephalus, limb defects, craniosynostosis, and pulmonary atresia [18–28], especially with doses over 1,000 mg/day [26]. Other neonatal complications like heart rate decelerations, liver toxicity, hypoglycemia, and reductions in neonatal fibrinogen levels have also been reported [29–32]. Children exposed to VPA prenatally have shown higher rates of low IQ, neurodevelopmental deficits, reduced verbal abilities, attention deficit hyperkinetic disorder and autism spectrum disorder [15, 33–36]. Recently, new interventions for advertisement about VPA use in women at childbearing age have been provided by the European Medicines Agency (EMA), prohibiting VPA use during pregnancy (EMA, 2018).

CBZ use has been associated with neural tube defects, craniofacial abnormalities, skeletal defects, developmental delay, growth retardation, microcephaly, hydrocephaly, spina bifida, gastroschisis, omphaloceles, cardiac abnormalities, and transient hepatic toxicity [37–41]. CBZ is also contraindicated during pregnancy [8].

OXC-related MCM include major cardiac and facial malformations, hydronephrosis, major urinary tract defect, spina bifida cystica, and clubfoot [14]. LTG has a favorable reproductive risk profile, and it is a preferred option for women of childbearing age [40, 42–45], although an increased risk of cleft lip and palate, heart malformations and hypospadias has been reported (being more frequent with doses over 300 mg/day). TPR use has been associated with micrognathia, phimosis [46], cleft lip, cleft palate, hypospadias, microcephaly, skeletal anomalies, respiratory and cardiovascular anomalies, SGA infants, preterm birth, and increased thickness of the placental barrier [15], especially with high doses (mean 400 mg) [14]. GBP have been related to delayed bone ossification, hydronephrosis, hydroureter, exencephaly, and skeletal malformations [15, 47], and also higher rate of preterm birth, low birth weight and more frequently requiring of neonatal intensive care treatment [48].

Whilst AEDs teratogenicity has been widely assessed in women with epilepsy (WWE), the risk in other populations has been poorly studied. AED doses used to treat epilepsy are generally higher than the doses used for BD. In addition, epilepsy might be associated with increased risk of MCM, so results reported from studies on epilepsy might not be applied to women with BD [49, 50].

To summarize the available evidence, we conducted a systematic review of studies that evaluated the adverse effects in pregnancy of AEDs used as mood stabilizers in BD and SAD, assessing those studies that included patients with any of these psychiatric disorders relating the use of different AEDs to adverse outcomes in pregnancy or MCM.

2. Procedures

This review has been conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [51]. Search Methods and Results are highlighted in Figure 1.

2.1. Literature search

We systematically searched the MEDLINE/PubMed, Cochrane Library, PsycINFO/PsycARTICLES, and clinicaltrials.gov databases from any time to January 18th, 2019, cross-checking the obtained references. The systematic search was performed by two blind independent research teams (led by Anna Giménez and Isabella Pacchiarotti), searching as follows:

MEDLINE/Pubmed/Index Medicus: authors used the following search strategy: *(teratogenic OR teratogenicity OR fetal malformations OR fetal development OR newborns development OR newborns malformations OR newborns outcomes OR offspring malformations OR offspring development OR pregnancy OR pregnant) AND (bipolar disorder OR bipolar depression OR mania OR manic OR schizoaffective)*, that produced 1,645 records. Of them, duplicates were 1, and selected for analysis 8.

For the Cochrane library we used the same search strategy, save for the use of square brackets, that the database's system does not accept; the search produced 94 records. It added no includible record to the PubMed search.

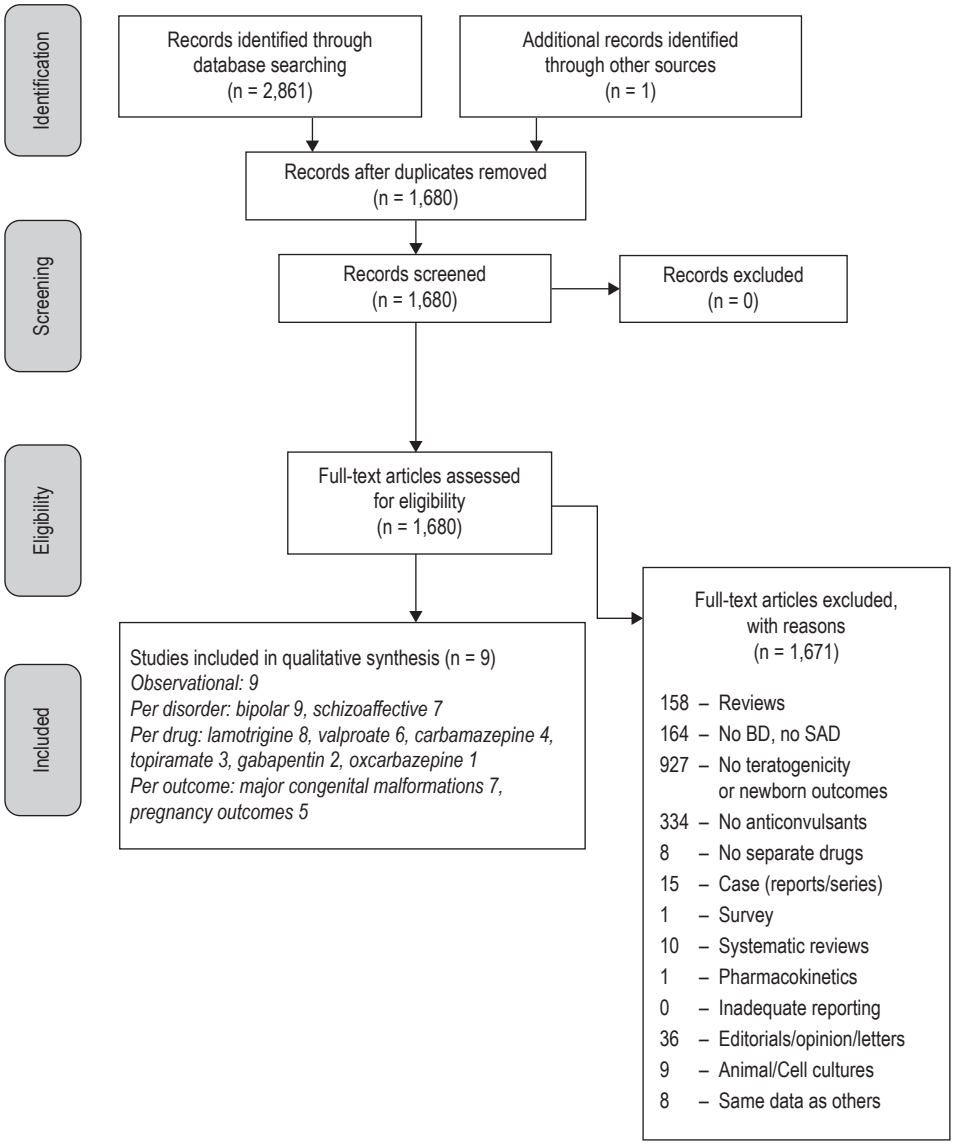
With the other databases we performed the same search as for PubMed. PsycINFO/PsycARTICLES yielded 1,117 records, not showing additional records to the PubMed search.

For the https://clinicaltrials.gov/ database, key words were: *anticonvulsants AND pregnancy* and produced 5 records.

From all databases used and 1 additional record that was identified through another source, just the additional article resulted includible to the pool of records identified by and selected from PubMed.

2.2. Study selection

We included longitudinal studies on the effect of AEDs in pregnancy outcomes and the incidence of MCM in children of women with BD or SAD. Studies could be experimental (randomized clinical trials (RCT), quasi-RCTs, nonRCTs), quasi-experimental (controlled before and after studies, interrupted time series), and observational (cohort, case-control, registry studies). We excluded animal and cell cultures studies, and also studies resulting from databases but not being relevant as to the adverse effects of anticonvulsants in newborns of mothers with BD or SAD. Excluded were also studies



PRISMA 2009 **Flow Diagram; Search carried out on January 18th, 2019. Databases: PubMed Cochrane → PsycINFO/PsycARTICLES → ClinicalTrials.gov**

on the effects of mood stabilizers without reporting results of each drug separately. Meta-analyses and reviews were used as evidence to support information that could not be drawn from individual studies. Open studies (unless they had a mirror design with a retrospective period equal to the longitudinal prospective one), case reports or

series, pharmacoeconomy studies, letters to the editor, author responses to criticisms, opinion papers, editorials, surveys, studies focusing only on biomarkers (like genetic investigations and brain imaging), pharmacokinetic studies, were excluded.

For this review, we filled-in the PICO worksheet [52], the AMSTAR form [53] and the PRISMA checklist [51][1]. We assessed the strength of our recommendations with the National Health and Medical Research Council (NHMRC) of the Australian Government's [54] NHMRC levels of evidence and grades for recommendations for developers of guidelines. Risk of bias was addressed with taking into account the Cochrane Risk of Bias Tool [55], classifying each study according to a high, low, unclear category for the selection, reporting, performance, detection, attrition, and other dimensions, which then affected the global quality of the paper.

3. Results

3.1. Systematic search results

The pooled records amounted to 1,680 Records (Figure 1). Excluded were: 158 Reviews, 164 NBSA, 927 No teratogenicity/newborn outcomes, 334 No anticonvulsants, 8 No separate drugs, 15 Case (reports/series), 1 Survey, 10 Systematic reviews, 1 PhK (pharmacokinetics), 0 Inadeq (inadequate design or outcomes), 36 E/O (editorials/opinion papers), 9 Animal/Cell cultures (studies on nonhumans or on isolated cell tissues), and 8 Same (reporting data elsewhere published better). This left 9 records to include (Figure 1).

All of them were observational cohort studies. 9 studies assessed BD, and 7 of them included other psychiatric disorders such as SAD. 8 studies assessed outcomes related to LTG, 6 the effects of VPA, 4 studies tested CBZ, 3 included TPR, and 2 of them GBP. According to the adverse effects, 7 reported rates of MCM and 5 pregnancy outcomes. The details of each study are reported in Table 1.

[1] available from the editors

Table 1. **Summary of included studies on AEDs use in BD and SAD during pregnancy**

Studies by first author and date in reverse order	Study design	Population, n (sites; sp. Y/N)	Duration	Drugs (treated women with BD)	Main outcomes	Quality (includes bias)
Richards et al., 2018	Cohort study (AEDs exposed and non-exposed women of childbearing age vs. pregnant women vs. women who had had a birth)	2,728 (1; N) including epilepsy	6 years	VPA (from 1.20 to 2.24 per 1,000) GBP (from 0.27 to 0.97 per 1,000) LTG (from 1.10 to 1.79 per 1,000) LEV (from 0 to 0.83 per 1,000) Included patients with epilepsy	Rates of AEDs prescription in a 6-year period. Spontaneous abortion: AEDs > non-AEDs pregnancies. Pregnancy termination: AEDs < non-AEDs pregnancies. More likely with GBP and VPA than LTG or CBZ.	3
Jazayeri et al., 2018	Cohort study (MCM in infants exposed to AEDs in WWE vs. non-epilepsy indications)	2,066 (1; N) including epilepsy	17 years	VPA (n = 9) GBP (n = 1) LTG (n = 9) TPR (n = 1) VPA+LTG (n = 1) VPA+LTG+GBP+TPR (n = 1)	Prevalence of use of anticonvulsants in non-epileptic patients. MCM: similar risks in women with BD (3%) and WWE (5%) taking AEDs. One case of cleft palate while taking VPA 1,700 mg per day for BD.	3

Hernández-Diaz et al., 2018	Cohort study (TPR exposure in pregnant women with epilepsy vs. non-epilepsy indications)	1,360,101 (1; N)	10 years	LTG (n = 1,086) TPR (n = 459)	TPR: dose-dependent increased risk of oral cleft. Median daily dose: 200 mg in WWE, 100 mg in women without epilepsy. Smoking, obesity: more common in TPR users. MCM overall: not increased in the TPR-exposed compared to the reference groups.	3
Bank et al., 2017	Cohort study (pregnant women with epilepsy or BD taking AEDs; no control group)	70 (1; Y) including epilepsy	4 years	CBZ (n = 8) LTG (n = 36) LEV (n = 37) OXC (n = 4) PHT (n = 3) TPR (n = 2) VPA (n = 6) CBZ+PHT (n = 1) CBZ+LEV (n = 1) LTG+LEV (n = 2) Included patients with epilepsy	Umbilical to maternal ratios between medications: no significant differences. Higher umbilical cord concentrations and umbilical to maternal ratios: not associated with adverse neonatal outcomes.	3

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Prakash et al., 2016	Cohort study (pregnant women with BD treated with LTG; no control group)	6 (1; N)	2 years	LTG (n = 5)	Gestational diabetes: two women. Gestational hypertension: one women with preexisting obesity. Lower caesarean sections: two women. Induced labor: four women. Tracheoesophageal fistula: one case. Mother with hypothyroidism poorly controlled in the first trimester. Low birth weights: two infants (2,060 g and 2,365 g) who required NICU admission. Length at birth, head circumference and Apgar scores were normal in all infants. Breastfeeding: no complications in four cases while treatment with LTG.	3-4

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Clark et al., 2013	Cohort study (serum levels of LTG during pregnancy in patients with BD; no control group)	8 (1; N)	12 months	LTG (n = 8)	Serial serum levels of LTG in pregnant patients. No MCM. Pregnancy outcomes: difficulty breast-feeding in one infant after delivery, admitted to the hospital for jaundice and dehydration, which resolved. At 12 days, mild hypotonia; no further complications.	3-4
Cassina et al., 2013	Cohort study (epileptic women exposed to AEDs vs. non-epileptic women exposed to AEDs vs. healthy women not exposed)	1,562 (1; N)	8 years	VPA (n = 107) CBZ (n = 40) LTG (n = 31) other AEDs (n = 96) VPA + other AED (n = 14) CBZ + other AED (n = 3) CBZ + VPA (n = 2) other AED polytherapy (n = 11) Includes other diagnoses (not epilepsy)	MCM: higher rates but not significant in the non-epileptic group vs control group. Spontaneous abortion: AED non-epileptic > AED epileptic or no AED. Cumulative incidence of spontaneous abortion: no significant differences. Elective termination of pregnancy: AED non-epileptic > AED epileptic > no AED. Preterm delivery: no significant differences. Low birth weight: AED epileptic > AED non-epileptic or no AED.	3

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Bodén et al., 2012	Cohort study (women without BD vs. treated women with BD vs. non-treated women with BD)	332,137 (3 in one country; N)	4 years	LTG (n = 116) VPA (n = 32) CBZ (n = 7)	Smokers, overweight, and misused alcohol or substances: BD > non-BD. Risks of caesarean delivery, instrumental delivery, a non-spontaneous start to delivery: BD > non-BD. Neonatal hypoglycaemia: BD > non-BD. No significant differences in MCM.	3
Diav-Citrin et al., 2008	Cohort study (VPA-exposed vs. non-exposed newborns)	1,469 (1; N) including epilepsy	10 years	VPA (n = 154) Included patients with epilepsy	Rate of major anomalies in VPA-exposed newborns with VPA doses >1,000 mg. MCM: cardiovascular, intellectual disability, hypospadias, VPA fetal syndrome.	3

MCM – major congenital malformations; AED – antiepileptic drugs; WWE – women with epilepsy; VPA – valproate; CBZ – carbamazepine; GBP – gabapentin; LTG – lamotrigine; TPR, –topiramate; LEV – levetiracetam; OXC – oxcarbazepine; PHT – phenytoin

Most studies were of good to satisfactory quality of evidence, but none was excellent, despite some studies had included large samples (Table 1). Reasons varied, with some studies not including a control group, a multisite study not addressing intersite variability issues, high rate of attrition bias, small samples, possible sponsor bias, lack of specification of psychiatric diagnoses and not assessing differences in outcomes according to diagnoses. Hence, the total strength of recommendations of this review according to the National Health and Medical Research Council (NHMRC) [54] is from satisfactory to good.

3.2. Content results

3.2.1. Major Congenital Malformations (MCM)

Seven studies have been included regarding rates of MCM in infants exposed to AEDs in BD or SAD. The first [61] was a cohort study in which 154 women exposed to VPA (96.1% at least in the first trimester) were compared with 1,315 women who were treated with non-teratogenic drugs in order to assess a major risk for MCM. The reported indications for treatment in the VPA-exposed group were epilepsy in 81.3% and others (including BD or migraine) in 18.7%. The rate of major anomalies in the VPA group exposed in the first trimester was higher compared with controls (6.7% vs. 2.5%). There were no cases of neural tube defect in the VPA-exposed group.

The most commonly observed MCM in the VPA group were cardiovascular abnormalities, with a 6-fold increased risk associated with VPA exposure (4.2% vs. 0.6%), intellectual disability (1.3%), hypospadias (1.3%), which show no significant differences, and some suspected VPA fetal syndrome (1.9%). A daily VPA dose of ≥ 1,000 mg was associated with the highest teratogenic risk (21.9% vs. 2.5%). Although number of BD or SAD patients included were not specified, all MCM were present in the group treated for epilepsy.

In a cohort study, Bodén et al. [49] included women treated (n = 320) or not treated (n = 554) with mood stabilisers for BD and women without BD (n = 331,263). In the treated mothers, 40% had used LTG during pregnancy, 12% VPA and 2% CBZ. The prevalence of MCM was 2.0% in infants born to women without BD, 1.9% in untreated women with BD, and 3.4% in women treated with AEDs. LTG treatment was associated with MCM in 3.5%, finding in 2 cases talipes equinovarus and heart malformations in the other 2. VPA treatment was associated with hypospadias in one case (3.1%), and CBZ treatment did not associate with any MCM. These findings did not show significant differences with patients without BD.

Cassina et al. [60] performed a prospective cohort study including 385 WWE treated with AEDs, 310 non-epileptic women treated with AEDs (including women with affective disorders) and 867 healthy women not exposed to AEDs. The sec-

ond group included 179 patients with BD or depression. The rates of MCM in the AEDs-exposed cohorts were higher than in the control group, being 7.7% in the epileptic cohort ($p < 0.001$), 3.9% in the non-epileptic cohort ($p = 0.534$) and 3.1% in the control group.

Among patients with BD, three congenital anomalies were found: one inguinal hernia in a newborn exposed to CBZ (400 mg/day), spina bifida in a child whose mother was treated with GBP (200 mg/day), and a ventricular septal defect after exposure to VPA (200 mg/day). The incidence of microcephaly was not significantly increased in treated patients. In all cases mothers were being treated with polypharmacy.

Clark et al. [42] conducted an observational study assessing LTG serum samples from eight mothers with BD taking doses from 100 mg to 300 mg and their infants at different time points during pregnancy and postpartum period. All infants whose mothers provided consent were full term and without MCM.

Prakash et al. [59] conducted a cohort study focused on pregnancy outcomes in six mothers with affective disorders who were being treated with LTG, including five women with BD. The daily dosage used was 100–400 mg, and three of them received additional psychotropic medication. Regarding MCM, one infant, whose mother had been receiving thyroxin replacement with poor control in the first trimester, had a tracheoesophageal fistula that required surgical repair in the immediate postpartum period.

One recent cohort study carried out by Hernández-Díaz et al. [57] assessed the prevalence of oral clefts in infants of epileptic and non-epileptic mothers, including 9,485 women with BD not taking anticonvulsants, 1,086 taking LTG and 459 receiving TPR during the first trimester of pregnancy. Maternal use of TPR during the first trimester was associated with an increased risk of oral cleft, finding higher relative risks at doses of TPR higher than 100 mg (0.73% vs. 0.24%). The risk in the LTG group was not significant. The risk of malformations overall was not increased in the TPR-exposed compared to the reference groups.

In a registry study, Jazayeri et al. [50] assessed the rates of MCM in children of 32 women taking AEDs for non-epileptic indications. Among these, 16 were women with BD. One case of cleft palate was found in a woman taking VPA (1,700 mg per day), which suggests that women without epilepsy treated with AED have a similar risk of having an infant with a MCM (3%) as WWE taking AEDs (5%).

3.2.2. Pregnancy outcomes and perinatal complications

We identified six observational studies that investigated the effects of anticonvulsants in pregnancy outcomes and perinatal complications in women with BD or SAD.

Bodén et al. [49] found an increased risk of caesarean delivery ($p < 0.001$), instrumental delivery ($p < 0.001$), a non-spontaneous start to delivery ($p < 0.001$), and preterm delivery ($p = 0.03$) in both untreated and treated women with BD. In the analysis of variation in very preterm deliveries no significant differences were found between VPA, LTG and CBZ users. Among infants of untreated or treated women the risk of being born very preterm was not significantly increased. Infants of treated or untreated women had no increased risks of a low Apgar score. The risk of neonatal hypoglycemia was increased in the infants of untreated and treated women ($p = 0.19$), but in treated women the risk estimates were imprecise. Neither untreated nor treated BD was associated with neonatal jaundice.

Cassina et al. [60] showed higher rates of spontaneous abortions in the non-epileptic group treated with AEDs compared to treated WWE and non-treated healthy women. The cumulative incidence of spontaneous abortions in the three cohorts was not statistically different. There was a higher rate of elective termination of pregnancy in the two AEDs-exposed groups compared to the control one ($p < 0.001$), which was statistically higher in the non-epileptic group than in the epileptic one ($p < 0.001$). No differences were observed between the rates of preterm deliveries in the three groups. Differently to the epileptic group, the rate of low birth weight in the non-epileptic group was not significantly higher in comparison with controls.

Clark et al. [42] assessed serum LTG levels before and after delivery in a cohort study on eight mothers with BD. Infant development, gestational duration, head circumference, length, and weight were also evaluated. Bayley Scales of Infant Development scores were within normal limits. At birth, all infants were within the normal range of growth percentiles. No rashes were reported in the infants exposed to LTG. The only complication was found in a newborn that had difficulty breast-feeding two days after delivery and was admitted to the hospital for jaundice and dehydration, which resolved with intravenous fluids and bilirubin light therapy. At 12 days, the infant had mild hypotonia but was otherwise normal on examination. The baby had no further complications after resuming exposure to LTG through breast milk, and his examination at 12 months was normal.

Prakash et al. [59] found that, among the six pregnant women with affective disorders treated with LTG, two of them developed gestational diabetes and one of them, who had a preexisting obesity, gestational hypertension. Two women had lower segment caesarean sections (LSCS): one of them at 36 weeks due to worsening pre-eclampsia, growth restriction and breech presentation, and the other mother at 39 weeks gestation due to previous LSCS. Labor was induced in the other 4 subjects between 38–39 weeks gestation. Two infants with low birth weights (2,060 g and 2,365 g) required neonatal intensive care unit (NICU) admission. Length at birth, head circumference and Apgar scores were within normal limits in all infants. Four

infants were breastfed with no complications while the mothers received uninterrupted treatment with LTG.

Bank et al. [58] conducted a study in pregnant women with epilepsy or BD in which total drug levels were measured in umbilical cord for patients taking CBZ (n = 8), LTG (n = 36), levetiracetam (n = 7), OXC (n = 4), phenytoin (n = 3), TPR (n = 2), and VPA (n = 6). Four mothers took polytherapy combinations that included CBZ and phenytoin (n = 1), CBZ and levetiracetam (n = 1), and LTG and levetiracetam (n = 2). Logistic regressions were performed in order to assess the correlation between AED levels and neonatal complications.

Regarding exposure to the different anticonvulsants, among the 8 infants exposed to CBZ, 2 were premature (25%), one was SGA (12.5%), one had an Apgar score less than 7 at 1 minute (12.5%), 2 were admitted to the NICU or special care nursery (25%), and one had a major malformation (12.5%). In the group of 36 children who were exposed to LTG, there were: one premature newborn (2.8%), 3 SGA infants (8.3%), 2 newborns with an Apgar score less than 7 at 1 minute (5.6%), and 6 admitted to the neonatal intensive care unit or special care nursery (16.7%). From the OXC group, which included 4 newborns, one of them was SGA (25%). Of the two children exposed to TPR, one was premature (50%), one was SGA (50%) and one was admitted to the NICU or special care nursery (50%). There were 2 out of 6 infants exposed to VPA who were SGA (33.3%). Among the 4 patients exposed to polytherapy, one of them was SGA (25%), 3 had an Apgar score less than 7 at 1 minute (75%), 2 were admitted to the NICU or special care nursery (50%) and one had a MCM (25%).

Neither higher umbilical cord concentrations of the total drug as a percentage of the upper limit of the therapeutic range nor higher umbilical to maternal total ratios were associated with increased likelihood of prematurity, low birth weight, NICU or special care nursery admission, MCM or Apgar score lower than 7 at 1 minute after delivery.

Recently, a cohort study published by Richards et al. [56] assessed in a 6-year period the increase in the number of women of childbearing potential with prescribed AEDs – from 9 per 1,000 women in 2008 to 11.4 per 1,000 women in 2014. It also showed that women who had been dispensed an AED had an increased rate of spontaneous abortion (9.0%) than those not dispensed an AED (6.3%), and a decreased rate of pregnancy termination (18.5% compared to 19.6%). Only a small proportion of pregnant women dispensed AEDs during pregnancy were on polytherapy (10.7%).

Analysis of pregnancy outcomes by AED revealed no difference in the rate of spontaneous abortions between AEDs. Women that had a termination were more likely to be taking GBP or VPA than LTG or CBZ.

4. DISCUSSION

The present systematic review examined and compared the safety of different AEDs in pregnant patients with mood disorders (BD and SAD). We found 9 observational studies to be included in our review. We rated it according to the AMSTAR system and we found it to be of low-moderate quality [53]. No clinical trials were found during the systematic research. Actually, the scarcity of studies included in our review assessing specifically BD and SAD patients is understandable considering the large number of studies on the use of AEDs in epileptic samples from which the effect of these drugs on pregnancy and on perinatal period can be extrapolated. Moreover, amongst the included studies, we found no data specifying the number of patients with SAD in their sample, and regarding BD studies, four of them did not separate BD from other diagnoses. Nevertheless, some data can be highlighted by examining the available studies for the AEDs use in patients with affective disorders. We found that LTG is the drug with more data in BD patients. This is probably due to ethical issues and clinical contraindications that might limit studies on CBZ and VPA during pregnancy.

Seven studies included in our review reported the rates of MCM in infants exposed to AEDs for the treatment of BD or SAD. Those assessing VPA showed a 6-fold increase of cardiovascular malformations at doses of 1,000 mg or higher [61]. Other studies focused on women with BD treated with LTG, VPA or CBZ did not show significant differences with women without AED treatment or AED treatment for other indications [49], whilst another study comparing WWE and non-epileptic women treated with LTG, VPA or CBZ showed that the rates of MCM were significantly higher in an epileptic cohort than in the control group, but not in the non-epileptic group compared with controls [60]. Among studies assessing the incidence of oral clefts in children of women with BD, current evidence showed an increased risk with TPR, especially at doses higher than 100 mg, and found one case during VPA treatment at a dose of 1,700 mg among 16 pregnancies [50, 57], which suggests that women without epilepsy treated with AEDs might have a similar risk of having an infant with a MCM as WWE.

Overall, it maybe underlined that, at least with VPA use, the risk of MCM appears to be dose dependent and this would also explain the higher rate of teratogenic effects in epileptic women in which notoriously higher doses are used than in women with affective disorders.. LTG was the AED that showed the highest safety profile during pregnancy. Two small studies [42, 59] showed no MCM in treatment with LTG at doses from 100 mg to 400 mg. A case of a tracheoesophageal fistula was reported in one infant, which could be related to concomitant treatment with thyroxin and poor control of patient's hypothyroidism.

With respect to complications during pregnancy or the perinatal period, the included studies showed increased risks of caesarean delivery, instrumental delivery, a non-spon-

taneous start to delivery, and preterm delivery in women with BD receiving or not AED treatment with VPA, LTG or CBZ, with no differences between these drugs [49, 60]. Similarly, other studies showed a higher rate of spontaneous abortions in patients treated with AEDs [56], especially in non-epileptic patients treated with VPA LTG or CBZ compared to treated WWE and non-treated healthy women. A higher rate of elective termination of pregnancy in patients exposed to AEDs was also reported, which was statistically higher in non-epileptic patients and especially in those taking GBP or VPA [56]. Again, studies assessing only LTG treatment showed no developmental abnormalities in exposed children of mothers with BD, but reported one case of a newborn with difficulty breast-feeding two days after delivery requiring an admission to the hospital for jaundice and dehydration, which was resolved by intravenous fluids and bilirubin light therapy [42]. Few cases of gestational diabetes, gestational hypertension, low birth weight and LSCS were also reported with LTG treatment [59]. However, since the sample sizes of these studies were small, the association of the adverse outcomes with LTG exposure during pregnancy was controverted.

A study assessing umbilical cord concentrations of different AEDs showed no increased likelihood of adverse outcomes with concentrations near the upper limit of the therapeutic range or higher umbilical to maternal total ratios [58]. One study assessing adverse outcomes of AEDs separately, including patients treated with CBZ, LTG, VPA, OXC or TRP, showed cases of prematurity, SGA infants, Apgar score less than 7 at 1 minute and admissions to the NICU. Nevertheless, this sample was small, with no control group and including pregnant women with AED treatment with no distinction between epileptic and non-epileptic patients, what limits the possibility to associate the use of each drug to specific adverse outcomes [58].

These results of an increased risk of perinatal period complications in non-epileptic women, regardless of the treatment with AEDs, could suggest the presence of an increased risk of perinatal anomalies that is intrinsic and related to the diagnosis of affective disorders, but the lack of comparative studies between treated and untreated women with BD keeps this evidence only on an empirical level.

Limitations

The limitations of this review include small sample sizes, lack of control group, lack of comparison of outcomes between epileptic and psychiatric patients, between treated and non-treated patients with BD or SAD and no studies assessed differences between the specific AEDs, relevant variables were not included, with an overall low-moderate level of evidence.

5. Conclusions

Summarizing, the level of evidence for the use of AEDs in the maintenance treatment of BD and SAD during pregnancy is still limited, considering the lack of randomized controlled clinical trials mainly due to ethical aspects. Actually, evidence-based recommendations on the AED use during pregnancy are provided by epileptic populations. Studies focused on patients with BD or SAD point at LTG as the safest option during pregnancy. VPA and to a lesser extent CBZ have shown the highest risk of MCM, especially with higher doses. Given the intellectual impairment in offspring exposed to *in utero* VPA, there is concern with its use in pregnancy even beyond the first trimester. CBZ should also be avoided where possible because of its teratogenicity.

Further studies with larger samples of BD and SAD patients treated with AEDs as mood stabilizers should be carried out, taking into account other relevant variables to assess the safety of these drugs according to the dosage used in psychiatric conditions. In addition, comparative studies between treated and untreated women with BD could strengthen the evidence on the effects of AEDs use in this specific population. Further research should also assess the effect of specific AEDs other than VPA and CBZ, such as LTG, to investigate their safety profile, which could increase the accuracy of current recommendations.

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