Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v31i3.5068

NEW ANTI-EPILEPTIC DRUG USAGE WHILE PREGNANT AND THE POSSIBILITY OF ADHD IN OFFSPRING

Fatima Soomro[1], Sangeet[2*], Fnu Simran[3], Suresh Kumar[4], Jai Chand[5], Aisha Chohan[6]

[1]Post Graduate Resident, Department of Psychiatry, Jinnah Post Graduate Medical Centre Karachi
[2*]FCPS Post Graduate Resident, Jinnah Post Graduate Medical Center, Karachi
[3]Ghulam Muhammad Mahar Medical College Sukkur
[4]Ghulam Muhammad Mahar Medical College Sukkur
[5]Medical Officer, Khairpur Medical College
[6]FCPS Psychiatry Resident, Liaquat University of Medical and Health Sciences and Sir Cowasjee Jahangir Institute of Psychiatry and Behavioural Sciences Hyderabad

[*]**Corresponding Author:** Dr Sangeet,
Email: manik_tahliyasangeet@yahoo.com

ABSTRACT

Introduction: Three to seven out of every 1,000 expectant mothers suffer from epilepsy. Antiepileptic medicines (AEMs) are the mainstay of treatment. Many AEMs are related to neurodevelopmental defects in children when used by pregnant females. **Objective:** The current study examined the relationship between a mother's use of AEMs throughout her pregnancy and the likelihood that her unborn child may experience ADHD. **Method** The study's data came from babies born to epileptic mothers who received new anti-epileptic medications at any time during their pregnancy. From January 1, 2018, to December 31, 2019, we tracked babies born in our hospital, and we continued to make regular telephonic calls to assess their child status until December 31, 2023. **Results** ADHD was more prevalent in the babies of mothers belonging to the Valproic acid group, with incidence ranging up to 8.87%. The Lamotrigine group had a lower incidence of ADHD as compared to the Valproic acid group (5.71%). The lowest incidence was reported by the babies of mothers belonging to no anti-epileptic usage group (1.42%). **Conclusion** We found an association between maternal valproic acid use and an increased risk of ADHD**.** The results of the current investigation did not show any evidence linking the use of Lamotrigine during pregnancy to the onset of ADHD in the unborn child. We suggest that during pregnancy, Lamotrigine may not be as dangerous as other new anti-epileptic medications.

Keywords: Lamotrigine, Valproic acid, Pregnancy, Attention deficient hyperkinetic disorder (ADHD)

Introduction

Three to seven out of every 1,000 expectant mothers have epilepsy (Błaszczyk et al., 2022; de Lima Leite et al., 2022). Antiepileptic medicines (AEMs) are the mainstay of treatment (Hu et al., 2023). Since studies have indicated a risk of unfavorable birth outcomes, questions are being raised over the safety of AEM during pregnancy (Marxer et al., 2021) and neurodevelopmental conditions, which include attention-deficit/hyperactivity disorder (ADHD) (Cohen et al., 2024).

Many studies have been done to evaluate the effects of certain new anti-epileptic medicines on offspring (Birnbaum et al., 2020),(Meador et al., 2021). More recently, new research has suggested that exposure to VPA during pregnancy may potentially result in neurodevelopmental disorders (NDD), which are characterized by cognitive and behavioral issues in children (Marxer et al., 2021; Sharma et al., 2022). No precise results are established regarding using AEM, which drug is better for having low or negligible neurological effects in offspring.

The present research looked at links between a mother's usage of AEMs during her pregnancy and her child's chance of developing ADHD. This study is unique in our area since it considers several variables other studies haven't considered. We looked at correlations between offspring born to epileptic mothers who used AEMs throughout pregnancy and those who did not. We considered exposure to valproate and Lamotrigine, the two AEMs most often used in our area.

Methods

The research project was approved by the Institutional Review Board and Ethical Committee of - Jinnah Post Graduate Medical Center Karachi. Informed consent was obtained from all participants in the study. The research was based on data from infants delivered to women with epilepsy who were taking new anti-epileptic drugs at any point before delivery. We identified infants born in hospitals between January 1, 2018, and December 31, 2019, and tracked them until December 31, 2023.

All pregnant females with epilepsy were enrolled in this study with a history of anti-epileptic medicine usage during pregnancy. Only females who did not have a proper record of anti-epileptic medicine usage and those who did not want to participate in the study were excluded. Children of such pregnant mothers were followed up via telephonic calls to ask for the signs and symptoms of attention deficient hyperkinetic disorder (ADHD).

We divided the study population into three groups. The valproic acid group, in which anti-epileptic medicine was Valproic acid used by the pregnant females, and the next group was the Lamotrigine group, in which the anti-epileptic medicine was Lamotrigine used by the pregnant females. The last group comprised those pregnant females who didn’t take any anti-epileptic medicine throughout the pregnancy. The infants born to mothers of both groups were tracked for four years via telephonic calls to check for the signs and symptoms of ADHD. Although the diagnostic standards for ADHD have changed over time, the testing and evaluation procedures have remained the same. ADHD remains primarily a medical diagnosis. Present guidelines for diagnosing suspected ADHD include a complete history of prenatal and perinatal history, family history, performance in school, environmental variables, and a thorough physical assessment. During a physical checkup, particular attention should be given to vital indicators (cardiac and skin). Thyroid and neurological systems, mainly motor coordination testing, are used to establish a diagnosis of ADHD.

Values were shown using SPSS version-21 as a percentage for qualitative data and a mix of standard deviation and mean for quantitative data. The Student t-test was utilized for continuous parameters in each group, while the chi-square test was employed for categorical data in the two groups. Finally, Cox regression analysis was performed to check the association of various drugs with ADHD. A p-value of <0.05 illustrates statistical significance.

Results

Out of the 240 pregnant women enrolled in the study, 30 cases were excluded further due to non-compliance with follow-up; thus, 210 pregnant females completed the study. All cases were comparable in demographics, as shown in the following table.

Table 1 Patient demographics

Variable	**Lamotrigine group N=70**	**Valproic acid group N= 70**	**Nonepileptic group N=70**
Age Mean+ SD(years)	24.24 ±11.3	21.29 ±12.6	23.82 ±13.7
Marital status			
Married	66(94.28)	67(95.7)	65(92.8)

Unmarried/divorced	4(5.71)	3(4.28)	5(7.14)
Residence			
Urban	23(32.9)	21(30)	24(34.3)
Rural	47(67.1)	49(70)	46(65.7)
Pregnancy plan			
Wanted	64(91.4)	62(88.5)	65(92.8)
Unwanted	6(8.6)	8(11.5)	5(7.2)

The mean age of the Lamotrigine group was 24.24 ±11.3 while that of the Valproic acid group was 21.29 ±12.6 and the non-epileptic group was 23.82, ±13.7.majority of the study population belonging to the rural residence with 67.1% in Lamotrigine group,70% in Valproic acid group and 65.7 in the non-epileptic group were residents of rural areas. All groups were comparable in demographics with no disparity, as shown in Table 1.

Table 2: Incidence of ADHD among groups

Variable	**ADHD diagnosis (Age 2yr or more)**	
	Present N,%	**Not present N,%**
Valproic acid, N=70	6(8.87)	64(91.4)
Lamotrigine, N=70	4(5.71)	66(94.2)
No anti-epileptic usage N=70	1(1.42)	69(98.57)

ADHD was more prevalent in the babies of mothers belonging to the Valproic acid group, with incidence ranging up to 8.87%. The Lamotrigine group had a lower incidence of ADHD as compared to the Valproic acid group (5.71%). The lowest incidence was reported by the babies of mothers belonging to the group with no anti-epileptic usage (1.42%).

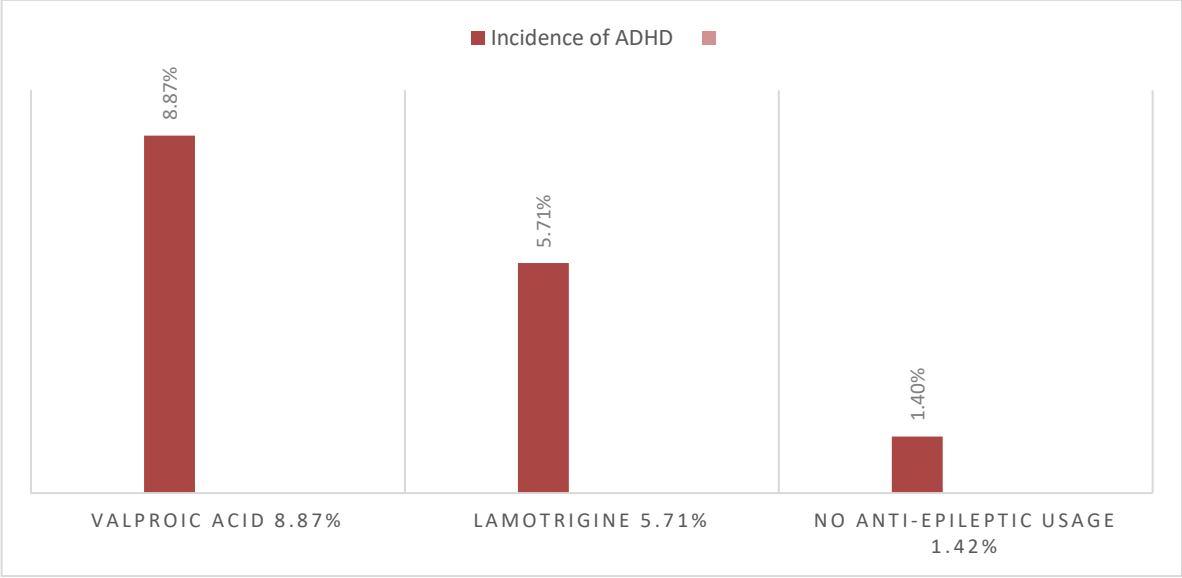

Figure 1 shows the incidence of ADHD among groups.

Table 3: Correlation between new anti-epileptic medicines and the prevalence of ADHD.

Variable	**Un adjusted**	**Adjusted**
	HR (95%CI)	
Valproic acid, N=70	1.81(1.43-2.36)	1.76(1.54-2.8)
Lamotrigine, N=70	1.43(0.83-2.16)	1.21(0.84-1.59)
No anti-epileptic usage N=70	0.63(0.23-1.21)	0.41(0.14-1.03)

Table 2 presents correlations between the maternal intake of anti-epileptic medications and ADHD in children whose mothers have epilepsy. Children in this population whose mothers reported using Valproic acid had a higher likelihood of developing ADHD (HR 1.81, 95% CI (1.43-2.36). Confounder correction had little effect on these correlations, as shown in Table 3. The Lamotrigine group had a relatively lower risk of developing ADHD (HR 1.43, 95% CI (0.83-2.16). The least likelihood was present in those epileptic mothers who did not take any epileptic medicines (HR 0.63, 95% CI (0.23-1.21) The.

Discussion

We found correlations in this relatively small sample between the mother's reported usage of anti-epileptic medications during pregnancy and increased risks for ADHD in their kids. However, Examining certain antiepileptic types produced inconsistent results, emphasizing the need to study individual medications. Our findings, in turn, corroborated the theory that some antiepileptic medications may pose a higher danger to fetal development.

We discovered that, even after controlling for several significant variables (such as the severity of seizures or epilepsy and parental mental health issues), mother-reported Valproic acid use was mainly linked to a higher risk of ADHD in offspring. However, we did not find any evidence of a direct link between Lamotrigine usage and an increased risk of ADHD among children born to epileptic mothers who reported using the drug during pregnancy; instead, all of the relationships were corroborated by confounding variables. Despite conflicting results in the literature about the relationship between Lamotrigine usage during pregnancy and the incidence of cleft lip/palate in infants (Kaplan and Demir, 2021; Laspro et al., 2024), the overwhelming body of research has also indicated that Lamotrigine use during pregnancy does not raise the risk of birth abnormalities (Veronika et al., 2017). These findings may further reassure the consumption of Lamotrigine during pregnancy for both clinicians and expectant mothers.

Because of its link to birth issues (such as birth abnormalities), medical experts strongly advise against using Valproic acid for the treatment of seizures in women who are or may become pregnant unless extremely important (Veronika et al., 2017); our study is in line to the previous researches which have shown that the use of Valproic acid by pregnant females during pregnancy can lead to significant developmental defects and delays in their babies (Daugaard et al., 2020; Reynolds and Green, 2020). The Lamotrigine group had a relatively lower risk of developing ADHD (HR 1.43, 95% CI (0.83-2.16) as compared to the use of Valproic acid. Our study's results are reinforced by previous studies showing developmental and neurological defects in children exposed to Lamotrigine in vivo (Peron et al., 2024; Yeh et al., 2021). Relatively most minor risk of ADHD was found in children of pregnant females who were healthy and did not take any anti-epileptic drugs, which shows that the epileptic drugs do impact fetal development (Pennell et al., 2022) and significantly less incidence of ADHD in this group may be explained due to the presence of confounding variables which were unable to eliminate in our investigation completely.

Many limitations of our study should be kept in mind while analyzing the results. Due to the small sample size of the research, the results of this study cannot be generalized. Since these conditions are inherited (Shimizu et al., 2022), this might have influenced the results of the current study. More thorough research in this area is needed.

Conclusions

The current study found no evidence to indicate a link between a pregnant mother's usage of Lamotrigine and the development of her baby's ADHD. Although we could not rule out all possible confounding variables, our results add to the expanding body of research suggesting that Lamotrigine might be less risky than other anti-epileptic medicines during pregnancy. We identified an increased likelihood of ADHD connected to maternal usage of Valproic acid.

Reference

1. Birnbaum, A. K., Meador, K. J., Karanam, A., Brown, C., May, R. C., Gerard, E. E., Gedzelman, E. R., Penovich, P. E., Kalayjian, L. A., and Cavitt, J. (2020). Antiepileptic drug exposure in infants of breastfeeding mothers with epilepsy. *JAMA neurology* **77**, 441-450.
2. Błaszczyk, B., Miziak, B., Pluta, R., and Czuczwar, S. J. (2022). Epilepsy in pregnancy—management principles and focus on valproate—international *journal of molecular sciences* **23**, 1369.
3. Cohen, M. J., Meador, K. J., Loring, D. W., Matthews, A. G., Brown, C., Robalino, C. P., Birnbaum, A. K., Voinescu, P. E., Kalayjian, L. A., and Gerard, E. E. (2024). Behavioral Outcomes and Neurodevelopmental Disorders Among Children of Women With Epilepsy. *JAMA neurology* **81**, 19-29.
4. Daugaard, C. A., Pedersen, L., Sun, Y., Dreier, J. W., and Christensen, J. (2020). Association of prenatal exposure to valproate and other antiepileptic drugs with intellectual disability and delayed childhood milestones. *JAMA network open* **3**, e2025570-e2025570.
5. de Lima Leite, M., Toporcov, T. N., Pai, J. D., and da Silva, J. C. (2022). Socio-demographic profiles and obstetrics outcomes of pregnant women with epilepsy in a vulnerability State, Brazil. *Plos one* **17**, e0271328.
6. Hu, T., Zhang, J., Wang, J., Sha, L., Xia, Y., Ortyl, T. C., Tian, X., and Chen, L. (2023). Advances in epilepsy: mechanisms, clinical trials, and drug therapies. *Journal of Medicinal Chemistry* **66**, 4434-4467.
7. Kaplan, Y. C., and Demir, O. (2021). Use of phenytoin, phenobarbital carbamazepine, levetiracetam lamotrigine and valproate in pregnancy and breastfeeding: risk of major malformations, dose-dependency, monotherapy vs polytherapy, pharmacokinetics and clinical implications. *Current neuropharmacology* **19**, 1805.
8. Laspro, M., Brydges, H. T., Verzella, A. N., Schechter, J., Alcon, A., Roman, A. S., and Flores, R. L. (2024). Association of Commonly Prescribed Antepartum Medications and Incidence of Orofacial Clefting. *The Cleft Palate Craniofacial Journal*, 10556656241237679.
9. Marxer, C. A., Rüegg, S., Rauch, M. S., Panchaud, A., Meier, C. R., and Spoendlin, J. (2021). A review of the evidence on the risk of congenital malformations and neurodevelopmental disorders in association with antiseizure medications during pregnancy. *Expert Opinion on Drug Safety* **20**, 1487-1499.
10. Meador, K. J., Cohen, M. J., Loring, D. W., May, R. C., Brown, C., Robalino, C. P., Matthews, A. G., Kalayjian, L. A., Gerard, E. E., and Gedzelman, E. R. (2021). Two-year-old cognitive outcomes in children of pregnant women with epilepsy in the maternal outcomes and neurodevelopmental effects of antiepileptic drugs study. *JAMA neurology* **78**, 927-936.
11. Pennell, P. B., Karanam, A., Meador, K. J., Gerard, E., Kalayjian, L., Penovich, P., Matthews, A., McElrath, T. M., Birnbaum, A. K., and Cohen, M. (2022). Antiseizure medication concentrations during pregnancy: results from the maternal outcomes and neurodevelopmental effects of antiepileptic drugs (MONEAD) study. *JAMA neurology* **79**, 370-379.
12. Peron, A., Picot, C., Jurek, L., Nourredine, M., Ripoche, E., Ajiji, P., Cucherat, M., and Cottin, J. (2024). Neurodevelopmental outcomes after prenatal exposure to lamotrigine monotherapy in women with epilepsy: a systematic review and meta-analysis. *BMC Pregnancy and Childbirth* **24**, 103.
13. Reynolds, E. H., and Green, R. (2020). Valproate and folate: Congenital and developmental risks. *Epilepsy & Behavior* **108**, 107068.
14. Sharma, A. R., Batra, G., Saini, L., Sharma, S., Mishra, A., Singla, R., Singh, A., Singh, R. S., Jain, A., and Bansal, S. (2022). Valproic acid and propionic acid modulated mechanical pathways associated with autism spectrum disorder at prenatal and neonatal exposure. *CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders)* **21**, 399-408.

15. Shimizu, H., Morimoto, Y., Yamamoto, N., Tayama, T., Ozawa, H., and Imamura, A. (2022). Overlap between epilepsy and neurodevelopmental disorders: insights from clinical and genetic studies. *Exon Publications*, 41-54.
16. Veroniki, A. A., Cogo, E., Rios, P., Straus, S. E., Finkelstein, Y., Kealey, R., Reynen, E., Soobiah, C., Thavorn, K., and Hutton, B. (2017). Comparative safety of anti-epileptic drugs during pregnancy: a systematic review and network meta-analysis of congenital malformations and prenatal outcomes. *BMC medicine* **15**, 1-20.
17. Yeh, T.-C., Bai, Y.-M., Hsu, J.-W., Huang, K.-L., Tsai, S.-J., Chu, H.-T., Liang, C.-S., and Chen, M.-H. (2021). Bipolar women's antepartum psychotropic exposure and offspring risk of attention-deficit/hyperactivity disorder and autism spectrum disorder. *Journal of Affective Disorders* **295**, 1407-1414.