# EFFECT OF ANTIEPILEPTIC DRUGS ON SERUM LIPIDS IN EPILEPTIC CHILDREN

## By

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## ABSTRACT

***Background:*** *Several studies have reported that antiepileptic drugs increase serum High Density Lipoproteins Cholesterol (HDL-C) levels, while others documented no such effect. Further, some researchers also observed that valproic acid (VPA) and other newer antiepileptic drugs have no influence on serum lipid profile.*

***Aim and objectives:*** *To study the effect of chronic intake of Antiepileptic Drugs (AEDs) in epileptic children on serum lipid profile including: Total Cholesterol (TC), Triglycerides (TGs), High-Density Lipoprotein (HDL-C), and Low-Density Lipoprotein (LDL-C).*

***Subjects and methods:*** *This is a cross sectional analytic study that was carried out on 50 epileptic children attending the Pediatric Neurology Clinics of Sayed Galal and El-Shatby university hospitals using AEDs: Carbamazepine, Na valproate, and Levetiracetam during the period from February 2021 to January 2022 , they were selected by simple random method. All the studied patients were subjected to: Detailed history taking with special emphasis on their seizure record, Clinical examination with special emphasis on CNS and Laboratory evaluation of Lipid profile including (TC, TGs, HDL-C and LDL-C).*

***Results:*** *There was a statistically significant difference in cholesterol in Na valproate group as it was higher in females than in males (p-value=0.013). There was a statistically significant difference in LDL cholesterol in Na valproate group as it was higher in females than in males (p-value=0.011) , and no statistically significant difference in other antiepileptic drugs regarding sex of the patient, There was no statistically significant difference in any of the antiepileptic drugs regarding lipid profile between groups with different disease duration. Also, no statistically significant difference in any of the antiepileptic drugs regarding lipid profile between groups with different age.*

***Conclusion:*** *Epilepsy and antiepileptic drugs are not considered risk factors of dyslipidemia. The results didn't show significant adverse effect on lipid profile in patients on long term antiepileptic drugs therapy.*

***Keywords:*** *Epilepsy; Antiepileptic Drugs; Lipid Profile; HDL-C.*

## *INTRODUCTION*

Epilepsy is a common heterogeneous neurological problem in children. It exerts a significant physical, psychological, economic and social toll on children and their caregivers. Fifty million people have epilepsies globally; more than half of them are children. In the USA, between 25,000 and 40,000 children will have a first non-febrile seizure each year. The problem is further compounded in developing countries as they add about 75-80% of new cases of epilepsy **(The Global Campaign against Epilepsy, 2001)**.

The seizures and epilepsies in children are extremely diverse, differing markedly in age of onset, seizure characteristics, associated co morbidities, treatment and prognosis. Without a firm understanding of the complexities of childhood epilepsy, physicians may not be able to make an accurate diagnosis and plan an effective treatment strategy, so it is important for the general pediatrician to be aware of the evaluation and management of these patients **(Guerrini R. Epilepsy, 1997)**.

Epileptic seizures affect 1-2 % of the population and 4% of children. Developing countries have higher prevalence due to the poorer perinatal care and standards of nutrition and public hygiene and the greater risk of brain injury, cerebral infection or other symptomatic cerebral conditions.

Incidence of seizures is age dependent. The highest incidence rate (100 per 100,000) is observed in the first year of life, declining to approximately 20 cases per 100,000 per year in adolescence. Childhood epilepsy has a prevalence of approximately 0.5-0.8% and comprises a heterogeneous group of disorders, including a variety of epilepsy syndromes that range in severity from benign to progressive and catastrophic.

Focal epilepsies predominate (59-63%) than generalized epilepsy (12-29%). In about 20% classification may change on follow up **(Hauser and Banerjee, 2008**; **Cross et al., 2013)**.

Epidemiological, clinical and experimental investigations have demonstrated that serum lipids and apolipoproteins are intimately related to atherogenesis **(Newman et al., 1986**; **Berenson et al., 1988)**.

Many studies, mainly comprising adult patients, have provided the evidence that there is a significant influence of long-term antiepileptic drugs (AEDs) therapy on total cholesterol (TC),

triglycerides (TGs), high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C), very low-density lipoprotein (VLDL-C) and apolipoprotein levels **(Verrotti et al., 1997, 1998**; **Sudhop et al., 1999)**.

## *AIM OF THE STUDY*

The study's goal was to study the effect of chronic intake of antiepileptic drugs in epileptic children on serum lipid profile including: Total Cholesterol (TC), Triglycerides (TGs), High-Density Lipoprotein (HDL-C), and Low-Density Lipoprotein (LDL-C).

**Sample size:**

This study is based on a study carried out by **Mujgan Sonmez et al., 2006**. Epi Info STATCALC was used to calculate the sample size by considering the following assumptions: - 95% two-sided confidence level, with a power of 80%. & an error of 5%. The final maximum sample size taken from the Epi- Info output was 44. Thus, the sample size was increased to 50 subjects to assume any drop out cases during follow up.

$x = Z(c/100)\ ^2\ r\ (100-r)$

$n = N\ x/\ ((N-1)\ E2 + x)$

$E = Sqrt\ [(N - n)\ x/n\ (N-1)]$

Where N is the population size, r is the fraction of responses that you are interested in, and Z(c/100) is the critical value for the confidence level c.

**Ethical Considerations:**

1. The study was done after being approved by the Institutional Ethical Committee, Al-Azhar University.
2. Informed consent was obtained from the parents before enrollment of the study.
3. All data was kept confidential.
4. All participants have the right to withdraw from the study without affecting their management.
5. All participants in the study were blinded to keep patient privacy.
6. Exclusion of patients who develop side effects related to the study and stopping the study in case of repeated side effects.

## *PATIENTS AND METHODS*

This study is a cross sectional analytic study conducted on 50 children of epileptic children attending the Pediatric Neurology Clinics of Sayed Galal and El-Shatpy university hospitals and started to use AEDs: Carbamazepine (CBZ), Na valproate (VPA), Levetiracetam (LEV). They were selected by simple random method during the

period from February 201 to January 2022.

**Inclusion criteria:**

1. All children are more than 4 years old.
2. All children were on AEDs for more than 6 months.
3. All children were consuming a normal diet.
4. All children did not change their physical activity during the period of treatment.

**Exclusion criteria:**

1. Patients received chronic drugs that could affect lipid metabolism as corticosteroids, thiazides, or oral anticoagulants.
2. Patients who had neurological deficits other than epilepsy as cerebral palsy or gross developmental delay.
3. Patients with hepatic, renal, or cardiac diseases.

**All patients were subjected to:**

1. Complete history taking with stress on:
    - Detailed seizure record. The clinical description of the events included clinical signs and duration.
2. Complete physical examination with emphasis on neurological examination.
3. BMI.
4. Laboratory studies: Venous blood samples were taken; lipid profile was evaluated in these blood samples [Total cholesterol (TC), triglycerides (TG), high density lipoprotein (HDL-C) and low-density lipoprotein (LDL-C)]

Serum samples were stored at –70°C until the time of analyses. Serum cholesterol levels were measured by a cholesterol oxidase enzymatic method, triglycerides by a glycerol oxidase enzymatic method, high-density lipoprotein cholesterol by a cholesterol oxidase enzymatic method in the supernatant after precipitation with phosphor-tungstic acid–MgCl2, low-density lipoprotein cholesterol by the Fried Ewald formula (total cholesterol – triglycerides/5+ high-density lipoprotein cholesterol).

**Statistical analysis:**

IBM SPSS 26 for windows software was used for the analysis. Descriptive statistics are presented in the form of mean and standard deviation for numerical variables and numbers and percentages are used for the categorical variables. One way ANOVA was used to compare lipid profile across the three antiepileptic drugs. Independent samples t-test was used to compare lipid profile

across different patient categories in antiepileptic drugs, while Mann-Whitney test was used for not normally distributed values. A two tailed p-value < 0.05 was considered statistically significant.

## *RESULTS*

Our results will be demonstrated in the following tables:

**Table (1): Drugs used in the study sample**

| Drug | N | % |
|---|---|---|
| **Na valproate (VPA)** | 15 | 30.0 |
| **Carbamazepine (CBZ)** | 15 | 30.0 |
| **Levetiracetam (LEV)** | 20 | 40.0 |

**Table (2): Demographic data of the studied patients**

| | | Group | | | | | | Total | |
|---|---|---|---|---|---|---|---|---|---|
| | | (Na valproate) | | (Carbamazepine) | | (Levetiracetam) | | | |
| | | N | % | N | % | N | % | N | % |
| Sex | Male | 7 | 46.7% | 6 | 40.0% | 12 | 60.0% | 25 | 50.0% |
| | Female | 8 | 53.3% | 9 | 60.0% | 8 | 40.0% | 25 | 50.0% |
| Age in years | 4-8 | 10 | 66.7% | 11 | 73.3% | 12 | 60.0% | 33 | 66.0% |
| | more than 8 | 5 | 33.3% | 4 | 26.7% | 8 | 40.0% | 17 | 34.0% |
| Drug intake Duration | 1 year or less | 6 | 40.0% | 6 | 40.0% | 7 | 35.0% | 19 | 38.0% |
| | More than 1 year | 9 | 60.0% | 9 | 60.0% | 13 | 65.0% | 31 | 62.0% |

**Table (3): Mean value of the lipid profile for all patients (n=50)**

| | Mean | SD |
|---|---|---|
| Cholesterol (mg/dl) | 135.97 | 40.82 |
| Triglyceride (mg/dl) | 97.26 | 43.44 |
| HDL cholesterol (mg/dl) | 48.28 | 17.25 |
| LDL cholesterol (mg/dl) | 71.42 | 29.21 |

**Table (4): Comparison of lipid profile in the antiepileptic drugs groups**

| | | N | Mean | SD | P-value |
|---|---|---|---|---|---|
| Cholesterol (mg/dl) | (Na valproate) | 15 | 143.40 | 23.69 | 0.205 |
| | (Carbamazepine) | 15 | 145.33 | 49.48 | |
| | (Levetiracetam) | 20 | 123.37 | 42.43 | |
| Triglyceride (mg/dl) | (Na valproate) | 15 | 97.33 | 45.14 | 0.482 |
| | (Carbamazepine) | 15 | 107.60 | 51.57 | |
| | (Levetiracetam) | 20 | 89.45 | 35.44 | |
| HDL cholesterol (mg/dl) | (Na valproate) | 15 | 49.60 | 18.12 | 0.354 |
| | (Carbamazepine) | 15 | 52.47 | 21.31 | |
| | (Levetiracetam) | 20 | 44.15 | 12.54 | |
| LDL cholesterol (mg/dl) | (Na valproate) | 15 | 74.47 | 17.31 | 0.592 |
| | (Carbamazepine) | 15 | 75.00 | 37.98 | |
| | (Levetiracetam) | 20 | 66.45 | 29.56 | |

This table shows insignificant difference regarding lipid profile in the different AED groups.

**Table (5): Comparison of lipid profile regarding sex in different antiepileptic drug groups**

| Group | | Sex | N | Mean | SD | P-value |
|---|---|---|---|---|---|---|
| (Na valproate) | Cholesterol | Male | 7 | 128.14 | 22.48 | 0.013* |
| | | Female | 8 | 156.75 | 15.89 | |
| | Triglyceride | Male | 7 | 89.57 | 48.82 | 0.553 |
| | | Female | 8 | 104.13 | 43.81 | |
| | HDL cholesterol | Male | 7 | 46.71 | 17.20 | 0.583 |
| | | Female | 8 | 52.13 | 19.68 | |
| | LDL cholesterol | Male | 7 | 63.71 | 15.46 | 0.011* |
| | | Female | 8 | 83.88 | 13.34 | |
| (Carbamazepine) | Cholesterol | Male | 6 | 168.33 | 51.84 | 0.147 |
| | | Female | 9 | 130.00 | 44.08 | |
| | Triglyceride | Male | 6 | 130.33 | 45.09 | 0.171 |
| | | Female | 9 | 92.44 | 52.33 | |
| | HDL cholesterol | Male | 6 | 49.17 | 20.39 | 0.642 |
| | | Female | 9 | 54.67 | 22.84 | |
| | LDL cholesterol | Male | 6 | 85.50 | 25.50 | 0.352 |
| | | Female | 9 | 68.00 | 44.49 | |
| (Levetiracetam) | Cholesterol | Male | 12 | 125.08 | 26.04 | 0.831 |
| | | Female | 8 | 120.79 | 61.72 | |
| | Triglyceride | Male | 12 | 90.00 | 39.22 | 0.935 |
| | | Female | 8 | 88.63 | 31.49 | |
| | HDL cholesterol | Male | 12 | 41.83 | 13.89 | 0.325 |
| | | Female | 8 | 47.63 | 10.03 | |
| | LDL cholesterol | Male | 12 | 65.33 | 20.47 | 0.512 |
| | | Female | 8 | 68.13 | 41.32 | |

*: significant as P value < 0.05.

There was a statistically significant difference in cholesterol in VPA group as it was higher in females than in males p-value=0.013. There was a statistically significant difference in LDL cholesterol in VPA group as it was higher in females than in males p-value=0.011.

**Table (6): Comparison of lipid profile regarding age in different antiepileptic drug groups**

| Group | | Age | N | Mean | SD | P-value |
|---|---|---|---|---|---|---|
| (Na valproate) | Cholesterol | 4-8 | 10 | 150.00 | 18.71 | 0.131 |
| | | More than 8 | 5 | 130.20 | 29.15 | |
| | Triglyceride | 4-8 | 10 | 103.80 | 42.93 | 0.453 |
| | | More than 8 | 5 | 84.40 | 51.69 | |
| | HDL cholesterol | 4-8 | 10 | 51.30 | 19.77 | 0.625 |
| | | More than 8 | 5 | 46.20 | 15.74 | |
| | LDL cholesterol | 4-8 | 10 | 78.10 | 15.85 | 0.220 |
| | | More than 8 | 5 | 67.20 | 19.61 | |
| (Carbamazepine) | Cholesterol | 4-8 | 11 | 142.00 | 51.65 | 0.682 |
| | | More than 8 | 4 | 154.50 | 48.76 | |
| | Triglyceride | 4-8 | 11 | 109.73 | 46.46 | 0.514 |
| | | More than 8 | 4 | 101.75 | 71.81 | |
| | HDL cholesterol | 4-8 | 11 | 54.00 | 20.72 | 0.661 |
| | | More than 8 | 4 | 48.25 | 25.63 | |
| | LDL cholesterol | 4-8 | 11 | 71.82 | 34.73 | 0.609 |
| | | More than 8 | 4 | 83.75 | 50.69 | |
| (Levetiracetam) | Cholesterol | 4-8 | 12 | 132.33 | 35.39 | 0.258 |
| | | More than 8 | 8 | 109.91 | 50.74 | |
| | Triglyceride | 4-8 | 12 | 88.00 | 38.40 | 0.830 |
| | | More than 8 | 8 | 91.63 | 32.93 | |
| | HDL cholesterol | 4-8 | 12 | 45.92 | 9.88 | 0.455 |
| | | More than 8 | 8 | 41.50 | 16.13 | |
| | LDL cholesterol | 4-8 | 12 | 68.83 | 34.83 | 0.671 |
| | | More than 8 | 8 | 62.88 | 20.97 | |

There was no statistically significant difference in any of the antiepileptic drugs.

**Table (7): Comparison of lipid profile regarding disease duration in different antiepileptic drug groups**

| Group | | Duration | N | Mean | SD | P-value |
|---|---|---|---|---|---|---|
| (Na valproate) | Cholesterol | 1 year or less | 6 | 141.33 | 17.36 | 0.794 |
| | | More than 1 year | 9 | 144.78 | 28.07 | |
| | Triglyceride | 1 year or less | 6 | 115.00 | 44.48 | 0.229 |
| | | More than 1 year | 9 | 85.56 | 44.04 | |
| | HDL cholesterol | 1 year or less | 6 | 40.00 | 10.71 | 0.064 |
| | | More than 1 year | 9 | 56.00 | 19.69 | |
| | LDL cholesterol | 1 year or less | 6 | 78.50 | 16.40 | 0.482 |
| | | More than 1 year | 9 | 71.78 | 18.33 | |
| (Carbamazepine) | Cholesterol | 1 year or less | 6 | 128.67 | 51.38 | 0.304 |
| | | More than 1 year | 9 | 156.44 | 47.82 | |
| | Triglyceride | 1 year or less | 6 | 77.50 | 28.72 | 0.062 |
| | | More than 1 year | 9 | 127.67 | 54.83 | |
| | HDL cholesterol | 1 year or less | 6 | 55.67 | 11.52 | 0.652 |
| | | More than 1 year | 9 | 50.33 | 26.44 | |
| | LDL cholesterol | 1 year or less | 6 | 56.00 | 43.55 | 0.116 |
| | | More than 1 year | 9 | 87.67 | 29.79 | |
| (Levetiracetam) | Cholesterol | 1 year or less | 7 | 126.71 | 24.07 | 0.803 |
| | | More than 1 year | 13 | 121.56 | 50.51 | |
| | Triglyceride | 1 year or less | 7 | 105.00 | 36.14 | 0.155 |
| | | More than 1 year | 13 | 81.08 | 33.45 | |
| | HDL cholesterol | 1 year or less | 7 | 41.71 | 9.30 | 0.538 |
| | | More than 1 year | 13 | 45.46 | 14.16 | |
| | LDL cholesterol | 1 year or less | 7 | 64.00 | 18.78 | 0.794 |
| | | More than 1 year | 13 | 67.77 | 34.66 | |

There was no statistically significant difference in any of the antiepileptic drugs.

## *DISCUSSION*

Epilepsy is a common neurological disorder of childhood and requires long-term use of antiepileptic therapy. The interaction between thyroid hormones and epilepsy is complex **(Tamijani et al., 2015)**.

In agreement with our results **Nishiyama et al., 2019** reported that the TC, TG, HDL-C and LDL-C levels were none significantly differed between carbamazepine and levetiracetam groups. TC, TG, HDL-C and LDL-C levels were non significantly higher in levetiracetam group at baseline, one month and 6 months of treatment.

As well the study by **Ali et al., 2020** who reported that Serum TC, LDL were significantly higher in

epileptic children treated with old (VPA and CBZ namely) and new generation (LEV) AEDs than other groups, TG and VLDL were higher in epileptic children treated with old AEDs than other groups, while newly diagnosed epileptic children have higher LDL than control group, on the other hand there is a significant higher HDL in epileptic children treated with new antiepileptic drugs than newly diagnosed epileptic children and epileptic children treated with old antiepileptic drugs. The difference with our results may be due to the differences in sample size and characteristics.

In contrast to our results **Eltom et al., 2021** found that there was significant difference in mean TC, TG, HDL, and LDL-C levels in the group receiving phenytoin for more than six months when compared with control group P value (0.00) for all lipid profile. Also, significant difference between the mean of TC, TG, HDL-C and LDL-C levels in the group receiving oxcarbazepine for more than six months when compared with control P value (0.00) for all lipid profile. This disagreement may be due to the difference in sample size and inclusion criteria.

In agreement with the current study **Attilakos et al., 2019** aimed to investigate prospectively the effect of levetiracetam (LEV) monotherapy on serum lipid profile and thyroid hormones levels in children with epilepsy.

Also, in line with our results **Karatoprak & Tosun O., 2020** included a total of 75 patients with epilepsy receiving either valproic acid or levetiracetam monotherapy for more than 12 months. The study reported that there were none significantly differed between the studied groups as regard TC, TG, HDL-C and LDL-C levels.

In a cross-sectional comparative study, **El-Farahaty et al., 2015** found significantly higher LDL-C and LDL-C/HDL-C ratio and lower HDL-C in 12 children, when compared with healthy subjects, after LEV treatment for a period of 2.2 ± 0.45 years. Interestingly, in this study, LEV-treated children had the lowest mean TGs levels among the other antiepileptic-drug groups and the control group.

The study by **Rai et al., 2010** reported that there was a significant increase serum level of triglyceride, total cholesterol, HDLc and VLDLc in patients receiving combination therapy of either Phenytoin and Phenobarbitone or Phenytoin and Carbamazepine or Phenytoin

alone. Patients receiving Carbamazepine alone had significant increase in serum levels of triglyceride and VLDLc but no significant changes in serum levels of total cholesterol & HDLc in this group.

Furthermore, **Kumar et al., 2003** the effect of anticonvulsant Drugs on Lipid Profile in Epileptic Patients, found a significant increase in serum levels of triglyceride, total cholesterol, HDL-C and VLDL-C in patients receiving combination therapy of either Phenytoin and Phenobarbitone or Phenytoin and Carbamazepine or Phenytoin alone. Patients receiving Carbamazepine alone had significant increase in serum levels of triglyceride and VLDL-C but no significant changes in serum levels of total cholesterol & HDL-C in this group.

In disagreement with the present results **Vafaee-Shahi et al., 2022** 30 children between 3 and 8 years of age who suffered from newly diagnosed epilepsy and received sodium valproate as monotherapy. The study reported that there were no statistically significant differences in TC, LDL, HDL and TG between males and females before and after using Sodium valproate. This disagreement may be due to the difference in inclusion criteria and samples size.

We did not found more studies assessed the relation between gender and lipid profile in children treated with antiepileptic drugs. To our knowledge there were no studies found in literature assessed the relation between gender and lipid profile in children treated with antiepileptic drugs.

In agreement with our results, **Eltom et al. 2021** reported that there was no correlation between drug duration with lipid profile in on oxcarbazepine and valproic Acid groups. But there was positive correlation between drug duration with TC in phenytoin group p value (0.00) R= 0.811. In contrast with our findings **Rai et al., 2010** reported that there was a significant correlation between duration of anticonvulsant therapy and lipid profile was established. Also, **Kumar et al., 2003** a significant correlation between duration of anticonvulsant therapy and lipid profile was established in this study. These conflicting results may be due to the differences in patients' characteristics including severity of disease and sample size.

## *CONCLUSION*

Epilepsy and antiepileptic drugs are not considered risk factors of dyslipidemias. The

results didn't show significant adverse effect on lipid profile in patients on long term antiepileptic drugs therapy. No significant correlation between age, sex, duration of disease and lipid profile was established except for the Na Valproate (VPA) treatment which showed a significant correlation between sex and Cholesterol as well as LDLc.

## *LIMITATION OF THE STUDY*

We ignored usage of different drugs other than anti-epileptic drugs for short period as antibiotic and anti-inflammatory drugs. However we aimed to overcome this point by excluding cases who reported usage of drugs that affect serum lipids. We did not evaluate effect of duration on extend of affection of each drug on lipid profile. Also, we evaluated limited number of drugs.

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