

## SODIUM VALPROATE AND PHENOBARBITOL: WEIGHT COMPLICATIONS OF TREATMENT IN EPILEPTIC CHILDREN

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### Abstract

#### Objective

The aim of this study was to evaluate and compare the effects of Na Valproate and Phenobarbital on changes in the weight of epileptic patients following treatment for their condition using the drugs mentioned.

#### Materials and methods

Sixty epileptics were assigned into two groups of 30 patients each, the case and controls. The diagnosis was made on the basis of the International League Against Epilepsy (ILAE) characteristics. BMI was defined. In the case group, the patients received 20mg/kg/day of Na Valproate, while the 30 controls received 5mg/kg/day of Phenobarbital for 6 months. Using the Mc Nemar and Chi-2 tests, BMI changes were compared after 6 months between the groups. Fisher's exact test was used to evaluate the role of age, sex, and primary weight on the weight increase due to Na Valproate usage.

#### Results

There were no specific changes in age, sex, primary BMI and fatness between the 2 groups; in the case group, 20 patients(66.7%) and in the controls 4(13.3%) gained weight ( $P < 0.001$ ). There were higher chances of weight gain in children who were older and fatter at the beginning of the study ( $P < 0.2$ ).

#### Conclusion

The results indicate that epileptic children, aged over 10 years, and those who are overweight have more chances of gaining weight or becoming fatter, following treatment with Na Valproate. Further studies investigating the issue are warranted.

**Keywords:** Valproate, Phenobarbital, Epilepsy, Weight, BMI

### Introduction

A major problem encountered in most societies by children is fatness (1).

In children, the prevalence ranges between 16 to 34% in children. Weight gain is also an important complication of epileptic medications, such as Valproate (2), which was introduced to the medicine world in 1970 (3). Fatness is one of the most important side effects of this medicine seen in 40% of children and 57% of adults (4,5). Therefore, the medication compliance is low, often resulting in increased blood pressure, serum levels, diabetes, and coronary artery disease; Increases in weight make patients discontinue medication and/or use alternative medicines which may again have their own complications/side effects. Literature shows studies that have investigated the issue and suggested solutions for the problem (6,7,8). It also needs

to be determined whether the culture and related patterns of eating habits play a role and what other factors, if any affect the problem. To assess and compare the effects of Na Valproate and Phenobarbitol, we investigated epileptic children, referring to the Mofid hospital during 2005, treated with Valproate and Phenbarbitol.

**Materials & Methods**

In this sequential randomized matched double blind trial, 60 epileptic children, aged between 3 to 15 years and being treated with Valproate or Phenobarbital monotherapy, were investigated. Exclusion criteria were: 1. Cessation of medication within 2 months of initiation. 2. Any history of illness constituting a contraindication for Valproate usage. 3. Concurrent use of these medications leading to weight gain. 4. Gastrostomy tube. 5. Mental retardation. Diagnosis was based on ILAE criteria; age, sex, and primary BMI were documented. Those with a BMI higher than the 95% percentile curve were considered ‘fat’(1).

Patients were randomly assigned into two groups of cases, using Valproate, and controls given Phenobarbital; Phenobarbital was administered at a dose of 5mg/kg/day for 6 months, while valproate was given 20mg/kg/day for 6 months.

Patients were followed for six months, after which BMI changes were evaluated and recorded and compared to the previous data. Changes between -0.1 to 0.1, less than -0.1, and over 0.1 were considered to be ‘without change’, ‘reduction’ and ‘increase’ respectively.

The parents were educated on other side effects of Valproate, and taught that 2 months is the minimum period required to demonstrate any weight change. Data were evaluated using the Mc Nemar test for increase in

the weight in the patients of each group, and the Chi-2 test for comparison between the two groups. The association between “age over 10 years old and high BMI” and weight gain was evaluated using Fisher’s exact test.

**Results**

Prior to treatment initiation, both groups were similar regarding age, sex, BMI before the treatment (P<0.2, Table 1).

Following therapy, results of the group receiving Phenobarbital showed that 6-7%, 80% and 3% had “reduced, no change and increased BMI respectively; 26 patients who had normal weight before the treatment, remained as such after; three, who had normal weight previously gained weight after the treatment, and those who had been fat prior to treatment remained the fat after (P<0.6).

In the Valproate consuming group, 33.3% remained without any change and 66.7% gained weight. Ten patients who had normal weight before treatment remained normal after treatment. Eighteen, who had normal weight, prior to treatment gained weight after; 2, who were fat before treatment, remained fat after (P<0.0001). Of patients that gained weight, 2 (10%) were previously fat, whereas among those without any gain or change, none were previously fat (P<0.4).

The percentages of weight gain were 66.7 and 13.3% in the case & control groups respectively (P<0.0001) (Table 2).

Of the Valproate users, among those who gained weight, 6(30%) were over 10 years old; among patients who gained weight, 5 (25%) were female. Of those without any weight gain, 3 (80%) were females and one (10%) was over 10 years old (P<0.2) and (P<0.2) (Table 3).

Table 1: Characteristics of study patients.

Medication	Age(yr)	Sex		BMI	Weight		
		girl	boy		thin	appropriate	fat
Phenobarbital (n=30)	8±3.1	14(46.7)	16(53.3)	15.8±1.8	1	28	1
Valproate (n=30)	8.±3.2	8(26.7)	22(73.3)	16.4±2.4	2	26	2
Results	P<0.8	P<0.2		P<0.4	P<0.4		

Table 2: Changes in the BMI of patients

BMI \ Changes	Reduced	Without change	Increased	Total
Phenobarbital	2 (6.7)	24(80)	4(13.3)	30(100)
Valproate	0(6)	10(33.3)	20(66.7)	30(100)

Table 3: Characteristics of children on Valproate therapy

Weight gain	Positive (n=10)	Negative (n=20)
<b>Age</b>		
< 10y	9(90)	14(70)
> 10y	1(10)	6(30)
<b>Sex</b>		
female	3(30)	5(25)
male	7(70)	15(75)
<b>Primary BMI</b>		
normal	10(100)	18(90)
high	0(0)	2(10)

**Discussion**

Our study have demonstrated more weight gain in children using Na Valproate as compared to Phenobarbital (P<0.0001), a finding that is in agreement with others (4,9).

Many factors result in weight gain; although it results in an increased appetite, it does not effect the total calorie and carbohydrate intake (6). Another factor is damaged termogenesis caused by sympathetic activities dysfunction. Valproate usage affects the hypothalamic neurons and reduces the catecholamine response to carbohydrates(7).

The Leptin protein produced by the OB gene in fat cells, increases with fatness or increased weight; other factors,are including the reduced level of blood sugar due to the increased insulin level, reduced gluconeogenesis,and fatty acids oxidation, and decreased albumin affinity (10).

The direct effect on hunger or appetite center has ruled out and carnitine level has not a great important role (6).

Regarding limitations of this study, the finding, not statistically significant, that chances of gaining weight following use of Valproate, are higher in epileptic children aged over 10 years, could be a consequence of the small sample size of our study; this is similar to the findings of the study conducted by Wirrell and colleagues (9).

Novak and associates, in a study conducted on 55 patients, age range 1.8 to 16.9 years, showed weight and BMI increase have a direct relation with BMI at initiation of treatment, although are not related to ages, sex, time of treatment start and the medication dose (11).

Again in our study, as revealed, the possibility of weight gain is higher in children on Valproate, difference not statistically significant; this finding agrees with those of the Novak study (1), although it differs with those of the Dinesen study, which revealed no such difference; Dinesen found that only patients with a familial disposition to fatness and diabetes

mellitus had higher risks of gaining weight following Valproate therapy (5).

In all these studies the reason for the differences in findings was the small sample sizes; hence any evaluation of the risk factors of weight gain following Valproate therapy, needs investigation of larger sample sizes.

According to our results no significant difference in weight gain was observed between male and female patients; (63% in females and 68% in males), this is in accordance with results of previous studies (5-11).

### Conclusion

Usage of Valproate in epileptic patients results in weight gain, especially in those in their teen years and with higher BMIs. More studies with larger sample sizes are necessary to determine and clarify the risk factors affecting weight gain in epileptic patients.

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