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REVIEW ARTICLE

Valproic acid and weight gain in patients receiving antiepileptic treatment: a systematic review

Ácido valproico y ganancia de peso en pacientes con tratamiento antiepiléptico: una revisión sistemática

Ácido valpróico e ganho de peso em pacientes recebendo tratamento antiepiléptico: uma revisão sistemática

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ABSTRACT

Introduction: valproic acid is a drug used in the treatment of various diseases, including epilepsy. Although it is considered a safe drug, it presents different adverse effects, among them the most common is the considerable increase in body weight. **Objective:** to identify the relationship between the use of valproic acid in patients with antiepileptic treatment and weight gain. **Method:** systematic review carried out at the Universidad Abierta Interamericana, Argentina, in which an exhaustive search of studies was carried out in the PubMed database with MeSH terms on Valproic acid AND weight gain. Once the articles were selected after applying the inclusion and exclusion criteria, 17 remained, which were useful to carry out this research. **Results:** the information from the articles found reveals that the mechanisms through which valproic acid can generate this increase in body weight are still not fully clarified. Several hypotheses have been proposed; the most frequent in the literature are: hyperinsulinemia and insulin resistance, as well as hyperleptinemia and leptin resistance, among others. Patients who present weight gain have important health consequences, particularly the development of obesity and the association with dyslipidemia, arterial hypertension, type 2 diabetes mellitus, and atherosclerosis. In addition, by generating changes in body image, it can bring depression, decreased self-esteem and self-confidence, which causes non-compliance and abandonment of treatment. **Conclusion:** the causal relationship of valproic acid on weight gain in patients with epilepsy is observed.

Keywords: antiepileptics; valproic acid; weight gain; leptin; insulin

RESUMEN

Introducción: el ácido valproico es un fármaco que se utiliza en el tratamiento de varias enfermedades, entre ellas la epilepsia. Aunque se lo considera un fármaco seguro presenta distintos efectos adversos entre ellos el más común es el aumento considerable de peso corporal. **Objetivo:** identificar la relación entre el uso de ácido valproico en pacientes con tratamiento antiepiléptico y la ganancia de peso. **Método:** revisión sistemática realizada en la Universidad Abierta Interamericana, en la que se realizó una búsqueda exhaustiva de estudios en la base de datos PubMed con términos MesH sobre Valproic acid AND weight gain. Una vez seleccionados los artículos tras la aplicación de criterios de inclusión y exclusión quedaron 17, los que fueron útiles para llevar a cabo esta investigación. **Resultados:** la información de los artículos hallados revela que los mecanismos a través del cual el ácido valproico puede generar este incremento de peso corporal aún no están del todo esclarecidos. Se han propuesto varias hipótesis; las más frecuentes en la literatura son: la hiperinsulinemia y resistencia a la insulina, así como también la hiperleptinemia y la resistencia a la leptina, entre otros. Los pacientes que presentan ganancia de peso tienen importantes consecuencias para la salud, en particular, el desarrollo de obesidad y la asociación con dislipidemia, hipertensión arterial, diabetes mellitus tipo 2 y aterosclerosis. Además, al generar cambios en la imagen corporal puede traer aparejada depresión, disminución de la autoestima y confianza en sí mismo, lo que provoca el incumplimiento y abandono del tratamiento. **Conclusión:** se observa la relación de causalidad del ácido valproico sobre la ganancia de peso en pacientes que padecen epilepsia.

Palabras clave: antiepilépticos; ácido valproico; ganancia de peso; leptina; insulina

RESUMO

Introdução: o ácido valpróico é um fármaco utilizado no tratamento de diversas doenças, entre elas a epilepsia. Apesar de ser considerado um medicamento seguro, apresenta diversos efeitos adversos, dentre eles o mais comum é o aumento considerável do peso corporal. **Objetivo:** identificar a relação entre o uso de ácido valpróico em pacientes em tratamento antiepiléptico e o ganho de peso. **Método:** revisão sistemática realizada na Universidad Abierta Interamericana, na qual foi realizada uma busca exaustiva de estudos na base de dados PubMed com termos MeSH sobre ácido valpróico AND ganho de peso. Uma vez selecionados os artigos após a aplicação dos critérios de inclusão e exclusão, restaram 17, que foram úteis para a realização desta pesquisa. **Resultados:** as informações dos artigos encontrados revelam que os mecanismos pelos quais o ácido valpróico pode gerar esse aumento de peso corporal ainda não estão totalmente esclarecidos. Várias hipóteses foram propostas; os mais frequentes na literatura são: hiperinsulinemia e resistência à insulina, assim como hiperleptinemia e resistência à leptina, entre outros. Pacientes que apresentam ganho de peso trazem importantes consequências para a saúde, principalmente o desenvolvimento de obesidade e associação com dislipidemia, hipertensão arterial, diabetes mellitus tipo 2 e aterosclerose. Além disso, por gerar alterações na imagem corporal, pode trazer depressão, diminuição da autoestima e da autoconfiança, o que ocasiona a não adesão e abandono do tratamento. **Conclusão:** observa-se a relação causal do ácido valpróico com o ganho de peso em pacientes com epilepsia.

Palavras-chave: antiepilépticos; ácido valpróico; ganho de peso; leptina; insulina

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INTRODUCTION

Valproic acid (VPA) or valproate is a broad spectrum antiepileptic drug effective against all types of seizures and, as it is useful in both adults and children, it has become the most prescribed drug in the world in recent years[1], although it is also used in other indications such as migraine prophylaxis and bipolar psychiatric disorder.[2]

Valproate is available in different dosage forms for both parenteral and oral use, with the usual effective dose in adults being 500 to 2500 mg/day and in children 10 to 30 mg/kg/day divided in two or three doses.[3]

The mechanism of action of this active is to increase the synthesis and release of gamma aminobutyric acid (GABA) and reduce the release of the excitatory amino acid β-hydroxybutyric acid, attenuate neuronal excitation mediated by activation of glutamate receptors, N-methyl-D-aspartate (NMDA), and also block voltage-dependent sodium channels.[3] It has also been observed that this drug modulates dopaminergic and serotonergic transmission, which could be relevant for its efficacy in some psychiatric disorders and in neurological disorders other than epilepsy. Therefore, VPA should not be considered a specific GABAergic drug.[4,5]

Although it is considered a safe drug, it has several adverse effects, the most common of which is considerable weight gain. Weight gain and obesity are important risk factors for dyslipidemia, hypertension, diabetes mellitus and atherosclerosis, but not only does it affect the patient physically, but also by presenting a change in body image the psychological part such as self-esteem and self-confidence is affected, leading to social isolation and indirectly to poor adherence to treatment.[6,7] This non-adherence to medication will, in turn, lead to an increased risk of breakthrough seizures that will affect the patient's daily activities.[8]

The incidence of suffering from this side effect according to authors Egger and Brett is 44 % of children treated with VPA(9); Dinensen reported a weight gain in 40 % of children and an increase of at least 4 kg in 57 % of adult patients.[10] The prospective study by Verotti showed that 37% of the women being studied developed obesity after starting therapy;[6,11,12] in the article published by Sharpe in 2009, his data indicated that a significant weight gain occurred in 24% of treated children, but it was found to be less common than in adults where the gain was in 50%-70% of patients.[13]

Risk factors associated with weight gain:

Duration of treatment with VPA: weight gain due to the use of this drug is generally observed during the first 3 months of treatment initiation, continues throughout treatment, and reaches a maximum peak after 6 months.[2,7]

Many authors make it clear that patients who gained weight received the medication for a longer time than those who had not suffered this adverse effect. Therefore, the long duration of therapy is directly proportional to the significant increase in body weight.[14]

Gender: A weight increase was observed in both sexes, being more frequent and pronounced in women than in men. This could be related to leptin resistance, as women had significantly higher serum leptin concentrations compared to the other group evaluated, or also to the high frequency of carbohydrate cravings (which was 25.8% in women and 14.3% in men included in this gender study). It was found that during this study women were trying to lose or control their weight through diet (22.6 % of women vs. 7.1 % of men), due to the socio-psychological burden they present, so special attention and therapeutic and preventive approaches are recommended in this group.[15]

Puberty: according to several authors, both prepubertal and postpubertal patients on VPA monotherapy experience an increase in body weight, although it was found to be more frequent in postpubertal patients.[9,16]

Anthropometric measurements: it has been shown that the higher the patient's weight at the beginning of treatment, the more it will increase during the course of treatment. Consequently, it is important to note the patient's body mass index (BMI) at the start of the treatment regimen and during follow-up.[8]

Seizure types and neurocognitive status: one study showed that patients with generalized seizures exhibited a higher risk of weight gain than those with partial seizures, while other studies found no difference between the incidence of one and the other. Those with abnormal neurocognitive status have been considered not to be a risk factor for obesity.[8,10,15]

Daily dose: no correlation has been found between the degree of weight gain and the daily dose of VPA and/or serum concentration of this drug.[17,18]

Mechanisms of production related to weight gain:

The mechanisms underlying weight gain associated with VPA treatment are not entirely clear. It is most likely multifactorial, as the control of food intake and energy expenditure is complex and is regulated peripherally and centrally by various appetite-regulating neuropeptides and cytokines acting in the hypothalamus.[11]

There are several hypotheses to explain this phenomenon which is described below:

Effect of the drug on the hypothalamus: It was suggested that at the level of the hypothalamus by a GABAergic agonist effect and increased levels of neuropeptide Y (NPY), VPA originates an increase in appetite, thirst and satisfaction with caloric beverages. However, this is not considered to be the process by which weight gain occurs, as other patients using GABAergic drugs have not been shown to suffer from this adverse effect.[7]

Effect on adipokines: in addition to the energy storage function, adipose tissue functions as an endocrine organ, which releases various mediating factors into the circulation, called adipokines, such as: leptin, adiponectin, soluble leptin receptor, ghrelin and visfatin. These adipokines are not only related not only to obesity and insulin resistance but also to obesity and cardiovascular diseases, hypertension and dyslipidemia.[1,19]

a) *Leptin:* Leptin is a peptide produced by adipose tissue and its levels are related to body fat and its secretion is influenced by food intake.[20] Leptin resistance is defined as reduced or complete sensitivity to leptin action which probably contributes to altered leptin signaling and decreased negative feedback.[1]

The increase in serum leptin concentrations in VPA-induced weight gain may be a consequence of increased adipose tissue. It has been suggested that VPA causes direct secretion of leptin by adipocytes; this is supported by the finding that VPA directly stimulates pancreatic cells, as shown in vivo studies, and potentiates androgen production through direct stimulation of ovarian theca cells.[11]

A significant increase in serum leptin levels was found in patients with epilepsy who became obese after treatment with VPA, whereas patients also treated with this drug but who remained lean showed no significant change in leptin levels.

They reported serum leptin levels between obese patients taking VPA and obese control group, but not in lean.[7,20] Hyperleptinemia associated with obesity could represent a decrease in leptin sensitivity or leptin resistance.[1,20]

b) *Adiponectin:* adiponectin is abundantly secreted by adipose tissue and is important in glucose and insulin metabolism and the regulation of energy balance.[7] Plasma adiponectin has an inverse relationship with BMI. Plasma levels of this mediator are low in diseases such as type 2 diabetes mellitus, coronary artery disease and insulin resistance, while in obese patients who lose weight the concentrations are elevated, i.e., weight loss generates hyperadiponectinemia.[19] Therefore, it is objective in several studies that weight gain associated with VPA causes a decrease in serum adiponectin levels.[7]

c) *Ghrelin:* peptide hormone secreted by the stomach and has an important role in the regulation of food intake. Its main effect is at the level of the arcuate nucleus of the hypothalamus where it increases appetite by enhancing the expression of orexigenic molecules such as NPY, among others. Serum ghrelin levels increase before a meal, during fasting, in patients suffering from anorexia nervosa and decrease after meals; it also increases after an abundant caloric intake in patients with obesity.[7,15]

Several studies have examined whether there is a relationship between weight gain with VPA and ghrelin. Serum ghrelin levels were found to be low in adult patients with treatment-associated obesity.[20] It is thought that decreased ghrelin levels may be the result of increased leptin and insulin which, in turn, decreases adiponectin through a feedback mechanism occurring in adipose tissue.[21]

d) *Visfatin:* protein with insulin mimetic effects and lowers blood glucose levels. It is more frequently expressed in visceral fat, muscle, liver and bone marrow. Increased levels of this adipokine have been found in patients using VPA relative to patients in the control group, and this could be because it is related to decreased insulin sensitivity. Another article has shown that

no relationship is found between visfatin and glucose alterations associated with the use of VPA.[19]

Hyperinsulinemia and insulin resistance generated by VPA: VPA increases the availability of local free fatty acids; this statement finds support since insulin resistance (IR) is linked to high serum concentration of free fatty acids, motivated by the use of VPA.

Commonly, the state of insulin resistance is associated with increased lipolysis and decreased re-esterification of free fatty acids in adipose tissue, leading to increased serum levels of FFA.[6]

VPA increases the availability of FFA through different mechanisms:

- VPA a fatty acid derivative competes with palmitate for albumin binding sites. The increased availability of long-chain FFA stimulates insulin production, thereby increasing lipogenesis, decreasing lipolysis, increasing glucose consumption as fuel and decreasing serum glucose and increasing appetite through hypothalamic glucoreceptors.[6]
- Inhibits fatty acid oxidation, resulting in a higher level of non-esterified fatty acids, shifts the use of fatty substances to carbohydrates, which decreases glucose concentration.[6]
- It inhibits gluconeogenesis due to decreased serum carnitine a metabolite involved in the transfer of fatty acids across the inner membrane of mitochondria for oxidation, and increases the proinsulin/insulin ratio. Carnitine deficiency may result in reduced fatty acid metabolism and increased glucose.[2,6]
- After initiation of VPA treatment, the catecholamine response to glucose loading was found to decrease. Another hypothesis proposed that VPA may inhibit GLUT-1, a cell membrane protein transporter of glucose activated at the end of insulin signaling. This study showed that GLUT-1 was inhibited at the level of astrocytes and fibroblasts by the drug, resulting in decreased glucose transport and low GLUT-1 mRNA expression. Finally, it has also been shown that VPA directly stimulates pancreatic islet cells, suggesting that it may itself induce hyperinsulinemia.[17,22]

In obese individuals, weight gain that is not associated with increased energy consumption has been explained by defective sympathetic activity.

VPA is a GABA agonist. The plasma level of GABA was found to increase with VPA treatment and this causes membrane depolarization, regulation of pancreatic cells and insulin secretion.[6,17]

Effects on NPY: is important in appetite regulation, food intake, energy homeostasis and in thermoregulation. It has been shown that this neuropeptide increases earlier than leptin in the early period of obesity. There is not much evidence between the relationship between VPA and NPY in the literature, only one study showed a significant increase in NPY, insulin and leptin levels at 6 and 12 months of treatment with VPA, so it could be said that these molecules are the main ones affecting body weight in patients following this treatment. However, this increase in NPY could be beneficial, since it is an endogenous anticonvulsant molecule and suppresses wave discharges in the electroencephalogram, therefore, it may be that it also intervenes with the anticonvulsant effect of VPA.[7]

METHOD

The present study is configured as a systematic review conducted at the Inter-American Open University, which seeks to answer whether weight gain is related to the use of VPA as antiepileptic treatment.

The study population was those patients suffering from epilepsy, without restriction in sex and age, which are using monotherapy with VPA as treatment of this pathology.

Inclusion criteria:
Patients suffering from epilepsy; patients with VPA monotherapy, as antiepileptic; patients of both sexes; without age restriction.

Exclusion criteria:
Patients under treatment for another pathology; patients with other associated diseases; articles in which other adverse effect than weight gain is treated.

The data analysis was obtained from a search in PubMed with the MesH terms Valproic acid AND weight gain. First, we opted for those articles that presented a title that was relevant to the objectives of the study and in accordance with the topic, then a more detailed reading of the abstracts was carried out and, once the articles were selected, the inclusion and exclusion criteria were applied, thus obtaining the 17 contributions that were useful to carry out this systematic review.

RESULTS

The filters applied to all the Mesh terms were Clinical Trial and Randomized Controlled Trial, with no time filter and no language restriction. Seventeen articles were selected after an exhaustive reading of the abstracts and consecutively of the whole article, with the application of the inclusion and exclusion criteria. These articles were:

1. Weight Gain Associated With Valproate in Childhood.[2]
   Ercan Demir, Sabiha Aysun
   Date: January 2000.
   The study included 24 patients diagnosed with primary generalized epilepsy without presenting any other disorder, of whom 14 were males and 10 were females; their ages ranged from 3 years 6 months to 15 years. They were randomly divided into two groups: group A was medicated with VPA plus carnitine while group B received VPA and placebo.
   It was observed that after 3 months of treatment, body mass index and ideal body weight had increased in both groups. The results obtained also confirmed that VPA decreases serum carnitine levels; this was observed in a significant number of patients who had not received supplementation of this amino acid. However, its deficiency is asymptomatic and does not seem to be related to weight gain. Therefore, the pathogenesis of this side effect is probably not through carnitine. Another finding is higher insulin and lower blood glucose levels, which do not correlate with increased BMI and body weight but may be involved in stimulating appetite.

2. Weight change associated with valproate and lamotrigine monotherapy in patients with epilepsy.[16]
   Biton V, Mirza W, Montouris G, Vuong A, Hammer AE, Barrett PS.
   Date: January 2001.
   This study was a randomized, double-blind study. A total of 133 patients were randomized, 65 treated with Lamotrigine monotherapy and 68 with VPA monotherapy. The mean age in the VPA-treated group was 30.1 years, while in the lamotrigine group it was 34.5 years. Both groups included patients of both sexes.
   The result observed was that weight remained stable among patients receiving lamotrigine monotherapy for a period of 8 months, while the group treated with VPA had significantly increased their body weight and the same was evident in the tenth week after the start of therapy. No differences in mean weight gain were observed between men and women within each group.

3. Polycystic ovaries, obesity and insulin resistance in women with epilepsy A comparative study of carbamazepine and valproic acid in 105 women.[23]
   Gerhard Luef, Irene Abraham, Michaela Haslinger, Eugen Trinka, Klaus Seppi, Iris Unterberger, Alexander Alge, Johannes Windisch, Monika Lechleitner, Gerhard Bauer.
   Date: December 2001.
   Included in this study were 105 women aged between 20 and 40 years, of whom 52 were treated with VPA while the other 53 women received carbamazepine.
   The data obtained by performing ultrasound on these patients were that only 28 of them had polycystic ovaries, of which 13 were in the group receiving VPA therapy and the remaining 15 women were in the carbamazepine-treated group.
   It was also found that the body weight and BMI in comparison between the two groups was higher in the VPA group.

4. Increase in Postprandial Serum Insulin Levels in Epileptic Patients With Valproic Acid Therapy.[24]
   Gerhard Luef, Irene Abraham, Friedrich Hoppichler, Eugen Trinka, Iris Unterberger, Gerhard Bauer, Monika Lechleitner.
   Date: October 2002.
   Forty-three age-matched women with different epileptic syndromes have been studied, of which 22 of the patients were treated with VPA and the remaining 21 women were treated with other antiepileptic drugs such as lamotrigine or carbamazepine.
   The results obtained were a higher BMI in those treated with VPA than in those who used the other antiepileptic drugs. Fasting and postprandial leptin levels were also higher in the VPA-treated group. Fasting and postprandial plasma glucose levels showed no differences between the groups. Fasting and postprandial levels showed a substantial increase in proinsulin levels in patients with VPA and not in those who used the other drugs; and with respect to fasting insulin levels, there were no changes between the two groups, but postprandial levels were increased in those who used VPA.

5. Higher androgens and weight gain with valproate compared with lamotrigine for epilepsy.[25]
   Martha J. Morrell, Jouko Isojärvi, Ann E. Taylor, Mogens Dam, Ricardo Ayala, Gema Gomez, Fiona O'Neill g, Pat Tennis, John Messenheimer.
   Date: April 2003.

This study sought to compare androgen levels and weight gain between patients receiving lamotrigine therapy and patients treated with VPA monotherapy. Therefore, 198 subjects were included, of whom 106 were treated with lamotrigine and 92 with VPA.

The results found were that the group using VPA as an antiepileptic drug had a weight gain of 3.7 kg since the start of treatment, while the other group did not change their body weight. The same was true for total serum testosterone and androstenedione levels, which were higher in the VPA group compared to the lamotrigine group.

6. Obesity and Plasma Concentrations of Alpha-Tocopherol and Beta-Carotene in Epileptic Girls Treated with Valproate [26]

Alberto Verrottia, Rita Grecoa, Giuseppe Latini, Michele De Simone, Francesco Chiarellia.

Date: April 2004.

Twenty girls with different types of epilepsy were prospectively studied, their age ranged from 8.5 to 11.2 years. To avoid interference from sex hormones, only prepubertal females were selected. In addition, only those treated with VPA monotherapy were included to exclude interference with other anticonvulsant drugs. Twenty healthy children of the same sex and age who had never been exposed to anticonvulsant drugs were also included in this study as controls. All patients and controls were studied before starting treatment, and a second evaluation one year after initiation.

After 1 year of VPA therapy, 7 of the 20 girls had developed obesity. Therefore, the study group was divided into group A those who had not changed their weight and group B those who had gained weight. In addition, it was also found that plasma concentrations of alpha-tocopherol and beta-carotene decreased in group B, but not in group A and control subjects. Girls in group B also had higher insulinemia values compared to baseline assessment.

Both groups also demonstrated lower triglyceride and LDL cholesterol levels and higher HDL cholesterol levels.

The 7 girls in group B underwent a third evaluation in which 5 of them were discontinued from the drug, and at 6 months all recovered a normal BMI. Antioxidant levels were also reevaluated and all values were found to be normal.

In conclusion, epileptic patients develop obesity during VPA therapy and, in addition, many metabolic changes such as: low levels of vitamins, antioxidants and hyperinsulinemia that may generate greater susceptibility to oxidative stress and contribute to the process of atherogenesis if obesity is not controlled. However, it has been shown that the changes induced by this anticonvulsant drug are transient and reversible with the discontinuation of therapy.

7. Serum Insulin, Leptin, and Neuropeptide Y Levels in Epileptic Children Treated With Valproate[27]

Kursad Aydin, Ayse Serdaroglu, Cetin Okuyaz, Aysun Bideci, Kivilcim Gucuyener.

Date: August 2004.

Twenty patients (10 males and 10 females) newly diagnosed with epilepsy, with an age range of 4 to 12 years were included in this study. BMI was measured, as well as blood levels of NPY, glucose, insulin, cortisol and leptin, before treatment and after the third and sixth months of VPA therapy.

At the end of 3 months of therapy BMI values and serum levels of insulin and NPY increased while those of glucose decreased. After a 6-month follow-up, increases in leptin and cortisol levels were also reflected. In turn, leptin was found to be higher in girls than in boys; no differences were found in NPY and cortisol concentrations.

8. Leptin, ghrelin, and adiponectin in epileptic patients treated with valproic acid.[20]
Greco R, Latini G, Chiarelli F, Iannetti P, Verrotti A.
Date: August 2005.
Forty post-pubertal Tanner stage V patients were studied. All patients were evaluated at the beginning of treatment and after at least 2 years of treatment.
After these 2 years of therapy, 15 patients had developed obesity and, in addition, had higher serum insulin and leptin levels than those who remained at the same weight. At the same time, plasma adiponectin levels were lower in obese patients than in lean and control subjects.

9. Characterization of Insulin Secretion in Valproate-treated Patients with Epilepsy.[28]
Virpi Pylv¨ anen, Arto Pakarinen, Mikael Knip, Jouko Isoj¨ arvi
Date: February 2006.
This study included 51 male and female patients (31 males and 20 females) on VPA treatment and 45 healthy control subjects (23 males and 22 females), their mean age was 30.9 ± 8.5 years.
Their results were that epileptic patients treated with VPA had significantly lower fasting plasma glucose concentrations and higher insulin than control subjects.

10. Valproate, weight gain and carbohydrate craving: A gender study.[15]
Firas El-Khatib, Markus Rauchenzauner, Monika Lechleitner, Fritz Hoppichler, Anis Naser, Markus Waldmann, Eugen Trinka, Iris Unterberger, Gerhard Bauer, Gerhard J. Luef
Date: December 2006.
The patients who participated in this study were 106 (55 women and 51 men) all approximately of the same age. The mean duration of treatment was 1.5 years in women and 1.8 years in men. The doses used in both groups were similar.
In the results a weight gain was observed in both genders, a high proportion of the patients who presented this adverse effect faced a gain of more than 5 kg. Another important finding was that this weight gain was significantly higher in women. Also in women, serum leptin levels and HDL cholesterol concentrations were found to be higher and triglyceride levels lower than in men.
Furthermore, in women the frequency of carbohydrate cravings was 25.8% and in men 14.3%. However, 22.6% of the female patients attempted to lose or control their weight by dieting and only 7.1% of the men also had this intention.

11. The Role of Ghrelin in Weight Gain and Growth in Epileptic Children Using Valproate [21]
Serdal Gungor, Gül Yücel, Ays¸ehan Ak¸, Yilmaz Tabel, Ibrahim Halil Ozerol, Saim Yologlu.
Date: December 2007.
A total of 17 female and 15 male epileptic patients were enrolled in the study group, of whom 20 are pubescent and 15 prepubertal, determined by Tanner staging. The ages ranged from 3 to 15 years. All of them have received monotherapy with VPA with a mean dose of 20 mg/kg/day. In addition, subjects without obesity, associated diseases or chronic drug use were enrolled in the control group.
Body weight and body mass index began to increase significantly from baseline to 6 months of treatments in all patients in the study group. In this study, in turn, an increase in serum ghrelin

levels and a decrease in insulin-like growth factor-1 and insulin-like binding protein-3 levels were detected 6 months after treatment.

It was concluded that weight gain in epileptic patients using VPA may be associated with increased ghrelin levels, since ghrelin stimulates appetite, food intake and thus leads to an increase in weight.

12. Adiponectin and visfatin concentrations in children treated with valproic acid.[29]

Markus Rauchenzauner, Edda Haberlandt, Sabine Scholl-B̈ urgi, Barbara Ernst, Fritz Hoppichler, Daniela Karall, Christoph F. Ebenbichler, Kevin Rostasy, Gerhard Luef.

Date: December 2007.

A total of 142 children over 6 years of age treated on an outpatient basis were enrolled in this study. The first group consisted of 84 patients receiving VPA monotherapy and the second group consisted of 58 children medicated with other antiepileptic drugs (lamotrigine in 12 patients, sulthiame in 12, and levetiracetam in 8 and oxcarbazepine in 26) who served as control subjects.

In the VPA group we found a significant increase in BMI, body fat percentage, serum levels of insulin, leptin and triglycerides than those children who were treated with the other antiepileptic drugs.

13. Effect of valproic acid treatment on body composition, leptin and the soluble leptin receptor in epileptic children.[1]

Rauchenzauner M, Haberlandt E, Scholl-B̈ urgi S, Karall D, Schoenherr E, Tatarczyk T, Engl J, Laimer M, Luef G, Ebenbichler CF.

Date: March 2008.

A total of 142 children with outpatient epilepsy participated in this study, of which 87 children and adolescents received VPA as treatment for at least 6 months and the other 55 patients received a different antiepileptic drug (control subjects).

The children who were treated with VPA had a significantly higher BMI than the control subjects. Also in this group when compared with that not receiving VPA, there was an increase in fasting serum insulin and leptin concentrations, similar soluble receptor concentrations in both, and lower levels of the leptin/soluble leptin receptor ratio. Serum glucose values did not differ between groups.

14. Body Mass Index and Serum Lipid Changes During Treatment with Valproic Acid in Children with Epilepsy.[30]

Salvatore Grosso, Rosa Mostardini, Barbara Piccini, Paolo Balestri.

Date: January 2009.

In this investigation 87 patients (39 females and 48 males) who received VPA as therapy for at least 3 months were included in this prospective longitudinal study. The median age at treatment initiation was 4.8 ± 0.8 years. The median follow-up time from the start of VPA therapy was 3.1 years.

Regarding the results obtained with respect to body weight and BMI, it was visualized that at the beginning of treatment only 6.9% of the patients were overweight, but after introducing this drug the percentage increased to 16% after its use as therapy, and a total of 3.5% and 5.7% were classified as obese before and after treatment, respectively.

15. New adipocytokines (vaspin, apelin, visfatin, adiponectin) levels in children treated with valproic acid.[19]
    Cihan Meral, Ferhat Cekmez, Sebahattin Vurucu, Emre Tascılar, Ozgur Pirgon, F. Emre Canpolat, Osman Metin Ipcioglu, Gokhan Aydemir, Secil Aydınoz.
    Date: May 2011.
    Forty-four children with idiopathic generalized epilepsy treated with VPA and 40 children in the control group were included in this study.
    The results found were that in the group doing VPA therapy BMI, the levels of triglyceride, apelin, visfatin and vaspin increased with respect to the control group. Likewise, HDL cholesterol and adiponectin concentrations were lower.

16. Serum Insulin, Cortisol, Leptin, Neuropeptide Y, Galanin and Ghrelin Levels in Epileptic Children Receiving Valproate.[31]
    Ali Cansu, Ayse Serdaroglu, OrhunÇamurdan, TubaHırfanoğlu, PeyamiCinaz
    Date: June 2011.
    The patients studied were 18 children (9 prepubertal and 9 pubescent), who were in the age range of 3.4 to 15.8 years. There was also a control group of 18 patients of the same sex and age.
    The results showed that the control group, which had started with an average initial weight of 39.95 ± 15.03 kg, at 18 months had an average weight of 44.82 ± 15.93 kg, that is, a difference of approximately 5 kg; while the subjects in the VPA treatment group started with an average initial weight of 38.72 ± 15.10 kg and ended after 18 months with 46.08 ± 16.34 kg, a difference of approximately 7.3 kg.
    This means that after 18 months of treatment with VPA the patients gained 2.3 kg more than expected in children of comparable age and sex. It was also revealed that insulin, leptin, NPY and galanin levels in the VPA group increased, while their ghrelin levels decreased.

17. Plasma leptin, neuropeptide Y, ghrelin, and adiponectin levels and carotid artery intima media thickness in epileptic children treated with valproate.[7]
    Huseyin Tokgoz, Kursad Aydin, Bulent Oran, Aysel Kiyici.
    Date: May 2012.
    This study included 20 children (8 females and 12 males) with a mean age of 8.75 ± 1.62 years treated with VPA monotherapy. Of these patients, 10 had idiopathic partial epilepsy and 10 had idiopathic generalized epilepsy.
    10 had idiopathic generalized epilepsy. Weight, height, BMI, plasma glucose, insulin, leptin, NPY, ghrelin, adiponectin and cortisol levels were measured before starting treatment and at 6 and 12 months after initiation of treatment.
    The results that could be appreciated were the increase in body weight and height at the end of the sixth and twelfth months. BMI also had a significant increase at the end of these same months, being higher after the second 6 months than after the first 6 months. Serum glucose levels did not vary statistically at the end of each measurement period. However, serum insulin levels were elevated at the end of the sixth and twelfth months.
    Compared to pretreatment measurements, there were significant increases in serum NPY and leptin levels at both the sixth and twelfth month. Cortisol levels also increased in the first six months, but

not in the twelfth month. Plasma ghrelin and adiponectin showed no major changes at the sixth and twelfth months.

There were no differences in plasma concentrations of total cholesterol, triglycerides, LDL, HDL in any of their measurements. There were also no differences between the parameters of boys vs. girls or between those with partial or total epilepsy.

DISCUSSION

The findings of importance in the present systematic review are that the results of the eligible studies analyzed show that treatment with VPA as an antiepileptic brings with it as an adverse effect a significant weight gain and increase in BMI in those who use it, whether they are adult or pediatric patients, regardless of their sex. In turn, it was found that women have a greater weight gain in relation to men, and it is believed that this is due to their greater frequency of carbohydrate craving.

It was also found that VPA in comparative studies with other antiepileptic drugs (lamotrigine, carbamazepine, among others), is the drug that causes the greatest increase in body weight, this is important because in those patients who already have some comorbidity, another anticonvulsant drug could be chosen.

As for the limitations of the present research on this subject is that it has not yet been possible to determine exactly what are the risk factors and pathophysiological mechanisms responsible for weight gain, although it is believed to be multifactorial and there are several proposals, such as the effect of the drug at the hypothalamic level, effect on adipokines, NPY, cortisol, what is most frequently manifested in several of the studies analyzed is that patients who develop overweight or obesity present increased serum levels of leptin and insulin, which would appear to be the main mechanisms involved in the development of weight gain. Further research into the pathogenesis of this unwanted side effect would be interesting and useful.

Overweight and obesity, by contributing negatively to both physical and psychological health, is a problem in the field of medicine, therefore, it would be interesting for the physician to properly select the patients to whom to indicate this treatment, inform them before starting the therapy about the adverse effect it produces, advise them on the care to be taken, and thus prevent the patient from having a poor adherence to the treatment and prevent relapses of their epilepsy.

CONCLUSIONS

After examining the existing studies, the causal relationship of VPA on weight gain in patients suffering from epilepsy is observed. The present review will provide new knowledge on this subject, since, as it has been proved, it has both physical and psychological consequences in patients with epilepsy. This, in turn, would lead to study what other preventive therapies for the increase of body weight or curative methods can be used in the processes of epileptic seizures and which are less harmful to health.

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