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# EVALUATE THE EFFECTS OF ANTIEPILEPTIC DRUGS ON REPRODUCTIVE ENDOCRINE SYSTEM IN NEWLY DIAGNOSED FEMALE EPILEPTIC PATIENTS RECEIVING EITHER VALPROATE OR LAMOTRIGINE MONOTHERAPY

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**Abstract:**

*This study has been conducted to analyze the growth of reproductive endocrine alteration in women suffering from epilepsy originating on either VPA (Valproate) or LTG (amotrigine) monotherapy.*

*Hormonal reproductive profiles, ovarian morphology, hirsutism by ultrasonography and data about the menstrual cycle, specifically in newly identified epilepsy suffered women taking VPA (n=34) or secondly LTG (n=32) with the mono-therapy comparison. There are no women who were getting hormonal contraception. All patients described the frequency, type of seizure and their medical history. We also measure fasting insulin, body weight, dehydroepiandrosterone sulfate (DHEAS), testosterone, androstenedione, luteinizing hormone LH, sex hormone-binding globulin SHGB, FSH follicle-stimulating hormone.*

*The mean level of testosterone was importantly boosted in VPA managed women at the time period of six months (p=0.03), the also at 12th month (p=0.01). With the comparison of women of LTG and VPA group the measurement of hirsutism growth (p=0.06), disturbances in the menstrual cycle *(p=0.02) and PCOS (p=0.001).*

*Long-term therapy of valproate in women suffered from epilepsy was linked with the connection of menstrual disturbance and increased PCOS risk development and also there are changes in reproductive hormonal function.*

**Keywords:** ***Testosterone, Menstrual disorders, Polycystic Ovarian Syndrome, Hirsutism***

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## 1.0 INTRODUCTION:

Throughout the globe, epilepsy is highly chronic adverse neurological disorder. Though therapeutic drugs effectively manage seizures in more than 70% of patients, therefore, medication is an enduring requirement and its side effects are common; these effects include on the reproductive endocrine female system. VPA, valproic acid is a common anti-epileptic medicine, having mood stabilizing and anticonvulsant properties. VPA is also effective in bipolar disorder, neuropathic pain and migraines (Brodie, Richens and Yuen, 2009).

Since the last twenty years, it has developed that Polycystic Ovarian Syndrome (PCOS) is developing constantly in those female patients who are taking VPA advising that medicine can disturb ovarian function and also perturb androgen synthesis. PCOS is commonly known endocrine reproductive disorder and affects reproductive age, but the elevated prevalence of 12-26% is described in epilepsy affected women. This disorder basically featured by polycystic ovarian morphology, galactorrhea, hirsutism, hyperandrogenism, infertility, and menstrual abnormalities (Hook, 2005).

The mechanisms of pathogenic causing the link between endocrine disorders and VPA have not been completely expounded. According to some researchers, epilepsy also plays a pathogenic role but others suggest that endocrines disorders have least partially credited to antiepileptic drugs usage (Jack, 2005).

## 2.0 METHODS:

### 2.1 Materials and methods

This study was directed at Neurology Department Database through a PubMed indexed search for EMBASE and MEDLINE was commenced, we also take Ethics committee approvals for this specific use of the database. The epilepsy type was organized according to the (ILAE) International League against Epilepsy (Kim et al., 2013).

2.1.1. Patients Groups

Newly diagnosed 66 female patients' record was taken for this research, accordingly, in newly diagnosed patients, two treatment weeks with any AED, not LTG or VPA is permitted before study enrollment. After the time period of two weeks, there may be benzodiazepines may associate acutely for handling the discovery seizures. This study is based on the data from October 2004 to May 2006 and the patients were between the ages of twelve to forty years. Thyroid function tests basically understood as normal. There is also all patients' history of the menstrual cycles (cycle ≥ 25 and ≤ 35 days). Urine pregnancy test also was done on all the patients at screening time and the criteria of eligibility were negative (McVearry and Meador, 2008).

### 2.2 Study protocol

Patients were allotted randomly in both groups of VPA (with 34 patients) and LTG (with 32 patients). Monotherapy respective drugs were necessary for all patients for at least one year.

2.2.1 Dosage

LTG group patients were instigated with LTG once a day at the ratio of 25 mg for the first fourteen days and then 50 mg daily for next fourteen days. On clinical response basis, the LTG dosage was titrated with a maximum dosage schedule of 550 mg daily. On the other side, all VPA group patients received 750 mg dose daily for a specific first week and increased to 1000 mg daily in next week (Sidhu, Srinivas and Sadhotra, 2017).

2.2.2 Examination of Initial Screening

Epilepsy affected patients who encountered the enclosure abovementioned criteria were physically and clinically examined by neurologists. Data of anthropometric like height and weight also measured. Patients were analyzed at inclusion with the 6$^{th}$-week ending time and also at the 3$^{rd}$-month end, 6$^{th}$-month end and then 9 and 12 month ends (Sidhu, Srinivas and Sadhotra, 2017).

2.2.3 Clinical and anthropometric data collection

Seizure type, age, BMI, menstrual history, drug dose, duration of illness, family history and antiepileptic therapy response clearly recorded in a specifically designed form. BMI (body mass index) was measured by Quetelet's indexing (kg weight/height (m2)). Hirsutism was scored and analyzed by "Ferryman Gallwey System". Eighty percent of patients with PCO expressed PCOS symptoms which twenty percent is expressed as symptoms free. The criteria of Rotterdam are:

a) Menstrual Disturbance (O)
b) Biochemical hyperandrogenism of acne (H)
c) Through ultrasound, polycystic ovarian morphology (P)

While using these criteria, PCOS patients classified into four multiple phenotypes:

Category 1 O+H+P
Category 2 H+O
Category 3 H+P
Category 4 O+P (Sidhu, Srinivas and Sadhotra, 2017)

2.2.4 Reproductive endocrine parameters collection

After twelve hours overnight fast, a blood sample was gathered 3 to 5 early follicular phase of the menstrual cycle. Parameters which measured while using radioimmunoassay kits: luteinizing hormone (LH), serum testosterone (T), prolactin (PRL), androstenedione (A), follicle-stimulating hormone (FSH), (SHBG) sex hormone binding globulin, DHEAS dehydroepiandrosterone sulfate. The estimation of serum testosterone was done by Adiva Centaur CP "Electro-chemiluminescent immunoassay" with 0.35 nmol/L sensitivity and the range of the assay is 0.39-49.8 nmol/L. Interassay and intraassay variation coefficients were 2.7% and 3.3% respectively (SCHIMSCHOCK et al., 2015).

2.2.5 Ultrasonography of Ovarian

Transabdominal pelvic ultrasound underwent patients gone with a conventional screening time full bladder and period of twelve month's study. Ultrasonography was accomplished in the phase of initial follicular (menstrual cycle one to seven days). Establishment of PCO morphology done by the detection of ≥12: measuring of follicles 2 to 9 millimeters in diameter and ovarian increased volume (> 10 milliliters) (SCHIMSCHOCK et al., 2015).

2.2.6 IR (insulin resistance) measurement

IR was projected using the "homeostasis model assessment" specifically for IR (HOMA-IR); FINS (fasting insulin) (mIU/L) x FBG (fasting glucose) (mg/d1)/405. IR is described as HOMA-IR level higher than 2.5.

**2.3 VPA with LTD Substitution**

At the ending phase of the study period, 11 female patients who were on the treatment of VPA; swapped to LTG and then again followed up in next six months. The initialization of LTG with 25mg daily for the first week and then dosage was increased with 25 mg per day till 200 mg maintenance dose was successfully achieved. After 200 mg per day, LTG dose was successfully achieved, the VPA dose was tapered "500 mg daily for a week" over three weeks (Sidhu, Srinivas and Sadhotra, 2017).

**2.4 Statistical Assessments**

We use SPSS software for data assessments, specifically with two-tailed, the particular level at $p < 0.05$. Expression of data was in mean ± SD for quantitative measures of parametric while adding to (range) median for nonparametric quantitative measures and both percentage and numbers for categorized data. $\chi 2$ and "Fisher's" exact test also utilized for categorical data analysis. RANOVA "Repeated-measure analysis of variance" with a test of least significant difference of Fisher was utilized to achieve assessment of the outputs. Nominal data outputs or not exactly distributed data were assessed using "Mann-Whitney U Test" and "Wilcoxon Signed-Ranked Test". Bonferroni correction test with ANOVA also used; where involved groups are more than two. Correlation Analysis of Spearman was executed for obesity and IR correlation with menstrual abnormalities occurrence and hormonal and PCO changes (Sidhu, Srinivas and Sadhotra, 2017).

## 3.0 RESULTS:

**Table 1**
The clinical characteristics of the patient groups studied.

| Characteristic | VPA | LTG |
|---|---|---|
| Number | 34 | 32 |
| Age (years) | 27(14–40) | 30 (15–42) |
| Age at onset (years) | 21 (14–28) | 19 (15–32) |
| Type of epilepsy[10] | | |
| a. Generalized motor (%) | 11 (32) | 14 (44) |
| b. Focal aware (%) | 11 (32) | 9 (28) |
| c. Focal impaired awareness (%) | 4 (12) | 3 (9) |
| d. Awareness unknown (%) | 1 (2) | 2 (6) |
| e.Focal motor seizure (%) | 7 (21) | 4 (12) |
| Dose (mg/day) | 1240 (400–2000) | 275 (50–550) |
| Seizures in last 6 month | 3 (1–13) | 7 (1–19) |
| Newly diagnosed/untreated (%) | 70/30 | 56/44 |
| Monotherapy at last visit (no.) | 30 | 27 |
| Seizure control at last visit (no.) | 28 | 23 |

Values are median and range, percentage; VPA, valproate; LTG, lamotrigine.

(Source: Sidhu, Srinivas and Sadhotra, 2017)

Ninety patients were randomized for specific medication after the basic screening, 24 patients were prematurely withdrawn from the study (as shown in figure 1)

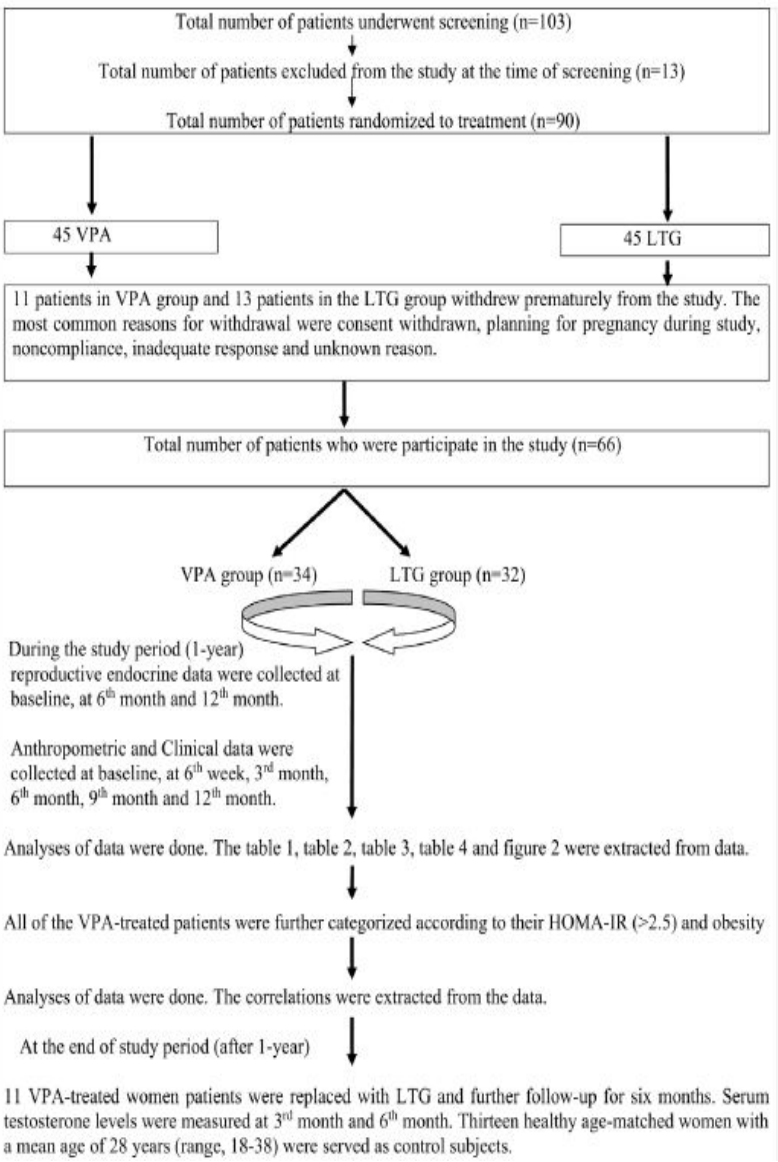


**Fig. 1.** Flow diagram of patient disposition and extraction of data during the study.

Source: Sidhu, Srinivas and Sadhotra, 2017)

Finally, there were 66 patients left in the study. With the median age of 28 years (range 14-42) total 66 females with epilepsy (25 idiopathic generalized and 41 focal-onset) were associated. Of these total 66 patients, 32 were taking LTG and 43 were taking VPA with the minimum period of time of one year. At insertion, 32% (11 female patients) in the group of VPA treatment and 32% (10 female patients) in LTG treatment group were overweight (BMI > 25). In the VPA treated group mean testosterone level was promptly high as compared with LTG group at sixth month (4.41 ± 2.23 vs. 3.61 ± 1.08; p =0.03) and at the end of the 12$^{th}$ month (4.84 ± 1.56 vs 3.48 ± 1.40; p = 0.01). The compared data with the baseline so the serum testosterone levels mean promptly high gradually in the patients of VPA medicated group patients (3.10 ± 1.12 to 4.84 ± 1.56 nmol/L, P < 0.01). DHEAS, LH, FSH, SHBG, and FAI have no important change and either with LTG or VPA the androstenedione also have not change. Thus, the treatment of VPA causes no important boom in SHBG and a decline in the levels of DHEAS. Hirsutism was assessed in three (which ratio is 10%) with the average HS score =14 of the VPA medicated females; but on the other group of LTG, no female develop any hirsutism. In 11 female patients there was menstrual disturbance found and among 11 (30%) nine received the treatment of VPA and (6%) two received LTG (P=0.02). Most of these female patients have oligomenorrhea. Reports showed that amenorrhea also saw in 3 VPA treatment receiving females. The menstrual disturbances incidence was greater in overweight

patients as compared to lean patients in both VPA and LTG group. Through ultrasonography 3 VPA treatment group females, who also had isolated disturbance of menstrual cycle, detected normal ovaries (Sidhu, Srinivas and Sadhotra, 2017).

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## 4.0 DISCUSSION:

This research suggested that VPA treated, specifically in a long-term basis, in epileptic women was linked with high risk of obese, menstrual abnormalities, hirsutism development, PCOS in reproductive hormonal function, specifically during the first 6 months of treatment and this alteration observed to be highly progressive over the last 6 months of therapy. Nineteen women from 34 (57%) in the VPA treated group gained weight (with the range, 1-10 kilograms) if we compare with 8 out of 32 (25%) women (range, 1-3 kilograms) in other LTG group (Rick, James and Olga, 2018).

This study the patients treated with VPA had greater pre-medication weight were more similar to increase their weight in the time of therapy course. All our results are in accordance with Elaine and Wirrel (2003) who clarified that higher weight before initiating any therapy was a forecaster of great BMI at the ending time of the study (P <0.0002). We also analyzed that elevated mean of serum testosterone degrees in all those women patients who fell in the VPA treatment group. There was both biochemical and clinical hyperandrogenemia, accordingly, some female patients had increased level of testosterone at a sixth month earlier to the menstrual abnormalities appearance (Rick, James and Olga, 2018).

Our findings also supported by some other studies which advise that VPA associated hyperandrogenemia occur in the initial stage in the first one to three months of initiation. In VPA treated female patients there were high occurrences of menstrual abnormalities found (30%) according to this study as compared to 7% general population prevalence. Several studies proved that therapy of VPA was linked with a high risk of menstrual disturbances (Zeng et al., 2010).

## 5.0 CONCLUSION:

According to this study, we advised that hormonal alterations and sexual dysfunction require to be tackled in inclusive epilepsy research programs of specifically managed nature, with broader samples and with longer periods of follow-up. The medication of those women who are in the age of child-bearing with epilepsy disease is typically challenging. Many points need to keep in mind while managing with mentioned distinctive cases such as AEDs effects on body weight, appearance, fertility, bone mineral density, contraception, sexual functions, developing embryo, breastfeeding, and pregnancy.

Evaluation of regular including endocrinologist, neurologist, psychiatrist, and gynecologist is required while handling epileptic patients. Longitudinal designed large sample size researches and longtime follow up is exclusively supportive in featuring the effects of time and length of exposure impacts of AESs on the function of reproduction. These researches should contain the new trends of AEDs. Presently, evidence-based medicine concept is gaining more attention. The AEDs choice will be further driven by highly accurate and complete deliberations to enhance the epileptic treatment specifically for individual patients.

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