

# Effects of antiepileptic drugs on sexual function and reproductive hormones of male epileptic patients

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## Keywords

Antiepileptic Drugs, Sexual Function, Male Reproduction, Epilepsy

## Abstract

**Background:** Diminished libido and sexual dysfunction are unusually common among male epileptic patients. The most important etiologic factor may be antiepileptic drugs (AEDs)-induced androgen deficiency. We compared reproductive hormone levels among men with epilepsy taking various AEDs and normal controls.

**Methods:** Subjects were 59 male epileptic patients who aged  $24 \pm 5$  years. They had been receiving lamotrigine (LTG) (n = 17), carbamazepine (CBZ) (n = 18), and sodium valproate (VPA) (n = 15) for at least 6 months. We also recruited 23 healthy controls. Testosterone, estradiol, dehydroepiandrosterone sulfate (DHEAS), sex hormone-binding globulin (SHBG), androstenedione (AND), luteinizing hormone (LH), and follicle stimulin hormone (FSH) levels and gonadal efficiency (testosterone/LH) were compared between the four groups. The patients and the control group were examined and evaluated for male reproduction by urology and endocrinology services.

**Results:** Subjects receiving CBZ, VPA, and LTG had significantly lower mean testosterone levels than the control group ( $P < 0.01$ ). In addition, patients receiving LTG had significantly higher mean testosterone levels than CBZ and VPA groups ( $P < 0.01$ ) and controls ( $P < 0.05$ ). There were not any significant differences between the groups in mean estradiol levels. The mean AND level in VPA was higher than CBZ, LTG, and control groups ( $P < 0.01$ ). Men receiving CBZ had significantly lower DHEAS levels than the other groups ( $P < 0.01$ ). Testosterone/LH ratio in the control group was more than other groups ( $P < 0.01$ ). On the other hand, this value in LTG group was higher than CBZ and VPA groups ( $P < 0.01$ ). However, CBZ and VPA groups were not significantly different in terms of testosterone/LH ratio.

**Conclusion:** Although the mean levels of reproductive hormones were lower in the LTG group compared to the controls, among traditional antiepileptic drugs, LTG had fewer side effects on reproductive hormones. Therefore, it is a good adjuvant and substitute drug for epilepsy control instead of CBZ and VPA.

## Introduction

Epilepsy, antiepileptic drugs (AEDs), and the reproductive system have complex interactions.

Fertility is lower in both men and women with epilepsy than in the general population.<sup>1-3</sup> Moreover, reproductive endocrine disorders are more common among patients with epilepsy than among the normal population.<sup>4,6</sup> While menstrual disorders, polycystic ovaries, and infertility have been described in women,<sup>7-9</sup> reduced potency, diminished libido, erectile dysfunction, lack of sexual satisfaction, and sperm abnormalities have been found in men.<sup>7,10,11</sup> In both sexes, sexual problems<sup>12</sup> and endocrine changes have been frequently described in previous studies.<sup>7-9</sup> These disorders have been attributed to both epilepsy itself and AEDs. This study compared sexual function and reproductive hormone levels among male epileptic patients taking various antiepileptic drugs and normal controls.

### Materials and Methods

In this study, 59 male epileptic patients, of whom 18 were on carbamazepine (CBZ), 15 were on sodium valproate (VPA), and 17 were on lamotrigine (LTG), were enrolled. The mean age of participants was  $24 \pm 5$  years. These patients had referred to the outpatient neurology and epilepsy clinics of Isfahan University of Medical Sciences, Iran.

All subjects were epileptic patients (generalized or focal) with idiopathic epilepsy whose diagnosis was made by an expert neurologist at least one year prior to the study. Patients were treated with CBZ, VPA, or LTG and had not changed their AED or its dose over the previous 6 months. Individuals with history of endocrine comorbidity, evidence of diabetes or thyroid dysfunction as determined by fasting serum glucose, thyroid stimulating hormone, and thyroxine (T4) measurements, pituitary abnormality on cranial magnetic resonance imaging (MRI), or evidence of depression as determined by the clinical assessment of a psychiatrist were not included. In addition, patients were not recruited if there was an evidence of anatomical disease of testes such as varicocele, spermatocele, cyst, or occult testicle in the clinical assessment by a urologist. On the other hand, 23 male age-matched subjects who had no known history of diseases were recruited as healthy controls (mean age:  $24 \pm 4$  years). None of the controls had a history of seizures or medical, neurologic, or endocrine illness, and none was receiving medication.

After receiving written informed consents from all subjects, morning blood samples were obtained to assess pituitary hormones including luteinizing hormone (LH), follicle stimulating hormone (FSH), and prolactin (PRL). Gonadal hormones, i.e. testosterone (T) and estradiol (E), sex hormone binding globulin (SHBG), androstenedione (AND), and dehydroepiandrosterone (DHEAS) levels were also

determined. Estimate of gonadal efficiency (T/LH) was calculated for each subject. Blood samples were centrifuged. After 20 minutes, the serum was separated and the samples were frozen at -20 degrees centigrade until hormone assays were performed. The examination and measurement of testes were conducted by an urologist. The length, depth, and width of testes were measured using a ruler, a pair of calipers, or ultrasound imaging. In addition, semen analysis was performed in 33 of our cases (about 60%).

The ethics committee of Isfahan University of Medical Sciences approved this study. Quantitative data was expressed as mean and standard deviation (SD). Categorical variables were described by relative frequencies. For comparisons of the quantitative variables the Student's t- test was used. Chi-squared test with Pearson modification was used for comparisons between the categorical variables. Intergroup comparisons of the quantitative variables were made by analysis of variance (ANOVA). The statistical significance criterion was set at  $P < 0.05$ .

### Results

The mean testicle length, breadth, and height were  $4.5 \pm 0.5$ ,  $2.0 \pm 0.5$ , and  $2.5 \pm 0.5$ , respectively. While 27 patients (92%) had normal semen analysis, four cases had reduced motility and sperm count of two cases was zero. The ages of the groups were not significantly different. In addition, the three epileptic patient groups did not significantly differ in duration of epilepsy and frequency of focal or generalized epilepsy (Table 1).

Hormone test results are shown in table 2. Men receiving CBZ, VPA, and LTG had significantly lower mean T levels than the control group ( $P < 0.01$ ). Subject receiving LTG had significantly higher mean T levels than the CBZ and VPA groups. While the CBZ group had significantly lower DHEAS levels than the other groups ( $P < 0.01$ ), there was no significant difference between other groups. Patients who were on VPA had significantly higher mean AND levels than CBZ, LTG, and control groups ( $P < 0.01$ ). However, the other groups were not significantly different in this regard. Serum levels of DHEAS in LTG treated group were significantly lower than the CBZ and VPA groups, but were in the same range as controls. The CBZ group had significantly higher mean LH levels compared to the other groups. The LTG group had significantly lower FSH levels than the other groups.

T/LH ratio in LTG group was significantly higher than CBZ and VPA groups ( $P < 0.001$ ) but lower than control subjects ( $P < 0.01$ ). There was no significant difference in PRL and E concentration between the groups.

**Table 1.** Age, types of epilepsy, and duration of epilepsy in different groups

Group	Age (years)	Focal Epilepsy	Generalized Epilepsy	Duration of epilepsy (years)
Carbamazepine	25.7 ± 4.7	9 (56.3)	9 (25.0)	7.9 ± 3.1
Sodium valproate	22.7 ± 5.5	3 (18.8)	14 (38.9)	5.8 ± 3.1
Lamotrigine	23.4 ± 3.7	4 (25.0)	13 (36.1)	6.4 ± 3.2
Control	23.8 ± 3.9	-	-	-

Values are expressed as mean ± SD or n (%).

**Table 2.** Serum hormone concentrations in patients who were treated with sodium valproate (VPA), carbamazepine (CBZ), or lamotrigine (LTG) for epilepsy, and in control (CON) subjects

Hormones	Medication Groups	Mean ± SD	P
Testosterone	CBZ	3.60 ± 1.70	> 0.05*
	VPA	3.30 ± 1.90	< 0.01†
	LTG	3.30 ± 1.80	< 0.01‡
	CON	6.60 ± 1.90	< 0.05§
Dehydroepiandrosterone sulfate	CBZ	0.86 ± 0.40	< 0.01*
	VPA	1.80 ± 0.53	< 0.01†
	LTG	1.51 ± 0.41	> 0.05‡
	CON	1.72 ± 0.39	> 0.05§
Androstenedione	CBZ	1.70 ± 0.84	< 0.05*
	VPA	3.21 ± 2.38	< 0.05†
	LTG	1.98 ± 1.02	> 0.05‡
	CON	1.83 ± 0.88	> 0.05**
Sex hormone-binding globulin	CBZ	41.10 ± 21.50	> 0.05*
	VPA	39.70 ± 10.30	< 0.05†
	LTG	20.30 ± 11.20	< 0.05‡
	CON	26.70 ± 9.90	> 0.05§
Luteinizing hormone	CBZ	3.57 ± 0.86	< 0.05‡
	VPA	2.62 ± 0.88	> 0.05†
	LTG	2.94 ± 0.85	> 0.05††
	CON	2.84 ± 0.87	> 0.05§
Follicle stimulating hormone	CBZ	4.48 ± 1.23	> 0.05*
	VPA	4.31 ± 1.87	> 0.05††
	LTG	3.11 ± 0.97	< 0.05§
	CON	4.29 ± 1.53	> 0.05**
Testosterone/luteinizing hormone	CBZ	0.97 ± 0.38	> 0.05*
	VPA	156.90 ± 18.00	< 0.05††
	LTG	153.20 ± 17.10	< 0.05†
	CON	155.30 ± 10.4	< 0.05§
Estradiol	CBZ	150.60 ± 11.60	> 0.05*
	VPA	156.90 ± 18.00	> 0.05†
	LTG	153.20 ± 17.10	> 0.05§
	CON	155.30 ± 10.40	> 0.05**
Prolactin	CBZ	229.00 ± 67.20	> 0.05‡
	VPA	192.90 ± 87.50	> 0.05*
	LTG	189.60 ± 105.70	> 0.05§
	CON	220.80 ± 77.00	> 0.05**

\* Comparison between CBZ and VPA groups

† Comparison between CBZ and LTG groups

\*\* Comparison between CON and CBZ groups

‡ Comparison between VPA and LTG groups

§ Comparison between CON and LTG groups

†† Comparison between VPA and CON groups

## Discussion

The potential effects of epilepsy on reproductive and endocrine function have been reviewed in previous studies. In 1954, Gastaut and Collomb evaluated a series of 36 patients who were mostly resident in institutions. They reported 27 of the patients to be sexually indifferent with infrequent or absent sexual contacts, dreams, and autoerotic behavior.<sup>13</sup> Since

then, there have been frequent reports of this phenomenon, especially in relation to complex partial seizures (CPSs).<sup>14-19</sup> There are a number of possible explanations for this observation. CPSs are associated with atrophy of the hippocampus and amygdale.<sup>20-22</sup> These structures are of fundamental importance for such basic behavioral patterns as feeding, drinking, reproduction, and social interaction.<sup>23</sup> Destruction of

temporal structures in humans results in marked changes in both sexual and social behaviors.<sup>24-28</sup> However, chronic use of AEDs has some side effects on multiple organs.<sup>29</sup> It is noticeable that AEDs may also alter endocrine function in both men and women with epilepsy and this alteration may lead to clinically significant reproductive endocrine disorders in certain cases. In recent years, the effects of enzyme-inducing AEDs (EIAEDs) on androgen metabolism have been invoked as a possible etiologic factor. These drugs have been found to cause an increase in total T (TT) and SHBG, but a decrease in free testosterone (FT) and free androgen index (FAI) in men.<sup>10,25</sup> This led to the suggestion that the reduction of FT and FAI induced by AED therapy is the cause of diminished libido observed in men with epilepsy.

The reproductive endocrine effects of CBZ in men with epilepsy appear to be similar to those observed during PHT medication, except that CBZ has not been reported to be associated with elevated serum TT or E concentrations; in addition, many cross-sectional and prospective studies have reported that an increase in serum SHBG concentrations results in decreased levels of bioactive free androgens (FAI).<sup>9</sup> Some studies have shown that the use of CBZ is associated with a progressive increase in serum levels of SHBG which in turn results in low FAI ratios and reflect decreased serum levels of free, bioactive T in male patients.<sup>28</sup> This progressive change appears to cause sexual dysfunction in some men with epilepsy after long-term CBZ treatment. Low serum DHEAS levels have also been reported in men on CBZ. DHEAS is a weak androgen secreted by the adrenal cortex. The clinical significance of decreased serum DHEAS concentrations is unknown. It has been suggested that the metabolism of hormones and synthesis of

hormone binding globulins is increased during medication with EIAEDs due to liver enzyme induction. No consistent abnormalities have been found in the basal or stimulated serum PRL or gonadotropin levels in men taking CBZ for epilepsy.<sup>28</sup>

VPA is not an EIAED. However, studies have suggested that in addition to reducing serum gonadotropin levels, VPA also increases serum AND concentrations in men with epilepsy. The mechanism by which VPA alters reproductive endocrine function in men with epilepsy is unknown. VPA modifies gamma-aminobutyric acid-ergic (GABAergic) neurotransmission and could alter the secretion of gonadotropins. On the other hand, a direct effect of VPA on testicular androgen synthesis is possible. Cases of infertility have been reported in male subjects taking VPA for epilepsy. An in vitro study suggested that VPA has direct effects on sperm motility.<sup>9</sup> Two recent clinical studies have also shown that VPA may reduce sperm motility, increase the frequency of morphologically abnormal sperm, and be associated with small testicular size in men with epilepsy.<sup>10,11</sup>

### Conclusion

Although the mean levels of reproductive hormones were lower in LTG group than controls, among of traditional AEDs, LTG had fewer side effects on reproductive hormones. Therefore, it is a good adjuvant and substitute drug for epilepsy control instead of CBZ and VPA.

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