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**Hormonal consequences of epilepsy and its treatment in men**

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## **Abstract**

### Purpose of review

Epilepsy and anticonvulsant medications may substantially alter endocrine homeostasis, including the male reproductive hormonal system.

### Recent findings

Seizures in medial temporal lobe structures, through their connectivity to the hypothalamus, alter the secretion of gonadotropins. Levels of circulating bioavailable testosterone are affected by changes in the level of binding proteins, which in turn may be affected by seizure medications. The use of older generation medications which induce the cytochrome P450 system is associated with an increase in sex hormone binding globulin and lower bioactive testosterone. Sexual dysfunction, including decreased libido and decreased potency, and infertility, is seen commonly in men with epilepsy. However, its relation to sex hormone levels remains unclear. Co-morbid depression and anxiety may be important confounding factors. Testosterone and sexual function appear not to be affected by the newer generation (non-inducing) anticonvulsants.

### Summary

Epilepsy and its drug treatments are associated with alterations in hormonal and sexual function in men. Further study is needed to clarify the precise mechanisms behind these alterations, as some of the data conflict. More attention should be paid to this issue in male patients with seizures; when appropriate, treatment for psychiatric co-morbidity and switches in anticonvulsant therapy may be worth consideration.

Key words: Epilepsy, sex hormones, antiepileptic drugs, testosterone, male sexual function

Disclosures: Dr. Sivaraaman has nothing to disclose.  
Dr. Mintzer has engaged in promotional speaking for UCB Pharma and GlaxoSmith-Kline, and has been a consultant for Sunovion, SK Pharmaceuticals, and Eisai. Dr. Mintzer is also a member of the Epilepsy Trial Consortium, through which he has performed advisory work on clinical trials for Sunovion, Pfizer, and Upsher-Smith.

## **Introduction**

Epilepsy is a condition with complex systemic effects, among them those on the endocrine system. There appears to be a bidirectional interaction, with seizures affecting hormonal levels and hormones in turn affecting and modulating seizures. Hormones in patients with epilepsy might conceivably be affected by a) the seizures themselves; b) the underlying brain pathology; or c) by antiepileptic drugs (AEDs). In this review we address the changes in the male reproductive hormonal system associated with all of these factors.

## **Hormonal changes in epilepsy**

Gonadotropins are significantly altered by seizures. An increase in levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH) has been demonstrated following generalized seizures. In fact, the elevation of LH appears to be longer-lasting than the well-known post-ictal rise in levels of prolactin [1]. While LH levels are elevated following seizures in both men and women, FSH levels rise only in women. This effect is seen not just following generalized seizures, but is also seen with partial seizures. The same study also demonstrated an elevation of LH levels following complex partial seizures in women [1].

In addition to the post-ictal hormonal changes shown above, persistent abnormalities of the reproductive hormone system have been shown in men with epilepsy [2-4]. Interictally, men with epilepsy have a slower LH pulse rate, lower mean concentrations and a higher peak amplitude than controls [5]. Furthermore, men with epilepsy have an abnormal LH response curve to gonadotrophin releasing hormone (GnRH) infusion and show greater variability in mean baseline secretion of LH and in pulse frequency. These effects appear to be independent of the type of AED used [3;4]. Interestingly, there appears to be a difference in this response depending on the laterality of the electrical activity, with right sided epileptiform discharges producing a greater alteration in gonadotropin levels [3;6]. In addition, amygdaloid seizures are associated with an increase in activity in regions of ipsilateral hypothalamus associated with reproductive endocrine functioning [7;8] and left and right sides of the limbic system and hypothalamus appear to be physiologically different [8;9](See below). This is corroborated by studies showing that right

temporal lobe epilepsy appears to be associated with a greater sexual dysfunction [8;10-12] and right temporal lobectomy appears to be associated with a better return of sexuality [11;13].

In line with the change in gonadotropin levels, men with epilepsy have been shown to have androgen deficiency. Testosterone in circulation is present in 3 forms: bound to sex hormone binding globulin (SHBG), loosely bound to albumin, and unbound (free). The albumin bound and free forms are available to tissues and constitute the bioactive fragment of the hormone. Investigators have found both a lower bioactive testosterone (BAT) and a greater age-related decline of the hormone in men with epilepsy relative to normal controls [6;14]. The change in dihydrotestosterone, a metabolite of testosterone, which could possibly have important roles in sexual function, has not been well studied in men with epilepsy [15-17].

## **Mechanism of hormonal changes in epilepsy**

The medial temporal lobe structures, especially the amygdala, have extensive reciprocal connections with the ventromedial nucleus of the hypothalamus and thus are important for modulation of pituitary function [18]. Hence, a seizure in the limbic circuits can interrupt the hypothalamic regulation of pituitary hormone secretion. The release of gonadotropins from the pituitary requires a pulsatile release of GnRH from the hypothalamus. A disruption of this pattern of release is associated with abnormal gonadotropin secretion and the resulting decrease in androgen levels and reproductive change [8].

From an endocrine standpoint, the amygdala can be functionally separated into two regions which have an opposing influence on pituitary hormone secretion [19;20]. Lesions in the basolateral region of the amygdala are associated with an increase in GnRH secretion, while lesions of the medial amygdala have the opposite effect [21]. This potential for bidirectional change underscores the fact that the limbic system acts as a regulatory feedback center for the endocrine system; thus, the disruption of this system, whether due to the paroxysmal electrical discharges or the underlying neuronal abnormality, is the presumptive explanation for the hormonal changes seen in temporal lobe epilepsy [4;22].

There is ample evidence from experimental animals to support this concept. Seizures in the limbic system in male rats have been shown to be associated with disruption of androgen levels as well as gonadal structure and function [23]. At the cellular level, unilateral amygdaloid seizures have been shown to activate regions of hypothalamus involved with reproductive endocrine functioning [7]. Electrical stimulation of the amygdala affects activity in hypothalamic neurons as well as endocrine-related sexual behavior and gonadal development [4;20].

This framework notwithstanding, the hypogonadism seen in men with epilepsy is likely multifactorial in etiology, since other factors aside from low gonadotropin levels, such as hyperprolactinemia and changes in SHBG, can affect gonadal function [24]. The contribution of each of these factors to androgen deficiency remains uncertain; for example, while tonically elevated prolactin can itself cause hypogonadotropism, it is unclear whether the transient elevation in the prolactin levels following seizures has a similar effect [3]. Several studies have shown a correlation between the levels of BAT and sexual function in men [6;14;25-27]. Other studies have shown that men with epilepsy may show evidence of sexual dysfunction even in the presence of normal BAT levels, arguing that higher BAT levels may be needed for normal sexual function in the context of epilepsy [3;19]. Changes in BAT may also be mediated by the drugs used to treat seizures (see below).

Though detailed discussion regarding the effects of steroid hormones on seizures is beyond the scope of this review, there is a bidirectional interaction between the hormones and seizures that is illustrated by emerging evidence of the role of testosterone in etiology and pathophysiology of seizures [28]. The mechanism by which testosterone influences seizure activity is complex and in part appears to depend on its metabolites  $17\beta$ -estradiol and  $3\alpha$ -androstenediol [29]. Aromatization of testosterone converts it to  $17\beta$ -estradiol while  $5\alpha$ -reduction yields dihydrotestosterone and

subsequently  $3\alpha$ -androstenediol. Estradiol appears to be proconvulsant while androstenediol demonstrates anticonvulsant properties [29,30]. Recent studies have shown androstenediol to activate  $GABA_A$  by allosteric modulation, and this in turn causes neuronal inhibition [31]. Because of these competing effects, the impact of testosterone supplementation on seizures can be difficult to predict. In concordance with this, some animal studies have reported that testosterone has seizure protective effects[32] while others have shown that they can enhance development of seizures [33]. Data in humans are but lacking though some studies have shown that treatment with testosterone causes a decrease in seizure frequency [27, 38].

### **Clinical features of the hormonal alterations associated with epilepsy**

The disruption of hormonal homeostasis due to epilepsy may result in several clinical features. Patients with epilepsy have altered sexual and reproductive function, psychiatric disturbances such as depression, and weight change, all of which resemble endocrine disturbances [4]. A range of studies have shown that men with epilepsy have a 31-67% incidence of sexual dysfunction, with decrease in libido and potency [11;19;24;34-36]. Newer studies with better structured questionnaires have shown a lower but still significant incidence of sexual dysfunction on the order of 20% [19]. There is also a high incidence of infertility, with abnormal sperm count, motility and morphology in men with epilepsy [8;19;35].

Despite the number of studies independently showing sexual dysfunction and hormonal changes associated with epilepsy, there is a lack of consensus regarding the correlation between the two. While some studies have shown a clear relationship between sex hormone levels and sexuality in men with epilepsy [6;14;25;27], others have failed to find such a correlation [15;17;37]. Indirect support for the hormonal causation theory came from a recent pilot study demonstrating that treatment with testosterone was associated with an improvement in sexual function in men with epilepsy [38]. The drawback in this study is that it did not have a control population. However, the improvement in sexual function was significantly greater in patients who had normalization of testosterone levels, again arguing for a hormonal causation of sexual dysfunction. There was also a significant improvement in mood (and even in seizure frequency) with testosterone treatment. In line with this, the same study showed that combining anastrozole (an aromatase inhibitor which prevents the conversion of testosterone to estradiol) with testosterone therapy was associated with a trend toward even greater improvement in sexual function scores. The fact that SHBG appears to be more consistently associated with poor sexual quality of life in men is another piece of indirect evidence in support of the hormonal theory since SHBG binds to testosterone and avidly decreases its bioavailability [39]. However, this may not be the only mechanism for the sexual dysfunction caused by SHBG, as some investigators have shown a poor correlation with SHBG and BAT [40]. Altered levels of SHBG are predominantly associated with the use of enzyme-inducing AEDs (see below).

In spite of the aforementioned evidence, it would be an over-simplification to assume that the sexual dysfunction seen in patients with epilepsy is wholly hormone-mediated. Epilepsy is associated with substantial psychiatric comorbidity, and this, along with other comorbid conditions, represent some of the major confounding factors pertaining to epilepsy and sexual dysfunction. Affective disorders are overrepresented in the epilepsy population and may contribute to the sex-

ual dysfunction seen [41;42]. A recent study has shown that interictal anxiety and depression could have a significant impact on sexual function in this population [17]. In this regard it is interesting to note the complex interplay between sexuality and depression, as hypogonadism in epilepsy can also manifest as an affective disorder with loss of energy, mood and competitive drive [19;38]. In line with this, treatment with testosterone is associated with a significant improvement in mood as mentioned above [38].

### **Effects of treatment on hormones and sexuality in men with epilepsy**

Because the vast majority of patients with epilepsy are treated with medications, the effects of drugs become virtually intertwined with those of the disease itself. This is of particular importance because of the wide variety of AEDs available currently (Table) [43]. One important property shared by several of these agents - including phenytoin (PHT), carbamazepine (CBZ), and the barbiturates - is that they are potent inducers of the cytochrome P450 (CYP450) enzyme system (Table), which may have significant metabolic implications [44]. The so-called “newer generation” AEDs which have been introduced since the 1990s do not, by and large, affect the CYP450 system. This property may have substantial bearing upon hormonal function.

A consistent finding in the literature has been that epilepsy patients who are treated with inducing agents have lower levels of free and bioactive testosterone than patients treated with non-inducing AEDs such as lamotrigine (LTG) or levetiracetam (LEV) [14;15;45-47]. There are two possible mechanisms for this, the most straightforward being that the drugs induce the metabolism of testosterone into other entities. However, total testosterone levels generally do not differ among subject groups in these studies; what clearly does differ is SHBG, which is significantly elevated among inducer-treated patients in all the aforementioned investigations. Thus, it appears that among the reactions induced by the inducing agents is the production of SHBG, which in turn leads to lower levels of unbound hormone and could conceivably have additional effects of its own.

Regarding the newer (non-inducing) agents, there are some conflicting data. One study which, importantly, included a cohort of untreated men with epilepsy, found that free testosterone levels in LTG-treated men did not differ from controls and concluded that changes in testosterone were clearly drug-related [14]. Another investigation with a more diversely-treated group of patients also found lower free testosterone levels among inducer-treated patients than among non-inducer-treated patients[15]. However, one group found that men treated with CBZ, LTG, or LEV all had reduced free testosterone relative to controls [47]. To complicate matters further, a recent study reported in abstract form using prospective repeated-measures methodology found that 3 of 5 men experienced an increase in testosterone after being treated with LEV [48]. It is worth noting that all of these investigations were cross-sectional in design; prospective repeated-measures studies would likely go a long way toward clarifying these findings. It also bears mention that most studies have shown no differences in total testosterone among the various AED-treated groups, so that one's view of the relevance of this data may depend upon how much credence is given to the importance of free or bioactive testosterone fractions. These caveats notwithstanding, the balance of data suggest that treatment with CBZ or PHT reduces free testosterone.

Ascertaining the functional consequences of drug-induced hormonal changes has proven considerably more complex. A landmark study in men with epilepsy taking PHT, CBZ, or LTG in monotherapy found not only that PHT- and CBZ-treated patients had reduced sexual function relative to LTG-treated and untreated men, but also that sexual function was significantly correlated with BAT levels [14]. This appeared to provide fairly solid evidence that the hormonal alterations caused by inducing AEDs had true adverse clinical effects.

Talbot et al begged to differ [15]. The latter investigators found that indeed, patients taking inducers had lower free testosterone than those taking non-inducers, but that virtually all still had levels which should be adequate for sexual function. Furthermore, they found no significant correlation between testosterone levels and sexual function, and no difference in sexual function between inducer- and non-inducer-treated men; instead, they found that sexual function appeared significantly correlated with levels of anxiety and depression. They concluded that focusing on inducing AEDs was an overly simplistic as an explanation for sexual dysfunction in men with epilepsy. This study has some drawbacks, among them that the newer drugs oxcarbazepine and topiramate were both classified as inducing agents, a claim which we would consider dubious and which might have contaminated the data in their small sample. This is all the more pertinent since there was, in fact, a sizable difference in sexual function scores between the two groups; it failed to reach statistical significance, which might have been simply a function of statistical power. On the other hand, reinforcing these authors' viewpoint was another recent study which found no differences in sexual function in men on CBZ relative to LTG-treated, LEV-treated, and control subjects [47].

Another curious wrinkle was provided by Gil-Nagel et al [49], who found that in a group of men who were switched from another AED to LTG, certain categories of sexual function improved. These authors suggested the possibility that LTG might actively improve sexual function. Additional potential support for this is seen in the Herzog study [14], in which lower-than-average sexual function scores were seen in 20% of untreated epilepsy patients, but only 4% of LTG-treated patients. LTG is well-established to have antidepressant effects, and in light of the findings of Talbot et al [15], one might speculate that improvement in mood due to LTG treatment could have led to enhanced sexual function. Any such hypothesis remains speculative at present, particularly since the most recent study found no evidence of enhanced sexual function in LTG-treated men [47].

Since about a third of patients with epilepsy prove resistant to medical therapies, surgical resection is an important mode of treatment, particularly for those with focal seizures. Studies of sexual function following epilepsy surgery are few; the most thorough one done to date found that changes in sexual function are quite common after temporal lobectomy, but not after resection of other brain regions [13]. In this cohort, changes occurred in either direction and were often (but not always) characterized by patients as in the direction of "more normal". Another study by Bauer et al. has demonstrated normalization of serum androgens after a temporal lobectomy [50]. These findings imply a role for the temporal lobes in reproductive and sexual behavior, but it remains unclear the extent to which these findings in patients with disease are applicable to those with normal brains.

## Conclusion

Epilepsy and some of its drug treatments -- particularly the older enzyme-inducing medications such as PHT and CBZ -- alter the gonadal hormone axis in men and lead to elevated incidence of sexual and reproductive dysfunction. Clinical confounds such as depression make it difficult to ascertain that the former is truly responsible for the latter. Since epilepsy is a very heterogeneous disease, and AEDs are a very heterogeneous drug class, more study will be necessary to sort out the effects of individual drugs and to separate them from the effects of the disease itself. Genetic variability in both the disease and drug response could be responsible for some of the conflicting data seen in this area.

## Bullet Points

- Both epilepsy and some of its treatments appear to have significant effects on male reproductive and sexual function.
- The extent to which these effects stem from the seizures themselves, the underlying brain abnormality (often in the temporal lobes), or co-morbid conditions (e.g. depression) remains to be determined.
- The older, enzyme-inducing anticonvulsants clearly increase sex hormone binding globulin and decrease bioactive testosterone, but the issue of whether this is responsible for any alterations of sexual function has been subject to conflicting reports and requires further study.

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**Table: Major antiepileptic drugs with their mechanism of action and effects of the cytochrome P450 system**

<b>Drug</b>	<b>Presumptive mechanism of action</b>	<b>CYP450 effects</b>
<b>Phenytoin</b>	Voltage- & frequency-dependent blockade of Na <sup>+</sup> channels	Inducer
<b>Phenobarbital</b>	Enhancement of GABA-mediated Cl <sup>-</sup> channel opening duration	Inducer
<b>Primidone</b>	Enhancement of GABA-mediated Cl <sup>-</sup> channel opening duration	Inducer
<b>Carbamazepine</b>	Voltage- & frequency-dependent blockade of Na <sup>+</sup> channels	Inducer
<b>Valproic acid</b>	Uncertain	Inhibitor
<b>Oxcarbazepine</b>	Voltage- & frequency-dependent blockade of Na <sup>+</sup> channels	Partial Inducer <sup>a</sup>
<b>Topiramate</b>	Uncertain	Partial inducer <sup>b</sup>
<b>Lamotrigine</b>	Voltage- & frequency-dependent blockade of Na <sup>+</sup> channels	No effect
<b>Levetiracetam</b>	Binds to synaptic vesicle protein SV2A	No effect
<b>Zonisamide</b>	Voltage- & frequency-dependent blockade of Na <sup>+</sup> channels; possibly others	No effect
<b>Gabapentin</b>	Binds to α <sub>2</sub> δ subunit of presynaptic Ca <sup>2+</sup> channel, reducing neurotransmitter release	No effect
<b>Pregabalin</b>	Binds to α <sub>2</sub> δ subunit of presynaptic Ca <sup>2+</sup> channel, reducing neurotransmitter release	No effect
<b>Lacosamide</b>	Enhancement of slow inactivation of Na <sup>+</sup> channels	No effect

<sup>a</sup>Oxcarbazepine has been shown to induce CYP3A4/3A5, and likely induces the CYP450 enzymes that metabolize 25-hydroxyvitamin D, but has not been shown to have other CYP450 effects.

<sup>b</sup>Topiramate induces the metabolism of oral contraceptive pills at high doses (400 mg/day) but not at low doses (≤200 mg/day). It has not been shown to have other enzyme-inducing effects.