

LOW FERTILITY IN MEN WITH EPILEPSY: UNHAPPY, UNINTERESTED, UNABLE

Sexual Function in Men with Epilepsy: How Important Is Testosterone? Talbot JA, Sheldrick R, Caswell H, Duncan S. *Neurology* 2008;70(16):1346–1352. **OBJECTIVE:** To ascertain the effects on sexual function of men with epilepsy (MWE) of testosterone levels and indices of anxiety and depression. **METHODS:** Sixty MWE taking one antiepileptic drug only (AED), with no comedication, were compared with 60 control men. Total testosterone (TT), free testosterone (FT), bioactive testosterone (BAT), dehydroepiandrosterone sulfate (DHEAS), androstenedione, and sex hormone-binding globulin (SHBG) were measured. Each man also completed validated questionnaires exploring sexual desire (Sexual Desire Inventory [SDI]), sexual response (Sexual Response Inventory [SRI]), erectile function (Sexual Self-Efficacy Scale [SSES]), and anxiety and depression (Hospital Anxiety and Depression Scale). **RESULTS:** MWE reported lower levels of sexual desire and lower erectile function compared with controls. They had significantly higher levels of anxiety, depression, and psychological distress. MWE had significantly higher SHBG levels and significantly lower DHEAS. There were no significant differences between the groups' TT, FT, or BAT levels. BAT levels were significantly lower in men taking enzyme-inducing AEDs than in those taking non-enzyme-inducing AEDs. Visual inspection of TT and BAT levels showed that the majority of MWE and controls had TT and BAT levels above the "androgen threshold" levels of 12 nmol/L TT or 3.8 nmol/L BAT considered necessary for normal sexual function. There was a significant correlation (Spearman rank and simple linear regression) between sexual function and indices of anxiety and depression. There was no significant relationship between SDI and SSES and TT, FT, or BAT (Spearman rank correlation). **CONCLUSIONS:** Concentrating on hormone levels alone as an explanation of sexual dysfunction in epilepsy represents an overly simplistic approach to the problem. Future studies should include measures of quality of life, anxiety, and depression.

COMMENTARY

Men who have epilepsy, particularly those with focal epilepsy, are far less likely to ever father a pregnancy than unaffected males (1). Sexual dysfunction, as manifested by decreased libido, erectile dysfunction, and anorgasmia, occurs in 20 to 50% of men with epilepsy (1,2). A loss of pubic hair, gynecomastia, and testicular atrophy are among the possible physical signs. In some patients, sexual dysfunction may relate to hypogonadism, that is, lower biologically available testosterone (BAT), and abnormal or decreased sperm production. Testosterone exists in three principal forms: 1) tightly bound to sex hormone-binding globulin (SHBG; 45–50%), 2) loosely bound to albumin (50–55%), and 3) unbound to albumin (1–2%) (1). Albumin-bound and unbound testosterone comprise the clinically important BAT, whereas testosterone bound to SHBG is not biologically available (1). Some studies, including the current one by Talbot and colleagues, have found decreased BAT and increased SHBG associated with enzyme-inducing antiepileptic drugs (AED), such as carbamazepine and pheny-

toin, but no alteration of these testosterone components with nonenzyme-inducing AEDs, such as lamotrigine (3,4). Among men with focal epilepsy, BAT levels are normal in 89% of men who are 20 to 30 years of age and in 73% of men between 30 and 40 years of age; thus, the percentage within normal levels is much higher than what would be expected, given the previously mentioned relative infertility incidence (1).

This discrepancy and the results of the Talbot et al. study indicate that other elements must be interposed in any link between epilepsy and males with infertility. The Talbot et al. study offered one example: "a significant correlation . . . between sexual function and indices of anxiety and depression." Stress, depression, and stigma-induced social isolation impair the ability to attract partners and marry (2,5). Psychosocial stress also may influence the development of hypogonadism, as stress may activate the hypothalamo-pituitary axis, increasing the formation of adrenocorticotrophic hormone (ACTH) and endorphin; both of these hormones inhibit gonadotrophin secretion and reproductive function (1,6).

The effect of epileptic discharges on fertility (particularly when abundant) merits consideration. Patients with focal epilepsy are more disadvantaged reproductively than those with primary generalized seizures (7,8). Temporal lobe epileptic

discharge likely disrupts hypothalamic functions associated with reproduction, but direct proof of any contribution to male hypogonadism and, therefore, to the loss of male fertility, is lacking. Afferents from the medial amygdaloid nucleus and the amygdaloid–hippocampal area project directly into the medial preoptic area of the hypothalamus—an area principally involved in reproductive functions (9). Electrical kindling of the rat amygdala increased serum testosterone in one study (10). However, the fact that kindled male rats have far fewer seizures than do patients with temporal lobe epilepsy diminishes the value of the kindling model for human male reproductive assessment (11). Of interest, the medial preoptic area also is involved in motivational aspects of male copulatory behavior; thus, lesions of this area may diminish interest and sexual arousal (9).

Enzyme-inducing AEDs (e.g., carbamazepine and phenytoin) decrease BAT in two ways: 1) by suppressing gonadal testosterone synthesis, and 2) by increasing hepatic production of SHBG (1). While the Talbot et al. study confirmed these effects, their finding that BAT levels exceeded the “androgen threshold” for normal sexual function in both patients and controls suggests that, as with most side effects, AED dose exerts a significant influence. Some types of epilepsy and patients with refractory epilepsy require substantially higher AED dosing than others. For example, the percentage of patients who fall into various epilepsy syndromes or subtypes and who have been seizure-free for more than 1 year ranges from over 80% (e.g., idiopathic generalized epilepsy) to between 24 and 54% (e.g., other focal epilepsies) to 3% (e.g., temporal lobe epilepsy, with dual pathology) (12,13). Moreover, enzyme-inducing AEDs generally are preferred by prescribing physicians for focal epilepsies, whereas nonenzyme-inducing AEDs are selected for generalized epilepsies (14–16). When combining data on seizure severity and AED preferences, it appears that enzyme-inducing AEDs used at higher doses may underlie the higher incidence of infertility in males with focal seizure disorders (7).

The following provides several epilepsy management implications for male patients with epilepsy:

- Establishing whether the seizure disorder is focal or primary generalized, using ictal semiology and one or more EEGs, is important.
- Depression is often hidden by men with epilepsy. Judicious enquiry of the patient and those living with him may be required to ascertain a diagnosis.
- Probing for the presence of sexual dysfunction through history and physical examination can be helpful.
- Reproductive endocrine levels can be measured by determination of the bioactive portions of total BAT and SHBG.

- Patients with seizures that originate focally and are intractable can be considered for resective surgery.
- If economic, employment, and driving factors permit, an attempt can be made to replace the patient’s enzyme-inducing AEDs with nonenzyme-inducing ones.

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References

1. Herzog A. Disorders of reproduction and fertility. In: Engel J Jr, Pedley TA, eds. *Epilepsy: a Comprehensive Textbook*, 2nd ed. Philadelphia: Lippincott, 2007:2053–2059.
2. Pack AM, Gidal BE. Long-term adverse events. In: Engel J Jr, Pedley TA, eds. *Epilepsy: a Comprehensive Textbook*, 2nd ed. Philadelphia: Lippincott, 2007:1209–1212.
3. Herzog AG, Drislane FW, Schomer DL, Pennell PB, Bromfield EB, Dworetzky BA, Farina, EL, Frye CA. Differential effects of antiepileptic drugs on sexual function and hormones in men with epilepsy. *Neurology* 2005;65:980–981.
4. Vining EPG. Drug treatment in adolescents. In: Engel J Jr, Pedley TA, eds. *Epilepsy: a Comprehensive Textbook*, 2nd ed. Philadelphia: Lippincott, 2007:1259–1262.
5. Schupf N, Ottman R. Likelihood of pregnancy in individuals with idiopathic/cryptogenic epilepsy: social and biologic influences. *Epilepsia* 1994;35:750–756.
6. Sapolsky RM. Stress-induced suppression of testicular function in the wild baboon: role of glucocorticoids. *Endocrinology* 1985;116:2273–2278.
7. Schupf N, Ottman R. Reproduction among individuals with idiopathic/cryptogenic epilepsy: risk factors for reduced fertility in marriage. *Epilepsia* 1996;37:833–840.
8. Olafsson E, Hauser WA, Gudmundsson G. Fertility in patients with epilepsy: a population-based study. *Neurology* 1998;51:71–73.
9. Gloor P. The amygdaloid system. In: Gloor P. *The Temporal Lobe and Limbic System*. Oxford: Oxford University Press, 1997:591–722.
10. Edwards HE, Burnham WM, MacLusky NJ. Partial and generalized seizures affect reproductive physiology differentially in the male rat. *Epilepsia* 40:1490–1498.
11. Burnham WM, Edwards HE. Intractable epilepsy, hormonal and reproductive problems: human and animal studies. *Adv Neurol* 2006;97:351–355.
12. Semah F, Picot MC, Adam C, Broglin D, Arzimanoglu A, Bazin B, Cavalcanti D, Baulac M. Is the underlying cause of epilepsy a major prognostic factor for recurrence? *Neurology* 1998;51:1256–1262.
13. Andrade DM, Zumsteg D, Sutula TP, Wennberg RA. Clinical aspects of temporal/limbic epilepsy and their relationships to intractability. *Adv Neurol* 2006;97:39–44.
14. Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Chadwick D, Guerreiro C, Kalviainen R, Perucca E, Tomson T. ILAE treatment guidelines: evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial therapy for epileptic seizures and syndromes. *Epilepsia* 2006;47:1094–1120.
15. Bergey GK. Evidence-based treatment of idiopathic generalized epilepsies with new antiepileptic drugs. *Epilepsia* 2005;46(suppl 9):161–168.
16. Burneo JG, McLachlan RS. Treating newly diagnosed epilepsy: the Canadian choice. *Can J Neurol Sci* 2007;34:230–236.