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Review

Interactions between antiepileptic drugs and hormones

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ABSTRACT

Antiepileptic drugs (AEDs) are known to have endocrine side effects in both men and women. These can affect fertility, sexuality, thyroid function, and bone health, all functions of major importance for well-being and quality of life. The liver enzyme inducing antiepileptic drugs (EIAEDs), like phenobarbital, phenytoin, and carbamazepine, and also valproate (VPA), a non-EIAED, are most likely to cause such side effects. AED treatment can alter the levels of different sex hormones. EIAEDs increase sex hormone binding globulin (SHBG) concentrations in both men and women. Over time, this elevation can lead to lower levels of bioactive testosterone and estradiol, which may cause menstrual disturbances, sexual problems, and eventually reduced fertility. VPA can cause weight gain in both men and women. In women, VPA can also lead to androgenization with increased serum testosterone concentrations, menstrual disturbances, and polycystic ovaries.

Lamotrigine has not been shown to result in endocrine side effects. The newer AEDs have not yet been thoroughly studied, but case reports indicate that some of these drugs could also be suspected to cause such effects if endocrine changes commence after treatment initiation.

It is important to be aware of possible endocrine side effects of AEDs as they can have a major impact on quality of life, and are, at least partly, reversible after AED discontinuation.

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1. Introduction

Epilepsy can have major impacts on several important aspects of life. The severity of the disease varies from good seizure control or seizure freedom (50–60%) with minor side effects from medication, to a debilitating disease with several daily seizures, the need for polytherapy, the occurrence of major side effects, and problems with drug interactions. Many patients also suffer from an underlying brain disease and co-morbidity, with depression or psychiatric disorders, for example, occurring frequently.

The epilepsy itself, with frequent epileptic discharges, can interact with cerebral function and affect memory and other cognitive aspects. Alterations in hormone levels are a direct effect of epileptic discharges, both in animals and humans [1–5].

Distinguishing the side effects of antiepileptic drugs (AEDs) from the many other factors that influence the patients can be difficult. *In vitro* experimental studies, *in vivo* animal studies, and studies in humans using the same medication for diagnoses other than epilepsy, can be helpful. In order to avoid the possible complexity from multiple interactions, monotherapy studies are important.

Despite these investigative difficulties, AEDs have been clearly demonstrated to have several hormonal side effects that can influence important areas in life, such as fertility, sexual function, and bone health. Some side effects may also be of a more cosmetic nature, such as weight gain, hair loss, acne, or a more masculine hair distribution in women. The various drugs affect the hormonal system differently, and cause specific and different types of hormonal disturbances.

2. Reproductive endocrine function in men

2.1. Enzyme-inducing drugs

The AEDs phenobarbital (PB), phenytoin (PHT), and carbamazepine (CBZ) are all inducers of hepatic microsomal enzymes, and thus accelerate the metabolism of other drugs, and also the breakdown and production of sex hormone binding globulin (SHBG). This increases SHBG concentrations and reduces concentrations of free, circulating androgen and estrogen, resulting in

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decreased levels of biologically active sex hormones [6–9]. Elevated estradiol levels have also been found in men with epilepsy taking PHT [7,10].

Low serum dehydroepiandrosterone sulfate (DHAES) concentrations have also been reported in men and women taking PHT and CBZ [6,8,11]. DHAES is a weak androgen that is secreted from the adrenal cortex, but the clinical implication of low DHAES levels is unknown.

Associations between high estradiol levels and sexual dysfunction have been found in men taking PHT [10]. In some men, sexual dysfunction has also been described after long-term CBZ or PHT treatment and is related to low bioactive testosterone levels [12]. Furthermore, both CBZ and PHT have been associated with changes in semen quality [13] and CBZ has been linked with reduced sperm motility and increased frequency of morphologically abnormal sperm [14,15].

Despite these findings, there is no obvious significant reduction in fertility in patients using enzyme-inducing AEDS (EIAEDs) [16].

Oxcarbazepine: Oxcarbazepine (OXC) has a different metabolic pathway to that of CBZ. Instead of oxidation, OXC is metabolized by reduction to its active metabolite, 10,11-dihydro-10-hydroxy-carbamazepine, and induces the liver P450 enzyme system only at high doses [17]. OXC taken in high doses may affect serum testosterone and SHBG levels, and may also induce changes in sperm morphology [18]. However, these findings should be confirmed in further studies before conclusions on their clinical significance can be reached.

2.2. Valproate

Valproate (VPA) does not induce liver enzymes, but, nevertheless, does reduce serum gonadotropin levels and increase concentrations of serum androstenedione [15,19]. These effects may be caused either by a centrally mediated modification of GABA-ergic neurotransmission in the hypothalamus or by a direct effect of VPA on endocrine tissue, in particular in the testis. A direct effect on the testis is supported by studies in dogs, rats, and goats that have demonstrated a reduction in testicular size and altered testicular morphology after VPA treatment [14,19,20]. Similarly, small testicular volumes have also been found in some [14], but not all [14], studies of men taking VPA. Further, semen morphology and motility are affected by VPA. In humans, the number of motile sperms is reduced, and several morphological parameters are changed [14,15]. In contrast to findings with CBZ, sperm from men that have been treated with VPA have been found to show increased tail pathology [14]. A number of studies of infertile men without epilepsy have shown these types of sperm tail abnormalities; bent or coiled sperm tails were found to occur significantly more frequently when pregnancy did not occur [20–22]. These findings suggest that sperm tail changes observed with VPA may affect fertility. Carnitine is important for sperm motility, and reduced sperm motility has been noted in men on VPA, and in whom the free *versus* total carnitine ratio is reduced [23,24].

2.3. Lamotrigine

To date, lamotrigine (LTG) has not been associated with reproductive endocrine disturbances in men with epilepsy nor in non-epileptic animals [12,25–28].

2.4. Levetiracetam

The mode of action levetiracetam (LEV) is mostly unknown, and differs from that of other AEDs. The drug binds to a synaptic vesicle protein, SV2A, which is widely distributed in the central nervous system and in most endocrine tissues. In a paper from Harden et al. [29] from 2010 testosterone levels increased in eight men after LEV treatment. However, this study was uncontrolled and included a very heterogeneous group of patients. In a clinical study by Svalheim [28], 30 men treated with LEV did not differ from controls regarding reproductive hormones or sexual function. Normal levels of sexual hormones were also found in a recent Chinese study by Xiaotian [30], but more sperm abnormalities were reported in LEV-treated males. Further studies are therefore needed before any conclusions can be drawn regarding the effects of LEV on reproductive endocrine function in men.

2.5. Topiramate

Sexual dysfunction has rarely been described in association with treatment with the newer AEDs, but there has been growing evidence of a correlation between topiramate (TPM) treatment and erectile dysfunction [31–33] and dose dependent reversible anorgasmia (both men and women) [34,35]. A non-hormonal, vasogenic mechanism has been suggested to explain these associations [33].

3. Reproductive endocrine function in women

3.1. Enzyme-inducing drugs

As in males, EIAEDs in females reduce the free fractions of steroid hormones, increase SHBG, and may also lower DHEAS. No consistent abnormalities in basal or stimulated serum gonadotropin or prolactin levels have been reported [36]. The clinical consequences of these endocrine changes are unknown. To date, no large study has demonstrated any increased frequency of menstrual disorders or other reproductive endocrine disorders in women treated with these drugs [27].

3.2. Valproate

The first report suggesting a high incidence of menstrual disorders linked to obesity, hyperandrogenism, and polycystic ovaries (PCO) in women taking VPA for epilepsy was published in 1993 by Isojärvi et al. [37]. This was a cross-sectional study of 238 women on VPA monotherapy. These women had significantly more menstrual disorders than controls, and these were frequently associated with PCO and/or hyperandrogenism. PCO and hyperandrogenism were especially common if VPA medication had been started before the age of 20 years. Moreover, the serum mean androgen levels were increased in women on VPA. These findings have been confirmed in later studies [38]. In a large, three-center study, with patients from Finland, Norway and Netherlands, hyperandrogenism and/or PCO were detected in 70% of VPA-treated women, 20% of CBZ-treated women, and 19% of women acting as controls. Menstrual disorders were reported by 59% of women on VPA, compared with 12% of CBZ-treated women and 15% women in the control group [39].

The age dependency, found by Isojärvi in 1993 [37] was later confirmed by others [38]. Furthermore, increases in serum androgen levels were detected before and during pubertal development in young girls taking VPA for epilepsy [40]. A five-year follow-up of these girls showed that of the girls/women who were still on VPA 5 years later (during the follow-up study), 60% had polycystic ovary syndrome (PCOS) as compared with 25% of the girls/women who had stopped taking VPA and switched to other AEDs [41]. These observations indicate that the young ovary is more vulnerable to the effects of VPA.

Similar endocrine changes induced by VPA were also seen in non-epileptic rats in a long-term monotherapy study [25]. A significant, dose-dependent increase in the number of follicular cysts in the ovaries was observed after VPA treatment, together with a reduction in the number of corpora lutea. Blood samples

showed a marked increase in the testosterone: estrogen ratio and a decrease in estrogen levels, with an absence of, or only minor, effects on gonadotropins [42].

Endocrine side effects of VPA have also been seen in women using VPA for bipolar disorders [43,44]. Endocrine side effects caused by VPA seem to be at least partly reversible [45,46] (Table 1).

PCO and hyperandrogenism are not only caused by the weight gain that many VPA users experience, as they also occur in lean VPA-treated women without hyperinsulinemia [39]. However, obesity and related hyperinsulinemia can be caused by VPA and may exacerbate the VPA-related reproductive endocrine disorders [38].

VPA is thought to have a direct effect on follicular steroidogenesis in the ovary. This was studied by Taubøll et al. [47–50], in a series of studies using both porcine and human ovary cells that were exposed to different concentrations of VPA, which was shown to increase testosterone and reduce estradiol secretion. The conversion of testosterone to estradiol at therapeutically relevant concentrations was reduced, indicating an effect on aromatase activity. A direct effect of VPA is further supported by the work of Hattori et al. [51] who demonstrated the presence of the enzyme microsomal epoxide hydrolase (mEH) in human ovaries. mEH is important in detoxification of several substances. Hattori and co-workers showed that human granulosa cells expressed mEH and that inhibition of mEH suppressed conversion of testosterone to estradiol. Given that VPA is a mEH inhibitor, this may be a mechanism by which VPA reduces serum estrogen levels and thereby increases the testosterone: estrogen ratio. This effect would result in an androgen-dominant microenvironment in the ovary and thereby possibly lead to polycystic changes without an increase in levels of luteinizing hormone.

VPA has also been found to affect gene expression. Nelson-DeGrave et al. [52] found that VPA increased expression of CYP17 and CYP11A genes. This occurs in PCOS and implies that VPA treatment may convert normal ovarian theca cells to a PCOS phenotype. In line with this, Gustavsen et al. [53] used a model of human adrenal carcinoma cells, which are capable of full steroidogenesis, to show that VPA resulted in a general down-regulation of expression of genes encoding for enzymes early in steroidogenesis. Using the same cell line, gene analyses suggested that VPA affects NR0BI expression [54], inhibiting promoters of other genes involved in steroidogenesis. Altered expression of NR0BI might explain the observed down-regulation in hormone production.

Table 1
Endocrine effects of antiepileptic drugs.

Drug		Men	Women
EIAED	Tot. testosterone	↔	↔
	Tot. estradiol	↔ (↑?PHT)	↔
	SHBG	↑	↑
	FAI	↓	↓
	DHEAS	↓	↓
	FSH	↔	↔
	LH	↔	↔
VPA	Tot. testosterone	↔	↑
	Tot. estradiol		↓ (?)
	SHBG	↔	↑
	Androstenedione	↔/↑	↑
	DHEAS	↑	
	FAI	↔	↑
	Insulin	↑	↑
	FSH	↓	↔
	LH	↓	↔

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The table shows the most frequently reported findings. Differences between studies do occur. EIAED: enzyme inducing antiepileptic drugs; VPA: valproate; PHT: phenytoin; FAI: total testosterone/SHBG × 100.

3.3. Lamotrigine

Lamotrigine has not been found to have endocrine side effects [26–28,55]. On the contrary, switching from VPA treatment to LTG treatment resulted in normalization of endocrine function during a one-year follow-up of women with a previously identified reproductive endocrine disorder that was likely to be related to VPA medication [46].

3.4. Levetiracetam

In a paper from 2006, we showed for the first time that LEV affected basal, but not gonadotropin-stimulated, testosterone and estrogen secretion from porcine ovarian follicular cells [49]. This observation suggests that LEV may affect reproductive endocrine function. The clinical consequences of this observation are difficult to determine, but it is possible that LEV might only affect reproductive endocrine function in prepubertal female subjects with low serum gonadotropin levels, whereas fertile-aged women might not be at risk because the ovaries are stimulated by higher levels of gonadotropins. In a paper from 2009, no endocrine changes were found in 21 LEV-treated women [28].

3.5. New AEDs

Randomized studies on newer AEDs are lacking, and little is known about their possible endocrine side effects. There have only been a few case reports, and this provides a positive indication that such side effects are rare. However, further studies are required.

4. Menstrual regularity

Women with epilepsy generally experience more menstrual irregularities than healthy women [56]. This is thought to be due both to the epilepsy itself and to the use of AEDs. Menstrual disorders are especially frequent in women on VPA treatment and in women using polytherapy [27,39].

5. Fertility

Fertility rates have been found to be lower in epilepsy patients than in the general population. In the Rochester study, fertility was considered to be reduced to 80% in males and 85% in females [57]. However, in a population-based study from Iceland, no difference in birth rate was found between female epilepsy patients and the reference group [58]. However, genuine infertility is not easy to measure in clinical studies because it depends on the frequency of unprotected intercourse. Social and psychological factors will also affect birth rate, which, erroneously, is often taken as being equivalent to fertility. While the frequency of marriage is lower among epilepsy patients, birth rate is also reduced among the married patients [59,60]. Epilepsy is a symptom of an underlying disease in many patients, and it can be that underlying disease (inherited diseases, cancer, cerebrovascular diseases, etc.) that is the cause of reduced fertility, rather than the epilepsy itself.

The medication taken for epilepsy can still be of importance. As previously noted, semen quality in men and ovarian function in women can be disrupted by AEDs, and changing medication should be considered for epilepsy patients with genuine fertility problems.

6. Sexuality

Several studies have shown that sexual problems are common in people with epilepsy, and a wide range of different problems has been described [61,62].

The reasons for the sexual problems are multifactorial, and both psychological and epileptological factors are probably important. In a large study on otherwise healthy outpatients on monotherapy and with few seizures, sexual problems were as frequent in the control group as in those being treated with LEV or LTG [28]. Psychological factors and the burden of seizures are probably critical, and for many patients are probably of greater importance than the drug treatment itself. Therefore, the specific role of the different AEDs is difficult to ascertain. In general, EIAEDs reduce the free fractions of peripheral sex steroid hormone concentrations, and this is well known to affect sexual function, including reduced libido, and potency problems in men. Herzog et al. [12] found reduced sexual function in men using CBZ or PHT for localization-related epilepsy, while sexual function was normal in men on LTG. The decreased sexual function in men on CBZ or PHT correlated with lowered bioactive testosterone levels. In a paper from Svalheim et al. [28], men and women treated with CBZ reported being less satisfied with their sex lives than those treated with LEV or LTG. In a randomized study by Mattson et al. [63], impotence and decreased libido were reported in 16% of epilepsy patients after starting monotherapy with PB, 12% after starting PHT, and 13% after starting CBZ.

A few cases of anorgasmia have also been described that are apparently associated with gabapentin treatment [64]. LTG, however, was shown not to affect sexual function [12,28,65]. AEDs can affect sexuality through different mechanisms. First, certain AEDs induce liver enzymes that lead to reductions in the free fractions of peripheral sex steroid hormones. Second, a more general, depressive effect of AEDs on brain excitability may have a negative impact on sexual function. It is possible that the more sedative AEDs have greater impact in this respect than some of the newer AEDs with less sedative effects. A negative impact of AEDs on cognitive function may also be important. In order to obtain a better understanding of the possible impacts of different AEDs on sexuality and to elucidate the underlying mechanisms further research on these aspects is essential.

7. Bone health

In comparison with the general population, patients with epilepsy have a 2–6 times greater risk of fractures. In a Danish population-based study from 2004, which included 124,655 fracture cases and 373,962 controls, the fracture risks related to AED exposure were examined [66]. In an unadjusted analysis, all AEDs were associated with an increased risk of fracture. After adjustment for prior fracture, exposure to corticosteroids, comorbidity, social variables, and diagnosis of epilepsy, some drugs were significantly associated with increased fracture risk: CBZ (odds ratio (OR): 1.18); OXC (OR: 1.14), clonazepam (OR: 1.27); PB (OR: 1.79), and VPA (OR: 1.15). For CBZ, PB, OXC, and VPA, a dose–response association was seen. The risk was more pronounced in those who used EIAEDs than in those who used non-inducing drugs.

The results from various studies strongly indicate that AED use may have negative impact on bone health. The older EIAEDs, particularly phenytoin (PHT), are most consistently associated with fractures and reduced bone mineral density (BMD). Pack and Walczak assessed several studies on the effects of individual AEDs on bones [67]. Decreased BMD was found to be associated with PHT use in four of five studies, PB use in two of two studies, and VPA use in three of four studies. CBZ use was only associated with low BMD in one of five studies. Short-lasting treatment with LTG in 93 premenopausal women was apparently not associated with reduction in BMD or with changes in bone turnover markers.

The traditional theory for explaining the bone loss associated with EIAEDs is that turnover of vitamin D and its metabolites is accelerated, owing to increased activity in the cytochrome P-450 system. This results in low vitamin D, reduced intestinal absorption of calcium, low serum calcium, secondary hyperparathyroidism, decreased BMD, and, eventually, fractures [68,69].

Several AEDs, including PHT, PHB, CBZ, and VPA, also appear to have a direct effect on bone cells, resulting in increased bone turnover [67,68,70].

Interaction with vitamin K has also been proposed as a possible mechanism for osteoporosis in patients with epilepsy. Vitamin K is an important co-factor in the synthesis of osteocalcin, an important marker of bone formation. Enzyme-inducing AEDs have been found to reduce vitamin K levels [71].

EIAEDs may also increase the metabolism of sex steroids, resulting in decreased levels of bioavailable endogenous estradiol and testosterone. An increased rate of bone loss may therefore be a consequence of this increased steroidal metabolism [69,72].

Several other mechanisms have also been suggested. These include disruption of brain regulation of bone metabolism *via* increased leptin [67], AED-induced increase in homocysteine [73], and reduction in insulin-growth factor 1 [72].

The mechanisms involved in AED-associated bone loss are likely to be multifactorial and are not yet fully understood. For the individual patient with epilepsy, the risk of developing bone disease is probably determined by a combination of several factors, including genetic factors, epilepsy syndrome, age, gender, lifestyle, and AED treatment.

8. Thyroid function

Some AEDs are associated with alterations in thyroid function. This was first shown in 1981 by Strandjord et al. [74]. In 42 patients on long-term CBZ treatment, thyroxine (T4), free T4-index (FT4), and triiodothyronine (T3) concentrations in serum were found to be significantly lower than in controls, while T3 uptake and thyrotropin (TSH) concentrations did not differ between patients and controls. A study of 90 men with epilepsy taking either CBZ, VPA, or OXC and 25 control men demonstrated that serum T4 and FT4 concentrations were low in men taking CBZ or OXC, with 45% and 24% falling below the reference range, respectively, but serum T3 and TSH levels were normal. In men taking VPA, the concentrations of thyroid hormones and TSH were normal [75].

Another study in children with new-onset epilepsy [76] was performed prospectively with baseline thyroid testing prior to drug administration, followed by testing at 3, 6, and 12 months after initiation of CBZ or VPA treatment. CBZ-treated patients demonstrated significantly lower serum T4 and FT4 levels than at baseline evaluation and compared with control subjects, but normal serum T3 and TSH response in a thyrotropin releasing hormone (TRH) test. This difference could be identified after only 3 months treatment. Some of the CBZ-treated children were withdrawn from CBZ for other reasons, and reevaluation 6 months later revealed that their thyroid hormone values had normalized. All values remained normal in the VPA treatment group. The patients were found to be clinically euthyroid, also in the CBZ group. The authors conclude that thyroid hormone alterations are not associated with clinical or subclinical hypothyroidism.

Another study of 35 patients on long-term PHT or CBZ treatment [77] reported that the mean concentrations of T4, FT4, FT3, and reverse triiodothyronine (rT3), but not T3, of these patients were significantly lower than those of 19 controls. Clinical examination of these patients did not reveal clinical signs of functional hypothyroidism. The authors also assessed response to thyroxine treatment in a smaller subset of patients, and the clinical parameters they examined were found to be unchanged after treatment. On the basis of the data from the cross-sectional and thyroxine treatment studies, the authors concluded that patients receiving AEDs chronically are eumetabolic and do not need thyroxine supplementation.

A recent prospective study on 23 children receiving OXC [78] showed that FT4, but not FT3, was significantly reduced after 8 and 18 months treatment, while TSH was significantly increased.

Alterations in thyroid function seem to be reversible after withdrawal of medication. Lossius et al. [79] showed significant increases in FT4 serum concentrations 4 months after CBZ withdrawal, in both men and women.

For patients with hypothyreosis prior to initiation of AED treatment, use of EIAEDs should probably not be recommended. Otherwise, the clinical importance of the interactions between AEDs and thyroid hormones appears to be minor, if any.

9. Conclusion

Many AEDs may affect an epilepsy patient's hormones and this may result in menstrual disturbances, sexual problems, fertility difficulties, or osteoporosis. In particular, the use of EIAEDs and VPA has been associated with such side effects. The newer drugs, however, have been investigated less and, although current data may imply a lack of such associations, should also be considered if new symptoms arise after initiation of treatment with such drugs. Increased awareness of these side effects will improve the possibility of tailoring treatment regimes to the characteristics of individual patients, paying particular regard to patient age and gender.

Conflict of interest statement

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

References

[1] Edwards HE, Burnham WM, Ng MM, Asa S, MacLusky NJ. Limbic seizures alter reproductive function in the female rat. Epilepsia 1999;40:1370–7.
[2] Edwards HE, Burnham WM, MacLusky NJ. Partial and generalized seizures affect reproductive physiology differentially in the male rat. Epilepsia 1999;40:1490–8.
[3] Feeney DM, Gullotta FP, Gilmore W. Hyposexuality produced by temporal lobe epilepsy in the cat. Epilepsia 1998;39:140–9.
[4] Herzog AG. A relationship between particular reproductive endocrine disorders and the laterality of epileptiform discharges in women with epilepsy. Neurology 1993;43:1907–10.
[5] Banczerowski P, Csaba Z, Csernus V, Gerendai I. Lesion of the amygdala on the right and left side suppresses testosterone secretion but only left-sided intervention decreases serum luteinizing hormone level. J Endocrinol Invest 2003;26:429–34.
[6] Macphee GJ, Larkin JG, Butler E, Beastall GH, Brodie MJ. Circulating hormones and pituitary responsiveness in young epileptic men receiving long-term antiepileptic medication. Epilepsia 1988;29:468–75.
[7] Isojärvi JI, Pakarinen AJ, Ylipalosaari PJ, Myllylä VV. Serum hormones in male epileptic patients receiving anticonvulsant medication. Arch Neurol 1990;47:670–6.
[8] Isojärvi JI. Serum steroid hormones and pituitary function in female epileptic patients during carbamazepine therapy. Epilepsia 1990;31:438–45.
[9] Murialdo G, Galimberti CA, Gianelli MV, Rollero A, Polleri A, Copello F, et al. Effects of valproate, phenobarbital, and carbamazepine on sex steroid setup in women with epilepsy. Clin Neuropharmacol 1998;21:52–8.
[10] Herzog AG. Reproductive endocrine considerations and hormonal therapy for men with epilepsy. Epilepsia 1991;32(Suppl. 6):S34–7.
[11] Levesque LA, Herzog AG, Seibel MM. The effect of phenytoin and carbamazepine on serum dehydroepiandrosterone sulfate in men and women who have partial seizures with temporal lobe involvement. J Clin Endocrinol Metab 1986;63:243–5.
[12] Herzog AG, Drislane FW, Schomer DL, Pennell PB, Bromfield EB, Dworetzky BA, et al. Differential effects of antiepileptic drugs on sexual function and hormones in men with epilepsy. Neurology 2005;65:1016–20.
[13] Chen SS, Shen MR, Chen TJ, Lai SL. Effects of antiepileptic drugs on sperm motility of normal controls and epileptic patients with long-term therapy. Epilepsia 1992;33:149–53.
[14] Røste LS, Taubøll E, Haugen TB, Bjørnenak T, Saetre ER, Gjerstad L. Alterations in semen parameters in men with epilepsy treated with valproate or carbamazepine monotherapy. Eur J Neurol 2003;10:501–6.
[15] Isojärvi JI, Löfgren E, Juntunen KS, Pakarinen AJ, Päivänsalo M, Rautakorpi I, et al. Effect of epilepsy and antiepileptic drugs on male reproductive health. Neurology 2004;62:247–53.
[16] Artama M, Isojärvi JI, Auvinen A. Antiepileptic drug use and birth rate in patients with epilepsy—a population-based cohort study in Finland. Hum Reprod 2006;21:2290–5.
[17] Löfgren E, Tapanainen JS, Koivunen R, Pakarinen A, Isojärvi JIT. Effects of carbamazepine and oxcarbazepine on the reproductive endocrine function in women with epilepsy. Epilepsia 2006;47:1441–6.
[18] Rättyä J, Pakarinen AJ, Knip M, Repo-Outakoski M, Myllylä VV, Isojärvi JI. Early hormonal changes during valproate or carbamazepine treatment: a 3-month study. Neurology 2001;57:440–4.
[19] Krogenæs A, Taubøll E, Stien A, Oskam IC, Lyche JL, Dahl E, et al. Valproate affects reproductive endocrine function, testis diameter and some semen variables in non-epileptic adolescent goat bucks. Theriogenology 2008;70:15–26.
[20] Escalier D, David G. Pathology of the cytoskeleton of the human sperm flagellum: axonemal and peri-axonemal anomalies. Biol Cell 1984;50:37–52.
[21] Toyama Y, Sumiya H, Fuse H, Shimazaki J. A case of an infertile man with short-tailed spermatozoa. Andrologia 1986;28:81–7.
[22] Jouannet P, Ducot B, Feneux D, Spira A. Male factors and the likelyhood of pregnancy in infertile couples, I. Study of sperm characteristics. Int J Androl 1988;11:379–94.
[23] Morand R, Todesco L, Donzelli M, Fischer-Barnicol D, Mullen PJ, Krähenbühl S. Effect of short- and long-term treatment with valproate on carnitine homeostasis in humans. Ther Drug Monit 2012;34:406–14.
[24] Røste LS, Taubøll E, Mørkrid L, Bjørnenak T, Sætre ER, Mørland T, et al. Chronic valproate treatment reduces free carnitine vs total carnitine ratio in men – of importance for semen quality? Epilepsia 2004;45(Suppl. 7):127–8.
[25] Røste LS, Taubøll E, Berner A, Isojärvi JI, Gjerstad L. Valproate, but not lamotrigine, induces ovarian morphological changes in Wistar rats. Exp Toxicol Pathol 2001;52:545–52.
[26] Røste LS, Taubøll E, Isojarvi JI, Berner A, Berg KA, Pakarinen AJ, et al. Gonadal morphology and sex hormones in male and female Wistar rats after long-term lamotrigine treatment. Seizure 2003;12:621–7.
[27] Svalheim S, Taubøll E, Bjørnenak T, Røste LS, Mørland T, Saetre ER, et al. Do women with epilepsy have increased frequency of menstrual disturbances? Seizure 2003;12:529–33.
[28] Svalheim S, Taubøll E, Luef G, Lossius A, Rauchenzauner M, Sandvand F, et al. Differential effects of levetiracetam, carbamazepine, and lamotrigine on reproductive endocrine function in adults. Epilepsy Behav 2009;16:281–7.
[29] Harden CL, Nikolov BG, Kandula P, Labar DR, Pannullo S. Effect of levetiracetam on testosterone levels in male patients. Epilepsia 2010;51:2348–51.
[30] Xiaotian X, Hengzhong Z, Yao X, Zhipan Z, Daoliang X, Yumei W. Effects of antiepileptic drugs on reproductive endocrine function, sexual function and sperm parameters in Chinese Han men with epilepsy. J Clin Neurosci 2013;20:1492–7.
[31] Holtkamp M, Weissinger F, Meierkord H. Erectile dysfunction with topiramate. Epilepsia 2005;46:166–7.
[32] Calabrò RS, Bramanti P, Italiano D, Ferlazzo E. Topiramate-induced erectile dysfunction. Epilepsy Behav 2009;14:560–1.
[33] Civardi C, Collini A, Gontero P, Monaco F. Vasogenic erectile dysfunction Topiramate-induced. Clin Neurol Neurosurg 2012;114:70–1.
[34] Sun C, Lay C, Broner S, Silberstein S, Tepper S, Newman L. Reversible anorgasmia with topiramate therapy for headache: a report of 7 patients. Headache 2006;46:1450–3.
[35] Coebergh JA, Waldinger MD. Reversible anorgasmia with topiramate for migraine prophylaxis. J Neuropsychiatry Clin Neurosci 2012;24:E30–1.
[36] Isojärvi JIT. Disorders of reproduction in patients with epilepsy: antiepileptic drug related mechanisms. Seizure 2008;17:111–9.
[37] Isojärvi JIT, Laatikainen TJ, Pakarinen AJ, Juntunen KTS, Myllylä VV. Polycystic ovaries and hyperandrogenism in women taking valproate for epilepsy. N Engl J Med 1993;329:1383–8.
[38] Isojärvi JIT, Tauboll E, Herzog A. Effect of antiepileptic drugs on reproductive endocrine function in individuals with epilepsy. CNS Drugs 2005;19:207–23.
[39] Isojärvi JIT, Taubøll E, Pakarinen AJ, Van Parys J, Rättyä J, Flinstad Harbo H, et al. Altered ovarian function and cardiovascular risks in valproate treated women. Am J Med 2001;111:290–6.
[40] Vainionpää LK, Rättyä J, Knip M, Tapanainen JS, Pakarinen A, Lanning P, et al. Valproate-induced hyperandrogenism during pubertal maturation in girls with epilepsy. Ann Neurol 1999;44:444–50.
[41] Mikkonen K, Vainionpää LK, Pakarinen AJ, Knip M, Järvelä I, Tapanainen JS, et al. Long-term reproductive endocrine health in young women with epilepsy during puberty. Neurology 2004;62:445–50.
[42] Røste LS, Taubøll E, Isojärvi JI, Pakarinen AJ, Huhtaniemi IT, Knip M, et al. Effects of chronic valproate treatment on reproductive endocrine hormones in female and male Wistar rats. Reprod Toxicol 2002;16:767–73.
[43] Akdeniz F, Taneli F, Noyan A, Yüncü Z, Vahip S. Valproate-associated reproductive and metabolic abnormalities: are epileptic women at greater risk than bipolar women? Prog Neuropsychopharmacol Biol Psychiatry 2003;27:115–21.
[44] O'Donovan C, Kusumakar V, Graves GR, Bird DC. Menstrual abnormalities and polycystic ovary syndrome in women taking valproate for bipolar mood disorder. J Clin Psychiatry 2002;63:322–30.
[45] Lossius MI, Taubøll E, Mowinckel P, Mørkrid L, Gjerstad L. Reversible effects of antiepileptic drugs on reproductive endocrine function in men and women

with epilepsy—a prospective randomized double-blind withdrawal study. Epilepsia 2007;48:1875–82.
[46] Isojärvi JI, Rättyä J, Myllylä VV, Knip M, Koivunen R, Pakarinen AJ, et al. Valproate, lamotrigine, and insulin-mediated risks in women with epilepsy. Ann Neurol 1998;43:446–51.
[47] Tauboll E, Wójtowicz AK, Ropstad E, Gregoraszczuk EL. Valproate irreversibly alters steroid secretion patterns from porcine follicular cells in vitro. Reprod Toxicol 2002;16:319–25.
[48] Taubøl E, Gregoraszczuk EL, Kołodziej A, Kajta M, Ropstad E. Valproate inhibits conversion of testosterone to estradiol and acts as an apoptotic agent in growing porcine ovarian follicular cells. Epilepsia 2003;44:1014–21.
[49] Taubøll E, Gregoraszczuk EL, Tworzydło A, Wójtowicz AK, Ropstad E. Comparison of reproductive effects of levetiracetam and valproate studied in prepubertal porcine ovarian follicular cells. Epilepsia 2006;47:1580–3.
[50] Taubøll E, Gregoraszczuk EL, Wojtowicz AK, Milewicz T. Effects of levetiracetam and valproate on reproductive endocrine function studied in human ovarian follicular cells. Epilepsia 2009;50:1868–74.
[51] Hattori N, Fujiwara H, Maeda M, Fujii S, Ueda M. Epoxide hydrolase affects estrogen production in the human ovary. Endocrinology 2000;141:3353–65.
[52] Nelson-DeGrave VL, Wickenheisser JK, Cockrell JE, Wood JR, Legro RS, Strauss JF, et al. VPA increases androgen biosynthesis in human ovarial theca cells by affecting gene expression. Endocrinology 2004;145:799–808.
[53] Gustavsen MW, von Krogh K, Taubøll E, Zimmer KE, Dahl E, Olsaker I, et al. Differential effects of antiepileptic drugs on steroidogenesis in a human in vitro cell model. Acta Neurol Scand 2009;Suppl189:14–21.
[54] von Krogh K, Harjen H, Almás C, Zimmer KE, Dahl E, Olsaker I, et al. The effect of valproate and levetiracetam on steroidogenesis in forskolin stimulated H295R cells. Epilepsia 2010;51:2280–8.
[55] Morrell MJ, Flynn KL, Seale CG, Done S, Paulson AJ, Flaster ER, et al. Reproductive dysfunction in women with epilepsy: antiepileptic drug effects on sex-steroid hormones. CNS Spectr 2001;6:783–6. 771-2.
[56] Herzog AG. Disorders of reproduction in patients with epilepsy: primary neurological mechanisms. Seizure 2008;17:101–10.
[57] Webber MP, Hauser WA, Ottman R, Annegers JF. Fertility in persons with epilepsy: 1935–1974. Epilepsia 1986;27:746–52.
[58] Olafsson E, Hauser WA, Gudmundsson G. Fertility in patients with epilepsy: a population-based study. Neurology 1998;51:71–3.
[59] Schupf N, Ottman R. Reproduction among individuals with idiopathic/cryptogenic epilepsy: risk factors for reduced fertility in marriage. Epilepsia 1996;37:833–40.
[60] Dansky LV, Andermann E, Andermann F. Marriage and fertility in epileptic patients. Epilepsia 1980;21:261–71.
[61] Harden CL. Sexual dysfunction in women with epilepsy. Seizure 2008;17:131–5.
[62] Hellmis E. Sexual problems in males with epilepsy – an interdisciplinary challenge! Seizure 2008;17:136–40.
[63] Mattson RH, Cramer JA, Collins JF, Smith DB, Delgado-Escueta AV, Browne TR, et al. Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic–clonic seizures. N Engl J Med 1985;313:145–51.
[64] Brannon GE, Rolland PD. Anorgasmia in a patient with bipolar disorder type 1 treated with gabapentin. J Clin Psychopharmacol 2000;20:379–81.
[65] Husain AM, Carwile ST, Miller PP, Radtke RA. Improved sexual function in three men taking lamotrigine for F epilepsy. South Med F J 2000;93:335–6.
[66] Vestergaard P, Rejnmark L, Moeskilde L. Fracture risk associated with use of antiepileptic drugs. Epilepsia 2004;45:1330–7.
[67] Pack AM, Walczak TS. Bone health in women with epilepsy: clinical features and potential mechanisms. Int Rev Neurobiol 2008;83:305–28.
[68] Pack AM, Morrell MJ, Marcus R, Holloway L, Flaster E, Doñe S, et al. Bone mass and turnover in women with epilepsy on antiepileptic drug monotherapy. Ann Neurol 2005;57:252–7.
[69] Petty SJ, O'Brien TJ, Wark JD. Anti-epileptic medication and bone health. Osteoporos Int 2007;18:129–42.
[70] Nakken KO, Taubøll E. Bone loss associated with use of antiepileptic drugs. Expert Opin Drug Saf 2010;9:561–71.
[71] Onodera K, Takahashi A, Sakurada S, Okano Y. Effects of phenytoin and/or vitamin K2 (menatetrenone) on bone mineral density in the tibiae of growing rats. Life Sci 2002;70:1533–42.
[72] Ensrud KE, Walczak TS, Blackwell T, Ensrud ER, Bowman PJ, Stone KL. Antiepileptic drug use increases rates of bone loss in older women: a prospective study. Neurology 2004;62:2051–7.
[73] Apeland T, Mansoor M, Strandjord RE. Antiepileptic drugs as independent predictors of plasma total homocysteine levels. Epilepsy Res 2001;47:27–35.
[74] Strandjord RE, Aanderud S, Myking OL, Johannessen SI. Influence of carbamazepine on serum thyroxine and triiodothyronine in patients with epilepsy. Acta Neurol Scand 1981;63:111–21.
[75] Isojärvi JIT, Turkka J, Pakarinen AJ, Kotila M, Rättyä J, Myllylä V. Thyroid function in men taking carbamazepine, oxcarbazepine, or valproate for Epilepsy. Epilepsia 2001;42:930–4.
[76] Verrotti A, Laus M, Scardapane A, Franzoni E, Chiarelli F. Thyroid hormones in children with epilepsy during long-term administration of carbamazepine and valproate. Eur J Endocrinol 2009;160:81–6.
[77] Tiihonen M, Liewendahl K, Waltimo O, Ojala M, Välimäki M. Thyroid status of patients receiving long-term anticonvulsant therapy assessed by peripheral parameters: a placebo-controlled thyroxine therapy trial. Epilepsia 1995;36:1118–25.
[78] Garoufi A, Koemtzidou E, Katsarou E, Dinopoulos A, Kalimeraki I, Fotinou A, et al. Lipid profile and thyroid hormone concentrations in children with epilepsy treated with oxcarbazepine monotherapy: a prospective long-term study. Eur J Neurol 2014;21:118–23.
[79] Lossius MI, Taubøll E, Mowinckel P, Gjerstad L. Reversible effects of antiepileptic drugs on thyroid hormones in men and women with epilepsy: a prospective randomized double-blind withdrawal study. Epilepsy Behav 2009;16:64–8.
[80] Taubøll E, Isojärvi JIT, Gjerstad L. Gender-specific side-effects of antiepileptic drugs. In: Schwartzkroin PA, editor. Encyclopedia of basic epilepsy research, vol. 3. Elsevier, UK: Academic Press; 2009. p. 1485–90.