# Gender differences in epilepsy: perceived or real?

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**Educational aims**

- To provide an overview of the gender issues in epilepsy
- To highlight the reasons as to why epilepsy affects males and females differently
- To demonstrate precautions to be taken in females on AEDs
- To enhance interdisciplinary care in the treatment of epilepsy in both men and women

**Key words**
Epilepsy, gender, hormones, anti-epileptic drugs

**Abstract**

**Epilepsy is the third most common chronic neurological condition across all ages, affecting around 1% of the population world wide. While epidemiological studies do not indicate any differences in the incidence of epilepsy in males and females, there may be significant differences in the impact and effect the condition may have between males and females across all ages.**

**These differences may not only be due to possible differences in antiepileptic drug (AED) efficacy, AED drug-drug interactions due to hormonal differences, and possible teratogenetic effects in women of child bearing age, but also differences in the social impact of the condition. These issues challenge both the woman with epilepsy, and the various health care professionals involved in her care.**

**Introduction**

Epilepsy is the third most common neurological condition, and annual incidence is estimated as 43 cases per 100,000 of the population worldwide. It is characterized by occurrence of unprovoked seizures accompanied by complex symptoms, due to disorders of brain function.[1] Despite extensive research on epilepsy and seizure mechanisms, treatment is still limited to symptomatic rather than mechanism-oriented approaches. In fact, the emerging genetic basis of some of the epilepsies, indicate that epilepsy will eventually be recognised as several different conditions.

There is now also an increased understanding of gender differences in the epidemiology of epilepsy and of specific epilepsy syndromes. Various published studies indicate that females have a marginally lower incidence of epilepsy and unprovoked seizures than males. This difference is usually attributed to a greater exposure to risk factors for lesional epilepsy and acute symptomatic seizures in males. Males also have a higher incidence of status epilepticus, sudden unexpected death in epilepsy (SUDEP), prognosis, and mortality. However, idiopathic generalized epilepsies (IGEs) are more common among female.[2] These differences may be due to the influence of sex hormones on seizures and epilepsy, as well as changes in the endocrine system and levels of sex hormones by epileptiform activity.[3]

Conversely, seizures may be sensitive to changes in sex hormone levels, which in turn may affect the seizure-induced

neuronal damage. Animal studies indicate that the effects of reproductive hormones on neuronal excitability, seizures, and seizure-induced damage are complex because of the multifaceted action of steroid hormones. These can induce genomic effects involving modulation of multiple genes by their up- or down-regulation and rapid non-genomic effects by activation of membrane orphan G-protein coupled receptors, specific membrane hormone receptors, or by direct binding to neurotransmitter receptors.[4]

**Choice of AEDs and sexual development**

Relative to males, females with epilepsy face unique challenges. Epilepsy affects sexual development, menstrual cycle, can influence choice of contraception, and may affect pregnancy outcomes. These factors will have an impact of the choice of an AED in patients with epilepsy, due to differences in the efficacy and safety of each drug, and also on the patient's acceptability of the drug.[1] Although most pregnancies are uneventful in women with epilepsy, preconception advice should be given to all women with epilepsy who are considering pregnancy, such as folic acid and vitamin K supplements. The lowest effective dose of the most appropriate AED should be used. A study carried out in France among epileptologists indicated a consensus for the selection of AEDs, mainly based on the epilepsy syndrome and gender. Sodium valproate and lamotrigine were found to be the two drugs of choice for generalized epilepsies, with lamotrigine often preferred for women of childbearing age. Carbamazepine was first line AEDs in men with partial epilepsy, with lamotrigine preferred in females.[5] However, other studies found that the combination of valproate and lamotrigine is particularly teratogenic. Moreover, lamotrigine was found to cross into breast milk and thus could accumulate in the child.[6]

AEDs which are nonenzyme-inducing, such as valproate, benzodiazepines and levetiracetam, do not interact with oral contraceptives (OCs). However, inducing AEDs, such as phenytoin, barbiturates, carbamazepine, topiramate, will affect the efficacy of OCs.[3] In another study looking at a cohort of 212 females, depression, female gender, symptomatic etiology, younger seizure onset age, ≥2 seizures, and history of febrile seizures were found to be associated with a higher adverse effect profile. Menopause was also found to affect seizure frequency and type and women with epilepsy. In addition, women on AEDs were found to be at increased risk of fractures, osteoporosis, and osteomalacia.[7]

**Co-morbidities in epilepsy**

Co-morbidities in epilepsy are very common. These can include behavioural changes in children, and anxiety and depression in adults. Wilner et al., (2014) assessed the prevalence of the most common co-morbidities in 6621 women and men with epilepsy (52% women, 48% men).[8] More women (50%) than men (43%) with epilepsy were found to have comorbidities ($p<0.05$). The most common co-morbidities found in women were psychiatric diagnosis (16%), hypertension (12%), asthma (11%), hyperlipidemia (11%), headache (7%), diabetes (6%), urinary tract infection (5%), hypothyroidism (5%), anemia (5%), and migraine (4%). For men, these co-morbidities were found to be psychiatric diagnosis (15%), hyperlipidemia (12%), hypertension (12%), asthma (8%), diabetes (5%), headache (4%), cancer (4%), coronary artery disease (3%), anemia (3%), and gastroesophageal reflux disease (3%). Psychiatric diagnosis was the only comorbidity among the top five comorbidities across all age groups in both men and women.

AEDs are often blamed for these co-morbidities, although they may not always be at fault. Indeed, it is crucial for patients that their care should include a wider perspective than merely reduction in seizure frequency, but also consider the broader aspects of epilepsy and its effects on quality of life.

**Epilepsy surgery**

Epilepsy surgery can also be perceived differently by males and females. In a study among a cohort of 389 men and women who underwent epilepsy surgery, both genders highlighted the possible impact on driving and memory, as the most important presurgical concerns. However, females fatigue and pregnancy as major concerns, while males rated driving, physical activity limitations, and economic worries as more important ($p \leq 0.05$).[9]

**Quality of life**

Despite advances in the understanding and effective management of epilepsy (more than 70% of persons with epilepsy have their seizures controlled with AEDs), there is often a mismatch between visible disability and perceived disability in these persons. This is because for many patients, while their seizures are controlled and they appear to be perfectly well and healthy, epilepsy can have a huge impact on the social, psychological, and physical health due perceived and real stigma as well as due to the side effects of AEDs.[7] Moreover, persons with refractory epilepsy face many challenges such as the unpredictability of seizures, problems with employment, learning and cognitive difficulties, physical activity limitations, and pregnancy concerns. In addition, epilepsy can impact on certain aspects of education and employment, mood changes, lifestyle choices.[8]

Patient-reported outcome measures are increasingly being used in assessing quality of life in persons with epilepsy. Using the World Health Organization Quality-of-Life Questionnaire - Brief (WHOQOL-Bref), the Health Related Quality of Life (HRQoL) in a cohort of men with epilepsy, was compared to seven other groups with chronic diseases. Multiple linear regression showed that mood was the most important independent predictor of the WHOQOL-Bref score.[10] Yet, various other studies have indicated that factors influencing quality of life in females are far more complex. While choice of treatment should be based on the individual patient's specific clinical characteristics, selection of AEDs and other treatment should also consider the patient's particular lifestyle and priorities, which may be far more heterogenous in women.[11]

**How can pharmacists help?**

Various studies have shown that the best approach in caring for women with epilepsy is a multidisciplinary one.[1] In a chronic condition, such as epilepsy, pharmacists can serve an important function in the health care of patients with this chronic disease. In a study among 175 pharmacists in the US, which used the Knowledge of Women's Issues and Epilepsy II (KOWIE-II) tool, nearly 75% of pharmacists scored correctly for the statement inquiring about the drug interaction between enzyme-inducing AEDs and contraceptives.[12] Slightly less knew about AED-induced bone loss. Almost one-third of the respondents answered incorrectly when asked about the frequency of sexual dysfunction in women with epilepsy, though an even higher percentage chose "don't know." Most of the pharmacists (69.1%) stated "don't know" when asked about the relationship between hormones and seizure control. More than 70% correctly

answered four of six pregnancy-related statements (use of folic acid=77.0%, healthy babies=82.9%, continued AED adherence during pregnancy=86.8%, choice of AED during pregnancy=71.1%). Fewer pharmacists knew about vitamin K supplementation (57.9%), and even fewer answered the question on breastfeeding correctly (33.6%). The pharmacist has a key role in ensuring continuity of care in persons with epilepsy especially in females. This can only be addressed through continuing professional education.

**Conclusions**

As has been seen from this brief review, differing effects of sex hormones can lead to significant differences between men and women in prognosis, treatment and social impact of persons with epilepsy. These differences could range from the incidence of various types of seizures, decreased fertility rates in females, pregnancy-related complications, and social impact and quality of life. Gender also has an impact on the treatment of epilepsy, selection of antiepileptic drugs (AEDs) and incidence of co-morbidities.

To date, the focus on gender issues in epilepsy has been mostly on females, with few studies being carried out in males. Indeed, guidelines for the management of women with epilepsy have been available for many years.[13]. Yet, despite these guidelines, studies have indicated that their implementation needs to be improved, with much more information being given to patients in an interdisciplinary care approach. Pharmacists can be instrumental in this regard.

**Key points**

- Differences between men and women in epilepsy may be due to the influence of sex hormones on seizures and epilepsy, as well as due to changes in the endocrine system and levels of sex hormones by epileptiform activity.
- Epilepsy affects sexual development, menstrual cycle, can influence choice of contraception, and may affect pregnancy outcomes in females.
- Common co-morbidities between men and women differ.
- The choice of AED treatment should also consider the patient's particular lifestyle and priorities which may be far more heterogenous in females.
- Pharmacists can be instrumental in imparting information to men and women with epilepsy in an interdisciplinary care approach.

**References**


1. Wiebe S. Managing women with epilepsy. Guideline producers now need to pay attention to implementation. BMJ. 2000;1;320(7226):3-4.
2. McHugh JC, Delanty N. Epidemiology and classification of epilepsy: gender comparisons Int Rev Neurobiol. 2008;83:11-26.
3. Tatum WO, Liporace J, Benbadis SR, Kaplan PW. Updates on the treatment of epilepsy in women. Archives of Internal Medicine 2004;164:137–45.
4. Velíšková J, Desantis KA.Sex and hormonal influences on seizures and epilepsy. Horm Behav. 2013;63(2):267-77.
5. Semah F, Picot MC, Derambure P, Dupont S, Vercueil L, Chassagnon S, Marchal C, Thomas P, Ryvlin P. The choice of antiepileptic drugs in newly diagnosed epilepsy: a national French survey. Epileptic Disorders 2004, 6(4):255-265.
6. Crawford P Best Practice Guidelines for the Management of Women with Epilepsy Epilepsia 2005;46(Suppl. 9):117–124.
7. Perucca P, Jacoby A, Marson AG, Baker GA, Lane S, Benn EK, Thurman DJ, Hauser WA, Gilliam FG, Hesdorffer DC. Adverse antiepileptic drug effects in new-onset seizures: a case-control study. Neurology 2011;18;76(3):273-9.
8. Wilner AN, Sharma BK, Soucy A, Thompson A, Krueger A. Common comorbidities in women and men with epilepsy and the relationship between number of comorbidities and health plan paid costs in 2010. Epilepsy Behav. 2014;32:15-20.
9. Bower CM, Hays RD, Devinsky O, Spencer SS, Sperling MR, Haut S, Vassar S, Vickrey BG. Expectations prior to epilepsy surgery: an exploratory comparison of men and women. Seizure. 2009;18(3):228-31.
10. Greenway L, Ahern D, Leavy Y, Rawnsley M, Duncan S. Quality of life in a cohort of men with epilepsy compared to a healthy population and those with common chronic diseases in the UK using a generic patient-reported outcome measure Epilepsy Behav. 2013;29(3):497-503.
11. Trinka E. Ideal characteristics of an antiepileptic drug: how do these impact treatment decisions for individual patients? Acta Neurol Scand Suppl. 2012;(194):10-8.
12. McAuley JW, Casey J, Long L. An evaluation of pharmacists' knowledge of women's issues in epilepsy. Epilepsy Behav. 2009 ;14(1):243-6.
13. Kampman MT, Johansen SV, Stenvold H, Acharya G. Management of women with epilepsy: Are guidelines being followed? Results from case-note reviews and a patient questionnaire. Epilepsia. 2005;46(8):1286-92.