SEXUAL DYSFUNCTION IN EPILEPSY AND THE ROLE OF ANTI-EPILEPTIC DRUGS

Running title: AEDs and sexual dysfunction in epilepsy

Mahinda Yogarajah MBBS PhD and Marco Mula MD PhD

Atkinson Morley Regional Neuroscience Centre, St George's University Hospitals NHS Foundation Trust, London, United Kingdom

Institute of Medical and Biomedical Education, St George's University of London, United Kingdom

Correspondence:

Marco Mula MD, PhD

Atkinson Morley Regional Neuroscience Centre, St George's University Hospitals NHS Foundation Trust

Blackshaw Road

London SW17 0QT

United Kingdom

Tel. +442087254322

Fax +442087254591

Email: mmula@sgul.ac.uk

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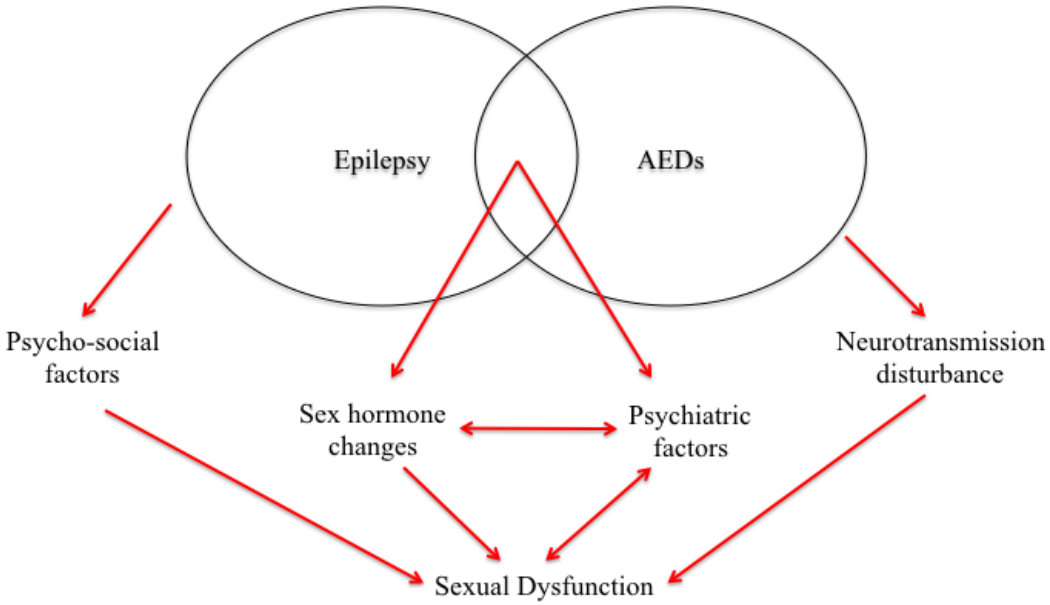
STRUCTURED ABSTRACT

Background: Sexual dysfunction is very common in patients with epilepsy. Objective: We sought to review the published literature around sexual dysfunction in epilepsy, and particularly the role played by anti-convulsant drugs. Method: We searched all related articles on PubMed using the search terms sexual dysfunction, various AEDs and epilepsy, and restricted the search to English language articles. Results: The most common manifestations of sexual dysfunction in patients with epilepsy are hyposexuality and erectile dysfunction. The cause of this dysfunction is multifactorial and overlapping, and includes changes in the levels of sex hormones, anti-convulsants, the epilepsy itself and psychosocial factors. Traditional anti-convulsants which induce the cytochrome P450 enzyme system have the highest rates of sexual dysfunction, which is primarily mediated by changes in sex hormone levels. Sexual dysfunction associated with newer anti-convulsants is likely to occur through different mechanisms. Some anti-convulsants such as oxcarbazepine and lamotrigine may improve sexual function, **but can also rarely be associated with sexual dysfunction**. Conclusion: Management of sexual dysfunction thought to be caused by anti-convulsants should include the cessation of the offending drug, and consideration of switching to alternative anti-convulsants that have been reported to improve sexual function such as oxcarbazepine, and lamotrigine.

GRAPHICAL ABSTRACT



Both epilepsy and AEDs causes sexual dysfunction mediated by changes in sex hormones. They can also cause mood disturbances, which can lead to sexual dysfunction. AEDs can also cause sexual dysfunction directly, by affecting neural transmission in pathways that are important for the sexual response.

1. INTRODUCTION

Epilepsy is one of the most common, serious, chronic neurological conditions in the world and it is becoming increasingly evident that a number of factors affect quality of life and well being in men and women with epilepsy beyond simple seizure control (1). However, historically, gender differences in epilepsy focused mainly on women with epilepsy, and issues around menstrual cycles, contraception and pregnancy. More recently there has been increasing awareness of the differing impact of epilepsy and antiepileptic drug (AED) treatment on sexual function in both men and women (1) and that sexual well-being is critical for a good quality of life in patients with epilepsy (2).

When discussing sexual dysfunction in epilepsy, the first step is to define both normal and abnormal sexual function (sexual dysfunction). Given the central, mechanistic role played by sex hormones in sexual dysfunction, it is also important to be aware of the basic metabolism and regulation of sex hormones. Furthermore, the aetiological basis of sexual dysfunction in patients with epilepsy is likely to be multifactorial and a number of different variables need to be considered such as the epilepsy itself, the AEDs used to treat it, and psychosocial factors. This is a narrative review on sexual dysfunction is epilepsy with special attention to the role of anti-epileptic drugs (AEDs). We searched all related articles on PubMed using the search terms sexual dysfunction, various AEDs and epilepsy, and restricted the search to English language articles.

2. SEXUAL DYSFUNCTION: DEFINITIONS AND CLASSIFICATION

Sexual dysfunction can be defined as a chronic inability to respond sexually in a way that is satisfying (3). Any discussion of sexual dysfunction demands oversight of the normal physiology of sexual function, and an understanding of the classification of sexual dysfunction.

The sequence of events that characterizes the progression from the sexually unaroused to the aroused state, and the resolution of these changes, has been described as the human sexual response cycle. It can be divided into several phases: desire, excitement, orgasm, and resolution (4). Sexual desire can be defined as a willingness to engage in sexual behaviour and can come about spontaneously (proceptive desire) or by activation through sexual excitation (responsive desire) in response to appropriate sexual stimuli (4). Androgens are thought to be essential to support sexual desire in both

men and women (5–8). Sexual excitement and its physiological counterpart, sexual or genital arousal, are defined as the capacity to respond to appropriate sexual stimuli which can be psychogenic (arising in the brain and triggered by input from the special senses or by conscious sexual fantasies) or reflexogenic arising from stimulation of genital and/or erotogenic sites (breasts, nipples, inner thighs, perineum) (4). It is mediated by androgens and estrogens, in men and women respectively (5–8), although testosterone is also important in women and there is laboratory evidence that it increases vaginal blood flow (9). Genital arousal consists of penile erection in men and clitoral tumescence, genital vasocongestion, and increased vaginal lubrication in women. The increase in heart rate, and blood pressure that occur during sexual arousal ensure there is increased blood flow to the genitals. These changes facilitate the sexual response in men, whose purpose is to allow the introduction of sperm into the vagina. The changes in women enable painless penile penetration and thrusting, and encourage sperm survival and transport (4).

A robust classification of sexual dysfunction in patients with epilepsy is critical not only for the diagnosis and management, but also for research, in these patients. However, many published studies in patients with epilepsy do not use any well-recognised classification systems. Given the multifactorial and often unknown basis of sexual dysfunction, a descriptive, rather than aetiologically based, organisation has been commonly used in defining sexual dysfunction. A significant problem associated with such a classification system is the assumption of mind versus body dualism whereby the disorder is either psychiatric or medical in aetiology (10). The most commonly used classification systems are the International Classification of Diseases, 10th Edition (ICD-10) (3) and the Diagnostic and Statistical Manual of Mental Disorders (fifth edition; DSM-V) (11) (Table 1). Although the DSM is a psychiatric system, some of its diagnostic criteria have been used to define conditions that are assumed to have an organic aetiology. This is a historical precedent. Before the advent of phosphodiesterase inhibitors, psychiatrists or psychologists initiated most treatment of sexual disorders, and it was widely presumed that most sexual disorders had psychological origins (12). The most recent version of the DSM (DSM-V) (11) separates out sexual dysfunction according to sex for the first time, and is no longer based on the sexual response cycle as proposed by Masters and Johnson (4).

Major Classification Systems of Sexual Dysfunction (adapted from McCabe et al(12)) – Table 1

ICD-10 Definitions of Sexual Dysfunction Not Caused by an Organic Disorder or Disease*	
Lack or loss of sexual desire	Loss of sexual desire is the principal problem and not secondary to other sexual problems such as erectile failure or dyspareunia. Lack of sexual desire does not preclude sexual enjoyment or arousal but makes initiation of sexual activity less likely.
Sexual aversion	Strong negative feelings associated with the prospect of sexual interaction resulting in avoidance of sexual activity.
Lack of sexual enjoyment	Sexual responses and orgasm occur normally but there is lack of appropriate pleasure.
Failure of sexual response	In men the principal problem is difficulty in getting and/or maintaining an erection (erectile dysfunction). Provided there is no organic aetiology to erectile dysfunction (eg diabetes or hypertension) erections may occur normally in certain situations such as masturbation, or sleeping with a different partner. In women the primary problem is vaginal dryness or failure of lubrication.
Orgasmic dysfunction	Orgasm does not occur or is markedly delayed.
Premature ejaculation	The inability to control ejaculation sufficiently for both partners to enjoy sexual interaction. In severe cases, ejaculation might occur before vaginal entry or in the absence of an erection.
Non-organic vaginismus	Spasm of the muscles that surround the vagina, causing occlusion of the vaginal opening and resulting in painful or impossible penile entry. Can often be due to local cause of pain in which case that should be coded.
Dyspareunia	Pain in women (or men) during sexual intercourse. Can often be due to local pathology in which case that condition should be coded. Category should only be used when there is no other primary sexual dysfunction (eg. vaginal dryness).
Excessive sexual drive	When excessive sexual drive is secondary to another disorder such as dementia or an affective disorder then the underlying disorder should be coded.
DSM-5 Definitions of Sexual Dysfunction**	
Female sexual interest-arousal disorder	Lack of, or significantly reduced sexual interest or arousal is manifested by at least three of the following characteristics: - absent or decreased interest in sexual activity - absent or decreased sexual or erotic thoughts or fantasies - no or decreased initiation of sexual activity - absent or decreased sexual excitement or pleasure during sexual activity in at least 75% of sexual encounters - absent or decreased sexual interest or arousal in response to any internal or external sexual or erotic cues - absent or decreased genital or non-genital sensations during sexual activity in at least 75% of sexual encounters
Female orgasmic disorder	Marked delay/infrequent/absent orgasms during at least 75% of sexual activity OR decreased intensity of orgasmic sensations during at least 75% of sexual activity
Female genito-pelvic pain-penetration disorder	Persistent or recurrent difficulties with at least one of the following - vaginal penetration during intercourse - vulvovaginal or pelvic pain during vaginal intercourse or penetration attempts - marked fear or anxiety about vulvovaginal or pelvic pain in anticipation, during or as a result of vaginal penetration - marked tensing or tightening of pelvic floor muscles during attempted vaginal penetration
Male hypoactive sexual desire disorder	Persistent or recurrent deficient (or absent) sexual or erotic thoughts or fantasies and desire for sexual activity.
Male erectile disorder	Experience during at least 75% of sexual activity of at least one of the following - difficulty in obtaining an erection - difficulty in maintaining an erection until completion of sexual activity - marked decrease in erectile rigidity
Male premature (early) ejaculation	Persistent or recurrent pattern of ejaculation within approximately 1 minute of vaginal penetration and before an individual wishes it.
Male delayed ejaculation	Either marked delay in ejaculation OR infrequent/absent ejaculation during at least 75% of sexual activity

*ICD-10 organic sexual dysfunction codes include erectile dysfunction, vaginismus, and dyspareunia of organic aetiology.

**DSM-V specifies that problems should have persisted for at least 6 months and have occured on approximately 75% or more of sexual occasions, and cause clinically significant distress, in order to be classified as sexual dysfunction. Symptoms should not be the consequence of a non-sexual mental disorder, severe relationship distress or attributable to the effect of a medication or illness.

2.1. Sex Hormone Synthesis and Metabolism (figure 1 adapted from (13))

The release of the sex steroid hormones is controlled by the hypothalamic-pituitary-gonadal axis. The major sex steroid hormones are testosterone from the testis and estrogen and progesterone from the ovaries. The adrenal gland also makes a significant contribution to androgen production. Peripheral conversion to other biologically active steroid forms occurs in the skin and adipose tissue.

The control centre of the reproductive system is the nuclei of the medial basal hypothalamus. Sex hormone synthesis is controlled by the pulsatile release of hypothalamic gonadotropin-releasing hormone (GnRH). At the pituitary gland GnRH stimulates the release of leuteinizing hormone (LH) and follicle simulating hormone (FSH) into the general circulation. LH binds to its target cells, which are the Leydig cells in the testes of the males, and theca cells in ovaries of females.

In men testosterone and other androgens such as dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulphate (DHEAS) and androstenedione are produced in the zona reticulate/fasciculata of the adrenal cortex, and the Leydig cells, which are adjacent to the seminiferous tubules of the testes. Testosterone itself exists in three different forms in the bloodstream, namely free (2-3%), albumin bound (53-55%) and sex hormone binding globulin (SHBG) bound (43-45%). While free testosterone and part of the albumin bound testosterone are available to tissues, the SHBG portion is unavailable to tissues and is not considered biologically active. Testosterone is converted to dihydrotestosterone (DHT) by the action of 5α-reductase in target tissues. Although this steroid is much less abundant than testosterone, it accounts for most of testosterone's biological action. Androgens are also synthesised in females either from circulating precursors in their target tissues, or in the zona reticularis of the adrenal glands, and the ovarian stroma. DHT is also produced in females, but in low quantities and is mainly produced in peripheral target tissues. Testosterone, but not DHT, is converted to estradiol (E2) by the action of aromatase in certain peripheral tissues, and is an important source of estrogens in some women.

In women estrogens are produced in the granulosa and theca cells of the ovaries as well as the corpus luteum. The theca cells are stimulated by LH to produce pregnenolone, which is eventually

converted to androstenedione. The androstenedione is converted to estrone (E1) by aromatase in the granulosa cells of the ovary, which is then converted to estradiol (E2) by 17β-HSD. The expression of aromatase and 17β-HSD is controlled by FSH stimulation. Aromatase is also expressed in non-gonadal tissue and facilitates the peripheral conversion of androgens to estrone (E1). Estrogens are also made in males in peripheral tissues that express aromatase (eg. Leydig cells and Sertoli cells in testes), which convert circulating testosterone to estradiol (E2) and androstenedione to estrone (E1). These estrogens act and are metabolised locally, which limits their systemic effects.

Progesterone is synthesized from pregnenolone by action of 3β-HSD in the corpus luteum, by the placenta during pregnancy, and by the adrenals, as a step in androgen and mineralocorticoid synthesis. Its actions are primarily mediated by an intracellular progesterone receptor, whose numbers increase in the presence of estrogen.

2.2. Sex Hormone Regulation (13) (figure 2)

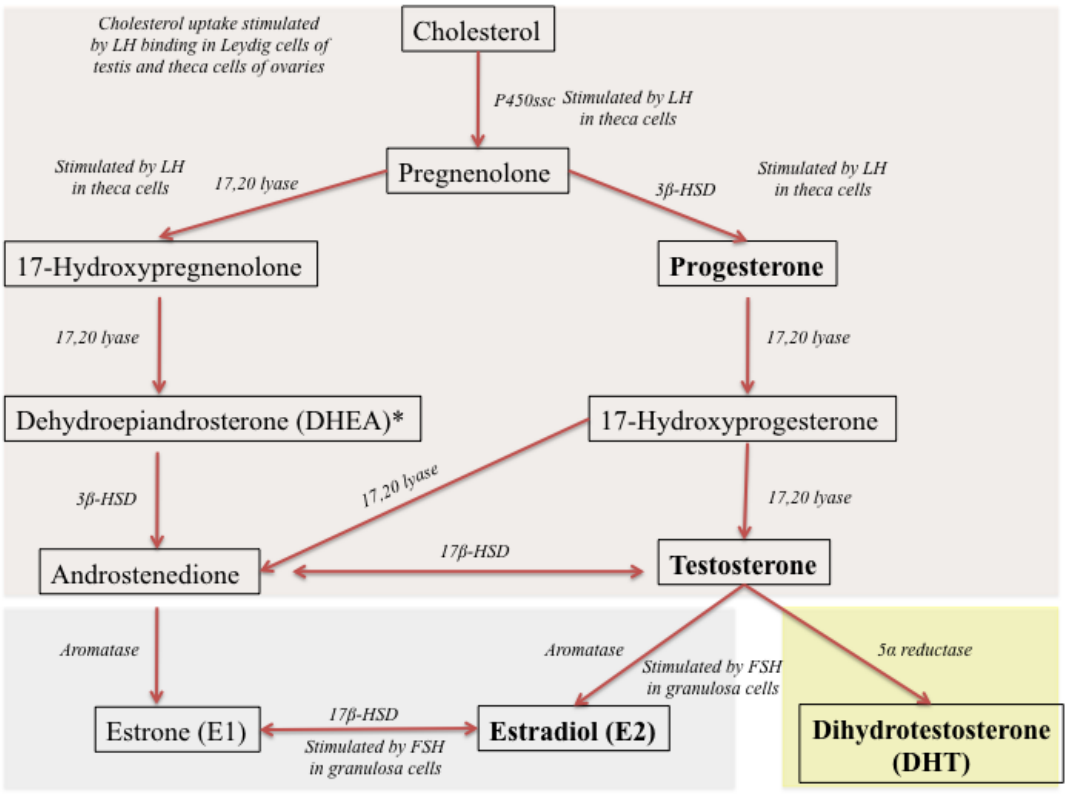
The sex hormones are regulated by the hypothalamic-pituitary-gonadal axis. Regions of the hypothalamus that are involved in the regulation, production, and secretion of gonadotrophin-releasing hormone (GnRH) receive direct connections from the cerebral hemispheres including the temporolimbic structures such as the amygdala (14,15). Functionally distinct regions of the amygdala exert opposing modulatory effects on pituitary hormone secretion (16). As a result of these intimate connections, epileptiform discharges from the temporal lobe may be transmitted through the amygdala-hippocampal pathways, and disrupt the normal pulsatile secretion of gonadotrophic hormones, and basal levels of dopamine secretion, resulting in hypogonadism and hyperprolactinaemia(17).

In men, the pulsatile release of GnRH from the hypothalamus causes the secretion of the gonadotropins LH and FSH into the circulation. While LH stimulates the release of testosterone from Leydig cells, the testosterone feeds back negatively on pituitary LH and hypothalamic GnRH. Estradiols generated by the peripheral aromatisation of testosterone may also give rise to negative feedback, although they can also contribute to sexual behaviour in a positive fashion in men (18). FSH stimulates the release of inhibin from Sertoli cells, which feeds back to inhibit the anterior pituitary release of FSH, and also stimulates spermatogeneis. Hormonal regulation in women is more

complicated than in men because the feedback effects of different hormones vary depending on the stage of the menstrual cycle. As in men GnRH release by the hypothalamus results in the release of LH and FSH at the anterior pituitary. Feedback from theca cells of the ovarian follicle occurs via the release of progestins, while feedback from the granulosa cells of the ovarian follicle occurs via the release of inhibin and estradiol. Progesterone and estradiol are also released by the corpus luteum which develops from the ovarian follicle in the post-ovulatory phase of the menstrual cycle.

2.3. Neuroanatomy of Sexual Function

Over the last 20 years, non-invasive functional imaging with positron emission tomography (PET) and magnetic resonance (fMRI) has highlighted those regions of the brain that are thought to be important for sexual function. They include, amongst others, the limbic and paralimbic regions, which are thought to be important for sexual motivation, and parietal areas that modulate emotional and motor responses (19). The autonomic nervous system connects the central nervous system to the genitalia and mediates genital engorgement, erections, ejaculation, and climax. Several components of the autonomic system are particularly important. The superior hypogastric plexus is a network of fibres anterior to the lower abdominal aorta and is connected with the pelvic (inferior hypogastric) plexus by the hypogastric nerves. The pelvic plexus itself has connections with sacral roots S2 to S4 through the pelvic splanchnic nerves, while the lumbosacral motorneurons also receive central projections from the ventral tegmental region of the brainstem which is thought to be important in sexual function (19).



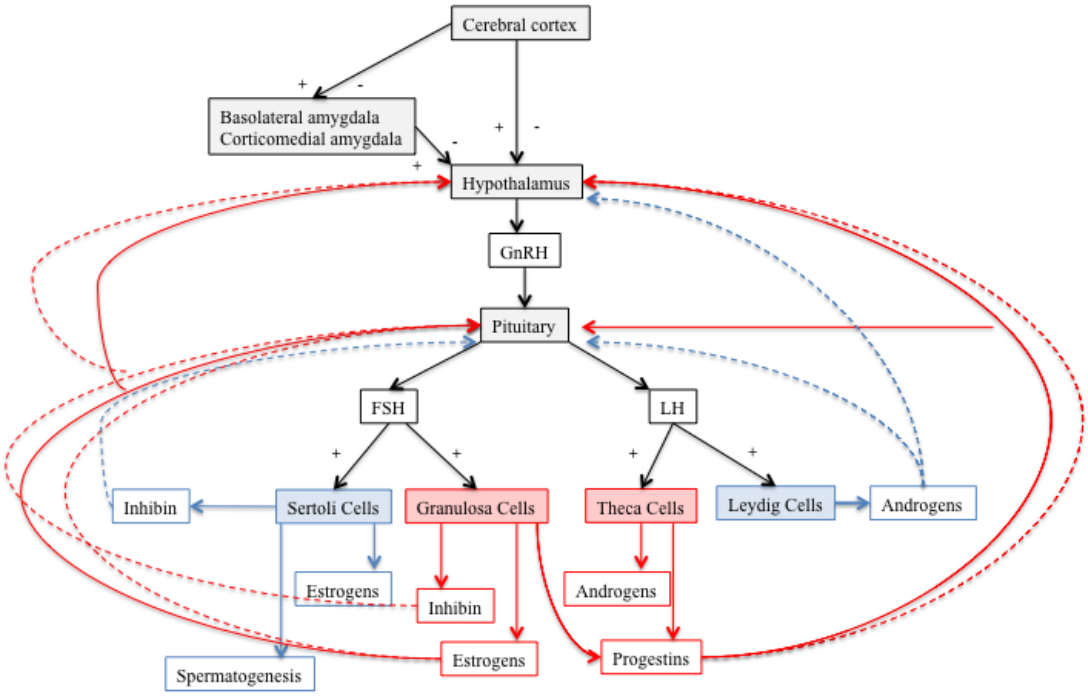
The metabolism of sex hormones - Figure 1

Pink – Early processing steps are common to multiple areas including the adrenal cortex, Leydig cells of the testes and theca cells of the ovaries.

Grey – These steps convert androgens from the theca cells into estogens in the granulosa cells of the ovary and peripheral tissues; the reactions are carries out by aromatase. Aromatase and 17β-HSD are found in peripheral tissues.

Yellow – These steps convert testosterone into more potent DHT and occur in peripheral tissues such as the skin, prostate and epididymis of the testis.

* Note DHEA is converted to DHEA-S in the adrenal cortex , which stimulates androgen secretion.



The hypothalamic-pituitary-gondal axis in males and females - Figure 2

Shaded boxes represent anatomical structures while unshaded boxes represent hormones. Unbroken lines indicate positive feedback, Dotted lines indicate negative feedback. Red colouring indicates structures or hormones found predominantly in females. Blue colouring indicates indicates structures or hormones found predominantly in males. Black/gray colouring indicates structures or hormones found in both sexes.

3. SEXUAL DYSFUNCTION IN MEN AND WOMEN WITH EPILEPSY: THE SIZE OF THE PROBLEM

Sexual dysfunction affects between 30 to 66% of men (20) with epilepsy and 14 to 50% of women (20). The variability in these figures is related to a number of limitations common to epidemiological studies and which include, lack of a control groups, selection bias, differing adopted clinical instruments and cultural backgrounds. Different groups or types of patients with epilepsy are assessed in different studies, and not always compared with control groups. Varying methods of assessment of sexual dysfunction are also used in patients, each with their own problems. Those studies that have used clinical interviews are often non-blinded, and unclear in their definitions of sexual dysfunction. Face-to-face interviews may result in a selection bias toward more sexually experienced subjects, and have higher drop out rates. There is some evidence to suggest that men are more likely to over-report and women to under-report sexual experiences (21). Conversely, the use of questionnaires is not without problems. Although there is a broad array of questionnaires that have been used in normative populations and subsequently applied to epilepsy patients, none have been formally validated in patients with epilepsy. Regardless of methodology, all types of studies are typically limited by confounding factors such as concurrent physical or psychiatric disease, and the location of the patient populations studied. These tend to be tertiary centres where patients either have refractory epilepsy, or are pre-surgical candidates. Theoretically therefore, the findings of these studies may not be representative of the epilepsy population at large. Finally, the cultural background of patients can influence results. For example, a cross-sectional study carried out in Egypt (22) reported no increase in sexual dysfunctions but all types of sexual dysfunction in women with epilepsy in Egypt were less common than in normal control women in the United States, suggesting that cultural factors may play a major role in the willingness to admit to, or even recognise, symptoms of sexual dysfunction.

3.1. Women with Epilepsy

At least 20 to 30% of women with epilepsy may suffer from sexual dysfunction (23). The nature of this sexual dysfunction consists primarily of reduced sexual desire, or orgasmic dysfunction. One of the earliest studies by Bergen et al. (24) evaluated 50 women with epilepsy in a tertiary epilepsy care centre, 32 of whom had focal epilepsy, and 28 of whom were taking only one AED. Patients and a

matched control group were asked how often they had the desire for sex, and how often they had sexual intercourse. Though equal proportions of women in both groups had a frequent desire for sex, more controls had a very frequent desire compared with none in the epilepsy group. In addition, a larger proportion of patients compared to controls had very infrequent sexual desire, and 20% of patients reported that they almost never had sexual desire. This difference could not be explained by access to a sexual partner, and there was no correlation with age, prescribed antiepileptic drugs, duration of epilepsy, or seizure type. The authors concluded that there was a significant proportion of patients with epilepsy who have markedly decreased sexual desire compared to the general population.

In contradiction to this finding other studies report that the main type of sexual dysfunction in patients with epilepsy is not a reduction in sexual desire, but orgasmic dysfunction or other physical symptoms. Morrell et al. (21) conducted a study of 116 women with epilepsy attending a tertiary centre, using patient self-report questionnaires, which included the Sexual Arousability Inventory Expanded (SAI-E), Sexual Behaviour Inventory (SBI), and Sexual Functioning Inventory (SFI). Compared with historical controls this group of women did not have less sexual desire, but did report less overall sexual satisfaction. Specifically, 18% (9%), 28% (7%), 39% (8%) and 42% (14%) of women with focal epilepsy had global anorgasmia, vaginismus, dyspareunia and arousal insufficiency respectively (figures in brackets represent controls). In women with generalised epilepsy, 31% (9%), 13% (7%), 19% (8%) and 33% (14%) had global anorgasmia, vaginismus, dyspareunia and arousal insufficiency respectively (figures in brackets represent controls). Although the women with epilepsy in this study did not have less sexual experience than controls, they reported more sexual anxiety, which may have contributed to problems with sexual arousal. Indeed, Duncan et al. (25) in a tertiary clinic based study of 195 women with epilepsy who completed the Frenken Sexuality Experience scale also reported higher levels of inadequate orgasmic satisfaction compared to healthy controls. They also reported that women with epilepsy desired intercourse as much as healthy controls, but were more ‘moral’ and less open to sexual experiences. Jensen et al. (26) studied sexuality in 48 women with epilepsy, and compared their findings to patients with diabetes mellitus and healthy controls. Although the authors found no difference in sexual desire between the three groups, 19% of the women with epilepsy had orgasmic dysfunction compared with 11% of the diabetes mellitus group and 8% of the controls. They found no correlation between sexual dysfunction and type and duration of epilepsy, or

AED use. A recent, large study (27) highlights both reduced sexual desire *and* orgasmic dysfunction and other physical symptoms in women with epilepsy. They used a study specific questionnaire to assess 171 in- and out-patients with epilepsy in a tertiary centre. The most common forms of sexual dysfunction in descending order were reduced sexual desire, problems with orgasm, vaginal dryness and pain during intercourse. They also reported that 75% of women compared with 12% of controls had sexual dysfunction, which was associated with a poorer quality of life and depression.

Despite the clear importance of psycho-sexual factors in sexual dysfunction as noted above, there is also direct support for physiological impairment of sexual function in women with epilepsy, including orgasmic dysfunction. Morrell et al. (28) measured genital blood flow in nine women with temporal lobe epilepsy as they watched erotic or neutral videos. Blood flow was significantly reduced in the women with epilepsy compared to healthy controls as they watched erotic material. There was no difference in mood between the two groups, but the women with epilepsy were less sexually experienced and more anxious when imagining specific sexual activities compared to controls.

3.2. Men with Epilepsy

Anywhere between 20 and 70% of male patients with epilepsy are affected by sexual dysfunction, which can include loss of sexual desire, reduced sexual activity or sexual arousal, anorgasmia and erectile dysfunction (29–31). Although the prevalence figures differ between studies (32), erectile dysfunction consistently appears to be more common in patients with epilepsy than healthy controls, **and indeed other neurological disorders (33).** In the study (27) described above, 63% of men suffered from sexual dysfunction compared with 10% of controls. This manifested as erectile dysfunction, reduced sexual desire, premature ejaculation and problems with orgasms in order of decreasing incidence. This finding is corroborated by other studies which have reported hyposexuality and erectile dysfunction in up to 80% of patients with refractory epilepsy (34,35). Reassuringly studies in different patient populations report similar findings. One community study (36) reported that 57% of men with epilepsy and attending their general practioner had erectile dysfunction compared with 18% of controls, and 39% had ejaculatory failure compared with 0% of controls.

Although erectile dysfunction appears to be common in men with epilepsy, it is also a

common problem in the general population and elderly men. It is associated with a number of variables including age, smoking, physical activity and educational level in individuals without co-existing medical conditions, in addition to common medical conditions such as diabetes and hypertension (37). This might explain why some studies report conflicting results in men with epilepsy suggesting no differences in sexual dysfunction between patients with epilepsy and healthy controls (26,32). In an attempt to resolve this problem a population-based case control approach has been taken by some groups (38). This study looked at 6,427 patients with erectile dysfunction and 32,135 controls matched for age. After adjusting for hypertension, diabetes, hyperlipidemia, renal disease, coronary heart disease, obesity, alcohol abuse/alcohol dependence syndrome, and socioeconomic status, conditional logistic regression analysis revealed that patients with erectile dysfunction were more likely to have been diagnosed with prior epilepsy than controls (OR = 1.83, 95% CI = 1.51-2.21). Compared with controls, the adjusted ORs for prior generalized epilepsy and focal epilepsy for cases were 2.13 (95% CI = 1.52-3.00) and 1.64 (95% CI = 1.31-2.06), respectively. The most pronounced associations were detected in erectile dysfunction cases aged between 30 and 39 who were 3.04 (95% CI = 1.67-5.50) times more likely than controls to have been previously diagnosed with epilepsy. Moreover, the authors of this study point out that these figures may be an underestimation, because erectile dysfunction remains a taboo subject in Taiwan where the study was based.

As was the case for women, despite the clear importance of psycho-sexual factors in sexual dysfunction, there is also direct evidence for physiological factors causing the impairment of sexual function in men with epilepsy, including erectile dysfunction. In addition to the nine women studied by Morrell et al. (28) discussed above, reduced genital blood flow compared to controls was reported in eight men with temporal lobe epilepsy as they watched erotic or neutral videos.

4. AETIOLOGY OF SEXUAL DYSFUNCTION IN EPILEPSY (Figure 3)

There is a significant body of evidence that demonstrates that sex hormone levels are altered in patients with epilepsy, and that patients have higher levels of endocrine reproductive disorders. In exploring the link between these observations and sexual dysfunction in epilepsy, two issues arise. Firstly, it is unclear how much of the alteration in sex hormones is due to AEDs (39), and how much is due to the ictal/interictal discharges associated with the epilepsy, or any underlying structural

abnormality, both of which are well recognised as causing reproductive endocrine disorders (16,31). On the one hand, there are studies that have demonstrated sexual dysfunction and reproductive endocrine abnormalities in drug naive patients highlighting the fact that epileptiform discharges or underlying structural abnormalities may be causative factors (17,40,41). Indeed, epileptic discharges can be associated with abnormal testosterone and gonadotrophin levels, altered LH response to GnRH stimulation and increased serum prolactin concentrations (42). In contrast, other studies have shown no difference in sex hormone levels between patients having seizures and those off AEDs with no seizures (43), suggesting that ictal and interictal discharges in epilepsy may only partly explain sex hormone abnormalities. Other studies highlight the role of AEDs in hormone levels in patients with epilepsy. For example one study prospectively measured hormone levels after enzyme inducing AED withdrawal in seizure free patients, and demonstrated increases in biologically active testosterone levels 4 months after drug withdrawal compared to baseline (44).

The second issue that arises is that despite the number of studies that independently demonstrate high levels of sexual dysfunction and reproductive endocrine disorders in patients with epilepsy, there is not a consistent correlation between the two observations (45,46). Indeed, it is clear that reproductive endocrine disorders do not always lead to sexual dysfunction in people without epilepsy (5–8). In patients with epilepsy, although some studies show a clear concordance between sex hormone levels and sexuality in patients with epilepsy (45,47,48), other studies have failed to show such a concordance (26,46,49). The reason for this discrepancy is likely to be the multi-factorial basis of sexual dysfunction in epilepsy, which includes not only changes in sex hormone levels caused by the epilepsy (ictal/interictal discharges +/- structural basis) itself and AEDs, but also psychosocial factors, and disturbances in neurotransmission, not all of which are mediated by changes in sex hormones (figure 3). Some of these other factors are related to AED use and will therefore be discussed in this review.

4.1. Effect of Antiepileptic Drugs on Hormone Levels

Evidence for a correlation between sexual dysfunction and hormonal changes in patients with epilepsy comes primarily from the multiple studies that have shown that changes in SHBG are associated with sexual dysfunction (50). A consistent finding is that patients treated with older AEDs (carbamazepine, phenytoin and barbiturates) which are potent inducers of the cytochrome P450

enzyme system typically have lower levels of free and bioactive testosterone than those treated with non-inducing AEDs such as lamotrigine or levetiracetam (39,46,51–53). While total testosterone levels do not differ among patient groups, SHBG is significantly elevated among patients on enzyme inducing AEDs. This, in turn, leads to lower levels of unbound, biologically active testosterone and higher serum gonadotrophin levels, which may contribute sexual dysfunction seen in this patient group (52,54–57). Enzyme inducing drugs may also induce aromatase, which converts testosterone to estradiol (E2), which inhibits LH secretion and may contribute to a drop in testosterone levels and sexual dysfunction (30). In a landmark study, Herzog et al. (45) studied a group of 85 men with a focal epilepsy syndrome (25 on carbamazepine, 25 on phenytoin, 25 on lamotrigine and 10 on no AEDs). Controls included men without epilepsy. Sexual function scores were obtained by a self-reported questionnaire (S-score questionnaire), and serum measurements included bioactive testosterone (BAT), bioactive estradiol (BAE), BAT:BAE ratio, sex hormone binding globulin (SHBG), and LH. Gonadal efficiency was defined as the ratio BAT:LH. Nearly 25% of men with epilepsy had sexual dysfunction, and S-scores were lower in men taking enzyme-inducing AEDs (EIAEDs), which in this study were men taking carbamazepine or phenytoin, compared to men with epilepsy taking lamotrigine or compared to controls. BAT levels correlated with S-scores for men with epilepsy taking EIAEDs. BAT, BAT:BAE and BAT:LH ratios were lower in men taking EIAEDs compared to controls or patients taking lamotrigine.

Similar findings are apparent in women with epilepsy. Morrell and et al. (58) studied 57 reproductive-aged women with either localization related (LRE) or primary generalized epilepsy (PGE) on antiepileptic drug (AED) monotherapy and 17 non-epileptic controls. They completed several questionnaires assessing sexual experience (sexual behaviour inventory), arousability (sexual arousability inventory), anxiety (sexual anxiety interview), and symptoms of depression. An endocrine assessment was performed during the early follicular phase of the menstrual cycle. Compared to non-epileptic controls, women with epilepsy had significantly higher sexual dysfunction scores, lower mean arousal, and higher depressions scores. Mean arousal scores were also lower in the PGE group. Women on EIAEDs (in this study defined as carbamazepine, phenobarbital and phenytoin) when combined into one group had significantly higher sexual dysfunction and lower sexual arousal compared to controls. This was not the case in women taking enzyme-inhibiting AEDs (sodium valproate) or enzyme neutral

AEDs (gabapentin, lamotrigine) Furthermore, estradiol levels negatively correlated with sexual anxiety, and dehydroepiandrosterone sulfate (DHEAS) was negatively correlated with sexual dysfunction and positively correlated with sexual arousal.

Other studies involving AEDs that do not induce cytochrome P-450 enzymes appear to support the concept that these AEDs have little effect on sex hormones (45,46). In a randomised prospective study of patients taking non-enzyme inducing AEDs and randomised to either valproate or lamotrigine monotherapy no changes in total testosterone or free testosterone were noted after 6 to 12 months of treatment in either treatment group (59).

4.2 Psychiatric Disorders

Despite the aforementioned studies, other reports have failed to demonstrate a correlation between hormonal changes in patients with epilepsy and sexual function (31). Part of the reason for this may be psychiatric comorbidities, which may also contribute to sexual dysfunction in patients with epilepsy (58,60). Talbot et al. (46) evaluated sexual function, anxiety and depression with the Hospital Anxiety and Depression scale in 60 men with epilepsy receiving AED monotherapy and 60 controls. They reported that while patients taking EIAEDs did have lower levels of free testosterone compared to patients taking newer anti-convulsants, most patients had levels of testosterone that should be adequate for sexual functioning. Moreover, they found no correlation between testosterone levels and sexual function, and no difference in sexual function between men taking enzyme inducing and non-enzyme inducing medications. Instead they found that sexual function correlated with levels of anxiety and depression, suggesting that reductions in sexual desire and self-belief in being able to behave sexually were related to a patient's mood. Although this study classified oxcarbazepine and topiramate as enzyme inducing drugs, which may have confounded results, other reports have also shown that anxiety and depression can have an impact on sexual desire and erectile function in patients with epilepsy (49). Conversely, other studies have shown that hypogonadism in epilepsy can manifest as an affective disorder with loss of energy and competitive drive (16,61), and that testosterone treatment in epilepsy patients with hypogonadism can lead to significant improvements in mood (61). More recently, a systematic review has confirmed for the first time a bidirectional association between depression and sexual dysfunction (62). Given that it is well documented that a number of AEDs

including barbiturates, vigabatrin, and topiramate can cause adverse mood effects (63), this therefore is a potential mechanism by which AEDs can cause sexual dysfunction.

4.3. Epileptic Factors

Aside from AEDs and psychiatric factors, structural and physiological factors associated with the epilepsy itself may also contribute to sexual dysfunction in patients with epilepsy. Patients with focal seizures, and especially temporal lobe epilepsy (TLE) appear to be more prone to hypogonadism and sexual dysfunction than patients with generalised epilepsy syndromes (14,15,24,54,64,65). This finding is corroborated by both animal (66), and clinical studies that have shown that a significant proportion of patients develop an improvement in sexual function after temporal, but not extra-temporal lobe, surgery for their epilepsy (67), and that a normalisation of serum androgens can occur after surgery even in patients with maintained AEDs (68). This is perhaps not surprising given the links between mesial temporal lobe structures like the amygdala and the hypothalamus-pituitary-gonadal axis. Fixed lesions or epileptiform discharges affecting these areas may therefore predispose to sexual dysfunction. Moreover, some studies suggest that there is a lateralisation effect such that patients with right sided lesions and right TLE are more likely to have sexual dysfunction, and this may relate to lateralisation in the central regulation of gonadotrophin secretion and its disruption by ictal and interictal discharges (69,70). These findings suggest that beyond seizures and AEDs, structural and physiological factors associated with the epilepsy, may also have a role to play in the development of hormonal abnormalities that may mediate sexual dysfunction in patients with epilepsy.

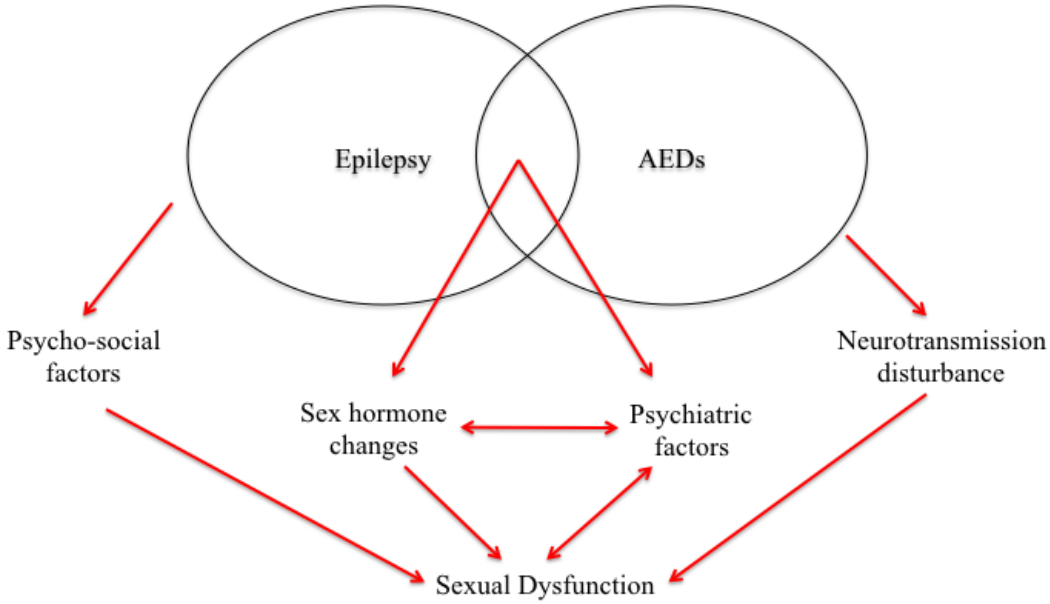
4.4. Neurotransmission changes

Calabro highlights another mechanism by which AEDs might cause sexual dysfunction in patients with epilepsy (30,71). He proposes that AEDs might inhibit and disrupt the normal neurotransmission of sexual excitement and arousal, which may lead to sexual dysfunction. These mechanisms which do not rely on changes in sexual hormone levels may be particularly relevant to newer, non-enzyme inducing AEDs. They include enhancement of GABAergic inhibition and unbalancing of the cerebral serotonin/dopamine ratio (carbamazepine, phenobarbital and phenytoin), AMPA receptor blockade through inhibition of the glutamatergic pathway (topiramate), the impairment of the complex interplay between serotonergic and nitrergic pathways (zonisamide), or the reduction of

central nervous system excitatory transmission by unbalancing the dopamine/serotonin ratio (oxcarbazepine, levetiracetam) (71,72).

4.5. Psychosocial factors

Psychosocial factors may also have a role to play in the aetiology of sexual dysfunction in patients with epilepsy. Stigmatization, psychological distress, low self-esteem and fear of rejection may lead to social isolation and feelings of inadequacy that contribute to sexual dysfunction. In a survey of quality of life of people with epilepsy in Europe, many subjects reported low levels of satisfaction with sexual relationships, partly because they felt stigmatized by having epilepsy (73).



The multi-factorial nature of sexual dysfunction in epilepsy - Figure 3

Both epilepsy (which includes ictal/interictal discharges +/- structural cause of epilepsy) and AEDs can give rise to sexual dysfunction which is mediated by changes in sex hormones.

However both epilepsy and AEDs can also cause mood disturbances which can lead to sexual dysfunction which may also be mediated by changes in sex hormones. Conversely, sexual dysfunction and hypogonadism may lead to mood disturbance. AEDs can also cause sexual dysfunction directly by

affecting neural transmission in pathways that are important for the sexual response. Finally, social factors caused by epilepsy can also lead to sexual dysfunction.

5. SPECIFIC AEDS AND SEXUAL DYSFUNCTION IN EPILEPSY (Table 2)

Having discussed the multiple mechanisms thorough which AEDs may affect sexual function, we will now describe the specific types of sexual dysfunction and how commonly they arise in patients with epilepsy. Given the multivariate nature of sexual dysfunction in epilepsy, sexual dysfunction can only reliably be ascribed to AEDs in several circumstances; where randomised clinical trials report sexual dysfunction as a side effect, where sexual dysfunction is reported in a comparative, cross-sectional study between patients on different AEDs, or between patients taking AEDs and healthy controls, and finally in case reports or series where sexual dysfunction arises after commencement of an AED and ceases when the AED is discontinued.

5.1. Carbamazepine

As the archetypical enzyme inducing AED, carbamazepine is probably the most common AED to cause sexual dysfunction in men and women. In the study by Herzog et al. (45) described earlier sexual function scores were below the control range in 32.0%, 24%, 20% and 4% of patients on carbamazepine phenytoin, no AEDs, and lamotrigine respectively. These findings are corroborated by other studies. In an observational, cross-sectional study of 90 men comparing the effects of valproate, carbamazepine and oxcarbazepine to healthy controls, 7 of the 18 men (18%) taking carbamazepine had diminished sexual dysfunction (52). These were the highest rates amongst the patients studied.

The most commonly reported types of sexual dysfunction reported in patients taking carbamazepine are decreased libido, erectile dysfunction and orgasmic dysfunction. In two multi-centre, randomised, controlled trials Matson et al. (74,75) reported that 7% of 231 and 13% of 101 patients with epilepsy taking carbamazepine developed decreased libido or impotence respectively during a one year follow-up period. Reis et al. (76) conducted a controlled cross-sectional study in 63 men receiving carbamazepine for temporal lobe epilepsy. Using the International Index of Erectile Function (IIEF-5) questionnaire they reported that 41/63 (65.1%) patients with epilepsy had erectile dysfunction compared with 4/55 (7.3%) control subjects, all of which were mild cases. Kuba et al. (77) evaluated the incidence of sexual dysfunction and hormonal profile in men with focal epilepsy. They prospectively analysed sexual function using the International Inventory of Erectile Function (IIEF), but without a control group. The authors noted that all patients with orgasmic dysfunction were being

treated with carbamazepine (CBZ) in monotherapy or combination therapy. In patients with at least one type of sexual dysfunction, they also found a higher proportion of valproate treatment in monotherapy or combination therapy in comparison with CBZ. The other AEDs patients were taking in this study included lamotrigine, levetiracetam, topiramate and valproate. The other types of sexual dysfunction that have been reported in the use of carbamazepine are much rarer and limited to single case reports, including ejaculatory failure (78) and hypersexuality (79).

5.2. Oxcarbazepine

Oxcarbaxepine is a carbamazepine derivative, but is metabolised by different pathways and unlikely to induce liver enzymes unless used at higher doses (>900mg/day) (80,81). Most studies indicate that it has a low incidence of sexual dysfunction associated with its use, and in some cases can improve sexual function. Rattya et al. (52) observed that in 29 patients with epilepsy taking oxcarbazepine monotherapy for an average of 2.4 years, 5 patients had diminished sexual function, while 1 had enhanced sexual function. Despite the limitations of this study in its lack of use a validated sexual function questionnaire, the study also showed that while valproate increased serum androgen concentrations in men with epilepsy, the endocrine effects of carbamazepine and oxcarbazepine were different. Carbamazepine appeared to decrease the bioactivity of androgens, whereas oxcarbazepine did not have this effect, which is consistent with its relative lack of adverse effect on sexual functioning at conventional doses. The other reports of sexual dysfunction caused by oxcarbazepine are limited to case reports and include anorgasmia (82), anejaculation (83), and a combination of both symptoms (84). In all of these cases symptoms resolved on discontinuation of oxcarbazepine, and in two of the three cases effects were seen only at 1800mg daily of oxcarbazepine.

Several studies have also suggested that oxcarbazepine can improve sexual function, especially if used in patients who have developed carbamazepine related sexual dysfunction. Luef et al. (85) conducted a prospective study in 228 male epileptic patients who had pre-existing sexual dysfunction and were treated with oxcarbazepine. After 12 weeks 181 (79.4%) of patients had improved sexual function, and 23 (10.1%) had no sexual dysfunction. In those patients who had been pre-treated with carbamazepine the improvement was most marked. Smaller case series report identical findings, namely resolution of erectile dysfunction when patients are switched from carbamazepine to oxcarbazepine (86).

5.3. Phenytoin

Phenytoin, like carbamazepine, has a high preponderance to causing sexual dysfunction. In the blinded, randomised controlled trial reported by Mattson et al. (74) 11% of 110 patients with focal or secondarily generalised seizures taking phenytoin experienced impotence during a 12 month treatment period. These findings are replicated in smaller cross-sectional studies. Herzog et al. (45) in the study described above, reported that after carbamazepine, phenytoin was the most likely drug to be associated with sexual dysfunction developing in 24% of male patients taking the drug, compared to 20% of patients with epilepsy and taking no AEDs. As an enzyme inducing drug phenytoin is associated with increased SHBG levels, and reduced serum levels of free testosterone. However, it is also associated with an increase in estradiol levels (64,87) suggesting that it may also induce aromatase, which converts free testosterone to estradiol. Although estradiol only makes up 1% of a male's total steroid sex hormone, it exerts powerful negative feedback on male LH secretion, and increases the synthesis of SHBG, all of which contribute to a hypogonadotrophic hypogonadism state (88).

Similar effects on sexual function are apparent in female patients with epilepsy. One study (58) reported that sexual dysfunction and anxiety were significantly higher, and sexual arousal significantly lower, in 27% of female patients taking phenytoin compared to healthy controls. There are also case reports that phenytoin may rarely cause retrograde ejaculation in male patients with epilepsy (89).

5.4. Phenobarbital

As an enzyme inducing AED, phenobarbital, and its structural analogue primidone, have been shown to increase SHBG levels and decrease free testosterone and estradiol levels (90). Correspondingly, cross-sectional studies have demonstrated prevalence rates of up to 22% patients suffering with decreased libido and impotence (74).

5.5. Sodium Valproate

Sodium valproate is a first generation AED that inhibits, rather induces, liver enzymes. In the randomised, controlled trail reported by Mattson et al. (75) 10% of the 240 patients taking sodium

valproate developed impotence or reduced libido during a one-year follow-up period. Cross-sectional, observational studies report similar results. One study (91) reported that a group of 25 male patients treated with sodium valproate reported worse erectile function as measured by a simplified version of the International Index of Erectile Function Scale (IIEF-5), when compared to healthy controls. Interestingly however, these patients also reported satisfactory sexual intercourse. This unexpected observation may be consistent with the finding by Rattya et al. (52) that in 21 male patients taking sodium valproate only 1 (5%) reported diminished sexual function, while 4 patients (19%) reported enhanced sexual function. In this study sexual function was considered enhanced if the patient reported increased libido, potency, or increased satisfaction with erection or orgasms, and was diminished if the patient reported no interest in sex, or decreased libido, potency, or decreased satisfaction with erection and orgasm. It is therefore possible that some of the patients reporting enhanced sexual function may also have had erectile difficulties, in addition to increases in other sexual domains. Given that androgen levels were increased as a group in these patients, it is possible that some of these effects may have been mediated by these hormonal changes. In women it is well documented that women can develop hyperandrogenic states and polycystic ovarian syndrome with the use of sodium valproate (ref drugs and sex/reproductive dysfunction review) but the link between these reproductive endocrine abnormalities and sexual function is much less clear (8).

5.6. Lamotrigine

There is an increasing body of evidence to suggest that lamotrigine may improve sexual function. Whether this is a direct effect of lamotrigine, or an indirect effect mediated by the mood enhancing effects of lamotrigine is less clear. Gil-Nagel et al. (92) conducted a prospective, unblinded study in 141 patients treated with lamotrigine over 8 months using the Changes in Sexual Functioning Questionnaire (CSFQ). Of these patients, 79 patients initiated treatment with lamotrigine monotherapy, and 62 were switched to lamotrigine because of lack of efficacy or adverse events to a previous AED. In women who started treatment with lamotrigine, a significant improvement was observed, both in total CSFQ score, and in the five dimensions of the scale (desire/frequency, desire/interest, pleasure, arousal/excitement and orgasm). In men, a significant improvement was only observed in the pleasure dimension. In the group of patients in whom a previous AED was substituted by lamotrigine, significant improvement was recorded in the dimensions of pleasure and orgasm in men and desire/frequency in women. Although the results of this study could be ascribed to direct or indirect

effects of lamotrigine, other factors that might be involved include improvement of the epilepsy, changes in quality of life, and elimination of side effects from other AEDs. However, the results of this study are also supported by two other important results. Herzog et al. (45) reported sexual dysfunction in 20% of untreated patients, but a lower rate of 4% of patients treated with LTG. In a cross-sectional study by Svalheim et al. (53) the sexual function of 40 women and 37 men receiving lamotrigine monotherapy for 6 months was evaluated using the Arizona Sexual Experience Scale Score (ASEX). The ASEX test is designed to assess five major aspects of sexual dysfunction: drive, arousal, vaginal lubrication/ penile erection, ability to reach orgasm, and satisfaction from orgasm. Sexual function across all categories was significantly better in female, but not male, patients taking lamotrigine compared to healthy controls and those patients taking carbamazepine. The findings of this study, despite its methodological differences, are in accordance with that by Gil-Nagel et al. (92) in suggesting that lamotrigine has an effect on improving sexual function, particularly in women. In addition to the large studies described, there are also a number of case reports, and case series describing improvements in sexual function when patients are switched from other AEDs to lamotrigine (93).

5.7. Levetiracetam

Levetiracetam is a relatively new, widely used, broad spectrum AED. Svalheim et al. (53) in the cross-sectional study described earlier also studied the effects of levetiracetam on sexual and hormonal function in 30 men and 26 women over 6 months using the ASEX rating scale. The authors reported that there were no specific hormonal changes associated with levetiracetam in men or women, but like lamotrigine it was associated with improved sexual function across almost all categories of the ASEX compared with controls in women only. However there are also reports of levetiracetam being associated with a decrease in sexual function such as decreased libido (94), but it should be noted that these are small case series or individual case reports, and interestingly all in men. In the study (91) described earlier, although hormonal levels were no different in 20 male patients taking levetiracetam compared to controls, the patient group as whole scored worse on International Index of Erectile Function Scale (IIEF-5).

5.8. Topiramate

Topiramate is an AED that is approved for the treatment of both focal and generalised epilepsy syndromes, and for migraine prophylaxis. Overall it appears to be associated with a low incidence of sexual dysfunction. Holtkamp et al. (95) were one of the first to report 2 cases of erectile dysfunction from their case series of 40 patients who had been treated with topiramate for focal epilepsy. The dosage of topiramate reached ranged from 100mg/day to 200mg/day, and symptoms resolved on discontinuation of the medication. This low rate of sexual side effects, despite its widespread use across two indications, is reflected in the small number of case reports documenting similar side effects (96–98).

5.9. Pregabalin

Pregabalin is an AED that is structurally related to gabapentin, and is used for pain and anxiety, as well as epilepsy. The incidence of sexual dysfunction appears to be low and is typically related to erectile dysfunction or anorgasmia. Hitiris et al. (99) reviewed the incidence of sexual dysfunction related to pregabalin in placebo-controlled trials across several of its indicated uses. In the placebo-controlled trials of pregabalin in epilepsy, 363 males received PGB and 156 males received placebo. Impotence was reported by 11 (3.0%) men taking PGB and three (1.9%) on placebo, which amounted to an insignificant difference between groups. The dose of pregabalin reached ranged from 150mg/day to 600mg/day. Across all placebo-controlled trials for all indications, a total of 2428 males received PGB, 71 (2.9%) of whom reported the adverse event of impotence. In these same trials, 1099 males received placebo with eight patients (0.7%) reporting impotence. Sexual dysfunction was not reported by female patients with epilepsy receiving treatment with PGB during the epilepsy trials and only in 3 patients (0.1%) across the entire population treated with PGB. A small number of case reports appear to support this finding of rare complications of angorasmia and erectile dysfunction, which are reversible on cessation of pregabalin (100,101).

5.1.0. Gabapentin

Gabapentin is widely used in migraines, paraesthesia, neuralgia, bipolar disorder and epilepsy. Sexual dysfunction is an uncommon side effect of gabapentin, and published data is limited to case reports despite its multiple indications. The most common symptom is anorgasmia, which can be seen at doses from 900mg/day to 3600/day in all indications, and may be more common in elderly patients

(102,103). Symptoms are reversible on cessation of the drug.

5.1.1. Other AEDs

Both zonisamide and lacosamide are relatively new AEDs. To date there is only one case report for each AED reporting sexual dysfunction (72,104). In both cases male patients reported erectile dysfunction, and a decrease in libido in the case of lacosamide. Symptoms resolved on cessation of the offending AED. To our knowledge no sexual dysfunction has been reported following use of brivaracetam, perampanel, felbamate and eslicarbazepine.

Drug	Most commonly reported types of sexual dysfunction	How common?	Nature of evidence
First generation AEDs			
Carbamazepine	Decreased libido Erectile dysfunction Orgasmic dysfunction	***	Randomised controlled trials Cross-sectional studies
Phenytoin	Decreased libido Erectile dysfunction	***	Randomised controlled trials Cross-sectional studies
Phenobarbital	Decreased libido Erectile dysfunction	***	Randomised controlled trials Cross-sectional studies
Primidone	Decreased libido Erectile dysfunction	***	Randomised controlled trials Cross-sectional studies
Sodium valproate	Decreased libido Erectile dysfunction	**	Randomised controlled trials Cross-sectional studies
Modern AEDs			
Oxcarbazepine	Improved sexual function	**	Cross-sectional studies
Lamotrigine	Improved sexual function	**	Prospective study Cross-sectional studies
Levetiracetam	Improved sexual function Decreased libido (men only)	* *	Cross-sectional studies Case series/Case reports
Topiramate	Erectile dysfunction	*	Case reports
Pregabalin	Erectile dysfunction	*	Randomised controlled trials Case reports
Gabapentin	Orgasmic dysfunction	*	Case reports
Zonisamide	Erectile dysfunction	*	Case reports
Lacosamide	Erectile dysfunction Decreased libido	*	Case reports

Summary of Anti-Convulsants and Effects on Sexual Function – Table 2
* = rare, ** = common, *** = very common

6. MANAGEMENT OF SEXUAL DYSFUNCTION RELATED TO AEDS

The use of AEDs in patients with epilepsy is clearly associated with the frequent occurrence of sexual dysfunction in both men and women. However, the relationship between sexual dysfunction, hormones, seizures and AEDs remains unclear. In addition, the psychosocial complications associated with epilepsy may also affect sexual health. Given the multifactorial nature of this problem, it is perhaps not surprising that there is little research in this challenging area, and there are no guidelines or expert consensus statement on the management of sexual dysfunction induced by AEDs in patients with epilepsy. Regardless of this, some general principles of management cab be applied to this population.

Firstly, when prescribing an AED to a patient with epilepsy there should be awareness that any pre-existing sexual dysfunction, depression or anxiety may facilitate the development and progression of sexual dysfunction. In any evaluation of a patient with epilepsy presenting with symptoms of sexual dysfunction, management of the patient should be guided by an awareness of the multifactorial nature of the problem. To this end, any history taking from the patient should also include a thorough medication history, sexual/relationship history and screening for anxiety and depression. Besides AEDs there are numerous other classes of drugs commonly prescribed in this patient population that can cause sexual side effects including anti-depressants, neuroleptics, sedatives, and beta-blockers. Questionnaires for assessing sexual dysfunction may prove a useful adjunct by allowing quantification of the problem, especially in patients who may be embarrassed to discuss their sexual problems. Two widely used scales are the Arizona Sexual Experience Scale (ASEX) and the International Index of Erectile Function score (IIEF). However, it should be noted that neither of these instruments nor others have been validated in an epilepsy population. Further assessment of the patient should include a general and urogenital as well as standard neurological examination, particularly as erectile dysfunction can be the first manifestation of cardiovascular disease. Blood tests should include a metabolic and endocrinological screen, including serum levels of testosterone, SHBG, DHEAS, estradiol, LH, FSH, prolactin, and thyroid function.

In those patients in whom sexual dysfunction is thought to be due to the AED, switching to an

alternative AED should be considered. As discussed above, the most commonly reported positive switch is from carbamazepine to oxcarbamazepine, although there is also some evidence to suggest that switching to lamotrigine may also be helpful. Phosphodiesterase type 5 inhibitors (PDE5) may also have a role in those patients with erectile dysfunction where a switch in AEDs is not possible or useful (29,86,105). However, caution is also needed because tonic-clonic seizures have been reported in patients taking PDE5 medications (106).

Ultimately, improvements in the management of sexual dysfunction secondary to AEDs in patients with epilepsy, is contingent on a deepening of our understanding of this area. Further research into the incidence and specific nature of sexual dysfunction for individual AEDs, and the dosages at which they occur, would enable better counselling of patients when they commence AEDs. A better understanding of the mechanisms that cause AEDs, especially non-enzyme inducing AEDs, to give rise to sexual dysfunction would help to improve treatment of these patients. These should be the areas of focus of robust, high quality research in the future.

CONFLICT OF INTERESTS

MM has received consultancy fees from UCB Pharma, Eisai, Pfizer, Elsevier and Springer. He has also received supports from Bial and Special Products Ltd. MY has no conflicts of interests

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