Review Article

Intake of Anti-Epileptic Drugs and their Influences on Sexual Dysfunctions

Roheela Yasmeen[1]* Nida Mobeen[1], Muhammad Amjad Khan[1], Irfan Aslam[1], Samia Chaudhry[2]

[1]Lahore Garrison University, Phase VI, Sector C DHA Lahore,

[2]Services Institute of Medical Sciences, Lahore

* roheelayasmeen@lgu.edu.pk

Abstract:

Epilepsy which is also called seizures disorder is an uncontrolled action of the central nervous system. It is not a single disease but a set of neurological disorders. Actually in this situation, the brain does not receive a precise signal and as a result an abnormal condition is produced that is usually involuntary in action. In this review, we aimed to focus on the relationship of anti-epileptic drugs with sexual dysfunction and adaptation of better remedies that improve a patient's family life. Sexual dysfunction is a common comorbidity in people with epilepsy which badly affects their quality of life. Sexual dysfunction is caused by different factors like psychiatric problems, anti-epileptic drugs (AEDs) and social factors etc. Sexual dysfunctions include ejaculatory failure, lessen libido, penile erection in men and irregular menstrual cycle in women. Common drugs such as Topiramate, Gabapentin (GBP), Valproate (VA), Carbamazepine (CBZ), Olanzapine (OL) and Risperidone (RTG) that are in practice to treat epilepsy usually produced adverse effect on sexual dysfunction. Even though a lot of studies have been carried out to control sexual dysfunction in epilepsy's patient, but still research is going on. Medicine such as Cyproheptadine, Mianserin, Buspirone, Yohimbine were found better to treat epilepsy with minimum side effects of sexual dysfunction. Moreover, it is also seen that certain vasodilators, folate , and vitamin supplements are effective in improving the quality of life.

Keywords: Epilepsy, psychiatric problems, anti-epileptic drugs (AEDs), social, sexual dysfunction

Introduction:

Sexual dysfunction is a condition in epilepsy which are produced due to excessive use of anti-epileptic drugs [1, 2]. The symptoms of sexual dysfunction that usually appear due to use of these anti-epileptic drugs include the sterility, low level of sexuality, hyper sexuality and ejaculatory failure [3]. It also comprises of hypoandrogenemia, hypogonadism and sperm aberrations which are mostly common in men. These anti-epileptic drugs in epilepsy affects the hormonal imbalances by lowering levels of testosterone, dehydroepiandrosterone, high sex hormone binding globulin, estradiol, prolactin, Luitenizing Hormone (LH), follicle stimulating hormone (FSH) levels and LH/FSH correlations [2]. According to Kaufman et al., Pavone [4] and [5] most frequent sexual dysfunction are erectile dysfunction, reduced libido, orgasamic and ejaculation dysfunction, high percentage of SD in persons with temporal lobe epilepsy (TLE) than primary generalized epilepsy. Moreover, various other symptoms like lessened libido, erectile dysfunction, ineffectiveness, ejaculatory retardation, overdue orgasm, anorgasmia, priapism, premature ejaculation and deteriorating ejaculation are also result of anti-epileptic drugs that are used in this disease. Lin et al. [6] also explained the signs such as declined libido, slash sexual stimulation, and sporadic orgasms seen in persons with epilepsy. While, Ocek et al. [7] specified that in epilepsy the surge of free testosterone and dehydroepiandrostenedione sulfate and the levels of sex hormone-binding globulin in male patients are reduced but prolactin levels are

increased in female patients. Hamed et al. [8] highlighted the penile arterial insufficiency in epileptic patients. In females, during menstrual cycle seizures are more probable to arise as compared to other days [9]. Menstrual abnormalities such as amenorrhea, oligomenorrhea, polymenorrhea and menometrorrhagia in epilepsy were reported in females by [10]. However, Herzog, [10] reported the loss of male escutcheon, gynecomastia, and testicular waste. According to Montejo et al. [11] in this disease complications occur in sexual arousal (penile erection), delayed orgasm, anorgasmia and vaginal lubrication which are the cause of Sexual Dysfunction. Hormones play a very important role in fertility as Al-Bishri, [12] depicted that the main fertility hormones testosterone, de-hydro-epi-androsterone, LH and FSH are significantly decreased in epileptic patients.

Anti-epileptic drugs as major cause of sexual dysfunction in epilepsy

Epilepsy is one of mental disorders and use of anti-epileptic drugs in this disease associated with sexual dysfunction. Different drugs like Topiramate, pregabalin and gabapentin become a cause of Sexual Dysfunction [3], [9]. Anti-epileptic drugs actually alter the liver functions that affect the psychological factor and ultimately gonads. One such study by Calabrò, [13] described that use of enzyme inducing anti-epileptic drugs such as phenobarbital and carbamazepine affects liver enzymes and causes problems in sexual desire. Luef and Madersbacher, also reported that Enzyme-inducing antiepileptic drugs influence the hepatic enzymes that enhance the levels of sex hormone-binding globulin (SHBG) which decrease sexuality in the patients of epilepsy [14]. According to Rathore and fellows mostly, patients with uncontrolled epilepsy, longer term of epilepsy, central epilepsy, higher seizure recurrence, and those receiving enzyme-inducing and various ASDs (antiseizure drugs) are bound to have sexual dysfunction [15]. Women generally have dysfunction in the domains of desire, while males usually have arousal disorders such as erectile dysfunction and premature ejaculation. Atif et al., highlighted aspects of anti-epileptic along with anti-hypertensive drugs, anti-psychotics, and anti-depressants drugs that affect the gonadotropin-releasing hormone (GnRH) which alter sexuality associated with epilepsy [16]. Wu and colleagues reported that renewal attacks in epilepsy can affect the size of gonads and reduce the sexual function [17]. Bangar et al., reported that Valproate is grievous as compared to Carbamazepine as it results in more menstrual disorders and also it decreases libido [18]. Valproic acid actually conquers the mitochondrial roles and affects the spermatozoa motility that results in sexual inability. However, Ocek et al., reported, use of Carbamazepine drug declines the free testosterone level while enhances the synthesis of Sex Hormone Binding Globulin and results in sexual dysfunction [7]. Use of Eslicarbazepine acetate also decreases the level of ethinyl estradiol and progesterone [19]. Factors such as irregularities in sperm concentration, morphology and motility, might play an important part in triggering fertility in men with epilepsy [20]. Antiepileptic drugs also lessens the sperm concentration. As it is explained by Hamed and cofellows that regular use of valproic acid in the epilepsy treatment lessens the number of sperms and motility [21]. This also ruins the testicular volume and erectile dysfunctions in men which may be caused by penile vascular flaws. Valproic acid (VPA) causes multiple sexual dysfunctions such as hyperandrogenism, polycystic ovarian syndrome and menstrual problems [22]. Stigmatization (*Stigma* involves negative attitudes or discrimination against someone based on a distinguishing characteristic such as a mental illness, health condition, or disability) also disturbs the sexual activity [23]. Epileptic patients have some other problems like fear, low self-confidence and these feelings are enhanced during sexual intercourse that lead to sexual dysfunction [24], [25]. SSRIs (selective serotonin

reuptake inhibitor) and SNRIs (serotonin-norepinephrine reuptake inhibitor) are anti-depressants that are commonly prescribed. They are involved in sexually opposing incidents like reduced libido, anorgasmia [26]. Hyperprolactinaemia-inducing antipsychotics including haloperidol, risperidone, paliperidone and amisulpride are related with reduced libido and arousal difficulties [11]. Some AEDs such as CBZ linked with the p450 enzyme system in the liver disturb the sex hormone levels by triggering structural irregularities in Leydig cells [27].

The incidence of oxidant disorder in the testes of epileptic patients triggered prolonged apoptosis in the germ cell layer [28]. Newer antipsychotic drugs, such as olanzapine and risperidone, are highest causing agents of erectile dysfunction (ED)[29]. Hormonal contraceptives may raise the removal of certain anticonvulsants such as lamotrigine which cause sexual dysfunction [30]. When a sexual happenstance marks in frustration and anxiety relatively than satisfaction, a vicious psych neuroendocrine cycle of distress and misery result in erectile dysfunction [31]. Catamenial epilepsy is a twofold or greater increase in seizure frequency during different phases of the menstrual cycle, perimenstrual phase, periovulatory phase, and luteal phase. Literature has stated that women with epilepsy may have increased rates of PCOS (poly cystic ovarian syndrome) that is a major cause of infertility. PCOS has been more frequently reported in women with genetic generalized epilepsy(GGE)[32]. Pennell et al., also focused on the POCS which occurs more commonly in those women, which use valproate for the treatment of idiopathic generalized epilepsy syndromes and they are also at high risk for miscarriage and their study highlighted that it occurred in women who are treated with AED monotherapy [33]. Persistent genital arousal disorder(PGAD)is a condition characterized by unrelenting, spontaneous, and uncontainable genital arousal, which is caused by Lamotrigine (LTG). Lamotrigine (LTG) is a second-generation anticonvulsant drug for the treatment of partial and secondarily generalized seizures. Mainly females are involved in PGAD [34]. Sidhu and fellows, elucidated in the study that there is an increased problems of polycystic ovarian syndrome (PCOS) [35]. However, it was more common in epileptic women than those taking VPA drugs which can disturb the ovarian function and androgen synthesis. Recent evidence suggests that VPA leads to hyperandrogenemia and PCOS-like features through direct effects on the ovary. Osuntokun et al., evaluated in his research that GBP (Guaifenesin) CBZ, and GBP-CBZ combination notably reduced the absolute weight of the testis, epididymis, and seminal vesicle [36]. Phenytoin which is also used as AEDs, increased metabolism of sex hormones which decreased the free androgen index. CBZ has direct effect on spermatogenesis, specifically its intrusion with acetylcholine-esterase and glucose and they both are required for the normal process of spermatogenesis. GBP caused the fewest adverse effects on serum testosterone while the greatest adverse effects were found with the GBP-CBZ combination. A predictable finding is that patients treated with more older AEDs(carbamazepine, phenytoin, and barbiturates) which are inducers of the cytochrome P450 enzyme system, commonly have lower levels of free and bioactive testosterone than those treated with noninducing AEDs, for example, lamotrigine or levetiracetam. SHBG (sex hormonebinding globulin) is essentially raised among patients taking enzyme inducing AEDs. This prompts lower levels of unbound, biologically active testosterone, which may contribute to sexual dysfunction [37]. According to Ceylan et al., males with epilepsy have lower fertility rates, hypo-sexuality and reduced potency [38]. According to them animal studies concerning the effects of LEV (levetiracetam) on sex hormones concluded that LEV may affect steroid hormone secretion. Moreover, [39] depicted that more seasoned antiepileptic drugs (AEDs) may cause SD by diminishing bioactive testosterone, accelerating sexual hormone digestion, and

animating binding hormone globulin activity, new AEDs are thought to cause sexual issues through complex and ineffectively understood mechanisms, presumably including brain neurotransmitters. Studies showed that depression in this disease is one of major reasons for the disturbing of sexual functions [4], [23].

Treatments commonly used in epilepsy

Epilepsy is a chronic disorder. It affects the different organs of the body at different stages of life. Sexual abnormalities are more adverse with epilepsy than other illnesses but a good treatment option for catamenial epilepsy is still unknown. AEDs like Oxcarbazepine, lamotrigine and levetiracetam has little effect on sexuality but oxcarbazepine, lamotrigine and levetiracetam may enhance sexual function [3]. Sex performance should be better but sometime it is affected by illness. To improve their function, different therapies and medicines are in use. Atif et al., studied the side effects of AEDs on sex performance [16]. They mentioned different medicines such as Buspirone, yohimbine, neostigmine, cyproheptadine, mianserin, amantadine and dexamphetamine, which are used to treat sexual dysfunction with epilepsy. Sexual dysfunctions are treated by using current methods in combination with previous methods. This includes anatomical induction of the penis to intensify spinal reflexes, and deprivation of blood can be intercepted by introducing elastic constricting bands at the base. Medication with oxcarbazepine stimulates the movement, rate and feasibility of sperm and levetiracetam and lamotrigine exhibit a marked increment on semen quality [17]. Hamed, explained, Tight seizure control, changing the AED, androgen therapy, genital vasodilators, L-carnitine supplementation, psychotherapy improve the sexuality [1]. Lamotrigine which shows a determined intensification in sexual desire in decreased libido as a credible medication are used for the treatment of sexual dysfunction [4], [18]. Psychotropics like escitalopram, mirtazapine and alprazolam are used for treatment [4] but psychoeducation for healthcare workers can support them and profile their arrogances by alerting them to the incidence of sexual difficulties, making them realize the importance of sexual health for overall quality of life [40]. Hameed and fellows described the importance of vasodilators and folate and vitamin supplements [8]. They are effective in improving the quality of life of a patient with epilepsy. Literature showed that epilepsy alters the pregnant woman's response [9] as pregnant women with epilepsy take folic acid along with AED during pregnancy to reduce teratogenesis in offspring. Swapping AED treatment from carbamazepine to oxcarbazepine in men may decrease the erectile dysfunction [10]. Herzog, also explained that combining testosterone with an aromatase inhibitor that intercept the conversion of testosterone to estradiol is related to seizure lessening [10]. Another inhibitor, phosphodiesterase inhibitor combined with a prostaglandin warrant used for the analysis of men with epilepsy who have sexual dysfunction. Montejo et al., explain the use of phosphodiesterase-5 (PDE-5) inhibitors that prove helpful in sexual problems like supplementary approaches with a dopamine agonist, add aripiprazole and substituting the antipsychotic [11]. Melatonin is the hormone that has the main function in the regulation of sleep cycle but it has influence on sexes. Melatonin is able to enhance the sperm motility by intensifying the total antioxidant level and also the Bupropion that is used as a drug has a good impact on cognition and improves sexual function [28]. Rezaei et al., explained most effective use of Bupropion. According to their study, bupropion has effects on erection and orgasm subscales and no substantial variations exhibited in libido, sexual arousal and ejaculation [41].

Conclusions:

It was concluded that sexual functions are influenced by anti-epileptic drugs. There is a strong link between various AEDs such as VPA,

Topiramate, pregabalin and gabapentin and sexual dysfunctions. As these drugs affect hormonal changes and enhance the depression in epiletic patients. However, in some studies CBZ like drugs have no effects on sexual dysfunctions which showed that in future there may be a possibility to get such drugs that will be used to control epilepsy with healthy physical and emotional effects. So, further studies are still recommended to get better alternates.

References:

1. *Hamed SA* (2016). The effect of epilepsy and antiepileptic drugs on sexual, reproductive and gonadal health of adults with epilepsy. Expert review of clinical pharmacology, **9**(6), 807-819.
2. *Yogarajah M, Mula M.* (2017). Sexual dysfunction in epilepsy and the role of anti-epileptic drugs. Current pharmaceutical design, **23**(37), 5649-5661.
3. *Yang Y, Wang X.* (2016). Sexual dysfunction related to antiepileptic drugs in patients with epilepsy. Expert opinion on drug safety, **15**(1), 31-42.
4. *Kaufman KR, Coluccio M, Sivaraaman K, Campeas M.* (2017). Lamotrigine-induced sexual dysfunction and non-adherence: case analysis with literature review. BJPsych open, **3**(5), 249-253.
5. *Pavone C, Giacalone N, Vella M, Urso L, Zummo L, Fierro B.* (2017). Relation between sexual dysfunctions and epilepsy, type of epilepsy, type of antiepileptic drugs: a prospective study. Urologia Journal, **84**(2), 88-92.
6. *Lin CY, Fung XC, Nikoobakht M, Burri A, Pakpour AH.* (2017). Using the Theory of Planned Behavior incorporated with perceived barriers to explore sexual counseling services delivered by healthcare professionals in individuals suffering from epilepsy. Epilepsy & Behavior, **74**, 124-129.
7. *Ocek L, Tarhan H, Uludağ Fİ, Sarıteke A, Köse C, Colak A, Zorlu F, Zorlu Y.* (2018). Evaluation of sex hormones and sperm parameters in male epileptic patients. Acta Neurologica Scandinavica, **137**(4), 409-416.
8. *Hamed SA, Hermann BP, Moussa EM, Youssef AH, Rageh TA, Elserogy YE, NasrEldin E.* (2015). Evaluation of penile vascular status in men with epilepsy with erectile dysfunction. Seizure, **25**, 40-48.
9. *Shawahna R, Atrash A, Jebril A, Khalaf A, Shaheen E, Tahboosh H.* (2017). Evaluation of pharmacists' knowledge of women's issues in epilepsy: a cross-sectional study in Palestinian pharmacy practice. Seizure, **46**, 1-6.
10. *Herzog AG.* (2015). Disorders of reproduction in patients with epilepsy. Zeitschrift für Epileptologie, **28**(4), 254-263.
11. *Montejo AL, Montejo L, Baldwin DS..* (2018). The impact of severe mental disorders and psychotropic medications on sexual health and its implications for clinical management. World Psychiatry, **17**(1), 3-11.
12. *Al-Bishri WM, Abdel-Reheim ES, Zaki AR.* (2017). Purslane protects against the reproductive toxicity of carbamazepine treatment in pilocarpine-induced epilepsy model. Asian Pacific Journal of Tropical Biomedicine, **7**(4), 339-346.
13. *Calabrò RS.* (2016). Sexual dysfunction in patients with epilepsy: disentangling the pathogenic mechanisms!. Epilepsy & Behavior, **64**, 294.
14. *Luef G, Madersbacher H.* (2015). Sexual dysfunction in patients with epilepsy. In Handbook of clinical neurology, **130**, 383-394. Elsevier.
15. *Rathore C, Henning OJ, Luef G, Radhakrishnan K.* (2019). Sexual dysfunction in people with epilepsy. Epilepsy & Behavior, **100**, 106495.
16. *Atif M, Sarwar MR, Scahill S.* (2016). The relationship between epilepsy and sexual dysfunction: a review of the literature. Springerplus, **5**(1), 2070.
17. *Wu D, Chen L, Ji F, Si Y, Sun H.* (2018). The effects of oxcarbazepine, levetiracetam, and lamotrigine on semen quality, sexual function, and sex hormones in male adults

with epilepsy. Epilepsia, **59**(7), 1344-1350.

18. *Bangar S, Shastri A, El-Sayeh H, Cavanna AE.* (2016). Women with epilepsy: clinically relevant issues. Functional neurology, **31**(3), 127..
19. *El Makawy AI, Ibrahim FM, Mabrouk DM, Ahmed KA, Ramadan MF.* (2019). Effect of antiepileptic drug (Topiramate) and cold pressed ginger oil on testicular genes expression, sexual hormones and histopathological alterations in mice. Biomedicine & Pharmacotherapy, **110**, 409-419.
20. *Asadi-Pooya A, Farazdaghi M, Ashjazadeh N.* (2015). Effects of carbamazepine on semen parameters in men with newly diagnosed epilepsy. Iranian journal of neurology, **14**(3), 168.
21. *Hamed SA, Moussa EM, Tohamy AM, Mohamed KO, Mohamad ME, Sherif TM, Abdellah MM.* (2015). Seminal fluid analysis and testicular volume in adults with epilepsy receiving valproate. Journal of Clinical Neuroscience, **22**(3), 508-512.
22. Verrotti A, Mencaroni E, Cofini M, Castagnino M, Leo A, Russo E, Belcastro V. (2016). Valproic acid metabolism and its consequences on sexual functions. Current drug metabolism, **17**(6), 573-581.
23. Krasuski T, Jędrzejczak J, Rysz A, Owczarek K. (2018). Sexual satisfaction of patients after the resection of an epileptic focus. Interdisciplinary Neurosurgery, **13**, 104-108.
24. Miller WR, Gesselman AN, Garcia JR, Groves D, Buelow JM. (2017). Epilepsy-related romantic and sexual relationship problems and concerns: Indications from Internet message boards. Epilepsy & Behavior, **74**, 149-153.
25. Singh M, Bathla M, Martin A, Aneja J. (2015). Hypoactive sexual desire disorder caused by antiepileptic drugs. Journal of human reproductive sciences, **8**(2), 111.
26. Kanner AM. (2016). Most antidepressant drugs are safe for patients with epilepsy at therapeutic doses: a review of the evidence. Epilepsy & Behavior, **61**, 282-286.
27. Basson R., Rees PM. (2018). Sexual Dysfunctions. The American Psychiatric Association Publishing Textbook of Psychosomatic Medicine and Consultation-Liaison Psychiatry, 405.
28. Shokri S, Kazemi M, Firouzjaei MA, Hemadi M, Moayeri A, Ganjkhani M, Nejatbakhsh R. (2015). Melatonin protects testes against lithium-pilocarpine-induced temporal lobe epilepsy in rats: a time course study. Andrologia, **47**(3), 343-353.
29. Matsui H, A Sopko N, L Hannan J, J Bivalacqua T. (2015). Pathophysiology of erectile dysfunction. Current drug targets, **16**(5), 411-419.
30. Sharma A, Boller F, Koubeissi M. (2016). Women with epilepsy. Functional neurology, **31**(3), 125.
31. Calabrò RS, Gervasi G, Naro A, de Luca R, Marullo M, Bramanti P. (2016). Erectile Dysfunction in Individuals with Neurologic Disability: A Hospital-based Cross-sectional Study. Innovations in clinical neuroscience, **13**(1-2), 10.
32. Voinescu PE, Pennell PB. (2017, December). Delivery of a Personalized Treatment Approach to Women with Epilepsy. In Seminars in neurology, **37**(6), 611-623. Thieme Medical Publishers.
33. Pennell PB, French JA, Harden CL, Davis A, Bagiella E, Andreopoulos E, Lau C, Llewellyn N, Barnard S, Allien S. (2018). Fertility and birth outcomes in women with epilepsy seeking pregnancy. JAMA neurology, **75**(8), 962-969.
34. Calabrò RS. (2017). Lamotrigine-induced persistent genital arousal disorder: an unusual side effect. Epilepsy & Behavior, **68**, 234-235.
35. Sidhu HS, Srinivasa R, Sadhotra A. (2018). Evaluate the effects of antiepileptic drugs on reproductive endocrine system in newly diagnosed female epileptic patients receiving either Valproate or Lamotrigine

monotherapy: A prospective study. Epilepsy research, **139**, 20-27.

36. Osuntokun OS, Olayiwola G, Oladele A, Ola I, AyokaAbiodun O. (2017). Chronic administration of gabapentin and a gabapentin-carbamazepine combination reversibly suppress testicular function in male Wistar rats (Rattus norvegicus). Pathophysiology, **24**(2), 63-69.

37. Yogarajah M. (2019). Epilepsy and sexual dysfunction. In The Comorbidities of Epilepsy: 51-76. Academic Press.

38. Ceylan M, Yalcin A, Bayraktutan OF, Karabulut I, Sonkaya AR.. (2016). Effects of levetiracetam monotherapy on sperm parameters and sex hormones: Data from newly diagnosed patients with epilepsy. Seizure, **41**, 70-74.

39. Calabrò RS. (2017). Sexual dysfunction and topiramate: What does lie beneath the tip of the iceberg?. Epilepsy & Behavior, **73**, 281-282.

40. Lin CY, Oveisi S, Burri A, Pakpour AH. (2017). Theory of Planned Behavior including self-stigma and perceived barriers explain help-seeking behavior for sexual problems in Iranian women suffering from epilepsy. Epilepsy & Behavior, **68**, 123-128.

41. Rezaei O, Fadai F, Sayadnasiri M, Palizvan MA, Armoon B, Noroozi M. (2018). The effect of bupropion on sexual function in patients with Schizophrenia: A randomized clinical trial. The European Journal of Psychiatry, **32**(1), 11-15.