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Review

Sexual dysfunction in people with epilepsy

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ABSTRACT

Sexual dysfunction is a common comorbidity in people with epilepsy (PWE) that adversely affects their quality of life. Nearly one-half of men and women with epilepsy have sexual dysfunction, but in the majority, this often goes unnoticed. The wide variation in the reported prevalence of sexual dysfunction in PWE is due to the significant heterogeneity among the studies with regard to patient population, type and severity of epilepsy, number and type of antiseizure drugs (ASDs) used, and the tools used for assessing sexual dysfunction. Generally, patients with uncontrolled epilepsy, longer duration of epilepsy, focal epilepsy, higher seizure frequency, and those receiving enzyme-inducing and multiple ASDs are more likely to have sexual dysfunction. Women generally have dysfunction in the domains of desire, while males usually have arousal disorders such as erectile dysfunction and premature ejaculation. There is limited evidence to indicate that sexual function improves in patients rendered seizure-free following epilepsy surgery. Multiple mechanisms including direct effects of epilepsy, effects of ASDs, and psychosocial factors contribute to sexual dysfunction in epilepsy. Circumstantial evidence indicates that seizures and interictal epileptiform discharges can directly affect the hypothalamic–pituitary axis as well as production of gonadal steroids. Enzyme-inducing ASDs cause sexual dysfunction by affecting the metabolism of gonadal steroids. Limited data suggest that newer ASDs including oxcarbazepine, lamotrigine, and levetiracetam cause no or minimal sexual dysfunction. Depression and anxiety significantly contribute to sexual dysfunction in PWE. A multipronged and multidisciplinary approach is essential for optimizing the sexual functions. Every effort should be made to identify and treat reversible causes including changing to nonenzyme-inducing ASDs and to provide symptomatic relief. Large, prospective studies are required to improve our understanding on prevalence and mechanisms of sexual dysfunction in PWE.

1. Introduction

Sexual functions play an important role in normal human life. Along with sleeping and eating, sexual functioning is one of the basic human drives. Sexual satisfaction and healthy sexual functioning are important factors in determining the quality of life in adults [1]. Sexual dysfunction has been identified as an important public health concern over the last two decades. Many common medical disorders such as diabetes, hypertension, and depression are known to cause sexual dysfunctions. The fact that epilepsy is associated with sexual dysfunction is known for the last 70 years [2]. In spite of this, the prevalence and nature of sexual dysfunctions in people with epilepsy (PWE), its causes, and optimal management strategies are poorly understood. Many factors contribute to this relative lack of data regarding sexual dysfunctions in PWE. Both physicians and patients are often reluctant to discuss sexual health in clinical encounters [3]. There is significant discomfort among the physicians in diagnosing and treating sexual dysfunctions in PWE, which often requires a multidisciplinary approach. Additionally, many patients, especially in developing countries, consider it a taboo to discuss sexual dysfunctions and in turn accept these as a part of their disease. For optimizing the sexual functioning and quality of life in PWE, physicians should have clear understanding of spectrum of sexual dysfunctions and their management strategies. In this review, we discuss the current status of information regarding sexual dysfunctions in PWE, why it often remains unnoticed, and outline the optimal management strategies.

2. Defining sexual dysfunctions

Sexual dysfunction is defined as difficulty experienced by an individual or a couple during any stage of a normal sexual activity which causes distress and strained interpersonal relationship. Several different

Abbreviations: ASDs, antiseizure drugs; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PWE, people with epilepsy; SHBG, sex hormone binding globulin.

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systems have been proposed for the classification of sexual disorders. The two most widely used classification systems are the International Classification of Diseases (ICD)-11 proposed by World Health Organization and the Diagnostic and Statistical Manual of Mental Disorders (DSM)-V proposed by the American Psychiatric Association [4,5]. These two systems divide sexual dysfunctions in four broad categories as follows: sexual desire disorders, sexual arousal disorders, orgasmic disorders, and sexual pain disorders (Table 1). These disorders are further classified as organic or functional in origin. In addition, there are other classification systems proposed by various societies [6]. However, all these are also based on the four sexual domains as described above.

A major limitation in identifying sexual disorders is the subjective nature of the dysfunctions. These are also influenced by the interpersonal relationship with the partner and sociocultural factors. Hyposexuality is defined as diminished sexual drive and is further quantified as sexual activity less than once per month [7]. However, sexual drive is often influenced by social, cultural, and environmental factors. The identification of sexual dysfunction also depends on the level of distress and interpersonal strain felt by a person which is again subjective. Moreover, sexual dysfunctions may not always fall into one definite category, i.e., disorders of arousal and desire may coexist in the same person. These factors need to be taken into account while diagnosing and classifying sexual dysfunctions in PWE.

3. Assessment of sexual dysfunction

Although clinical history is the most important tool to diagnose sexual dysfunctions, quantification of sexual dysfunctions is important to understand the severity of problem and to assess the response to treatment especially in research settings. On the whole, more than 50 questionnaires and screening tools have been developed to assess and quantify sexual dysfunctions in the general population and in several chronic diseases [6,8–11]. However, none of the scales has been validated in PWE, and there is no uniformly agreed sexual dysfunction rating scale for use in them. Various studies have used different rating scales depending upon the population under study and the questions one wished to address. For use in PWE, a sexual dysfunction rating scale should be simple, easy to administer, nonintrusive, measures all domains of sexual functioning, applicable to people of all genders and sexual orientations, and should have good validity and reliability. None of the available scales fulfills all these requirements. Based on the available literature, certain rating scales are suitable for use in PWE (Table 2). Overall, we feel that Arizona Sexual Experiences Scale (ASEX) is very useful initial screening tool for all the patients [17]. It is very brief, least intrusive, and has good validity and reliability. For further detailed evaluation, Derogatis Interview for Sexual Function [16] applicable to both genders, Sexual Function Questionnaire for women [13], and International Index of Erectile Function scale [18] for males can be used.

Table 1
Classification of sexual dysfunctions [4–6].

1. Sexual desire disorders
   A. Hypoactive sexual desire disorder
   B. Sexual aversion disorder
2. Sexual arousal disorders
   A. Female sexual arousal disorder
   B. Male erectile disorder
3. Orgasmic disorders
   A. Male orgasmic disorder
   B. Female orgasmic disorder
   C. Premature ejaculation
4. Sexual pain disorders
   A. Dyspareunia
   B. Vaginismus
   C. Other sexual pain disorders

4. Prevalence and type of sexual dysfunctions in epilepsy

The fact that PWE can have significant sexual dysfunctions is known for over seven decades. Gastaut and Collomb in 1954 described hyposexuality in 26 of 36 (72%) patients with complex partial seizures [2]. Likewise, Blumer and Walker in 1967 described marked hyposexuality in 11 of their 21 patients (52%) with temporal lobe epilepsy [19]. This hyposexuality manifested in the form of grossly decreased interest in all aspects of sexual life. Subsequently, numerous other reports have focused on the sexual dysfunctions in PWE. Nonetheless, the exact prevalence of sexual dysfunctions in PWE and their pattern are not well defined. The reported studies have been quite heterogeneous with respect to study populations especially the type and severity of epilepsy, use and type of antiseizure drugs (ASDs), age at epilepsy onset, and the methodology used for defining sexual dysfunctions. The majority of studies are epilepsy clinic-based observational studies without any control groups. Most of them have included either male or female patients, while other studies have included mixed populations. This makes the comparison between different studies very difficult. Nonetheless, certain broad conclusions can be drawn from the available data.

4.1. Sexual dysfunction in women with epilepsy

The prevalence of sexual dysfunction in females in general population varies from 25 to 63% [18,20]. Many investigators have tried to study sexual dysfunction in women with epilepsy (Table 3) [21–33]. The reported prevalence of sexual dysfunction in women with epilepsy varies from 10% to 75%. As can be learned from Table 3, studies have been variable with regard to number of patients, marital status of patients, type and severity of epilepsy, use of ASDs, and the type of screening instruments used for evaluating sexual dysfunctions. Majority of studies have used small number of patients which makes subgroup analyses difficult. This is likely to be the reason for many studies not being able to find the effects of epilepsy severity and use of ASDs on sexual functions. Overall, studies which involved patients with uncontrolled seizures, longer duration of epilepsy, higher seizure frequency, focal epilepsy, and patients receiving polytherapy have reported higher prevalence of sexual dysfunction. Similarly, studies which have used rating scales with standard cutoff values to quantify sexual dysfunctions have reported higher prevalence of sexual dysfunction as compared to studies relying on personal interviews or structured questionnaires probably suggesting that scales with standard cutoffs are more sensitive in detecting sexual dysfunctions. On the contrary, it appears that most women with well-controlled epilepsy and receiving single ASD have normal sexual function. However, studies with larger number of patients with different types of epilepsies and seizure severities are required to draw definite conclusions.

In women with epilepsy, all the four types of sexual dysfunctions are present. However, majority of women have dysfunctions in the domains of sexual desire (hyposexuality) and sexual arousal, while orgasmic- and pain-related sexual problems are less frequent.

Table 2
Tools used for screening and evaluation of sexual dysfunction in people with epilepsy.

Name of scale/reference	Target population	Items	Domains assessed	Time taken to administer	Validation	Reliability assessment	Cutoff scores	Comments
Brief Sexual Symptom Checklist for men and women (BSSC-M; BSSC-W) [11]	Both sexes	4 questions	Desire, arousal, orgasm, pain	5 min	No	No	NA	Brief screening questionnaire, easy to administer
Complaints Screener for men and women (SCS) [11]	Both sexes	10 questions for men; 11 questions for women; each graded on a scale of 5	Desire, arousal, orgasm, pain	10 min	No	No	NA	Brief screening questionnaire, easy to administer
Female Sexual Function Index (FSFI) [12]	Women	19 & 6 (abbreviated version)	Desire, arousal, orgasm, pain	10–15 min	Yes	Yes	Yes	Widely used; considered gold standard for evaluation of SD in women
Sexual Function Questionnaire (SFQ) [13]	Women	28	Desire, arousal, orgasm, pain	15–20 min	Yes	Yes	Yes	Good for evaluation of SD in females
International Index of Erectile Function (IIEF) [14]	Men	15 and 5	Erection, orgasm, desire, satisfaction, and overall satisfaction, ejaculation	10–15 min	Yes	Yes	Yes	Widely used; can be used to quantify treatment response
Premature Ejaculation Profile (PEP) [15]	Men	4	Ejaculation	5 min	Yes	Yes	NA	Assesses severity of premature ejaculation
Derogatis Interview for Sexual Function (DISF) [16]	Both sexes	25	Desire, arousal, orgasm, pain	15–20 min	Yes	Yes	Yes	Good tool for individual components and overall sexual functions
Arizona Sexual Experiences Scale (ASEX) [17]	Both sexes	5	Desire, arousal, orgasm, overall satisfaction	5 min	Yes	Yes	Yes	Good initial screening tool, easy to administer

NA - not applicable; SD - sexual dysfunction.

4.2. Sexual dysfunction in men with epilepsy

Many studies have reported the sexual dysfunction in men with epilepsy [30–36]. Approximately 20%–30% of males in general population have sexual dysfunction [18,20]. In contrast to women who generally have dysfunction in the domains of desire and pain, males usually have sexual dysfunction related to physical response which mainly includes erectile dysfunction and premature ejaculation. Similar to the studies in women, major methodological heterogeneity among the studies precludes any definite conclusions. Veterans Administration Cooperative Study, a randomized-controlled trial to assess the effectiveness of four ASDs, was one of the earliest studies to report sexual dysfunction in men with epilepsy [37]. In this study, decreased libido was reported by 22% of patients taking primidone, 16% of those taking phenobarbital, 13% of taking carbamazepine, and 11% taking phenytoin. A study from Taiwan which used longitudinal health insurance database and included 6427 males with erectile dysfunction and 32,135 controls found that patients with erectile dysfunction were 1.8 times more likely to have epilepsy than controls after adjusting for all the other known risk factors for erectile dysfunction [38]. Other studies have reported the variable prevalence of 3%–60%, largely related to methodological heterogeneity among the studies [30–36].

In spite of methodological limitations, these studies suggest that men with epilepsy are 1.5–2 folds more likely to have sexual dysfunction as compared to healthy controls. While erectile dysfunction is the most common sexual dysfunction in men with epilepsy, approximately 10%–20% patients also have decreased libido. Sexual dysfunction is more likely to occur in patients with uncontrolled epilepsy and those with associated anxiety and depression, while patients with well-controlled epilepsy have lower prevalence of sexual dysfunctions.

5. Sexual dysfunction and epilepsy surgery

There is a relative dearth of data regarding the effects of epilepsy surgery on sexual functions, and sexual function as an important outcome measure has not received much attention in epilepsy surgery literature. For example, two studies that have reported in detail the sexual outcome following epilepsy surgery, have not attracted more than four citations per year since their publication [39,40]. Intuitively, as epilepsy surgery is undertaken in patients with frequent seizures and on multiple ASDs (which are significant risk factors for sexual dysfunction), seizure freedom and ASD reduction following surgery should improve sexual functioning. However, there are only few longitudinal studies, published 50 years ago, which have evaluated the effects of epilepsy surgery on sexual dysfunction [19,41]. Other studies which have reported sexual functions in patients undergoing epilepsy surgery are cross-sectional studies undertaken in patients following surgery. As expected, these studies have significant recall bias where patients may find it difficult to recall preoperative experiences. Additionally, patients are more likely to express satisfaction rather than dissatisfaction after the surgical treatment introducing added bias.

As early as in 1967, Blumer and Walker reported the effects of temporal lobectomy on sexual functions in 21 patients with drug-resistant temporal lobe epilepsy [19]. Preoperatively, 11 of 21 patients exhibited marked hyposexuality. Postoperatively, 4 had no improvement in sexual functions, another 4 had lasting improvement in sexual functions, while 3 patients had temporary increase in sexual functions. Overall, seizure-free patients were more likely to have improvement in sexual functions. All 3 patients with increase in sexuality returned to baseline with recurrence of seizures. In a larger study, Taylor reported effects of temporal lobectomy in 100 patients with drug-resistant temporal lobe epilepsy using a qualitative sexual function rating scale [41]. Preoperatively, 72% of patients had sexual dysfunction. Following surgery, 62% of patients had either no or occasional seizures. In the postoperative period, 14 patients stayed in good sexual adjustment, 22 improved, and 14 worsened, while 50 remained poorly adjusted. However, postoperative change in sexual functions did not correlate with seizure outcome.

There are other studies which have assessed the postoperative change in sexual functions after epilepsy surgery. Baird and colleagues studied postoperative change in sexual functions through a semi-structured interview in 58 patients with temporal resections and 16 patients with extratemporal resections [39]. Of the temporal resection group, 40% reported a postoperative sexual increase, 24% reported a decrease, and 36% reported no postoperative sexual change. Only 25% of patients in extratemporal resection group reported change in sexual functions. The postoperative change appeared within three months of surgery and usually persisted for long periods in majority. Changes in sexual

Table 3
Major studies reporting sexual dysfunction in men and women with epilepsy.

References (first author/year)	Subjects	Type of epilepsy	Assessment tool	Prevalence of SD	Type of SD	Factors associated with SD	Comments
Demerdash et al., 1991 [21]	700 women; 100 controls	Mixed	Clinical interview	127 (18%)	Sexual dysfunction: 83% [desire (24%); arousal (25%); orgasm (22%); pain (12%); paraphilias (16%)]	Longer duration of epilepsy; focal epilepsy	Majority were on enzyme-inducing ASDs; seizure frequency and control were not reported
Bergen et al., 1992 [22]	50 women; age-matched controls	Mixed (64% focal epilepsy)	Self-reported questionnaire	17 (34%)	Hyposexuality; 20% with no desire at all.	None	Seizure control not reported; 44% on more than one ASD; 94% on enzyme-inducing ASD
Morrell & Guldner, 1996 [23]	116 women	Predominantly focal epilepsy (85%)	Sexual Arousability Inventory-expanded; Sexual Behavior Inventory; Sexual Functioning Inventory	30%	Desire (16%); arousal (42%); pain (25%); orgasm (18%)	None	Seizure not controlled in 62%; 27% on polytherapy; used published norms as control
Morrell et al., 2005 [24]	57 women; 17 controls	Mixed; on monotherapy	Sexual Arousability Inventory-expanded; Sexual Behavior Inventory; Sexual Anxiety Interview; hormonal assessment	20% vs. 9% in controls	Arousal and anxiety	Focal epilepsy; phenytoin therapy; associated depression; low levels of estradiol	Seizure control not reported; 43% on nonenzyme-inducing drugs
Duncan et al., 1997 [25]	195 women; 48 controls	Mixed; 36 not on ASD	Sexuality Experience Scales; hormonal levels	No difference between patients and controls	Not provided	None	75% on monotherapy; seizure control and frequency not mentioned
Zelena et al., 2011 [26]	78 women	Mixed	Female Sexual Function Index	23%	All domains mainly desire and arousal	Depression	Majority had uncontrolled epilepsy and were on polytherapy
Atarodi-Kashani et al., 2017 [27]	196 married women	Mixed	Female Sexual Function Index	74.5%	All 4 components; maximum dysfunction in orgasm and sexual satisfaction	Age more than 40 years; poor education and income status; higher seizure frequency; higher number of antiepileptic drugs; and use of enzyme-inducing drugs	56% had uncontrolled epilepsy; 45% on more than one ASD
Ogunjimi et al., 2018 [28]	70 women and 70 controls	Mixed	Arizona Sexual Experience Scale	50% in patients and 38% in controls; patients had high score in all domains	All domains	Lesional epilepsy; older age; motor weakness	50% had uncontrolled epilepsy
Tao et al., 2018 [29]	112 women and 120 controls	Mixed	Female Sexual Function Index	70% in patients and 24% in controls	Desire (85.7%); arousal (56.3%); lubrication (47.3%); orgasm (66.1%); satisfaction (58.9%); pain (41.1%)	Poor economic status; presence of anxiety; nonadherence to medicines	50% had uncontrolled epilepsy; 45% on more than one ASD
Jensen et al., 1990 [30]	86 (38 men; 48 women); historical controls	Mixed; 73% on single or no drug	Self-reported questionnaire; hormonal assessment	8% in men; 29% in women; normal hormones in both	Desire (22%); orgasmic (19%); erectile dysfunction (3); some had combination	None	Majority had good seizure control
Souza et al., 2000 [31]	60 patients of both genders and 60 controls	Mixed with majority (58) on monotherapy	Sexual Behavior Interview	50% patients and 25% controls	Not reported	Depression	50% had uncontrolled epilepsy
Herzog et al., 2003 [32]	36 patients; 9 untreated; 12 controls	Uncontrolled TLE	Arizona Sexual Experience Scale; hormonal analysis	39%	Not reported	Right TLE; low bioactive testosterone	Uncontrolled TLE
Henning et al., 2016 [33]	171 patients; 594 controls	Mixed	Self-reported questionnaire	75% vs. 12% in women; 63% vs. 10% in men	All domains mainly reduced desire in females (50%) and erectile dysfunction in men (34%)	None of the epilepsy-related factors predicted SD	Majority patients had uncontrolled epilepsy
Nikoobakht et al., 2007 [34]	80 married men	Mixed	International Index of Erectile Function-15	43% had erectile dysfunction; 11% had premature ejaculation	Desire and arousal	Higher seizure frequency; generalized seizures	70% had controlled epilepsy (seizure-free for 6 months)
Duncan et al.,	69 men and	Mixed on	Sexual Desire	Patients had	Desire and arousal	Anxiety and depression	Two-thirds of

Table 3 (*continued*)

References (first author/year)	Subjects	Type of epilepsy	Assessment tool	Prevalence of SD	Type of SD	Factors associated with SD	Comments
2009 [35]	50 controls	single ASD	Inventory; Sexual Self-Efficacy Scale—Erectile Function; Sexual response inventory	higher scores than controls			patients had uncontrolled epilepsy
Calabro et al., 2013 [36]	30 men and 30 controls	Mixed	Semi-structured questionnaire and sex-relation evaluation schedule assessment monitoring	28% in patients and 18% in controls	All domains; erectile dysfunction in 5%	High seizure frequency	Majority had well-controlled epilepsy. 70% were seizure-free for more than 5 years

ASD - antiseizure drug; SD - sexual dysfunction; TLE - temporal lobe epilepsy.

functions were more common in patients with right-sided resections and in women. A study from India evaluated the sexual behavior of 50 married male patients who had undergone temporal lobectomy using a self-reported quantitative questionnaire [40]. The sexual desire and satisfaction levels improved in the postoperative period but did not reach to the levels of control subjects. Postoperative seizure freedom, use of one or no ASD, and absence of interictal discharges on postoperative electroencephalogram were associated with better sexual functions. Another study comprising 63 operated patients also showed better sexual functions in seizure-free patients as compared to nonseizure-free patients [42]. Although these largely cross-sectional studies with small number of patients preclude any firm conclusion regarding the effect of epilepsy surgery on sexual functions, they do suggest that seizure freedom or even the anticipation of seizure freedom following surgery is associated with improved sexual outcomes. Further longitudinal studies with large number of patients focusing on the sexual functions before and after surgery are required.

Few studies have investigated the mechanisms of improved sexual functions following epilepsy surgery. Two studies have shown that serum androgen levels improve following surgery in seizure-free patients but remain low in nonseizure-free patients [43,44]. Baird and colleagues reported that those patients who showed sexual improvement following surgery had larger volumes of contralateral amygdale as compared to controls suggesting that contralateral amygdala might have controlling effect on sexual functions following temporal lobectomy [45]. Overall, it can be hypothesized that disappearance of seizures and interictal discharges following surgery may positively affect the pituitary–hypothalamic axis resulting in improved androgen levels and better sexual functions.

There have been rare reports of hypersexuality and deviant sexual behavior following unilateral temporal lobectomy [46]. This is largely explained as the result of partial Klüver-Bucy syndrome because of the presence of undetected contralateral temporal pathology. Majority of these cases are from premagnetic resonance imaging (MRI) era, and these occurrences are highly unlikely with modern presurgical evaluation strategies. Two of the reported patients developed hypersexuality because of other mechanisms. One young girl developed excessive masturbation as a part of severe depression which improved with treatment of depression [47], while another patient developed hypersexuality in the postictal phase possibly suggesting seizure-induced transient bilateral temporal dysfunction [48].

6. Mechanisms of sexual dysfunction in epilepsy

In spite of being a subject of study for seven decades, the mechanisms of sexual dysfunction in patients with epilepsy remain unclear. Most of the available data suggest that etiology of sexual dysfunction in epilepsy is related to multiple interdependent factors (Fig. 1). A combination of disease-related, drug-related, psychiatric, and psychosocial factors contribute to the pathogenesis of sexual dysfunction in epilepsy.

6.1. Direct effects of epilepsy on sexual functions

There is circumstantial evidence that sexual dysfunction can occur because of the direct effects of epilepsy. Sexual dysfunctions usually begin after the onset of seizures and are present in untreated patients with epilepsy [2,19,49,50]. Similarly, patients with focal epilepsy are four times more likely to have sexual dysfunction as compared to those with primary generalized epilepsy [20,51]. As discussed above, sexual dysfunctions are more common in patients with uncontrolled epilepsy, especially temporal lobe epilepsy. Studies have also suggested that sexual dysfunctions are more common in patients with right temporal lobe epilepsy [30,52]. A study from Italy involving 45 patients with epilepsy showed that both men and women with right temporal lobe epilepsy had higher prevalence of sexual dysfunction as compared to patients with left temporal lobe epilepsy and healthy controls [52]. In another study of 50 women with temporal lobe epilepsy, 20 of whom were not on ASDs, sexual dysfunctions were more common in women with right temporal lobe epilepsy [53]. These women with sexual dysfunction also had low levels of luteinizing hormone (LH). Same authors also reported sexual dysfunction in 11 (55%) of 20 males with temporal lobe epilepsy, nine of whom had reproductive endocrine disorders including hypogonadotropic hypogonadism in five, hyperprolactinemia in two, and hypergonadotropic hypogonadismn in two [54]. Authors also reported that in these patients, sexual dysfunction was

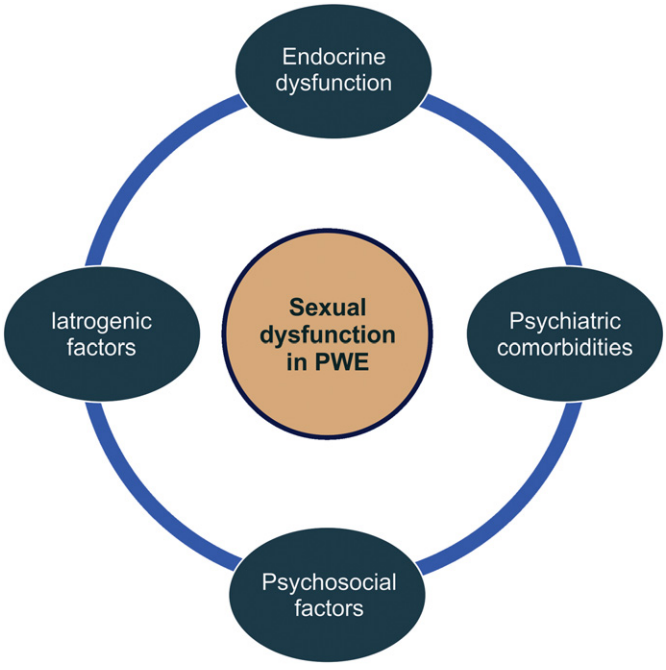

Fig. 1. Causal dimensions of sexual dysfunction in people with epilepsy (PWE).

independent of ASD usage or associated psychiatric comorbidity. All these factors suggest that central mechanisms interfering with pituitary–hypothalamic functions contribute to sexual dysfunctions in patients with epilepsy. It is proposed that epileptiform discharges propagating through amygdalo-hypothalamic pathways can interfere with pulsatile secretion of gonodatrophic hormones and dopamine [30,54]. This in turn causes hypogonadism, hyperprolactinemia, and sexual dysfunction. There is experimental evidence in rats to suggest that reproductive functions are more preferentially lateralized to right hypothalamus which can explain the higher prevalence of sexual dysfunction in right temporal lobe epilepsy [55].

Other studies have evaluated the role of testosterone in patients with epilepsy. Herzog and colleagues compared the sexual function and gonadal steroid levels in 36 women with epilepsy [30]. Sexual dysfunction was more common in patients with right temporal lobe epilepsy and with low levels of bioactive testosterone which was independent of ASD usage. However, this study had small number of patients, and authors did not report the association between LH levels and testosterone levels. In a larger study, Bauer and colleagues estimated hormonal levels in 200 patients with epilepsy who were receiving either one or no ASD and compared them with 105 healthy controls [50]. Of these, 90% had focal epilepsy, 58% had temporal lobe epilepsy, and 33 were not on ASDs. All the groups, including those not on ASDs had low levels of free testosterone. These low free testosterone levels were associated with high LH levels and low testosterone/LH ratio suggesting that epilepsy affects testicular testosterone production by mechanisms other than centrally induced low LH levels. Patients on carbamazepine had lowest levels of testosterone indicating that carbamazepine further aggravates the effects of epilepsy on testicular functions. However, another study of 60 patients with epilepsy who were taking single ASD reported normal levels of bioactive testosterone and no correlation between testosterone levels and sexual dysfunction [56]. All these variable results suggest significant methodological heterogeneity among the studies especially with regard to the type and severity of epilepsy and the use of ASDs. Although there is enough data to suggest that epilepsy can cause sexual dysfunctions, its mechanism remains controversial. The data provide only circumstantial evidence for the direct effects of epilepsy on sexual functions which are mediated by central and peripheral effects on various sex hormones. Further studies with large number of patients enabling subgroup analyses are required to clarify the issue.

6.2. Antiseizure drugs and sexual dysfunction

In contrast to the ambiguity regarding effects of epilepsy on sexual functions, there is more definitive evidence that ASDs, especially enzyme-inducing ASDs, influence sex hormonal levels and can produce sexual dysfunction [57]. Antiseizure drugs can produce sexual dysfunction by multiple mechanisms [57,58]. Antiseizure drugs, especially enzyme-inducing drugs, increase the levels of sex hormone binding globulin (SHBG) and thus reduce the levels of unbound active testosterone. Antiseizure drugs also increase the hepatic metabolism of gonadal and adrenal sex steroids. In addition, ASDs with overall inhibitory effect on brain are postulated to suppress the pituitary–hypothalamic axis thus producing hypogonadotrophic hypogonadism. Antiseizure drugs can also influence the sexual functions by their effect on serotoninergic pathways.

Carbamazepine has been shown to be associated with low levels of free testosterone and high levels of SHBG in healthy volunteers and in patients with epilepsy [50,59]. Herzog and colleagues studied sexual functions and sex hormonal levels in 85 men with focal epilepsy [60]. In this group, 25 patients each were on carbamazepine, phenytoin, and lamotrigine, while 10 patients were not on ASDs. Sexual function scores, bioactive testosterone levels, bioactive testosterone/bioactive estradiol, and bioactive testosterone/LH were significantly greater while SHBG levels were significantly lower in the control and lamotrigine groups than in the carbamazepine and phenytoin groups. Sexual function scores were associated with bioactive testosterone levels. The association between carbamazepine and low levels of sex steroids is further supported by a study which showed significant increase in serum testosterone levels and free androgen index in both men and women after carbamazepine withdrawal [61]. Thus, there is enough evidence to suggest that enzyme-inducing ASDs, especially phenytoin and carbamazepine, adversely affect sex hormone levels and sexual functions in PWE.

There is limited data available about the effects of newer ASDs on sexual functions. Overall, data suggest that majority of them cause either no or minimal sexual dysfunction. A study with 59 male patients showed that lamotrigine is least likely to adversely affect the sex hormonal levels compared to carbamazepine and valproate [62]. Another study which evaluated the effects of lamotrigine, carbamazepine, and levetiracetam on sexual functions and hormonal levels showed better sexual functions and sex hormonal profiles in patients receiving lamotrigine and levetiracetam as compared to those receiving carbamazepine in both males and females [63]. A study from China reported that patients on both valproate or levetiracetam monotherapy had higher risk of erectile dysfunction as compared to controls [64]. However, hormonal levels were adversely affected only in patients with valproate monotherapy in the form of low LH and follicle-stimulating hormone (FSH) levels. Limited data suggest that valproate can cause impotence in 10% of patients [65].

A systematic review of 17 studies, mostly case reports and small case series, by Chen and colleagues showed that topiramate can cause sexual dysfunctions in 7.4% to 12.5% patients [66]. It mainly causes orgasmic disorders in females and erectile dysfunction in males. A study of 141 patients on lamotrigine therapy, who were either initiated or switched to lamotrigine, suggested that lamotrigine can cause improvement in sexual functions [67]. Authors suggested that improvement in seizure control as well as improvement on mood might have caused improved sexual functions in these patients. There have been isolated reports that oxcarbazepine can cause sexual dysfunctions and adverse hormonal effects similar to carbamazepine [68]. However, other studies have suggested that patients with sexual dysfunction on carbamazepine improve after switching over to oxcarbazepine. Luef and colleagues reported that of the 228 patients with preexisting sexual function impairment at baseline, an improvement was observed in 181 (79.4%) patients after switching over to oxcarbazepine [69]. This is probably related to the fact that oxcarbazepine does not cause induction of liver P450 enzyme system. Regarding other newer ASDs, there are isolated case reports suggesting that gabapentine, pregabaline, zonisamide, levetiracetam, and lacosamide can cause hyposexuality, erectile dysfunction, and anorgasmia [70–74]. The mechanisms of sexual dysfunction caused by newer nonenzyme-inducing ASDs are poorly understood and likely to be multifactorial [73–76]. Many of them including topiramate, zonisamide, and levetiracetam have multiple antiseizure mechanisms, some of which may contribute to sexual dysfunction. Majority of these drugs reduce central excitatory transmission by acting on sodium and calcium channels and glutamate and gabanergic receptors. This reduced central excitatory transmission can cause hyposexuality [73–76]. In addition, by acting on the gabaminergic and glutaminergic neurons as well as calcium channels, these drugs can modulate the dopaminergic and serotoninergic neurons in specific brain regions. It is known that brain dopamine systems have excitatory effect on sexuality while serotonin has inhibitory effect on sexuality. Newer ASDs can cause sexual dysfunction by altering dopamine/serotonin ratio in hypothalamic limbic system. In addition, certain newer ASDs have specific mechanisms for causing sexual dysfunction. Both topiramate and zonisamide, by inhibiting carbonic anhydrase enzyme, interfere with the production of intracavernosal vasoactive compounds namely vasoactive intestinal peptide (VIP) and nitric oxide which play important role in peripheral erectile mechanisms [75]. Levetiracetam increases brainstem serotonin concentration by inhibiting presynaptic P/Q-type calcium channels thus causing reduced sexual drive [74].

In summary, it is evident that enzyme-inducing ASDs can cause sexual dysfunction by affecting metabolism of sex steroids while the risk of sexual dysfunction with newer ASDs is low. Patients experiencing sexual dysfunction with enzyme-inducing drugs may benefit by switching over to nonenzyme-inducing drugs.

6.3. Comorbid psychiatric issues and sexual dysfunction

People with epilepsy have significant associated psychiatric comorbidity. A systematic review of 23 studies has shown that prevalence of active depression in PWE is 23% with an odds ratio of 2.8 [77]. Likewise, studies have shown that PWE are 10 times more likely to develop psychosis as compared to healthy controls [78]. It is also well established that people with psychosis and depression have high prevalence of hyposexuality which can be further aggravated by the use of antipsychotic and antidepressant drugs. A systematic review has shown a bidirectional relationship between depression and sexual dysfunctions [79]. People with depression had a 50% to 70% increased risk of developing sexual dysfunction while those with sexual dysfunction had 130% to 210% increased risk of developing depression [79]. Thus, there is substantial evidence that depression can contribute to sexual dysfunction in PWE.

A study of 60 PWE showed that depression and anxiety were associated with sexual dysfunction rather than age of seizure onset and seizure frequency [33]. Other studies have also shown that psychological factors are the most important factors determining the sexual functioning in PWE [24,33,56].

Overall, there is ample evidence to suggest that depression, anxiety, and psychosis can significantly contribute to sexual dysfunction in PWE and all PWE should be screened for associated psychiatric comorbidity.

6.4. Psychosocial issues and sexual dysfunction

Various psychosocial factors can play important role in causing sexual dysfunction in PWE. They have low self-esteem, feeling of stigma, lower social development, and often feel social isolation [80]. These factors may contribute to heightened sense of rejection, sexual inadequacy, and sexual unattractiveness in these patients. Additionally, anxiety and fear of having a seizure during sexual intercourse can lead to avoidance of sexual activity which can cause feeling of rejection and dissatisfaction in partner.

7. Evaluation and management of sexual dysfunction in epilepsy

Keeping with the multifactorial nature of sexual dysfunction in PWE, the evaluation and management requires multipronged and multidisciplinary approach (Fig. 1; Table 4) [58,81].

7.1. Clinical and psychosocial evaluation and counseling

The first and foremost aspect of management of sexual dysfunction in epilepsy is to inquire about it during clinical interview. Majority of patients usually do not feel comfortable about discussing sexual problems, and majority of physicians do not inquire about it [3]. A practical approach may be to ask all the patients to fill a brief, nonintrusive questionnaire such as ASEX during the initial and follow-up visits. Patients detected to have sexual dysfunction on screening questionnaire should undergo a detailed clinical interview by a clinical psychologist, preferably along with the partner, to inquire about the nature of sexual dysfunction and likely factors contributing it. A distinction should be made between organic and psychogenic impotence by inquiring and evaluating for nocturnal tumescence. At this stage, patients should be screened and evaluated for the presence of depression, anxiety, or other psychiatric comorbidity. Patients found to have psychosocial issues, or underlying psychiatric comorbidity should be advised counseling and proper treatment of psychiatric illness should be initiated in consultation with a psychiatrist.

Table 4
A multidisciplinary approach to management of sexual dysfunctions in people with epilepsy.

- Assess all patients for sexual dysfunction using a screening questionnaire.
- Detailed clinical interview and counseling of those screened positive and their partner by a clinical psychologist.
- Screening and management for systemic causes such as hypertension and diabetes.
- Detailed drug history for contributory drugs, if any.
- Screening and treatment for local causes in association with urologist and gynecologist.
- Screening and treatment for associated anxiety and depression by a psychiatrist.
- Comprehensive hormonal evaluation for all patients with sexual dysfunction.
- Improve seizure control by optimizing antiepileptic drug therapy; switch to nonenzyme-inducing drugs.
- Consider epilepsy surgery in drug-resistant patients.
- Consider testosterone supplements in patients with low testosterone levels.
- In men with erectile dysfunction, consider symptomatic therapy with phophodiesterase type-5 inhibitor drugs.
- Consider paroxetine for premature ejaculation.

Patients, especially males with erectile dysfunction, should be screened for underlying disorders which can contribute to sexual dysfunction such as hypertension, diabetes, and coronary artery disease. A detail drug history is crucial as many drugs such as beta blockers, diuretics, and antidepressants can cause erectile dysfunction. Patients should also be evaluated for local urogenital problems by urologist and gynecologist.

Next step should be the optimization of epilepsy treatment. Seizure freedom is associated with low risk of sexual dysfunction, and this should be the goal in all patients. If possible, enzyme-inducing ASDs, especially phenytoin, carbamazepine, and phenobarbitone can be switched over to nonenzyme-inducing ASDs such as valproate, levetiracetam, and lamotrigine. Oxcarbazepine offers a good alternative in patients with focal epilepsy using enzyme-inducing ASDs. However, a balance should be maintained between optimal seizure control and optimization of sexual functions. Patients with drug-resistant epilepsy should be evaluated for epilepsy surgery to maximize the chances of seizure freedom and improving sexual functions.

7.2. Hormonal evaluation and symptomatic treatment

As PWE with sexual dysfunction have associated hormonal dysfunctions, a detailed screening metabolic and hormonal screening should be undertaken in all of them. Thyroid function tests, serum levels of total and free testosterone, SHBG, prolactin, estradiol, LH, and FSH should be done in all the patients. Patients with hypogonadism and low levels of testosterone may benefit with testosterone supplements. A study in 40 men with epilepsy and hypogonadism showed improved sexual functions with the combination of testosterone and aromatase inhibitor anastrozole, which blocks the conversion of testosterone to estradiol [82].

Male patients with erectile dysfunction can benefit by symptomatic therapy with phophodiesterase type-5 inhibitor drugs such as sildenafil, vardenafil, tadalafil, and avanafil. These drugs are safe and highly effective but it needs to be remembered that they will not improve hyposexuality. There are isolated case reports of seizure precipitation by these drugs in patients without epilepsy which should be kept in mind [83,84]. In resistant patients, further invasive treatment options like vacuum devices, intracavernous injections of prostaglandins and papaverine, and penile prostheses can be considered in consultation with a urologist.

There are limited options available for orgasmic and ejaculatory disorders. Recently, short acting selective serotonin reuptake inhibitors such as paroxetine have been shown to have beneficial effect in premature ejaculation in males [85]. Female patients with sexual pain

disorders should be managed by a gynecologist with the help of topical therapy, drugs such as gabapentin, botulinum toxin, and surgical therapy.

8. Conclusions

We wish to conclude that sexual dysfunction is common in PWE, but remains unrecognized in the majority of them because the physician is reluctant to inquire and the patient is hesitant to complain about it during routine clinic visits. Interplay of multiple causes including direct effects of epilepsy, effects of ASDs, and psychosocial factors contributes to sexual dysfunction in PWE. Patients with focal epilepsy, high seizure burden, those on multiple and enzyme-inducing ASDs, and depression are more likely to have sexual dysfunction. A multipronged and multidisciplinary approach is essential for optimizing the sexual functions in PWE. We hope that this review will prompt physicians to regularly quiz their patients about sexual health and stimulate clinical and basic science studies in this poorly understood and scantily researched field of epilepsy care.

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Declaration of competing interest

None of the authors have any competing interest related to this article.

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