Seizure: European Journal of Epilepsy 65 (2019) 80–88

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

Review

# Association between epilepsy and risk of sexual dysfunction: A meta-analysis

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ARTICLE INFO

*Keywords:*
Epilepsy
Sexual dysfunction
Risk
Meta-analysis

ABSTRACT

*Purpose:* Sexual functioning is an important factor influencing quality of life. Mounting evidence suggests that both male and female patients with epilepsy (PWE) have an increased risk of developing sexual dysfunction (SD). The aim of this meta-analysis was to quantify the association between epilepsy and the risk of SD.

*Methods:* PubMed, Embase, and Cochrane Library database were systematically searched to identify the pertinent studies focusing on the association between epilepsy and SD. Relative risk (RR) for SD with 95% confidence interval (CI) was calculated. The overall quality of the evidence was generated by applying the GRADE-profiler. This meta-analysis was registered on the PROSPERO (ID: CRD42018103572, http://www.crd.york.ac.uk/PROSPERO).

*Results:* Nine studies (3 cross-sectional, 5 case-control, and 1 cohort) were included in this meta-analysis, for a total of 1556 subjects and 599 cases of epilepsy. Synthetic results demonstrated that epilepsy was associated with an increased risk of female SD (6 studies, pooled RR = 2.69, 95%CI: 1.48–4.89, $P = 0.001$; heterogeneity: $I^2 = 88.9\%$, $P < 0.001$) as well as male SD (3 studies, pooled RR = 4.85, 95%CI: 2.01–11.7, $P < 0.001$; heterogeneity: $I^2 = 74.2\%$, $P = 0.021$). The GRADE-profiler showed that the rate of events of SD on average in the PWE and the controls were 383/659 (58.1%) and 168/1017 (16.5%), respectively. The quality of evidence across outcomes was MODERATE.

*Conclusions:* Epilepsy is significantly associated with an increased risk of SD in both sexes. These findings suggest that both clinicians and patients should recognize that epilepsy has a potential hazardous effect on sexual functioning.

## 1. Introduction

Epilepsy, which is characterized by recurrent and unprovoked seizures, is one of the most common neurodevelopmental diseases [1]. An estimated 50 million people worldwide have epilepsy. The prevalence of epilepsy varied between 1% and 5% in different countries [2,3]. Some specific types of epileptic seizures can be completely controlled by surgical therapies. However, this chronic neurologic disorder generally requires a long time and even lifelong antiepileptic drugs (AEDs) treatment in most cases due to its chronic nature [4]. Moreover, although many new AEDs are currently introduced, nearly 40% of all the patients with epilepsy (PWE) continue to have intractable seizures [5,6].

Because epilepsy and AEDs have direct impacts on the regulation of the hypothalamic-pituitary-gonadal axis, PWE are at high risk to develop ovarian or testicular dysfunctions [7–9]. Abnormalities in central control (i.e., interference of the medial temporal lobe) and sex steroid hormones metabolism (i.e., reduction of androgen) may affect various aspects of sexual functions in both male and female sufferers. In addition, epilepsy can also induce comorbid neuropsychiatric disorders (i.e. depression and anxiety) which are known to contribute to sexual dysfunction (SD) [6]. Taken together, an increased rate of SD is to be expected in the PWE.

Research data showed that the proportion of SD in PWE varied across the studies, ranging from 38% to 71% and 23% to 60% in male and female patients, respectively [10–13]. Erectile dysfunction (ED),

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https://doi.org/10.1016/j.seizure.2019.01.004
Received 17 July 2018; Received in revised form 6 January 2019; Accepted 8 January 2019

hyposexuality, and organic sexual problems were the common complaints in male PWE [14]. In female PWE, lack of sexual desire, orgasmic dysfunction, dyspareunia, and less sexual arousal were the prominent features among them [15]. However, results from different studies remain conflicted and inconclusive on the association between epilepsy and SD. A previous study indicated that only 8% of male PWE had SD as compared with 13% of the non-epilepsy control [16]. In line with this finding, de Vincentiis et al. failed to find a relationship between epilepsy and SD in the female subjects [17].

Although a high prevalence of SD in PWE has been observed, the evidence for this potential relation is still controversial among studies and the comprehensive information is limited. Therefore, we conducted the present meta-analysis in an attempt to explore whether epilepsy was a risk factor for SD.

## 2. Methods

The protocol of this systematic review and meta-analysis was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The PRISMA checklist was presented in Supplementary Table 1. In addition, we have registered a protocol for this meta-analysis on PROSPERO (ID: CRD42018103572, http://www.crd.york.ac.uk/PROSPERO).

### 2.1. Data sources and searches

Medline (PubMed), Embase, and the Cochrane Library databases were comprehensively searched for relevant studies from the inception to May 17, 2018. We restricted the search limit to English language and human participants. The following search subject headings and the text keywords were used for PubMed: (((((("Erectile Dysfunction"[Mesh]) OR sexual function) OR sexual dysfunction) OR "Sexual Dysfunctions, Psychological"[Mesh]) OR "Sexual Dysfunction, Physiological"[Mesh]) OR Impotence)) AND ((((((((((("Epilepsy"[Mesh]) OR Epilepsies) OR Seizure Disorder) OR Seizure Disorders) OR Awakening Epilepsy) OR Epilepsy, Awakening) OR Epilepsy, Cryptogenic) OR Cryptogenic Epilepsies) OR Cryptogenic Epilepsy) OR Epilepsies, Cryptogenic) OR Aura) OR Auras).

### 2.2. Measurement of epilepsy and SD

Definitions of epilepsy and SD were in compliance with the international classification of diseases codes. PWE were diagnosed according to different diagnosing criteria, such as International League Against Epilepsy criteria, clinical and EEG evidence, etc. Male patients with SD mainly manifested as erectile dysfunction, diminished libido, and abnormal ejaculation; while female patients with SD mainly manifested as desire, arousal, orgasmic, and sexual pain disorders. In the present meta-analysis, SD was confirmed by using any of the existing and validated instruments, including the Arizona Sexual Experience Scale, International Index of Erectile Function, Diagnostic and Statistical Manual of Diseases Classification, and Female Sexual Function Index (FSFI).

### 2.3. Study selection

Any available epidemiologic evidence met our inclusion criteria were included in this study. In compliance with the patient, intervention, comparison, outcome and study design (PICOS), the question guiding for this meta-analysis was: Does epilepsy increase the risk of SD? The combinations for the PICOS evidence were: males and/or females subjects with SD or sexual problems (P); a history of epilepsy (I); compared with the general population (C); the diagnosis of SD (O); no limitations on study designs (S). We also included the studies providing the relative risk (RR), hazard ratio, or odds ratios with 95% confidence intervals (CI). The excluded studies were as follow: (1) without the control population data; (2) review article, comment, editorial, letter, and case report, etc.; (3) duplicated data; (4) animal experiment.

### 2.4. Data extraction

A standardized data collection form was performed to extract the following relevant information by two authors independently: the first authors' names, publication year, country of origin, study design, disease duration, specific AEDs usage, the demographic and age of the study and the control sample, measurements of epilepsy and SD ascertainment, and variable adjustment for confounding factors.

### 2.5. Quality assessment

The reporting quality assessment of the cross-sectional study was depended on the cross-sectional study quality methodology checklist. The low quality, moderate quality, and high quality were judged with the scores at 0–3, 4–7, and 8–11, respectively. The methodological quality evaluation of the case-control/cohort study was based on the Newcastle–Ottawa Scale (NOS). NOS scores of 0–3, 4–6, 7–9 were regarded as low quality, moderate quality, and high quality, respectively. The grading of recommendations assessment, development, and evaluation (GRADE) approach was presented to exert the absolute estimates of the risk of SD in PWE and to rank the overall quality of the evidence.

### 2.6. Statistical analyses

The overall RR with its corresponding 95% CI was employed to assess the strength of the association between epilepsy and the risk of SD. In this analysis, results with a two-tail $P$ values $< 0.05$ were regarded as statistically significant. The $I^2$ statistic and the Cochrane $Q$ statistic were calculated to assess the heterogeneity of included studies (substantial heterogeneity was confirmed by $I^2 > 50\%$; statistical significance was validated by $P$ value of $Q$ test $< 0.10$). In the present study, a random effect model rather than a fixed effects model was applied due to the high likelihood of between-study variance for differences in study design as well as the study population. Sensitivity analyses were conducted to detect the potential source of heterogeneity. Begg's rank correlation test and Egger's regression asymmetry test were employed to evaluate the publication bias. The current statistical analysis was conducted by using the Stata (version 13.0, Stata Corp LP, College Station, Texas, USA).

## 3. Results

### 3.1. Literature search

Through the initial search, a total of 924 articles were identified (503 from MEDLINE, 311 from EMBASE, and 110 from the Cochrane Library). Based on the initial reviewing of titles and abstracts, 878 publications were excluded after removing duplicates, leaving 46 pertinent studies for further full-text review. Among them, 18 articles were excluded for failing to provide the control group; 8 articles for insufficient outcome data; 6 articles for not meeting the inclusion criteria; and 5 articles for inappropriate grouping. Finally, 9 observational studies [18–26] met the pre-defined eligibility criteria and were included in quantitative analysis. Fig. 1 showed the process of selection.

### 3.2. Study characteristic

The 9 included studies were published between 2000 and 2018. Three studies referred to cross-sectional designed [21,23,25], five to case-control designed [18–20,22,26], and one study to cohort designed [24]. There were 2 publications conducted in Brazil [18,21] and United States [19,20], respectively, as well as 1 publication conducted in Italy

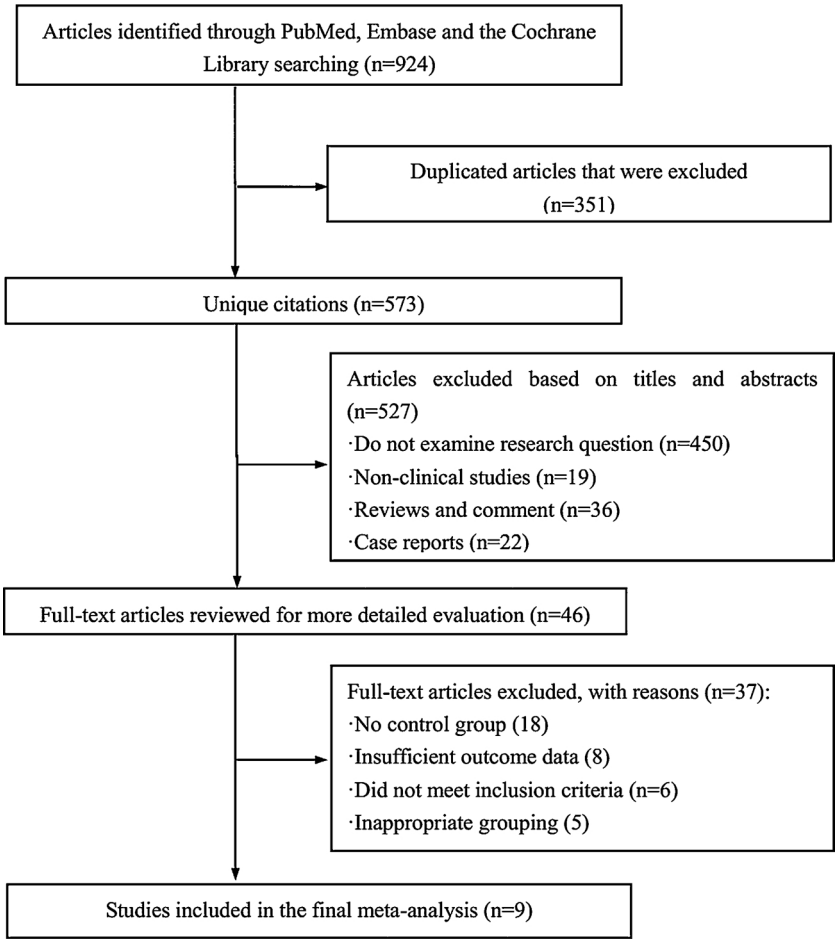


**Fig. 1.** Flow chart of study selection. A total of 924 publications were identified in 3 databases during the initial search. After reviewing of titles and abstracts, 878 publications were eliminating for duplicates and ineligible studies, leaving 46 pertinent studies for further full-text assessment. Finally, 9 articles were included in the current study.

[22], India [23], Norway [24], China [25], and Nigeria, respectively [26]. These included studies have enrolled a total of 1029 female participants and 527 male participants, of whom 418 women and 181 men were PWE, respectively. Among the 9 eligible studies, 1 study reported the combined results from both genders [18] and 1 study provided the data of both sexes independently [24]. Four studies reported the disease duration of epilepsy [18,19,23,25], ranging from 4 to 15.5 years. Six studies [19–23,25] mentioned the specific AEDs usage, including carbamazepine, phenobarbital, phenytoin, valproate, gabapentin, lamotrigine, clobazam, oxcarbazepine, levetiracetam, and topiramate, etc. The mean age of the female subjects and male subjects among studies ranged from 29.6 to 43.6 years and 30.5–43.6 years, respectively. The detailed characteristics of the 9 included studies were summarized in Table 1.

### 3.3. Study quality and overall quality of the evidence

The outcomes of the methodological quality of the 3 cross-sectional studies were shown in Supplementary Table 2, of which 2 studies [21,23] were judged as moderate quality and the remaining 1 study [25] was judged as high quality. In the case-control and cohort studies, 5 studies [18–20,24,26] were moderate quality and 1 [22] study was high quality (Supplementary Table 3).

As listed in Table 2, the GRADE-pro showed that the rate of events of SD on average in both female and male PWE was 383/659 (58.1%), whereas the general population was 168/1017 (16.5%). The absolute effect of epilepsy on SD was 344 more per 1000 (from 157 more to 641 more), and the overall quality of the evidence was judged as MODERATE. When the female individuals were analyzed independently, the rate of events of SD on average in PWE was 247/418 (59.1%), while the control group was 119/611 (19.5%); the absolute effect was 329 more per 1000 (from 93 more to 758 more); and the overall quality of the evidence was judged as LOW. When the male subjects were analyzed independently, the rate of events of SD on average in epilepsy was 106/181 (58.6%), while the rate of healthy subjects was 34/346 (9.8%); the absolute effect was 378 more per 1000 (from 99 more to 1000 more); and the overall quality of the evidence was considered to VERY LOW.

### 3.4. Synthesis of results

In these 9 included studies, 6 studies [19,20,23–26] provided the outcomes for females, 3 studies [21,22,24] for males and 1 study [18] for both sexes. When combined all the cases of both female and male subjects, synthetic results suggested that epilepsy was significantly associated with an increased risk of SD in both sexes (overall RR = 3.08, 95%CI: 1.95–4.88, $P = 0.007$; heterogeneity: $I^2 = 86.9\%$, $P < 0.001$). In the female individuals, synthetic RR from 6 studies [19,20,23–26] by using a random-effects model revealed that epilepsy conferred a 2.69-fold increased risk of SD compared to the general population (pooled RR = 2.69, 95%CI: 1.48–4.89, $P = 0.001$; heterogeneity: $I^2 = 88.9\%$, $P < 0.001$). Moreover, pooled results from 3 studies [21,22,24] investigating male subjects yielded a similar result (synthetic RR = 4.85, 95%CI: 2.01–11.7, $P < 0.001$; heterogeneity: $I^2 = 74.2\%$, $P = 0.021$).

**Table 1**
Characteristics of the included studies.

| Study | Study design | Gender | Mean disease duration (years) | AEDs usage | Study group case/total | Control group case/total | Mean age (years) study group | Mean age (years) control group | Diagnosis of epilepsy | Assessment of SD | Variable adjustment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Souza [18] 2000 Brazil | Case–control | Both sexes | 15.5 ± 8.7 | NA | 30/60 | 15/60 | 32.4 ± 6.62 | 34.1 ± 8.25 | EEG, CCT | 4th Edition (DSM IV) | Anxiety, depression, self-esteem |
| Herzog [19] 2003 United States | Case–control | Female | 8.2 ± 6.4 | CB,PHT,VPA,GBP | 14/36 | 1/12 | 30.9 ± 5.8 | 29.6 ± 6.1 | Clinical and EEG evidence | ASEX questionnaire | NA |
| Morrell [20] 2005 United States | Case–control | Female | NA | CBZ,PB,PHT,VPA,GBP,LTG | 12/57 | 2/17 | 31 ± 5.6 | 31 ± 5.6 | The Stanford Comprehensive Epilepsy Center | 4th Edition (DSM IV) | NA |
| Reis [21] 2012 Brazil | Cross-sectional | Male | NA | CBZ | 41/63 | 4/55 | 32.5 ± 1.0 | 30.5 ± 0.8 | Clinically Diagnosis at a University Hospital | IIEF | Age, BMI, hormone levels |
| Calabro [22] 2013 Italy | Case–control | Male | NA | CBZ, VPA | 8/30 | 5/30 | 38.8 ± 7.1 | 30.8 ± 7.5 | Physical and neurological examination, EEG, brain MRI | 4th Edition (DSM IV) | Duration of illness, Depression, Anxiety |
| Karan [23] 2015 India | Cross-sectional | Female | 4 | VPA,CBZ,PHT,CLB | 43/60 | 20/60 | 30.7 ± 6.4 | 29.9 ± 6.8 | International League Against Epilepsy criteria | FSFI | Age |
| Henning [24] 2016 Norway | cohort | Male/ Female | NA | NA | Male: 57/88 Female: 64/83 | Male: 25/261 Female: 40/332 | Total: 43.6 | Total: 43.6 | Norwegian National Centre for Epilepsy | Defined sexual functioning questionnaire | NA |
| Tao [25] 2018 China | Cross-sectional | Female | 7.18–9.51 | LTG,CBZ,OXC,VPA,LEV,TPM | 79/112 | 29/120 | 35.0 ± 10.2 | 35.2 ± 6.4 | International League Against Epilepsy criteria | FSFI | Age, education, income |
| Ogunjimi [26] 2018 Nigeria | Case–control | Female | Age at diagnosis:8–62 | NA | 35/70 | 27/70 | 41.7 ± 19.2 | 40.7 ± 16.8 | Clinically with electroencephalographic features | 5th Edition (DSM-V) | Age |

*Note:* AEDs = Antiepileptic drugs, SD = Sexual Dysfunction, NA = Not Available, RR = Relative Risk, CI = Confidence Interval, IIEF = International Index of Erectile Function, FSFI = Female Sexual Function Index, ASEX = Arizona Sexual Experience Scale, EEG = electroencephalography, CCT = computerized cranial tomography, DSM = Diagnostic and Statistical Manual of Diseases Classification, CBZ = carbamazepine; PB = phenobarbital; PHT = phenytoin; VPA = valproate; GBP = gabapentin; LTG = lamotrigine, CLB = clobazam, OXC = oxcarbazepine, LEV = levetiracetam, TPM = topiramate.

**Table 2**
GRADE summary of evidence for the effects of epilepsy and sexual dysfunction (SD).

| Quality assessment | | | | | | | No. of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No. of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Epilepsy | Control | Relative (95%CI) | Absolute | | |
| Sexual dysfunction (assessed with: International Index of Erectile Function, Female Sexual Function Index, etc.) | | | | | | | | | | | | |
| 10 (Both sexes) | Observational studies | Serious[1] | No serious inconsistency | Serious[2] | No serious imprecision | Strong association[3] Reduced effect for RR > > 1 or RR < < 1[4] Dose response gradient[5] | 383/659 (58.1%) | 168/1017 (16.5%) | RR 3.08 (1.95 to 4.88) | 344 more per 1000 (from 157 more to 641 more) | ⊕⊕⊕O MODERATE | CRITICAL |
| 6 (Female) | Observational studies | Serious[1] | No serious inconsistency | Serious[2] | No serious imprecision | Strong association[6] Dose response gradient[5] | 247/418 (59.1%) | 119/611 (19.5%) | RR 2.69 (1.48 to 4.89) | 329 more per 1000 (from 93 more to 758 more) | ⊕⊕OO LOW | CRITICAL |
| 3 (Male) | Observational studies | Serious[1] | Serious[7] | Serious[2] | No serious imprecision | Strong association[8] Dose response gradient[5] | 106/181 (58.6%) | 34/346 (9.8%) | RR 4.85 (2.01 to 11.7) | 378 more per 1000 (from 99 more to 1000 more) | ⊕OOO VERYLOW | CRITICAL |

CI: confidence interval; RR: relative risk;
GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate.

[1] selection bias, performance bias, and detection bias were detected in several included studies.
[2] some studies concluded that neuropsychiatric disorders and sex hormones disturbance might play roles in this association.
[3] large sample, total 1676 female and male participants from 10 studies were included.
[4] combined RR was 3.08 (95%CI: 1.95–4.88, $P = 0.007$).
[5] patients with long duration and severity of epilepsy in had a higher risk of SD.
[6] large sample, total 1029 female participants from 6 studies were included, the overall RR was 2.69 (95%CI: 1.48–4.89, $P = 0.001$).
[7] inconsistent association between epilepsy and male SD was reported within the included studies (i.e. Calabro et al's study).
[8] total 527 male participants from 3 studies were included, combined RR was 4.85 (95%CI: 2.01–11.7, $P < 0.001$).

### 3.5. Subgroup analyses

In this study, we performed the subgroup analyses to further elicit the association between epilepsy and the risk of SD and to explore the source of heterogeneity. Of note, the disease duration, specific AEDs, and mean age might serve as the confounding factors, by which might affect the actual role of epilepsy on the sexual functioning. However, because only a few studies provided the data of the mean duration of epilepsy and the specific AEDs, we did not conduct the subgroup analyses on these two factors.

In the included studies reporting female subjects, subgroup analysis on the study design indicated that the association between epilepsy and SD was existed in cross-sectional studies [21,23] (RR = 2.55, 95% CI: 1.89–3.43, $P < 0.001$) and no significant heterogeneity was detected ($I^2 = 25.3\%$, $P = 0.247$). However, such association was not found in the cohort/case-control studies [19,20,24,26] (RR = 2.83, 95% CI: 0.9–8.82, $P = 0.074$) and the substantial heterogeneity was observed ($I^2 = 92.8\%$, $P < 0.001$). Stratified analysis by geographical area revealed that there was no significant relationship between epilepsy and female SD in studies conducted in the United States [19,20] (RR = 2.49, 95% CI: 0.81–7.71, $P = 0.113$) and non-significant heterogeneity was found ($I^2 = 0.0\%$, $P = 0.429$). However, those studies conducted in other regions [21,23,24,26] confirmed a relationship between epilepsy and SD (RR = 2.7, 95% CI: 1.37–5.32, $P = 0.004$; $I^2 = 93.2\%$, $P < 0.001$). Based on the mean age, the results of subgroup analysis verified the positive association between epilepsy and the female SD, and such association seemed stronger in the PWE with age ≥35 years [24–26] (RR = 2.91, 95% CI: 1.19–7.12, $P = 0.02$) than those with age < 35 years [19,20,23] (RR = 2.18, 95% CI: 1.51–3.16, $P < 0.001$) (Table 3).

As shown in Table 3, the results of subgroup analyses for male studies showed that the association between epilepsy and male SD was detected in cross-sectional designed, study conducted in America, and mean age < 35 years. Great heterogeneity was observed in those studies designed by cohort/case-control and conducted in Europe, and in those PWE with mean age ≥35 years.

### 3.6. Sensitivity analysis

To evaluate the influence of individual study on the overall risk of SD, we have conducted the sensitivity analyses subsequently. Omitting any one of the 6 studies of female subjects did not substantially change the new overall synthesis RR [ranged from 2.07 (95%CI: 1.38–3.12) to 3.29 (95%CI: 1.87–5.76)] and the heterogeneity ($I^2$ ranged from 62.4% to 91.1%) (Table 4 and Supplementary Fig. 1 left panel).

**Table 4**
Sensitivity analysis after each study was excluded by turns.

| Study omitted | RR (95% CI) for remainders | Heterogeneity | |
|---|---|---|---|
| | | $I^2$ | $P$ |
| *Female:* | | | |
| Herzog et al (2003) [19] | 2.58 (1.38, 4.84) | 91.1% | < 0.001 |
| Morrell et al (2005) [20] | 2.82 (1.48, 5.35) | 91.0% | < 0.001 |
| Karan et al (2015) [23] | 2.85 (1.34, 6.03) | 90.5% | < 0.001 |
| Henning-2 et al (2016) [24] | 2.07 (1.38, 3.12) | 62.4% | 0.031 |
| Tao et al (2018) [25] | 2.64 (1.18, 5.91) | 91.1% | < 0.001 |
| Ogunjimi et al (2018) [26] | 3.29 (1.87, 5.76) | 81.9% | < 0.001 |
| *Male:* | | | |
| Reis et al (2012) [21] | 3.55 (0.87, 14.45) | 85.5% | 0.009 |
| Calabro et al (2013) [22] | 7.05 (4.86, 10.23) | 0.0% | 0.598 |
| Henning-1 et al (2016) [24] | 3.80 (0.70, 20.55) | 83.2% | 0.015 |

Abbreviation: RR = relative risk; CI = confidence interval.

In the studies of male individuals, however, there was substantial change in the new overall combined RR after excluding the studies of Reis et al. [21] (RR = 3.55, 95%CI: 0.87–14.45; heterogeneity: $I^2 = 85.5\%$, $P = 0.009$) or Henning et al. [24] (RR = 3.8, 95%CI: 0.7–20.55; heterogeneity: $I^2 = 83.2\%$, $P = 0.015$), and no significant association between epilepsy and SD was observed. Interestingly, the substantial heterogeneity was disappeared after omitting the study of Calabro et al. [22] ($I^2 = 0.0\%$, $P = 0.598$), indicating that the substantial heterogeneity of the included studies of male subjects might originate from this study (Table 4 and Supplementary Fig. 1 right panel) (Fig. 2).

### 3.7. Publication Bias

As shown in Fig. 3, visualization of the funnel plot suggested that Begg rank correlation test and the Egger linear regression yielded no evidence of publication bias among the included studies (Begg's, $P > |z| = 1.000$; Egger, $P > |t| = 0.812$, 95%CI: −5.3–4.28).

**Table 3**
Subgroup analyses of the association between epilepsy and sexual dysfunction.

| Category of variables | NO. of studies | Heterogeneity | | Random-effects model OR (95% CI) $P$ | |
|---|---|---|---|---|---|
| | | $I^2$ | $P$ | | |
| *Female:* | | | | | |
| Study design | | | | | |
| Cross-sectional [21,23] | 2 | 25.3% | 0.247 | 2.55 (1.89, 3.43) | < 0.001 |
| Cohort/Case-control [19,20,24,26] | 4 | 92.8% | < 0.001 | 2.83 (0.90, 8.82) | 0.074 |
| Geographical area | | | | | |
| United States [19,20] | 2 | 0.0% | 0.429 | 2.49 (0.81, 7.71) | 0.113 |
| Other regions [21,23,24,26] | 4 | 93.2% | < 0.001 | 2.7 (1.37, 5.32) | 0.004 |
| Mean age | | | | | |
| < 35 years [19,20,23] | 3 | 0.0% | 0.71 | 2.18 (1.51, 3.16) | < 0.001 |
| ≥35 years [24–26] | 3 | 95.1% | < 0.001 | 2.91 (1.19, 7.12) | 0.02 |
| *Male:* | | | | | |
| Study design | | | | | |
| Cross-sectional [21] | 1 | – | – | 8.95 (3.42, 23.39) | < 0.001 |
| Cohort/Case-control [22,24] | 2 | 85.5% | 0.009 | 3.55 (0.87, 14.45) | 0.077 |
| Geographical area | | | | | |
| America [21] | 1 | – | – | 8.95 (3.42, 23.39) | < 0.001 |
| Europe [22,24] | 2 | 85.5% | 0.009 | 3.55 (0.87, 14.45) | 0.077 |
| Mean age | | | | | |
| < 35 years [21] | 1 | – | – | 8.95 (3.42, 23.39) | < 0.001 |
| ≥35 years [22,24] | 2 | 85.5% | 0.009 | 3.55 (0.87, 14.45) | 0.077 |

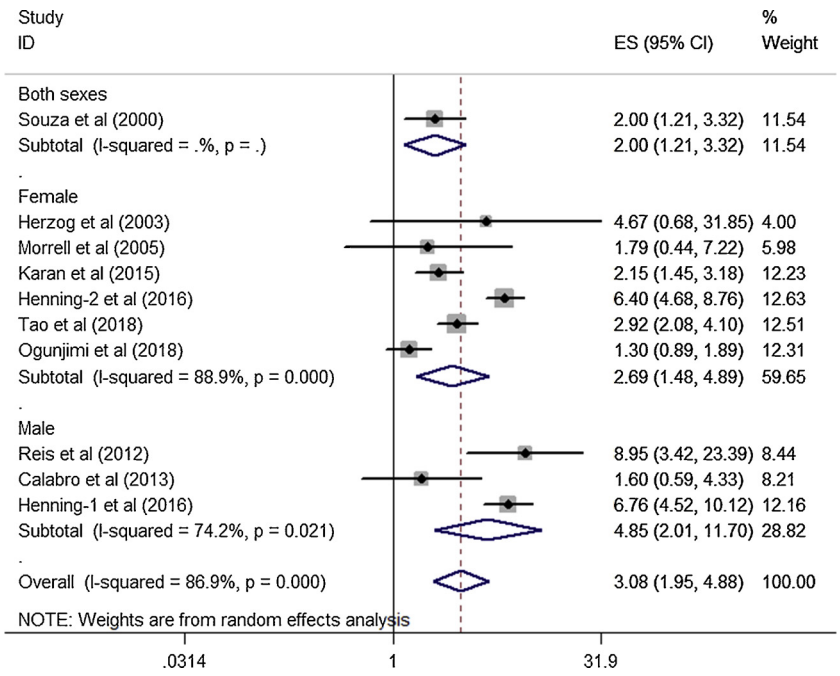


**Fig. 2.** Forest plots of meta-analysis of the included studies on the association between epilepsy and sexual dysfunction in both sexes. The synthesis relative risk using a random effect model showed that epilepsy was associated with a significantly higher incidence of sexual dysfunction in both genders. Substantial heterogeneity was detected across the studies.

## 4. Discussion

Since the first publication [27] reporting SD developing in two-thirds of untreated PWE, by Gastaut et al. in 1954, extensive studies were conducted to investigate the risk of SD development in epilepsy and to explore the underlying mechanism. Based on the combined RR from the 6 included studies reporting female subjects and 3 studies reporting male individuals, the present meta-analysis revealed that the prevalence of SD was remarkably higher among PWE than the general populations in both sexes. Female and male PWE might be at two-fold and four-fold higher risk of SD than the healthy female and male controls, respectively. Ascertained by GRADEpro, the rates of events of SD on average were 59.1% and 19.5% for female PWE and healthy individuals, respectively; and 58.6% and 9.8% for male PWE and the healthy controls, respectively. These results were in line with the findings of some other pertinent trials failing to meet our pre-defined eligibility criteria [13,28–31], which showed the suspicious association between epilepsy and SD. Sensitivity analyses suggested that the quantification of the risk for the SD in PWE remained prominently high in nearly all of the studies, indicating our findings were robust. However, there was substantial heterogeneity among studies. In addition to study design, geographical area, and the mean age which reflected by the subgroup analyses in this meta-analysis, the different mean disease duration of epilepsy, frequency and severity of the disease, AEDs usage, sample size, the assessment tool for SD, and variable characteristics of participants could all be partly responsible for the heterogeneity.

Although the current meta-analysis suggested that epilepsy might be linked with SD, no clear-cut etiology has been recognized to interpret this possible association. Multifactorial mechanisms may contribute to the development of SD in PWE, these include but are not limited to the innate nature of impairments in the nervous system (i.e., the site of origin of seizures, different types, duration and frequency of epileptic seizure), endocrine disorder, AEDs usage, psychiatric illness, and psychosocial deficits [15,32,33].

Sexual behavior is known to be controlled by the brain. Epilepsy is one of the diseases of brain lesions. The results of our study suggested an increased rate of SD in the PWE. The clinical manifestations of the impairment on sexual function in PWE seemed to depend on the site of the origin of seizures. Among the PWE, the occurrence of SD is distinctly higher in people with temporal lobe epilepsy (particularly on the right side) than those with extratemporal and primary generalized epilepsies [34–36]. A previous study [37] reported that anterior temporal lobectomy would result in postoperative seizure freedom in over 60% AED-resistant patients. Intriguingly, most patients who received the surgery have achieved an appreciable improvement in their sexual function postoperatively [38,39]. On the other hand, different types of

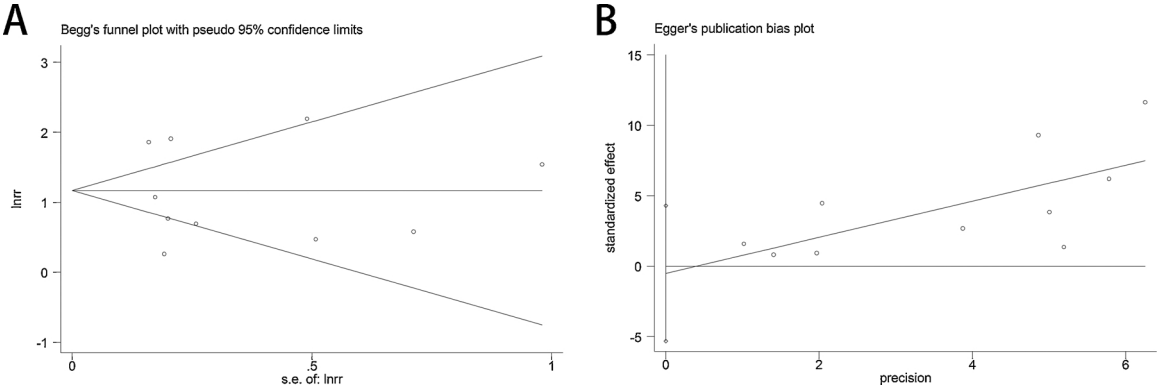


**Fig. 3.** Begg's and Egger's tests to detect publication bias. Both Begg's rank correlation test (left panel) and the Egger's linear regression (right panel) yielded no evidence of publication bias in this study.

epileptic seizure also have various effects on sexual functioning. Previous study suggested that the incidence of SD was higher in patients with focal epilepsy than those with generalized epilepsy [34]. FSFI is a 19-item questionnaire evaluating the sexual function of female, in which 6 domains of sexual desire, arousal, lubrication, orgasm, satisfaction, and dyspareunia are included, and a total scores less than 26.55 is considered as SD. In Karan et al.'s study [23], they observed that female patients with a longer duration of epilepsy had the remarkably low scores of FSFI. The effect of seizure frequency on sexual function was still controversial. Some investigators reported that seizure frequency was not related to the SD symptoms [18].

Abnormalities in the secretion of sex hormones are the important factors related to the etiology of SD in both male and female PWE. Mounting evidence has emerged suggesting that epilepsy could affect the hypothalamic–pituitary–testicular axis or the hypothalamic-pituitary-ovarian axis [40,41]. It is known that bioactive testosterone plays a key role in sexual functioning in both men and women. The bioactive testosterone was found to be significantly lower in both male and female PWE compared to the healthy controls, suggesting a consequent hyposexuality in the PWE [42]. In addition to the declination of testosterone, SD in male PWE might also be correlated with elevated levels of follicle-stimulating hormone / sex hormone-binding globulin / prolactin, and decreased levels of GnRH and dehydroepiandrosterone sulfate, thereby leading to hypogonadism [40,43]. As for female PWE, it was reported that SD might also be associated with the reduction in estradiol or dehydroepiandrosterone sulfate [20]. Interestingly, there seems to be a bidirectional interaction between seizures and sex hormones, in which seizures may affect sex hormones levels and in turn hormones modulated seizures, suggesting a vicious cycle between epilepsy and SD [44].

It was reported that both epilepsy and AEDs could be causally implicated in patients' sexual function [45]. AEDs have been demonstrated to be contributed to the development of sexual hormone disorders, thus resulting in SD. Those process might involve different mechanisms [46]. On the one hand, certain AEDs (i.e. phenobarbital, carbamazepine, and phenytoin) could induce liver enzymes, leading to direct suppression of gonadal testosterone synthesis and disturbance of other peripheral sex steroid hormones [47]. On the other hand, AEDs can also have a depressive effect on brain excitability, thus producing a deteriorative impact on sexuality. Due to the natural effect of AEDs is to control the seizure symptoms of the patients, it seems that the more sedative AEDs have a greater impact on the sexual functioning than those AEDs with less sedative effects [46]. Intriguingly, some clinicians found that oxcarbazepine (a keto-derivative of carbamazepine) not only had the beneficial effects on SD, but also was effective for well control in PWE [48]. In line with this finding, Atarodi-Kashani et al. reported that non-enzyme-inducing AEDs (i.e., Lamotrigine and Levetiracetam) could significantly improve the desire, orgasm, and satisfaction [30]. As for the possible association between AEDs and sexual functioning, both the clinicians and patients should take into account not only the seizure situation but also the sexual health to choose the optimum AEDs.

Psychiatric and psychosocial comorbidity might also play pivotal roles in the development of SD in PWE. Evidence from several epidemiological studies indicated that anxiety and depressive disorders were high in PWE, especially in those received AEDs treatment [49–51]. It is well known that both anxiety and depression can significantly reduce libido and orgasm of the sufferers [52]. Since many patients further received psychotropic medications, which were considered as the risk factors for sexual impairment, thus these anti-psychiatric medications usage might contribute to the development of SD symptoms [53]. Moreover, psychosocial stresses have also been identified as causes of SD in epilepsy. A large proportion of the PWE have complained about poor self-esteem, feelings of stigma, and limitation of social contacts, including family relations, work, and education [54–56]. These psychosocial constraints might be one of the explanations for SD among PWE.

To the best of our knowledge, this is the first meta-analysis to summarize all available evidence for pooling the odds on the association between epilepsy and the risks of developing SD in both male and female subjects. However, there were also several inherent limitations in the study. Firstly, substantial heterogeneity across the included studies was found. Subsequent sensitivity analyses indicated that the potential origin for the observed heterogeneity of male's studies might derive from Calabro's study. However, heterogeneity was consistent in the studies of female subjects after excluding any one of the relevant studies. Secondly, we did not conduct the stratification analyses for the disease frequency, severity, duration, and specific AEDs because these data were not available in all the studies. Thus, high-quality prospective cohorts with large sample size are still warranted to validate the evidence of epilepsy predisposing to the development of SD in both sexes.

## 5. Conclusions

In summary, this meta-analysis suggests a hazardous effect of epilepsy on the development of SD in both female and male patients. Possible interpretations for this association may be multifactors, these include but are not limited to neurological impairment, AEDs usage, psychiatric and psychosocial comorbidities. Therefore, sexual functioning assessment and the preferred treatment should be given when managing the PWE in clinical practice.

## Informed consent

The manuscript does not contain clinical studies or patient data.

## Conflicts of interest

The authors declare that they have no confict of interest.

## Ethical standard statement

For this type of study formal consent is not required.

## Acknowledgement

This work was supported by the grants from Science and Technology Planning Project of Guangdong Province (No.2017B030314108).

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.seizure.2019.01.004.

## References

[1] Heyne HO, Singh T, Stamberger H, Abou JR, Caglayan H, Craiu D, et al. De novo variants in neurodevelopmental disorders with epilepsy. Nat Genet 2018;50:1048–53.
[2] Centers for Disease Control and Prevention (CDC) Epilepsy in adults and access to care—United States, 2010. MMWR Morb Mortal Wkly Rep 2012;61:909–13.
[3] Sayehmiri K, Tavan H, Sayehmiri F, Mohammadi I, Carson K V. Prevalence of epilepsy in Iran: a meta-analysis and systematic review. Iran J Child Neurol 2014;8:9–17.
[4] Ocek L, Tarhan H, Uludag FI, Sariteke A, Kose C, Colak A, et al. Evaluation of sex hormones and sperm parameters in male epileptic patients. Acta Neurol Scand 2018;137:409–16.
[5] Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen HW, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010;51:1069–77.
[6] Spencer DD, Gerrard JL, Zaveri HP. The roles of surgery and technology in understanding focal epilepsy and its comorbidities. Lancet Neurol 2018;17:373–82.
[7] Pennell PB. Hormonal aspects of epilepsy. Neurol Clin 2009;27:941–65.
[8] Isojarvi JI, Lofgren E, Juntunen KS, Pakarinen AJ, Paivansalo M, Rautakorpi I, et al. Effect of epilepsy and antiepileptic drugs on male reproductive health. Neurology 2004;62:247–53.

[9] Roste LS, Tauboll E, Morkrid L, Bjornenak T, Saetre ER, Morland T, et al. Antiepileptic drugs alter reproductive endocrine hormones in men with epilepsy. Eur J Neurol 2005;12:118–24.
[10] Hamed SA. The effect of epilepsy and antiepileptic drugs on sexual, reproductive and gonadal health of adults with epilepsy. Expert Rev Clin Pharmacol 2016;9:807–19.
[11] Morrell MJ, Guldner GT. Self-reported sexual function and sexual arousability in women with epilepsy. Epilepsia 1996;37:1204–10.
[12] Morrell MJ, Sperling MR, Stecker M, Dichter MA. Sexual dysfunction in partial epilepsy: a deficit in physiologic sexual arousal. Neurology 1994;44:243–7.
[13] Zelena V, Kuba R, Soska V, Rektor I. Depression as a prominent cause of sexual dysfunction in women with epilepsy. Epilepsy Behav 2011;20:539–44.
[14] Hellmis E. Sexual problems in males with epilepsy—an interdisciplinary challenge!. Seizure 2008;17:136–40.
[15] Harden CL. Sexual dysfunction in women with epilepsy. Seizure 2008;17:131–5.
[16] Jensen P, Jensen SB, Sorensen PS, Bjerre BD, Rizzi DA, Sorensen AS, et al. Sexual dysfunction in male and female patients with epilepsy: a study of 86 outpatients. Arch Sex Behav Arch Sex Behav 1990;19:1–14.
[17] de Vincentiis S, Febronio MV, Da SC, Saito MI, Takiuti AD, Valente KD. Sexuality in teenagers with epilepsy. Epilepsy Behav 2008;13:703–6.
[18] Souza EA, Keiralla DM, Silveira DC, Guerreiro CA. Sexual dysfunction in epilepsy: identifying the psychological variables. Arq Neuropsiquiatr 2000;58:214–20.
[19] Herzog AG, Coleman AE, Jacobs AR, Klein P, Friedman MN, Drislane FW, et al. Relationship of sexual dysfunction to epilepsy laterality and reproductive hormone levels in women. Epilepsy Behav 2003;4:407–13.
[20] Morrell MJ, Flynn KL, Done S, Flaster E, Kalayjian L, Pack AM. Sexual dysfunction, sex steroid hormone abnormalities, and depression in women with epilepsy treated with antiepileptic drugs. Epilepsy Behav 2005;6:360–5.
[21] Reis RM, de Angelo AG, Sakamoto AC, Ferriani RA, Lara LA. Altered sexual and reproductive functions in epileptic men taking carbamazepine. J Sex Med 2013;10:493–9.
[22] Calabro RS, Grisolaghi J, Quattrini F, Bramanti P, Magaudda A. Prevalence and clinical features of sexual dysfunction in male with epilepsy: the first southern Italy hospital-based study. Int J Neurosci 2013;123:732–7.
[23] Karan V, Harsha S, Keshava BS, Pradeep R, Sathyanarayana RT, Andrade C. Sexual dysfunction in women with epilepsy. Indian J Psychiatry 2015;57:301–4.
[24] Henning OJ, Nakken KO, Traeen B, Mowinckel P, Lossius M. Sexual problems in people with refractory epilepsy. Epilepsy Behav 2016;61:174–9.
[25] Tao L, Zhang X, Duan Z, Wang Y, Liu J, Hou H, et al. Sexual dysfunction and associated factors in Chinese Han women with epilepsy. Epilepsy Behav 2018;85:150–6.
[26] Ogunjimi L, Yaria J, Makanjuola A, Ogunniyi A. Sexual dysfunction among Nigerian women with epilepsy. Epilepsy Behav 2018;83:108–12.
[27] GASTAUT H, COLLOMB H. Sexual behavior in psychomotor epileptics. Ann Med Psychol (Paris) 1954;1954(112):657–96.
[28] Keller J, Chen YK, Lin HC. Association between epilepsy and erectile dysfunction: evidence from a population-based study. J Sex Med 2012;9:2248–55.
[29] Hamed SA, Hermann BP, Moussa EM, Youssef AH, Rageh TA, Elserogy YE, et al. Evaluation of penile vascular status in men with epilepsy with erectile dysfunction. Seizure 2015;25:40–8.
[30] Atarodi-Kashani Z, Kariman N, Ebadi A, Alavi MH, Beladi-Moghadam N. Sexual function and related factors in Iranian woman with epilepsy. Seizure 2017;52:147–53.
[31] Toone BK, Edeh J, Nanjee MN, Wheeler M. Hyposexuality and epilepsy: a community survey of hormonal and behavioural changes in male epileptics. Psychol Med 1989;19:937–43.
[32] Lambert MV. Seizures, hormones and sexuality. Seizure 2001;10:319–40.
[33] Smaldone M, Sukkarieh T, Reda A, Khan A. Epilepsy and erectile dysfunction: a review. Seizure 2004;13:453–9.
[34] Shukla GD, Srivastava ON, Katiyar BC. Sexual disturbances in temporal lobe epilepsy:a controlled study. Br J Psychiatry 1979;134:288–92.
[35] Harden CL. Sexuality in men and women with epilepsy. CNS Spectr 2006;11:13–8.
[36] Luef G, Madersbacher H. Sexual dysfunction in patients with epilepsy. Handb Clin Neurol 2015;130:383–94.
[37] Tellez-Zenteno JF, Dhar R, Wiebe S. Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis. Brain 2005;128:1188–98.
[38] Baird AD, Wilson SJ, Bladin PF, Saling MM, Reutens DC. Sexual outcome after epilepsy surgery. Epilepsy Behav 2003;4:268–78.
[39] Ramesha KN, Radhakrishnan A, Jiayaspathi A, Padickaparambal S, Alexander A, Unnikrishnan JP, et al. Sexual desire and satisfaction after resective surgery in patients with mesial temporal lobe epilepsy with hippocampal sclerosis. Epilepsy Behav 2012;25:374–80.
[40] Xiaotian X, Hengzhong Z, Yao X, Zhipan Z, Daoliang X, Yumei W. Effects of antiepileptic drugs on reproductive endocrine function, sexual function and sperm parameters in Chinese Han men with epilepsy. J Clin Neurosci 2013;20:1492–7.
[41] Thomas SV, Sarma PS, Nirmala C, Mathai A, Thomas SE, Thomas AC. Women with epilepsy and infertility have different reproductive hormone profile than others. Ann Indian Acad Neurol 2013;16:544–8.
[42] Molleken D, Richter-Appelt H, Stodieck S, Bengner T. Sexual quality of life in epilepsy: correlations with sex hormone blood levels. Epilepsy Behav 2009;14:226–31.
[43] Kuba R, Pohanka M, Zakopcan J, Novotna I, Rektor I. Sexual dysfunctions and blood hormonal profile in men with focal epilepsy. Epilepsia 2006;47:2135–40.
[44] Sivaraaman K, Mintzer S. Hormonal consequences of epilepsy and its treatment in men. Curr Opin Endocrinol Diabetes Obes 2011;18:204–9.
[45] Herzog AG, Drislane FW, Schomer DL, Pennell PB, Bromfield EB, Dworetzky BA, et al. Differential effects of antiepileptic drugs on sexual function and hormones in men with epilepsy. Neurology 2005;65:1016–20.
[46] Svalheim S, Sveberg L, Mochol M, Tauboll E. Interactions between antiepileptic drugs and hormones. Seizure 2015;28:12–7.
[47] Herzog AG, Drislane FW, Schomer DL, Pennell PB, Bromfield EB, Kelly KM, et al. Differential effects of antiepileptic drugs on sexual function and reproductive hormones in men with epilepsy: interim analysis of a comparison between lamotrigine and enzyme-inducing antiepileptic drugs. Epilepsia 2004;45:764–8.
[48] Luef G, Kramer G, Stefan H. Oxcarbazepine treatment in male epilepsy patients improves pre-existing sexual dysfunction. Acta Neurol Scand 2009;119:94–9.
[49] Tellez-Zenteno JF, Patten SB, Jette N, Williams J, Wiebe S. Psychiatric comorbidity in epilepsy: a population-based analysis. Epilepsia 2007;48:2336–44.
[50] Lacey CJ, Salzberg MR, Roberts H, Trauer T, D'Souza WJ. Psychiatric comorbidity and impact on health service utilization in a community sample of patients with epilepsy. Epilepsia 2009;50:1991–4.
[51] Eddy CM, Rickards HE, Cavanna AE. Behavioral adverse effects of antiepileptic drugs in epilepsy. J Clin Psychopharmacol 2012;32:362–75.
[52] Kalmbach DA, Kingsberg SA, Ciesla JA. How changes in depression and anxiety symptoms correspond to variations in female sexual response in a nonclinical sample of young women: a daily diary study. J Sex Med 2014;11:2915–27.
[53] Maguire MJ, Weston J, Singh J, Marson AG. Antidepressants for people with epilepsy and depression. Cochrane Database Syst Rev 2014. CD010682.
[54] Pavone C, Giacalone N, Vella M, Urso L, Zummo L, Fierro B. Relation between sexual dysfunctions and epilepsy, type of epilepsy, type of antiepileptic drugs: a prospective study. Urologia 2017;84:88–92.
[55] Montouris G, Morris GR. Reproductive and sexual dysfunction in men with epilepsy. Epilepsy Behav 2005;7(Suppl 2):S7–14.
[56] Al-Khateeb JM, Al-Khateeb AJ. Research on psychosocial aspects of epilepsy in Arab countries: a review of literature. Epilepsy Behav 2014;31:256–62.