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The impact of medications and medical comorbidities on sexual function in people with epilepsy

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ABSTRACT

Objective: People with epilepsy experience increased rates of sexual dysfunction, often affecting quality of life. Sexual dysfunction may result from the underlying disorder, antiseizure or other medications, or comorbid psychosocial factors. This study evaluated the incidence and clinical associations of sexual dysfunction in adult epilepsy patients.

Methods: 89 epilepsy patients 18 years and older admitted to the New York University Comprehensive Epilepsy Center epilepsy monitoring unit between 2016 and 2018 completed a survey on sexual functioning. The survey included demographic, clinical, and sexual functioning information with a validated measure of sexual function (the Arizona Sexual Experiences Scale (ASEX).

Results: Of 89 surveys completed, 15 (16.9 %) patients had discussed sexual functioning with a medical professional and 20 (22.5 %) reported sexual dysfunction. For the group, the mean ASEX score was 13.6 (SD 4.8). 59 (66.3 %) participants reported not being asked about sexual health by their doctor or nurse practitioner in the last year. The two independent predictors of sexual dysfunction were self-identifying as overweight/obese (OR 6.1, CI 1.4−26.5, P = 0.02) or taking strong enzyme-inducing antiseizure medications (OR 7.8, CI 1.4−44.9, P = 0.02). Other factors such as age, relationship status, duration of epilepsy, the presence of depression or anxiety, cardiovascular risk factors, and opioid/stimulant use, did not predict sexual dysfunction.

Significance: Our study showed that sexual dysfunction is common in epilepsy patients but infrequently discussed by medical professionals. Two modifiable risk factors, being overweight or taking strong enzyme-inducing antiseizure medications, were independently associated with sexual dysfunction, suggesting interventions to potentially improve sexual health.

1. Introduction

Sexual health is an important aspect of life that strongly impacts quality of life, a World Health Organization basic human right (World Health Organization, 2020). Compared to the general population, people with epilepsy have increased rates of sexual health issues, including impairments in desire, arousal, and orgasm (Foundation E. Epilepsy and Sexual Relationships, 2014; Zhao et al., 2019; Henning et al., 2016). Despite its importance, sexual health is often a neglected topic by epilepsy healthcare providers, with few quality studies to guide assessment and management of sexual disorder in epilepsy patients (Kaufman et al., 2015; 't Hoen et al., 2017). The mechanisms of sexual dysfunction in epilepsy is poorly understood, but may be related to medication side effects, underlying etiology (e.g., genetic, vascular, autoimmune), and psychosocial issues (e.g., stigma, unemployment, psychiatric disorders) (Foundation E. Epilepsy and Sexual Relationships, 2014). Here, we studied we the prevalence of sexual dysfunction among epilepsy patients admitted for video-EEG monitoring at the New York University (NYU) Comprehensive Epilepsy Center and to identify potentially modifiable risk factors.

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2. Methods

2.1. Study population

A convenience sample of adult patients with epilepsy who were admitted to the NYU Comprehensive Epilepsy Center epilepsy monitoring unit between August 2016 and June 2018 were asked to voluntarily complete a survey on sexual functioning. Respondents were informed that completing the survey would imply consent for study participation. Inclusion criteria were admission to the epilepsy monitoring unit and being ≥ 18 years of age. Exclusion criteria included: unable to comprehend spoken and written English sufficiently to independently engage with study personnel (e.g., non-English speaking, severe intellectual disability), unable to independently use the study survey device to respond to study questions even after completing an instructional session. The NYU institutional research board approved this study.

2.2. The questionnaire

After the study team provided detailed instruction including a test survey, respondents completed an anonymous 37-item survey on a tablet (Apple iPad Mini) using Qualtrics survey software (Provo, UT) at their own pace over the course of a day during their hospitalization. Study tablets were collected the following day. Survey questions included demographic information (i.e., age, sex, racial identity, and level of education), medical history (e.g., years treated for epilepsy, medication use, and presence of any medical and psychiatric comorbidities), relationship and sexual history including history of prior sexual abuse, and sexual satisfaction and functioning. Subjects also completed the Arizona Sexual Experiences Scale (ASEX), a validated scale quantifying sex desire, arousal, vaginal lubrication/penile erection, ability to reach orgasm, and satisfaction from orgasm. Each item is scored from 1 to 6, and sexual dysfunction is present with a total score of ≥19, scoring ≥5 on any item, or ≥4 on three items (McGahuey et al., 2000).

2.3. Statistics

We analyzed group differences in variables including demographic and clinical characteristics between people with and without sexual dysfunction on the ASEX. For univariate analysis, some variables were categories. Higher education was education beyond high school. Cardiovascular risk factors were one or more of the following: hypertension, hyperlipidemia, diabetes, history of stroke, and active smoking. Use of strong enzyme-inducing antiseizure medication(s) included: carbamazepine, phenytoin, phenobarbital, and/or primidone. All variables were based on self-report by survey respondents, including relationship status, self-identifying as having depression and/or anxiety, and self-identifying as being overweight or obese. We used Pearson's chi-square tests for univariate analysis. Variables with $P < 0.1$ in univariate analysis were included in a multiple logistic regression in order to determine independent predictors of sexual dysfunction (ASEX score). 95 % confidence intervals were used, and a P-value of < 0.05 was considered statistically significant. Analyses were performed using JMP (Version 14.0; SAS Institute Inc., Cary, NC; 2016).

3. Results

3.1. Participants

Of the 103 of patients who agreed to participate, 89 (86.4 %) completed the survey and ASEX questionnaire and were included in this analysis. Of these, nearly all (88/89 or 99 %) were diagnosed with epilepsy for ≥1 year; one respondent had an uncertain time of diagnosis. Nine respondents (10 %) were on no antiseizure medications, and 17 (19 %) were on monotherapy. Pertinent demographic and clinical characteristics of participants are presented in Table 1, categorized into groups based on whether or not they had sexual dysfunction on ASEX scores.

3.2. Sexual function

Only 15 participants (16.9 %) reported ever having discussed concerns about sexual functioning with a medical professional, and 20 (22.5 %) met criteria for sexual dysfunction by ASEX score. Fifty-nine participants (66.3 %) reported they had not been asked about sexual dysfunction by their doctor or nurse practitioner in the last year, and of these, 14 (15.7 %) had an ASEX score indicating sexual dysfunction. Scores on individual ASEX questions were similar between men and women (Table 2). Most participants (60 or 67.4 %) were sexually active at least once per week and expressed a desire for sexual activity at least once per week (68 or 76.4 %).

3.3. Risk factors for sexual dysfunction

Univariate analysis showed significant risk factors for sexual dysfunction included: female sex (OR 3.7, CI 1.2−11.1, $P = 0.02$), ≥ 50 years (OR 3.7, CI 1.3−10, $P = 0.01$), overweight or obese (OR 6.9, CI 1.9−25, $P < 0.01$), and using one or more strong enzyme-inducing antiseizure medications (OR 7.4, CI 1.59−33.3, $P < 0.01$). Since these were significant findings in univariate analysis, they were included in multivariate testing. Multivariate analysis revealed that the only independent predictors of sexual dysfunction were overweight (OR 6.1, CI 1.4−26.5, $P = 0.02$), and taking strong enzyme-inducing antiseizure medications (OR 7.8, CI 1.4−44.9, $P = 0.02$); Table 3.

4. Discussion

A key finding from this study is that sexual health is not often discussed in clinic visits among patients with epilepsy. In fact, 66 % of the respondents in our study reported not being asked about sexual functioning within the past year by a doctor or nurse practitioner, despite the finding that 23 % reported sexual dysfunction. The emphasized the fact that discussing sexual function is a critical part of neurological care since certain risk factors can potentially be modified to help improve the sexual functioning of people with epilepsy.

Table 1
Demographic and clinical characteristics of respondents.

	Survey respondents (n = 89)
Sex	
Female, n (%)	46 (52)
Male, n (%)	43 (48)
Age category (Range: 18−80 years)	
18−49, n (%)	57 (64)
>50, n (%)	32 (36)
Level of education	
No higher education, n (%)	13 (15)
Higher education, n (%)	76 (85)
Relationship status	
Single, n (%)	40 (45)
In a relationship, n (%)	49 (55)
Years Treated for Epilepsy	
0−5, n (%)	30 (34)
>5, n (%)	59 (66)
Depression or Anxiety, n (%)	38 (43)
Overweight or obese, n (%)	12 (13)
Cardiovascular risk factors	
Hypertension, n (%)	7 (8)
Hyperlipidemia, n (%)	3 (3)
Diabetes (Type II), n (%)	1 (1)
Active smoking, n (%)	16 (18)
Prior stroke, n (%)	4 (5)
Strong enzyme inducing medication, n (%)	8 (9)
Opioid or stimulant use, n (%)	13 (15)

Table 2
Average Scores on ASEX Categories by Sex.

	Average ASEX Question Score	
	Male Score (SD)	Female Score (SD)
Desire	2.58 (1.0)	3.33 (1.15)
Arousal	2.79 (0.95)	3.2 (1.06)
Penile erection or vaginal lubrication	2.66 (1.33)	3.07 (1.12)
Orgasm	2.46 (1.05)	3.58 (1.2)
Satisfaction	1.87 (0.73)	2.7 (1.39)

The findings in our study are consistent with several questionnaire studies and a meta-analysis showing increased sexual dysfunction in epilepsy patients, though results vary widely based on study design and population, with sexual dysfunction rates up to 75 % (Zhao et al., 2019; Atarodi-Kashani et al., 2017; Davis et al., 2008; Dawson et al., 2019; Hamed et al., 2006; Karan et al., 2015; Mameniškienė et al., 2017; Pavone et al., 2017; Zelená et al., 2011). In contrast to community studies, we surveyed patients in an epilepsy monitoring unit at a tertiary referral center, with 70 % of patients surveyed being on 2 or more antiseizure medications. This could imply our population had a higher burden of seizures overall, which can have a negative impact on sexual functioning.

Patients who identified as being overweight/obese in our survey had significantly greater sexual dysfunction than those of normal weight, consistent with sexual dysfunction studies in the general population (McCabe et al., 2016). No cardiovascular risk factor independently predicted sexual dysfunction risk, which may be reflect the young age of our respondents. Anxiety, depression, or use of opioids or stimulants were not associated with sexual dysfunction, though these have been identified as risk factors in the general population (McCabe et al., 2016). Our study identified a significant association between sexual dysfunction and use of the enzyme-inducing drugs carbamazepine, phenytoin, phenobarbital, and primidone. This finding is consistent with some earlier studies but contrasts with a recent study where no difference in sexual dysfunction was identified for enzyme-inducing antiseizure medication (Henning et al., 2016, 2019; Herzog et al., 2005; Toone et al., 1983; Rättyä et al., 2001; Devinsky, 2005). These differences may reflect different patient demographics, epilepsy syndromes, adherence, dosing regimens, concomitant medications or medication subclasses.

Elevated BMI and enzyme-inducing medications can impair sexual dysfunction via several mechanisms. Disruption in the hypothalamus-pituitary-ovarian/testicular axis could result from the underlying cause of epilepsy, interictal epileptiform discharges or seizures, or antiseizure or other medications. Epilepsy patients have alterations in sex hormone levels compared to the general population (Kuba et al., 2006; Morrell et al., 2005). Enzyme-inducing antiseizure medications affect sex hormone levels through induction of sex hormone binding globulin and increased sex hormone metabolism (Herzog et al., 2005; Luef and Madersbacher, 2015). However, while some hormone level disturbances may be attributed to enzyme-inducing medications, alterations in sex hormone levels may be unrelated to medication (Kuba et al., 2006).

In a recent study, men with epilepsy reported increased levels of anxiety, depression, and psychological distress with reduced quality of life, physical health, sexual desire, and erectile function, but none of these factors correlated with seizure frequency or bioactive testosterone levels (Duncan et al., 2009). Another study found no differences in testosterone levels in epilepsy patients compared to controls despite people with epilepsy reporting lower levels of sexual desire and increased erectile dysfunction (Talbot et al., 2008). In a multicenter study of women with epilepsy, there was no difference in the proportion of women able to achieve pregnancy among women with epilepsy compared to controls despite increased rates of sexual dysfunction in those with epilepsy (Pennell et al., 2018). Although our study did not investigate hormone levels, the finding that enzyme-inducing anti-seizure medications were associated with sexual dysfunction suggests this may have affected some patients. Sexual dysfunction in epilepsy patients is likely multifactorial, with contributions from intrinsic properties of the disease itself, psychosocial issues, epilepsy, and other (e.g., psychiatric and medical) treatments (Hamed et al., 2006; Devinsky, 2005; Rathore et al., 2019; Luef and Madersbacher, 2015; Atif et al., 2016; Bangar et al., 2016; Gutierrez et al., 2008; Harden, 2002, 2006; Harden, 2008; Luef, 2008).

Factors related to overall health such as body weight were associated with sexual dysfunction, supporting that sexual health is deeply related to overall physical health. While we did not study psychiatric or psychosocial comorbidities, these can contribute to sexual dysfunction in epilepsy patients (Harden, 2008). Given the multiple factors that may contribute to sexual dysfunction in epilepsy patients, a personalized approach to recognize and treat this problem is critical to providing care and maximizing quality of life.

There were several limitations to our study, including the disadvantage of allowing patients to independently answer questionnaires (e.g. respondents failing to understand a question or unintentionally selecting a response). However, respondents may be more candid with surveys rather than an in-person interview due to potential embarrassment. Another limitation was our use of a convenience sample of people admitted to an epilepsy monitoring unit at a single center. Therefore, we did not capture the full spectrum of people with epilepsy, including less severely affected subjects who do not require inpatient monitoring. Also, our participants had the time and motivation to complete a survey on sexual functioning, with a possible selection bias underestimating the issue by not including people less willing to participate or capable of completing an electronic survey for physical, cognitive, or disease-specific reasons (e.g., those who are embarrassed by their sexual dysfunction or affected by frequent seizures).

Additionally, the nature of our survey maintaining patient anonymity meant that objective data from the medical record could not be linked to individual patients, and therefore we relied on patients self-reporting of comorbidities such as being overweight or obese, or having depression, anxiety, or other health issues for the results of this

Table 3
Patient characteristics associated with sexual dysfunction.

	Sexual dysfunction		*Univariate*		*Multivariate*	
Variable	*Yes (N = 20)*	*No (N = 69)*	*p-value*	*OR (95 % CI)*	*p-value*	*OR (95 % CI)*
Sex (female)	15	31	**0.02**	**3.7 (1.2–11.1)**	0.14	2.5 (0.72–8.83)
Age ≥ 50	12	20	**0.01**	**3.7 (1.3–10)**	0.08	2.8 (0.88–9.18)
Higher education	19	57	0.17	0.25 (0.03–2.05)		
In a relationship	10	39	0.61	0.77 (0.28–2.09)		
Epilepsy tx > 5 years	15	44	0.35	0.59 (0.19–1.81)		
Depression/anxiety	10	28	0.45	0.68 (0.25–1.86)		
Overweight or obese	7	5	**<0.01**	**6.9 (1.9–25)**	**0.02**	**6.1 (1.4–26.5)**
CV risk	8	16	0.14	0.45 (0.16–1.3)		
Strong enzyme-inducing ASMs	5	3	**<0.01**	**7.4 (1.59–33.3)**	**0.02**	**7.8 (1.4–44.9)**
Opioid/stimulant use	4	9	0.44	0.6 (0.16–2.2)		

study. Although this design may have improved patient participation, it limited our ability to analyze these factors in-depth and to confirm the severity of epilepsy (such as with seizure frequency and severity), which will require further studies for clarification. Although the ASEX questionnaire has been validated across a wide spectrum of patient populations and clinical settings, though not specifically in patients with epilepsy (Elnazer and Baldwin, 2020). By using relationship status as a general category, we were also unable to identify whether any specific relationship types (such as marriage or domestic partnership) may have impacted sexual health. Furthermore, strong enzyme-inducing antiseizure medications are uncommon in current practice, suggesting either intractability or very chronic use of these drugs; either could negatively impact on sexual health. There were also only a small number of participants (8) taking these medications, which limits generalizability of these findings. The complexity of sexual well-being makes it a complex and challenging task to study with a survey. Although our sample size was limited and involved only one center, it supports and extends findings in earlier studies.

Despite the prevalence of sexual dysfunction in patients with epilepsy and importance of sexual health to quality of life, healthcare providers appear to neglect this topic in outpatient discussions (Kaufman et al., 2015). The majority of respondents in our study (66 %) did not recall being asked about sexual functioning within the past year by their physician or another healthcare professional. Whether related to stigma, clinician knowledge gaps, or intrinsic to healthcare system inadequacies (visit time restrictions, billing codes, electronic health records), sexual health is a critical but often overlooked topic of discussion. Improved communication between patients and their healthcare team is the most important step to increase recognition and treatment of sexual dysfunction in people with epilepsy (Bartlik et al., 2005; Fishman et al., 2006).

Declaration of Competing Interest

Asya Wallach has received fellowship support from the National Multiple Sclerosis Society, and consulting fees from Biogen. Daniel Friedman receives salary support for consulting and clinical trial related activities performed on behalf of The Epilepsy Study Consortium, a non-profit organization. Daniel Friedman receives no personal income for these activities. NYU receives a fixed amount from the Epilepsy Study Consortium towards Daniel Friedman's salary. Within the past two years, The Epilepsy Study Consortium received payments for research services performed by Daniel Friedman from: Axcella, Biogen, Cerevel, Crossject, Engage Pharmaceuticals, Eisai, Pfizer, SK Life Science, Xenon, and Zynerba. He has also served as a paid consultant for Eisai and Neurelis Pharmaceuticals. He has received travel support from Medtronics, Eisai and the Epilepsy Foundation. He has received research support from the CDC, NINDS, Epilepsy Foundation, Empatica, Epitel, UCB, Inc and Neuropace unrelated to this study. He serves on the scientific advisory board for Receptor Life Sciences. He holds equity interests in Neuroview Technology and Receptor Life Sciences. He received royalty income from Oxford University Press. Orrin Devinsky has equity interests in Qstate Biosciences, Tevard Biosciences, Regel Therapeutics and Script Biosciences, Privateer Holdings, Tilray, Receptor Life Sciences, Empatica, Engage, Egg Rock/Papa & Barkley, Rettco, SilverSpike, and California Cannabis Enterprises (CCE). Orrin Devinsky receives grant support from NINDS, NIMH, MURI, CDC and NSF. He is an investigator for PTC Therapeutics, Inc., Stoke Therapeutics, Marinus, Ovid and GW Pharmaceuticals. The other authors have no disclosures to report.

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