Sex matters – also in epilepsy

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  - Eisai
  - UCB

Sex matters - also in epilepsy

- Prevalence and characteristics of sexual dysfunction
- Pathogenic mechanisms
- Our studies
- Management of sexual dysfunction

The Embrace, Egon Schiele, 1917

… talking about sex

- Physicians and patients are often reluctant to discuss sexual health
- The further medical students had come in their education, the less likely they were to have considered talking about sexuality in practice
- Possible reasons are lack knowledge and expertise and fear of being perceived as intrusive or asking inappropriate questions
- Patients might accept sexual dysfunctions as a part of their disease

Kaufman KR et al. Epilepsy Behav 2015, Henning O et al. Epilepsy Behav 2016, Fischer N et al. Scandinavian Psychologist 2016, Dyer K et al. J Sex Med 2013

…meet Ole

- 47 years old
- Temporal lobe epilepsy
- MR: unremarkable EEG: interictal spikes right temporal
- Seizurefree for at least 4 years on CBZ (used for many years)
- Coincidently talking about getting old and “things are not like they used to be”
- Problems getting an erection “Probably due to my age”

…meet Kari

- 47 years old
- Sleeprelated hypermotor epilepsy (paroxysmal arousal)
- MR: possible FCD left frontal EEG: interictal spikes left precentral
- Good seizure control after using OXCB low dosage
- Coincidently talking: difficulties at home, lost all interest in sex
- Had difficult times and depression, but better now

Definition Sexual health, Sexual dysfunction

- "…a state of physical, emotional, mental and social well-being in relation to sexuality"
- "Sexual dysfunction is characterized by a disturbance in the process that characterizes the sexual response cycle (Desire, Excitement, Orgasm and Resolution) or by pain associated with sexual intercourse".
- The sexual problem must have been persistent or recurrent and associated with significant distress in the patient.

WHO. The world health organization. Sexual and reproductive health
DSM Diagnostic and statistic manual of mental disorders. 5th ed. Washington, DC: American Psychiatric Assosiation2013.

Sexual problems in the general population

- Ranging from
  - 10 % to 52 % in men
  - 25 % to 63 % in women
- The range reflects:
  - differences in definition of sexual problems
  - different study populations
  - different methods for assessing sexual problems
  - cultural differences regarding sexuality

Embraching Women, Egon Schiele, 1915

Heiman JR. J Sex Res 2002, Laumann EO et al.. Int J Impot Res 2005, Laumann EO et al.. Jama 1999, Shifren JL et al.. Obstet Gynecol 2008

Assessment of sexual function

- Various studies have used different rating scales
- Ideally a sexual dysfunction rating scale should be
  - simple, easy to administer
  - nonintrusive
  - measuring all domains of sexual functioning
  - applicable to people of all genders and sexual orientations
  - have good validity and reliability

Assessment of sexual function

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

TOME II. — N° 5 DÉCEMBRE 1954

ANNALES
MÉDICO-PSYCHOLOGIQUES

MÉMOIRES ORIGINAUX

ÉTUDE DU COMPORTEMENT SEXUEL CHEZ LES EPILEPTIQUES PSYCHOMOTEURS

PAR

HENRI GASTAUT et HENRI COLLOMB

Sexual problems in men with epilepsy

- The rate of sexual problems varies from 28% to 43%
- Controlled studies show an increase in rates of sexual problems by factor 1.54 – 8.91
- A population based study found an OR 1.83 for prior epilepsy in men with erectile dysfunction
- Nevertheless, one study found a lower rate of sexual problems in men with epilepsy than in controls (8% vs. 13%)

Braun M et al., Int J Impot Res 2000, Calabro RS et al.. Int J Neurosci 2013, Herzog AG et al., Neurology 2005, Jensen P et al. Arch Sex Behav 1990, Keller J et al. Sex Med 2012, Nikoobakht M et al., Urol J 2007, Reis RM et al., J Sex Med 2013, Svalheim S et al., Epilepsy Behav 2009.

Sexual problems in women with epilepsy

- The rate of sexual problems varies from 18% to 75%
- More descriptive studies reporting
  - Less open to psychosexual stimulation
  - Decreased rate of sexual activity (hypoactive)
- Controlled studies show an increased rates by factor 1.29 – 2.91
  - One study found no differences
- *Problems with: Desire (libido), excitement and lubrication.*
- *Less sexual problems in women with well controlled epilepsy using monotherapy*

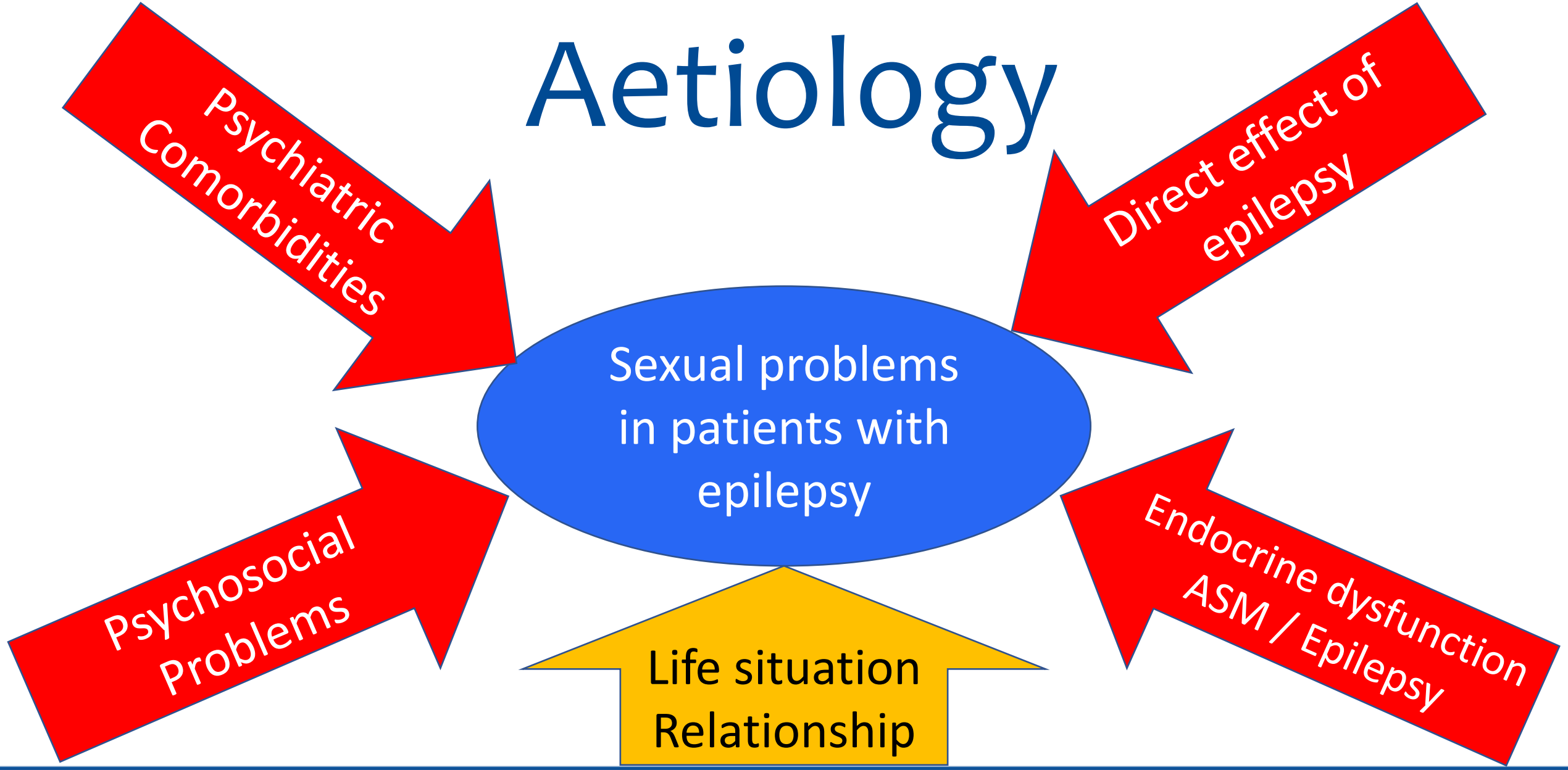
Atarodi-Kashani Z et al., Seizure 2017, Bergen D et al., Psychopathology 1992, Demerdash A et al., Epilepsia 1991, Duncan S et al., Epilepsia 1997, Jensen P et al., Arch Sex Behav 1990, Svalheim S et al., Epilepsy Behav 2009, Tao L et al., Epilepsy Behav 2018, Zelena V et al., Epileptic Disord 2007 and Epilepsy Behav 2011

Table III. Frequency and Symptoms of Sexual Dysfunction in 86 Epileptic Patients, 160 Insulin-Treated Diabetics, and 80 Healthy Controls

	Epileptics		Diabetics[a]		Controls[a]	
Dysfunction	*n*	%	*n*	%	*n*	%
Men	*n* = 38		*n* = 80		*n* = 40	
Erectile dysfunction	1	3	27	34	0	0
Inhibited sexual desire	1	3	25	31	1	3
Premature ejaculation	0	0	3	4	4	10
Retarded ejaculation	1	3	2	3	0	0
Total (at least one symptom)	3	8	35	44	5	13
Women	*n* = 48		*n* = 80		*n* = 40	
Inhibited sexual desire	9	19	19	24	9	23
Orgasmic dysfunction	9	19	9	11	3	8
General sexual dysfunction	1	2	6	8	0	0
Vaginismus	0	0	0	0	0	0
Total (at least one symptom)	14	29	22	28	10	25

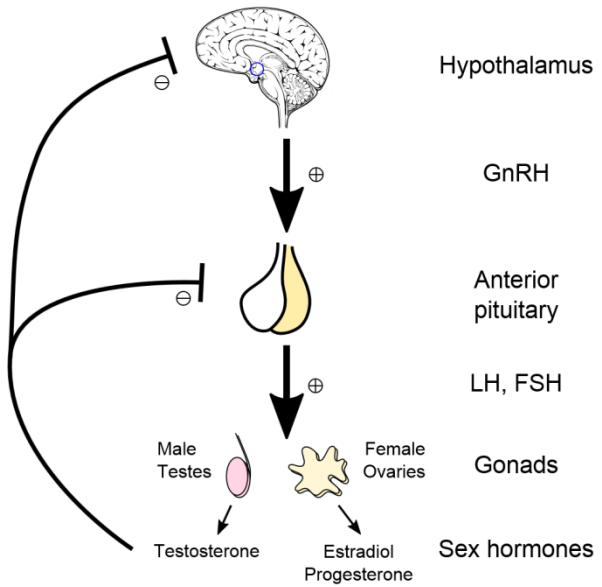
Jensen P, Jensen SB, Sorensen PS, et al., Arch Sex Behav 1990;19:1-14.

Aetiology


Psychiatric Comorbidities
Direct effect of epilepsy
Sexual problems in patients with epilepsy
Psychosocial Problems
Life situation Relationship
Endocrine dysfunction ASM / Epilepsy

Aetiology – direct effect of epilepsy

- Sexual dysfunctions usually begin after the onset of seizures and are present in untreated patients with epilepsy
- Patients with focal epilepsy are four times more likely to have sexual dysfunction as compared to those with primary generalized epilepsy
- Central mechanisms interfere with pituitary–hypothalamic functions? Epileptiform discharges propagating through amygdalo-hypothalamic pathway can interfere with pulsatile secretion of gonadotrophic hormones and dopamine. This in turn causes hypogonadism, hyperprolactinemia, and sexual dysfunction.



Bauer J et al. Neurology 2004, Shukla DG et al. Br J Psychiatry 1979, Herzog AG et al. Arch Neurol 1986,

Aetiology – direct effect of epilepsy

- Sexual dysfunction more common in patients with right temporal lobe epilepsy and with low levels of bioactive testosterone, independent of ASD usage
- MWE including those not on ASMs 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
- Serum androgen levels improve following surgery in seizure-free patients but remain low in non seizure-free patients regardless of ASM treatment

Herzog AG et al. Epilepsy Behav 2003, Bauer J et al. Neurology 2004, Bauer J et al. Neurology 2000,

Aetiology –effect of anti seizure medication

- ASMs, especially enzyme-inducing drugs, increase the levels of sex hormone binding globulin (SHBG) and thus reduce the levels of unbound active testosterone.
- EIASMs increase the hepatic metabolism of gonadal and adrenal sex steroids.
- EIASMs can induce aromatase converting testosterone to estradiol such inhibiting LH secretion contributing in a drop of testosterone levels
- ASMs with overall inhibitory effect on brain can suppress the pituitary–hypothalamic axis thus producing hypogonadotrophic hypogonadism.
- ASMs can also influence the sexual functions by their effect on serotoninergic pathways.

Calabrò RS et al. Expert Rev Neurother 2011, Atif M et al. Springerplus 2016, Luef et al. Handb Clin Neurol 2016, Herzog A et al. Neurology 2005

Aetiology –effect of anti seizure medication

Valproate	F,M: Androgens↑	F: Risk of PCOS↑ M: FSH↓				M: Fertility↓
Carbamazepine, Phenytoin	F,M: SHBG↑		F,M: DHEA↓	F: E↓	M: BAT↓	F,M: Fertility↓
Oxcarbazepine (>900 mg/d), Primidone, Phenobarbital	F,M: SHBG↑			F: E↓	M: BAT↓	F,M: Fertility↓
Levetiracetam, Lamotrigine Lacosamide						
F, female; M, male; SHBG, sex hormone-binding globulin; FSH, follicle-stimulating hormone; E, estradiol; DHEA, dehydroepiandrosterone; BAT, bioactive testosterone.						

Luef et al. Handb Clin Neurol 2016

Drug	Most common reported type of sexual dysfunction	How common?
Carbamazepine	Decreased libido, Erectile dysfunction, Orgasmic dysfunction	+++
Phenytoin, Phenobarbital, Primidone	Decreased libido, Erectile dysfunction	+++
Sodium valproate	Decreased libido, Erectile dysfunction, Increased libido	++ ++
Oxcarbazepine	Anorgasmia/anejaculation Improved sexual function (especially if switching from carbamazepine)	+ ++
Lamotrigine	Increased libido (especially in women switching to it from other antiepileptic drugs)	++
Levetiracetam	Improved sexual function (especially in women) Decreased libido (men only) and erectile dysfunction	++ +
Topiramate	Erectile dysfunction, Decreased libido, Orgasmic dysfunction	+
Pregabalin	Erectile dysfunction, Orgasmic dysfunction	+
Gabapentin	Orgasmic dysfunction	+
Zonisamide	Erectile dysfunction	+
Lacosamid	Erectile dysfunction, Decreased libido	+

Yogarajah M, THE COMORBIDITIES OF EPILEPSY, 2019

Aetiology –psychosocial problems

- Stigmatization, psychological distress, low self-esteem, and fear of rejection may lead to social isolation and feelings of inadequacy that contribute to sexual dysfunction.
- Patients reported low levels of satisfaction with sexual relationships, partly because they felt stigmatized by having epilepsy

Bishop M et al. Epilepsy Behav 2003, Baker GA e al. Epilepsia 1997

Aetiology –psychiatric comorbidity

- Psychiatric comorbidities can contribute to sexual dysfunction
- Sexual function correlated with levels of anxiety and depression and not with testosterone levels
- A bidirectional association between depression and sexual dysfunction has been confirmed

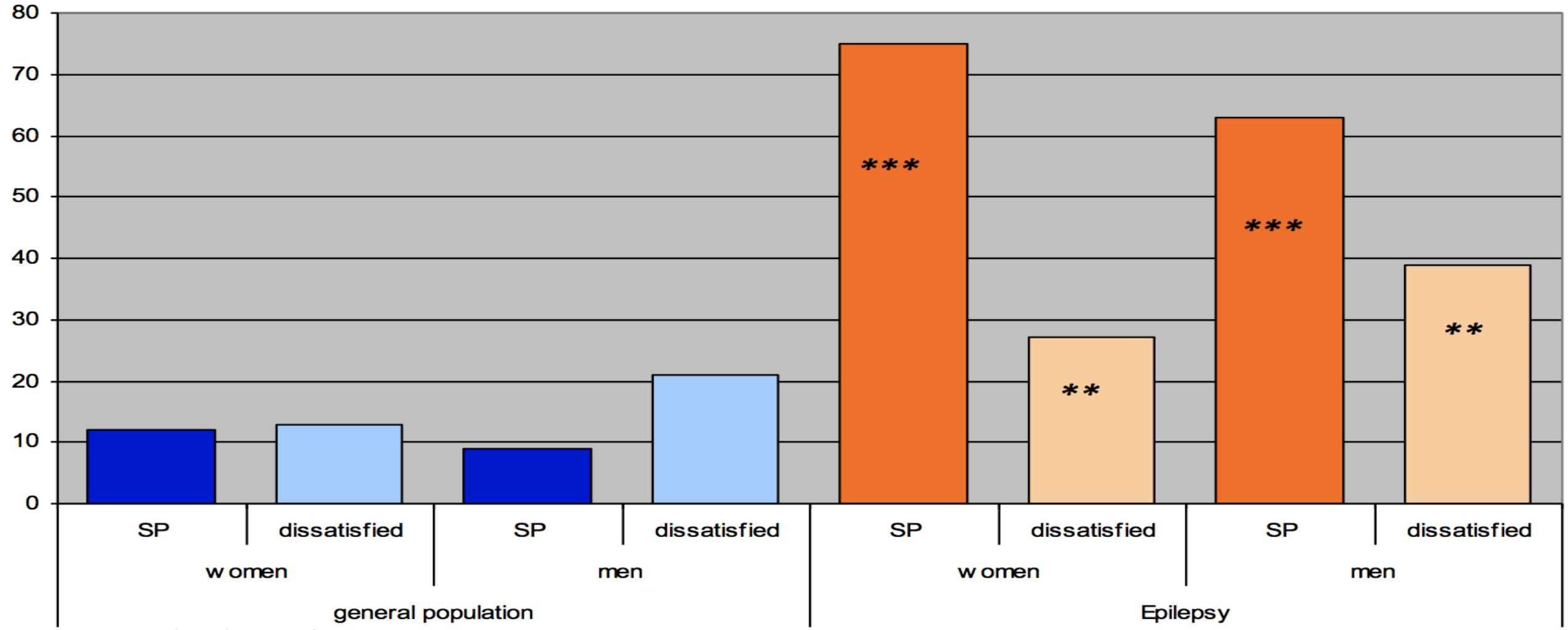
Morrell MJ et al. Epilepsy Behav 2005, Gilliam F et al. Epilepsy Behav 2003, Talbot JA et al. Neurology 2008, Atlantis E et al. J Sex Med 2012

Sexual problems in people with refractory epilepsy

- 171 consecutive adult inpatients and outpatients at the National Centre for Epilepsy in Norway
  - Focal epilepsy 126 (73.8%)
  - AED monotherapy 68 (39.8%)
  - 3 or more AEDs 22 (12.6%)
  - Use of enzyme-inducing ASMs 48 (28.0%)
  - BDI > 14 44 (25.7%)
- 594 adult Norwegians

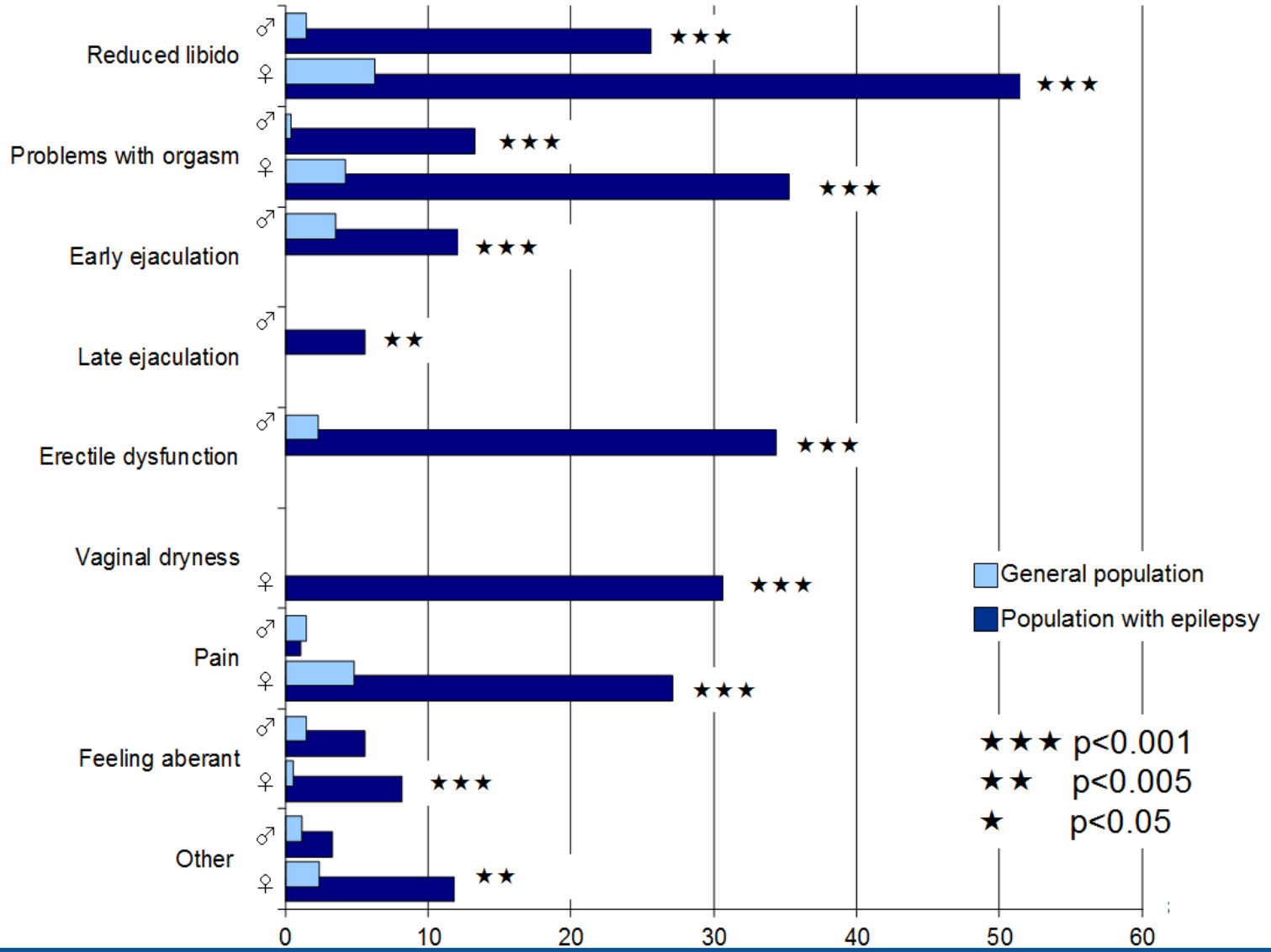
Henning O et al. Epilepsy Behav 2016

Sexual problems in people with refractory epilepsy



Henning O et al. Epilepsy Behav 2016

Type of sexual dysfunction



Sexual problems in people with refractory epilepsy

- Significant increase in lifetime or current SP
  - Patients scoring <66.25 on the overall QoL
  - Female patients scoring >14 on the BDI
- No significant associations
  - Types of epilepsy (focal vs. generalized)
  - Usage of enzyme-inducing ASMs
  - Usage of selective serotonin reuptake inhibitors (SSRI)
  - Being in a relationship vs. single

Henning O et al. Epilepsy Behav 2016

Sexual function in people with epilepsy: Similarities and differences with the general population

- 221 adult inpatients and outpatients, National Centre for Epilepsy
- 78 outpatients from a second line hospital
- 1671 adult Norwegians in the general population
- Perceived quality of life (QoL), seizure frequency, use of antiepileptic drugs (ASMs); CBZ, PB, DPH, PRM defined as enzyme-inducing ASMs
- Sexual problems, satisfaction with sex life, importance of sex in daily life, help-seeking behavior regarding sexual problems

Henning O et al. Epilepsia 2019

Sexual function in people with epilepsy: Similarities and differences with the general population

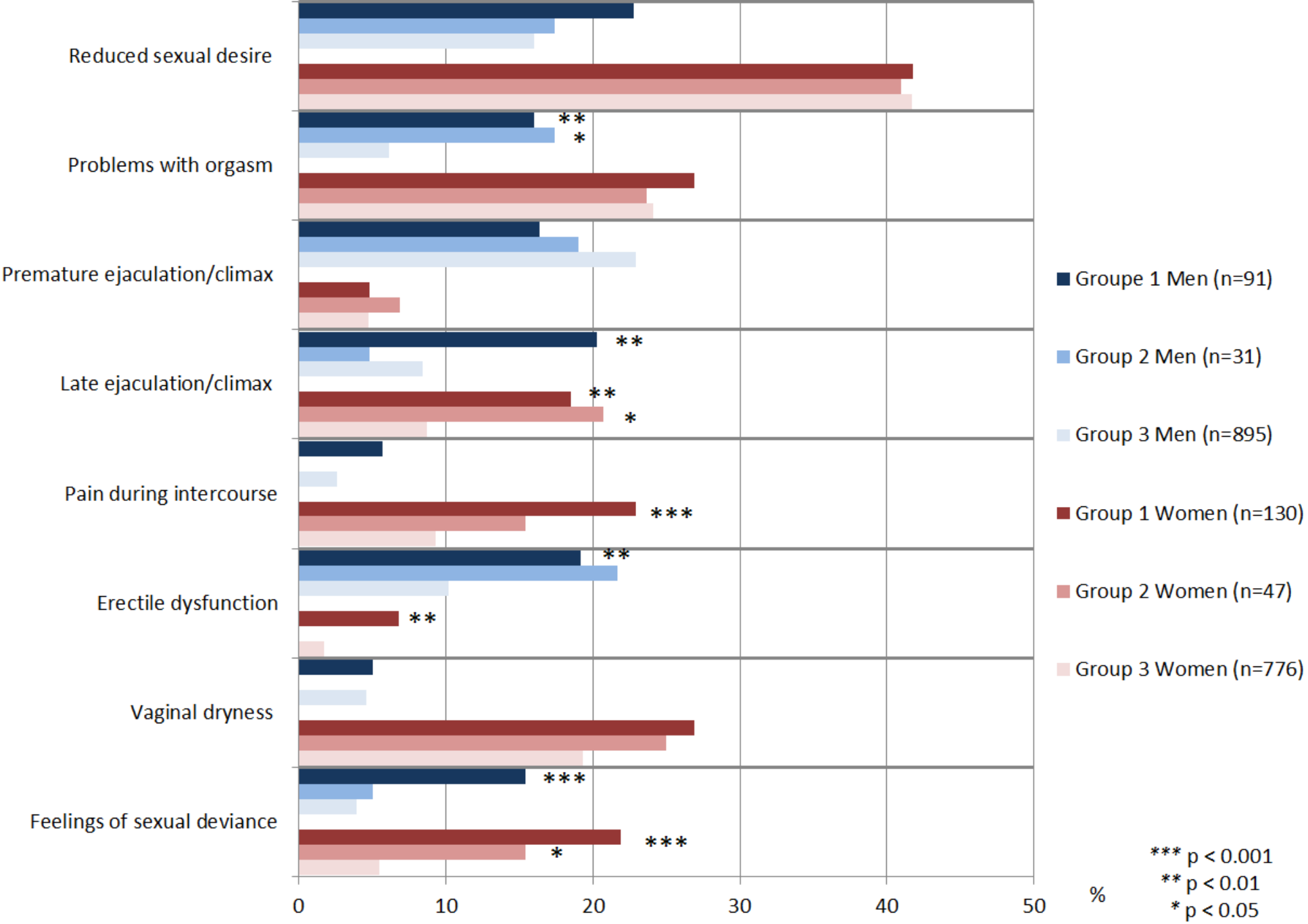
	National center (n = 221)	Second line hospital (n=78)	General population (n = 1671)
Gender Female n (%)	130 (58.8)	47 (60.3)	776 (46.4)
Age Mean (SD; min.-max.)	39.1 (13.5; 18-72)	43.3 (16.7; 18-77)	42.6 (12.2; 18-67)
Partnership Cohabitating or in a relationship, n (%)	142 (56.1)	54 (69.2)	1316 (78.8)
Have had intercourse n (%)	198 (90.8)	68 (93.2)	1620 (97.6)
Age of sexual debut Mean (SD; min.-max.)	17.7 (3.2; 12-36)	17.9 (3.4; 13-33)	18.0 (3.6; 7-65)

Henning O et al. Epilepsia 2019

Sexual function in people with epilepsy: Similarities and differences with the general population

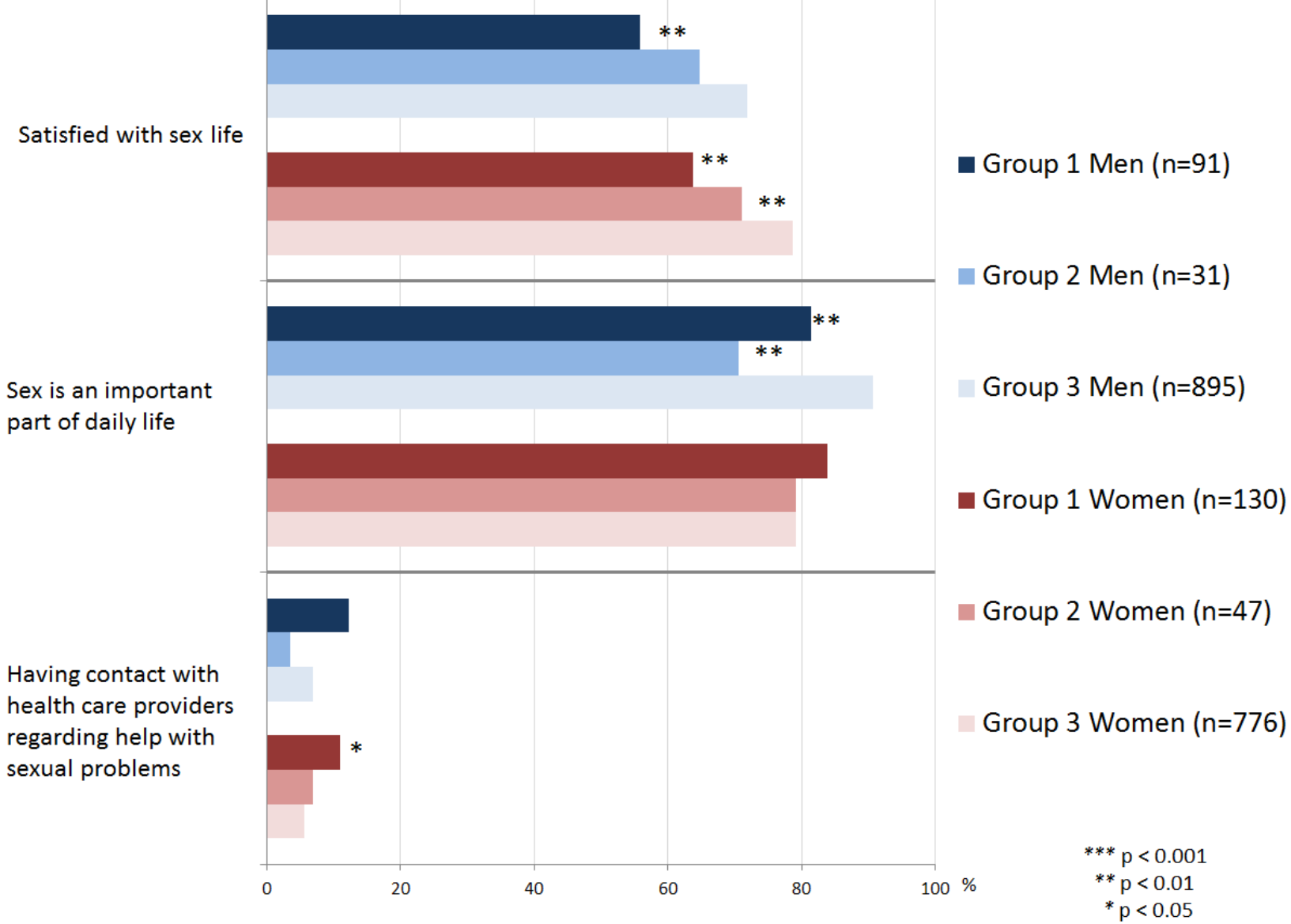
Epilepsy characteristics	Mostly refractory epilepsy patients (n = 221) n (%)	Well-controlled epilepsy patients (n=78) n (%)
Seizure-free during previous 12 months	51 (24.5)***	42 (60.0)
Enzyme inducingASMs	30 (13.6)	13 (16.7)
NDDI-E <15	156 (73.2)	55 (82.1)
AEP >44	77 (42.5)	19 (30.3)
QoL over mean (6.7)	104 (49.5)*	46 (63.9)

Henning O et al. Epilepsia 2019



Henning O et al. Epilepsia 2019

Group 1: mostly refractory epilepsy, Group 2: well-controlled epilepsy, Group 3: General population



Henning O et al. Epilepsia 2019

Group 1: mostly refractory epilepsy, Group 2: well-controlled epilepsy, Group 3: General population

Sexual problems in people with refractory epilepsy

- Reduced sexual desire in women with epilepsy
  - over the mean age (OR 2.744, CI 1.308-5.757; P = .008)
  - NDDI-E score over 14 (OR 3.904, CI 1.692-9.009; P = .001)
- Reduced sexual desire in men with epilepsy
  - QoL under mean (OR 3.484, CI 1.161-10.417; P = .026)
  - being in a relationship (OR 3.791, CI 1.018-13.586; P = .047)
- No significant associations
  - Being seizure-free during the previous 12 months
  - use of enzyme-inducing ASMs
  - use of lamotrigine, levetiracetam, or valproate
  - a high burden of adverse events (AEP > 44)
  - level of education

Henning O et al. Epilepsia 2019

Sexual problems affecting quality of life (n=1182)

Characteristics	
Age (years) Mean (SD)	41.8 (14.92)
Male gender n (%)	372 (31.5)
In a relationship n (%)	697 (59.0)
Seizure-free throughout the previous year n (%)	479 (40.6)

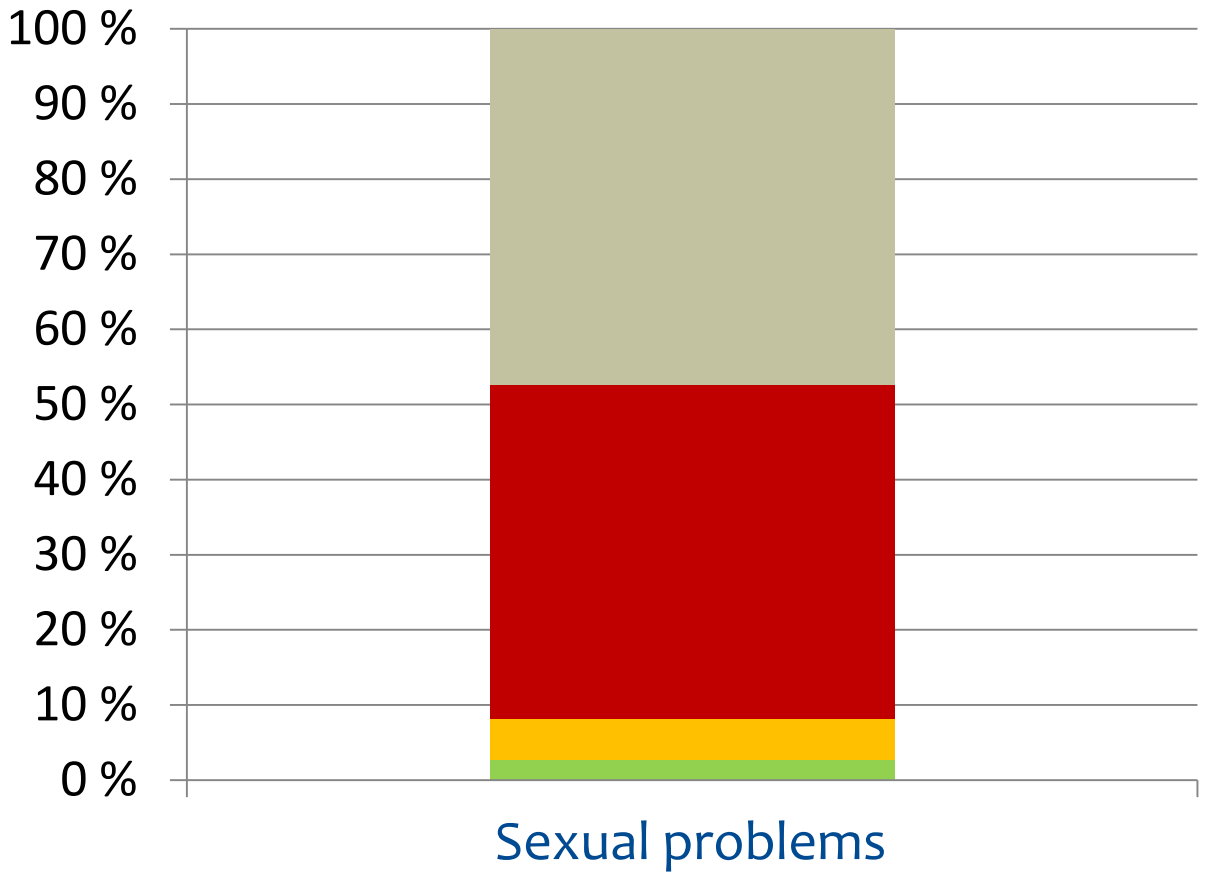
	Female	Male
Not at all	47.7%	42.7%
To a lesser degree	22.0%	24.4%
somewhat	19.1%	23.0%
To a considerable degree	11.2%	10.0%

70%

30%

Henning O et al., Acta Neurol Scand. 2019

Asking for help from health professionals



Data on file

Management – sexual dysfunction in epilepsy

- Sexual dysfunction is increased in both men and women with epilepsy
- The nature of this problem is multifactorial
- There are no guidelines or expert consensus statement on the management of sexual dysfunction in patients with epilepsy
- But there are some general principles of management

Management – sexual dysfunction in epilepsy

- Be open to talk about, if possible screen for sexual problems/dysfunction
- Questionnaires for assessing sexual dysfunction can be useful
- When starting or changing ASM treatment be aware that sexual problems/dysfunction can occur
  - preexisting sexual dysfunction, depression, or anxiety are risk factors
- The problem is multifactorial
  - thorough medication history, sexual/relationship history, and screening for anxiety and depression
- Besides ASM other classes of drugs can cause sexual side effects, including antidepressants, neuroleptics, sedatives, and beta-blockers
- Neurological but also general and urogenital examination
  - erectile dysfunction can be the first manifestation of cardiovascular disease.

Rathore C et al., Epilepsy Behav 2019, Yogarajah M THE COMORBIDITIES OF EPILEPSY, 2019, Yogarajah M et al. Curr Pharm 2017

Management – sexual dysfunction in epilepsy

- Blood tests: metabolic and endocrinological screen, including serum levels of testosterone, SHBG, DHEAS, E2, LH, FSH, prolactin, and thyroid function.
- Consider alternative ASM
- Consider Phosphodiesterase type 5 inhibitors (PDE5 inhibitors) (caution!)
- Consider paroxetine for premature ejaculation
- Consider referral to specialist (Gynecology, Sexual medicine)
- Consider testosterone supplements in patients with low testosterone levels

Rathore C et al., Epilepsy Behav 2019, Yogarajah M THE COMORBIDITIES OF EPILEPSY, 2019, Yogarajah M et al. Curr Pharm 2017

…meet Ole

- Possibly related to use of CBZ
- Changed from CBZ to LEV
- Improved sexual functioning

Lossius MI et al. Epilepsia 2007

…meet Kari

- Had started on SSRI because of depression
- Good effect but lost all interest in sex
- Stopped SSRI, in case of worsening of affective symptoms recommended cognitive behavioral therapy
- Restitution of libido

Take home message

- Sexual problems are increased in patients with epilepsy and are correlated to a reduced quality of life
- Both physicians and patients are often reluctant to discuss sexual health
- Causes are multifactorial
  - epilepsy itself, ASMs, and psychosocial factors
- Management is multifactorial/multidiciplinary

Friendship, Egon Schiele, 1913