Sexual Dysfunction Related to Psychotropic Drugs: A Critical Review. Part III: Mood Stabilizers and Anxiolytic Drugs

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Abstract

Introduction: Sexual dysfunction is a potential side effect of mood stabilizers and anxiolytic drugs: this article presents a critical review of the current literature. Although many studies have been published on sexual side effects of psychopharmacological treatment, only a minority relate to mood stabilizers and anxiolytic drugs. Most of these studies are not methodologically robust, few are RCTs and most did not use a validated rating scale to evaluate sexual functioning. In addition, many of the studies on sexual dysfunction associated with mood stabilizers and anxiolytic drugs are limited by other methodological flaws. While there is evidence to suggest that mood stabilizers, with some exceptions, negatively affect sexual functioning, there is still insufficient evidence to draw any clear conclusions about the effects of anxiolytic drugs on sexual function. There is some weak evidence to indicate that switching from enzyme-inducing to non-enzyme-inducing anticonvulsant drugs, could be clinically useful. Some researchers recommend that sexual dysfunction in patients taking antiepileptic drugs should in general be treated according to standard guidelines for the management of sexual dysfunction, since reliable data on special populations is not available. However, specific approaches may be useful, but cannot yet be recommended until further validating research has been conducted. We did not find evidence supporting the use of any specific treatment strategy for sexual dysfunction associated with anxiolytic treatment.

Methods: This study was conducted in 2013 using the paper and electronic resources of the library of the Azienda Provinciale per i Servizi Sanitari (APSS) in Trento, Italy (http://atoz.ebsco.com/Titles/2793). The library has access to a wide range of databases including DYNAMED, MEDLINE Full Text, CINAHL Plus Full Text, The Cochrane Library, Micromedex healthcare series, BMJ Clinical Evidence. The full list of available journals can be viewed at http://atoz.ebsco.com/Titles/2793, or at the APSS web site (http://www.apss.tn.it). In completing this review, a literature search was conducted using the key words "anxiolytic drugs", "mood stabilizers", "benzodiazepines", "psychotrophic drugs", "sexual dysfunction", "sexual side effects", "treatment-emergent sexual dysfunction". All resulting listed articles were reviewed.

Discussion: This review includes studies that investigated the relationship between mood stabilizer and anxiolytic drug treatment and sexual dysfunction. The purpose was to identify possible intervention strategies for sexual dysfunction related to these drugs.

Introduction: Sexual Dysfunction Induced by Mood Stabilizers

In recent years some studies have reported a relationship between mood stabilizers and sexual dysfunction [1–6]. However, these studies have similar methodological weaknesses to studies on sexual dysfunction caused by other drug groups [7]. A particular problem is the failure to adopt a standard definition for sexual dysfunction (such as those specified in ICD-10, DSM-IV-TR and currently in DSM-V) or to use validated rating scales for assessing sexual dysfunction.

In addition to these methodological problems, it is worth noting that many studies on sexual dysfunction induced by anticonvulsant drugs have been carried out on epileptic patients, while others have been conducted on non-epileptic patients.

It is difficult to interpret the data from studies examining sexual dysfunction in patients with epilepsy given the effect of the disease itself on

Table 1 Main conclusions of the studies that have investigated the relationship between epilepsy, sexual dysfunction (SD) and anticonvulsant drugs.

1. There is a wide range of reported sexual problems in patients (both male and female) with epilepsy: SD is more common in men. There is poor consensus regarding the prevalence of SD in males: a recent review found a prevalence that ranged between 3 and 80% [15]. In contrast, in women with epilepsy, the prevalence of SD ranged between 20 and 30% [16, 17].
2. The aetiology of SD in patients with epilepsy is multifactorial: in addition to various psychological and social factors (low self-esteem, comorbid mood disorders such as depression, anxiety, fear of rejection by partner), other important factors co-exist, such as an altered blood hormone profile (usually reduction of bioactive testosterone) as well as the negative effect of seizures (especially in temporal lobe epilepsy) and interictal epileptiform discharges on brain areas that regulate the sexual functions of desire, arousal and orgasm [18–20].
3. A high correlation between SD and sexual hormones has been reported in men [21–29]. Mölleken et al. [26] report that "quality of sex life" in men, seems to be adversely affected by endocrine factors including, blood levels of total testosterone (TT), follicle-stimulation hormone (FSH), SHBG (sex hormone-binding globulin), dehydroepiandrosterone sulfate (DHEAS), estradiol (E2), prolactin (PRL) and luteinizing hormone (LH). These authors suggest that biological endocrine factors may have a greater influence on the "quality of sexual life" in men, whereas in women sexual problems may be more associated with psychological factors.
4. Some studies [30–35] have shown that endocrine alterations induced by anticonvulsant drugs had clinical manifestations such as "polycystic ovary syndrome" and "abnormal sperm": these studies, however, did not search for a (possible) correlation with sexual dysfunction.
5. In general, women with epilepsy are more likely to experience low levels of sexual desire with dyspareunia, vaginismus and inadequate lubrication [16–18, 36–40], while men are more likely to report problems of erectile dysfunction and ejaculatory disorders [22, 24, 31, 41–43].
6. Anticonvulsant drugs have a negative effect on sexual function: the traditional anticonvulsants (barbiturates, phenytoin, carbamazepine and valproate) tend to have the highest percentage of sexual side effects compared to newer anticonvulsant drugs, probably because the latter do not seem to significantly change the hormonal balance. However, this observation should be interpreted with great caution, in order to avoid attributing sexual disorder to drug therapy alone [22, 44].

sexuality [2]. In the pioneering studies of Gastaut and Collomb [8], sexual dysfunction was identified in epileptic patients who were not taking antiepileptic drugs. The difficulty of distinguishing whether sexual dysfunction is a product of the disease itself or whether it is related to drug treatment of the disease has been described by other early researchers [9–11].

Several studies have documented alterations of sex hormones in epileptic patients during treatment with antiepileptic drugs: these changes appear to be reversible after withdrawal of these drugs [12–14].

In **Table 1** we have summarized the main conclusions of the studies that have investigated the relationship between epilepsy, sexual dysfunction and anticonvulsant drugs (many of which are also used as mood stabilizers).

Sexual dysfunction has in particular been reported with the use of the old anticonvulsants, i. e., carbamazepine, phenytoin and phenobarbital [15, 38, 45–47]. In fact, it has been suggested that these drugs may cause sexual dysfunction by reducing blood levels of free testosterone: the results of a study by Herzog et al. [22] seem to confirm this finding (particularly for carbamazepine) which has also been identified in previous studies. Circulating testosterone is highly bound to a specific transport protein (SHBG: sex hormone binding globulin), whose production is increased by drugs such as carbamazepine, that induce hepatic metabolism. The increase in plasma concentrations of SHBG results in a decrease in levels of free testosterone, partly contributing to hypogonadism [33].

In an observational, open-label study, that lacked a control group, 673 adult male patients with partial epilepsy who were prescribed oxcarbazepine monotherapy, were questioned about their sexual function at baseline and after 12 weeks of treatment. 228 patients (33.9%) complained of pre-existing sexual dysfunction prior to treatment: among whom 181 patients (79.4%) reported an improvement in sexual function after 3 months of treatment with oxcarbazepine and 23 patients (10.1%) experienced no sexual impairment at the final 12 week visit [48].

In contrast to the findings of this study, some case reports of dose-dependent oxcarbazepine-related anorgasmia and retrograde ejaculation have been published [49–51]. The pathophysiology underlying oxcarbazepine-induced anorgasmia is not fully understood.

Severely decreased libido and anorgasmia have been reported in woman treated with valproate for bipolar disorder [47]. The authors hypothesised that this dysfunction may be related to increased serotonergic transmission, frequently associated with the use of selective serotonin reuptake inhibitors (SSRIs) [47].

There are reports of endocrine disorders (possibly related to the presence of ovarian cysts in women, and reduced testicular volume in men), among those taking valproate [31]. The relationships between endocrine disorders and valproate are outlined in **Table 2**. A case report of retrograde ejaculation during treatment with valproate has also been described [52, 53].

Case reports of anorgasmia have been described with gabapentin in both men and women [54–56]. Kaufmann et al. [57] in addition to anorgasmia, also reported anejaculation, decreased desire and erectile dysfunction in a case report of a man taking gabapentin at a total daily dose of only 300 mg. Similar findings were reported by Labbate [58].

Calabrò [59] suggests that gabapentin-induced SD is most likely secondary to a central inhibitory effect on neurotransmission: the inhibition of calcium currents induced by gabapentin could lead to a decrease in neurotransmitter release and attenuation of postsynaptic excitability. However, we did not find evidence to support this hypothesis.

Lamotrigine does not seem to cause any alteration to SHBG levels, probably due to the fact that it does not cause hepatic enzyme induction: sexual activity in the group of patients treated with lamotrigine was found to be comparable to that of controls [21, 22]; in addition the sexual function scores, BAT (bioactive testosterone) and BAE (bioactive estradiol) levels, hormone ratios (BAT/BAE,) and gonadal efficiency (BAT/luteinizing hormone) were greater in the lamotrigine group compared to the carbamazepine and the phenytoin-treated groups [21, 22].

An improvement in sexual function was also reported in 3 case reports on men prescribed lamotrigine [60].

In an open-label, observational trial on 141 patients, lamotrigine was reported to be associated with improved sexual function in both men and women [44]. Patients were assessed using the "changes in sexual functioning questionnaire (CSFQ)". In women who commenced treatment with lamotrigine, a significant improvement was observed in both the total CSFQ score and in each of the five dimensions of the scale (desire/frequency,

Table 2 Antiepileptic drugs most frequently used as mood stabilizers: relationship between sexual dysfunction and effects on hepatic microsomal enzymes (CYP = cytocrome P-450; UGT = UDP-glucuronosyltransferase). Data from: Anderson [64], Andreasen et al. [65], Basson et al. [66], Shorvon [67], Spina et al. [68], Stimmel et al. [6], Verrotti et al. [69]. Changes in hormone levels could lead to sexual dysfunction induced by CBZ, OXCZ and VPA. Other less understood mechanisms are probably involved in sexual dysfunction induced by LTG, gabapentin and pregabalin.

Carbamazapine (CBZ)*	hepatic enzyme-inducing anticonvulsant drug (CYP1A2, CYP2C, CYP3A, UGTs)	non-inhibitor anticonvulsant drug
Oxcarbazepine (OXCZ)**	hepatic enzyme-inducing anticonvulsant drug (CYP3A4, UGTs)	hepatic enzyme-inhibiting anticonvulsant drug (CYP2C19)
Valproate (VPA)***	non-inducer anticonvulsant drug	hepatic enzyme-inhibiting anticonvulsant drug (CYP2C9, UGTs, epoxide hydrolase)
Lamotrigine (LTG)****	hepatic enzyme-inducing anticonvulsant drug (UGTs)	non-inhibitor anticonvulsant drug
Gabapentin*****	non-inducer anticonvulsant drug	non-inhibitor anticonvulsant drug
Pregabalin******	-	-
Enzyme-inducing anticonvulsant drugs (carbamazapine*, oxcarbazepine**):		
I. increase hepatic synthesis of sex hormone-binding globulin (SHBG), which reduces testosterone availability. Oxcarbazepine** is a much weaker enzyme inducer compared to carbamazepine: in the study by Andreasen et al. [65] the hepatic enzyme inducing effect of CBZ was about 46 % higher than that of OXCZ.		
II. increase the metabolism of sex hormones, including exogenous contraceptive hormones.		
III. Carbamazapine* is most often associated with sexual dysfunction [6].		
IV. The study by Herzog [22] supports the hypothesis that enzyme-inducing anticonvulsant drugs can impair sexual function [70].		
Enzyme-inhibiting anticonvulsant drug: valproate (VPA)***		
VPA can increase testosterone as well as estrogen levels [34, 70]. Decreased sexual desire and anorgasmia have been reported in some case reports on women treated with valproate for bipolar disorder. In some studies valproate has been associated with an increased incidence of menstrual disorders, polycystic ovarian syndrome and hyperandrogenism (with high serum testosterone concentrations) in women with epilepsy [30, 31]. However, in the study by De Vries et al. [71], long-term treatment with VPA in girls with epilepsy was associated with increased testosterone levels after menarche, and not with clinical hyperandrogenism or polycystic ovary syndrome. For a detailed discussion on this topic, the reader should refer to a recent critical review [69]. Valproate*** seems to reduce SHBG [66].		
Lamotrigine**** does not seem to have negative effects on sexuality [6, 20–22, 44, 60, 61]		
Gabapentin***** case reports of anorgasmia, decreased desire and erectile dysfunction have been described [54–58].		
Pregabalin****** does not bind to plasma proteins and has virtually no hepatic metabolism since 98 % of this drug is excreted unchanged in the urine [15]. Some case reports of erectile dysfunction, anorgasmia and delayed ejaculation during treatment with pregabalin have been described [62, 63].		

desire/interest, pleasure, arousal/excitement and orgasm). In men, a significant improvement was observed only in the pleasure dimension.

Two case reports of "hypersexuality" have been reported during treatment with lamotrigine, however the mechanism is unclear [61].

Some case reports of erectile dysfunction, anorgasmia and delayed ejaculation during treatment with pregabalin have been described [62, 63].

The aetiology of sexual dysfunction associated with anticonvulsant drugs is unclear: changes to sex hormone levels induced by anticonvulsants may be a possible cause, however, other mechanisms similar to those described for antidepressant drugs cannot be excluded, for example, mechanisms involving the numerous central and peripheral neurotransmitters (especially serotonin, dopamine, acetylcholine, norepinephrine) and vasodilatory substances (such as nitric oxide, which plays a key role in increased blood flow in the genitals) which can influence the phases of the sexual response cycle (desire, arousal and orgasm). We have summarized the main research findings on the relationship between SD and anticonvulsants used as mood stabilizers in **Table 2**.

In this section of the review we have dealt with anticonvulsants used as mood stabilizers and have not addressed anticonvulsants prescribed for non-pyschiatric disorders (e.g., phenytoin, topiramate) for which the reader may refer to the review by Calabrò [15].

In comparison to other psychotrophic drugs, there has been very little investigation on the sexual side effects induced by lithium. There have been reported cases of decreased sexual desire and erectile dysfunction in patients prescribed lithium [71, 72]. Lithium monotherapy was not associated with sexual dysfunction in a retrospective, non randomized study involving 104 patients with bipolar disorder, however, combined treatment with lithium and benzodiazepines was found to cause significantly higher rates of sexual dysfunction compared to lithium monotherapy [74]. Labbate [3] commenting on the findings of this study added that, if benzodiazepines cause sexual problems, it remains unclear if this effect is independent of lithium or due to a combined effect of benzodiazepine and lithium.

In a small open-label study of 35 bipolar and schizoaffective male patients prescribed only lithium, 11 patients (31.4 %) reported sexual dysfunction on at least 2 items of the sexual function questionnaire. Nevertheless, almost all patients reported preserved pleasure during sexual activity and were satisfied with their sexual performance: the authors concluded that the level of sexual dysfunction was not a source of distress to patients and did not lead to non-compliance [75].

Zuncheddu et al. [76] conducted a study on 51 bipolar patients on lithium monotherapy and compared them to a control group of 176 healthy subjects, using a questionnaire (self administered) designed by the researchers themselves. The questionnaire consisted of 6 items investigating: presence of sexual intercourse activity, "sexual pleasure", "sexual satisfaction", frequency of sexual intercourse, sexual fantasies and "desires".

Researchers found that patients taking lithium had significantly lower scores on all of the questionnaire items compared to controls, and concluded that lithium has a negative effect on sexual desire and sexual arousal. Unfortunately, the authors did not provide any data on the reliability, validity or sensitivity of the questionnaire used by them for assessing treatment-emergent sexual dysfunction: this may limit the conclusions of this study.

Sexual Dysfunction Induced by Anxiolytic Drugs

The research investigating the sexual side effects of benzodiazepines is weak. Our search of the current literature revealed mainly case reports and retrospective studies. Benzodiazepine use has been reported as being associated with *decreased sexual desire,* delay in reaching orgasm and erectile dysfunction [77–84]. Conversely, some case reports have described increased sexual desire with lorazepam [85] and "sexual disinhibition" [86,87] during treatment with clonazepam.

Recently, a multicenter comparative and double blind randomized study, was conducted in Argentina on 190 outpatients affected by panic disorder and on treatment with alprazolam (sublingual and oral formulations). The Arizona sexual experience scale (ASEX) was used for assessing sexual dysfunction. The authors found that the ASEX scores did not show statistically significant differences before and after treatment with alprazolam, inferring that alprazolam does not affect the sexual sphere [88].

Despite the findings of this study, the available evidence on benzodiazepines and their effect on sexual dysfunction is still insufficient to draw any definitive conclusions [89].

A possible positive effect on sexual function was observed with buspirone used as an augmentation treatment for sexual side effects caused by SSRIs (selective serotonin reuptake inhibitors). Buspirone is an anxiolytic drug and is a serotonin (5HT1A) partial agonist and also a partial alpha-noradrenergic antagonist [1]: at doses above 30 mg per day, buspirone appears to reverse sexual dysfunction caused by SSRIs [90–92]. However, this finding has not been consistently replicated [5].

Discussion and Conclusions

This review has highlighted the multifactorial aetiology of sexual dysfunction induced by anticonvulsants. As we have already pointed out, many studies have been conducted only on patients prescribed anticonvulsants for epilepsy, while just a few have been conducted on patients prescribed anticonvulants for psychiatric disorders. Furthermore, most of the patients in these studies were prescribed polytherapy, which makes it difficult to differentiate the specific effect of a particular drug on sexual function.

There is some evidence to suggest a correlation between an alteration of sex hormone levels induced by mood stabilizers and sexual dysfunction, therefore it is worth evaluating a patient's sexual hormonal profile before and during treatment. However, it should also be noted that some changes to hormonal levels may not be related to mood stabilizer drug treatment: for example, Herzog et al. [22] found that 20% of men with focalized epilepsy taking no anticonvulsant drugs have abnormally low sexual function. Therefore, caution is warranted before attributing an aetiological role to drug treatment alone, which may negatively influence a patient's attitude to treatment and lead to poor treatment compliance.

Sexual dysfunction induced by mood stabilizers may be dose dependent: therefore, where appropriate, dose reduction may improve sexual function. In patients treated with lithium, continuing the same treatment dose for a period of 2–3 months, may lead to a spontaneous remission of sexual dysfunction [89].

Doctors and patients should not underestimate the importance and the clinical benefits of conducting a thorough clinical assessment, which in many cases may result in the identification of effective treatments and the resulting improvement of symptoms. Heightened awareness of drug-induced sexual dysfunction by physicians and patient education, should be encouraged [6,93]. Furthermore, due to the multifactorial nature of sexual dysfunction, in most cases improvement of symptoms can be obtained by a using a multidisciplinary assessment and treatment approach involving where appropriate a psychiatrist, urologist, gynecologist, neurologist, or endocrinologist [6,24,93].

There is some weak evidence to indicate that CBZ may be more associated with sexual dysfunction, especially in comparison to lamotrigine. However, these findings, are not sufficiently robust to recommend switching to any particular mood stabilizer. In a recent study, Gutierrez et al. [45] concluded that switching from enzyme-inducing to non-enzyme-inducing anticonvulsant drugs such as valproate or lamotrigine, may be clinically appropriate.

Stimmel et al. [6] recommend that sexual dysfunction in patients taking antiepileptic drugs should in general be treated according to standard guidelines for the management of sexual disorders, since reliable data on special populations is not available. However, specific approaches (such as the use of testosterone in combination with aromatase inhibitors) may be useful, but cannot yet be recommended before conducting further confirmatory investigations on this topic. The same authors also suggest that the use of PDE-5 inhibitors to treat erectile dysfunction in patients taking anticonvulsant drugs may lead to some treatment benefits, however, no prospective trials on this drugs' efficacy or safety have been conducted in this patient population. Similar treatment conclusions are reached by Calabrò et al. [15]. We did not find evidence supporting any specific treatment strategy for sexual dysfunction occurring during treatment with anxiolytics.

In conclusion, no specific recommended treatment strategies have been identified for the management of sexual side effects induced by either mood stabilizers or anxiolytic drugs.

Further studies that use specific rating scales such as ASEX, FSFI, IIEF, CSFQ [94–97], are needed: failure to use such assessment questionnaires, reduces the detection of sexual dysfunction, and the probability of accurately diagnosing the specific type of sexual dysfunction involved (e.g., disorders of sexual desire, arousal, or orgasm), as well as preventing an objective monitoring of symptom improvement or worsening during the course of drug treatment.

Further studies are also needed to clarify the exact mechanisms underlying sexual dysfunction induced by mood stabilizers [98]. Future research should also be conducted on the newer antiepileptic drugs, such as leviracetam and topiramate, which are not usually prescribed for psychiatric disorders, and which in some case reports have been described as being associated with "hypersexuality" or "loss of libido", erectile dysfunction and anorgasmia [99–101].

In our opinion, large prospective, double-blind and placebo-controlled studies are warranted to help delineate the phenomenology, the dose relationship, the role of gender differences and the comorbid conditions involved in mood stabilizer-induced sexual dysfunction.

Conflict of Interest

The authors declare no conflicts of interest.

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