

## Short report

## Lamotrigine-induced sexual dysfunction and non-adherence: case analysis with literature review†

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**Background**

Optimal anti-epileptic drug (AED) treatment maximises therapeutic response and minimises adverse effects (AEs). Key to therapeutic AED treatment is adherence. Non-adherence is often related to severity of AEs. Frequently, patients do not spontaneously report, and clinicians do not specifically query, critical AEs that lead to non-adherence, including sexual dysfunction. Sexual dysfunction prevalence in patients with epilepsy ranges from 40 to 70%, often related to AEDs, epilepsy or mood states. This case reports lamotrigine-induced sexual dysfunction leading to periodic non-adherence.

**Aims**

To report lamotrigine-induced sexual dysfunction leading to periodic lamotrigine non-adherence in the context of multiple comorbidities and concurrent antidepressant and antihypertensive pharmacotherapy.

**Method**

Case analysis with PubMed literature review.

**Results**

A 56-year-old male patient with major depression, panic disorder without agoraphobia and post-traumatic stress disorder was well-controlled with escitalopram 20 mg bid, mirtazapine 22.5 mg qhs and alprazolam 1 mg tid prn. Comorbid conditions included complex partial seizures, psychogenic non-epileptic seizures (PNES), hypertension, gastroesophageal reflux disease and hydrocephalus with

patent ventriculoperitoneal shunt that were effectively treated with lamotrigine 100 mg tid, enalapril 20 mg qam and lansoprazole 30 mg qam. He acknowledged non-adherence with lamotrigine secondary to sexual dysfunction. With lamotrigine 300 mg total daily dose, he described no libido with impotence/anejaculation/anorgasmia. When off lamotrigine for 48 h, he described becoming libidinous with decreased erectile dysfunction but persistent anejaculation/anorgasmia. When off lamotrigine for 72 h to maximise sexual functioning, he developed auras. Family confirmed patient's consistent monthly non-adherence for 2–3 days during the past year.

**Conclusions**

Sexual dysfunction is a key AE leading to AED non-adherence. This case describes dose-dependent lamotrigine-induced sexual dysfunction with episodic non-adherence for 12 months. Patient/clinician education regarding AED-induced sexual dysfunction is warranted as are routine sexual histories to ensure adherence.

**Declaration of interest**

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Optimal anti-epileptic drug (AED) treatments for persons with epilepsy (PWE) and psychotropic treatments for persons with mood disorders maximise therapeutic response and minimise adverse effects (AEs).<sup>1,2</sup> The key to successful pharmacotherapies, whether AEDs or psychotropics, remains medicine adherence. The degree of non-adherence is often underappreciated both by patients and clinicians.<sup>3,4</sup> One review of treatment adherence in bipolar patients extracted from a VA database ( $N=44,637$ ) noted that only 54.1% of all patients were fully adherent.<sup>5</sup> A recent UK primary care study of PWE ( $n=398$ ) found that 36.7% had low adherence,<sup>4</sup> which is consistent with a US study addressing elderly PWE with data extracted from the Integrated Health Care Information Services Managed Care Benchmark Database ( $N=1278$ ) that reported a 40.7% non-adherence rate.<sup>6</sup>

In light of the degree of non-adherence and the associated negative effect on acute and long-term treatment outcomes for PWE and persons with mood disorders, especially when considering the direct and indirect costs of these illnesses to society,<sup>6–9</sup> research has focused on potential predictive and risk factors. Specific significant predictive and risk factor associations for medication adherence and non-adherence have been reported with, but not limited to, ethnicity, socioeconomics, education, culture, stigma, age, illness

status/duration, comorbid substance use disorders, understanding illness process, perceptions related to medication and AEs.<sup>4,5,10–13</sup>

AE severity is a critical determinant of non-adherence that can be readily addressed during meaningful clinical interactions wherein dosing, alternative pharmacotherapy or even treatment for a specific AE can be considered. Frequently, PWE and persons with mood disorders do not spontaneously report and clinicians do not specifically query critical AEs that lead to non-adherence, including sexual dysfunction.<sup>14–17</sup> Sexual functioning is an important marker of quality of life. Sexual dysfunction prevalence in PWE ranges from 40 to 70%, often related to the AEDs, epilepsy, hormonal status or mood states.<sup>18,19</sup> Similarly, sexual dysfunction prevalence in patients with mood disorders ranges from 25 to 80% with attribution to psychotropics, mood state and hormonal status.<sup>16,20–22</sup>

This case reports lamotrigine-induced sexual dysfunction leading to periodic lamotrigine non-adherence in the context of multiple comorbidities and concurrent antidepressant and antihypertensive pharmacotherapy.

**Method**

Case analysis with PubMed literature review was employed. Search terms utilised in the PubMed literature review included but were

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not limited to: (1) sexual dysfunction (expanded to all forms of sexual dysfunction – decreased libido, lack of libido, erectile dysfunction, impotence, ejaculatory inhibition, anejaculation, delayed orgasm, anorgasmia, priapism, premature ejaculation, retrograde ejaculation and hypersexuality); (2) general aetiologies (from general reviews this was expanded to reviews addressing neurologic disorders, hypertension, cardiovascular disease, hormonal disorders, psychiatric and substance use disorders, medication and psychotropics); (3) specific aetiologies by patient's psychiatric diagnoses (mood disorders, anxiety disorders, major depression, panic disorder and post-traumatic stress disorder (PTSD)); (4) specific aetiologies by the patient's medical diagnoses (epilepsy, complex partial seizures, psychogenic non-epileptic seizures (PNES), hypertension, gastroesophageal reflux disease (GERD) and hydrocephalus); (5) specific aetiologies by the patient's psychotropics (antidepressants, selective serotonin reuptake inhibitors (SSRIs), escitalopram, mirtazapine, anxiolytics, benzodiazepines and alprazolam); (6) specific aetiologies by the patient's pharmacotherapy utilised for medical conditions (anticonvulsants, AEDs, lamotrigine, antihypertensive agents, angiotensin converting enzyme (ACE) inhibitors, enalapril, proton pump inhibitors (PPIs) and lansoprazole); (7) lamotrigine and drug interactions; (8) adherence (therapeutic drug monitoring (TDM), discontinuation syndrome and reporting of AEs) and (9) probability rating scale.

## Results

A 56-year-old male patient with major depression, panic disorder without agoraphobia, and PTSD was well-controlled with escitalopram 20 mg bid, mirtazapine 22.5 mg qhs and alprazolam 1 mg tid prn. Comorbid medical conditions included complex partial seizures, PNES, hypertension, GERD and hydrocephalus with patent ventriculoperitoneal shunt that were effectively treated with lamotrigine 100 mg tid, enalapril 20 mg qam and lansoprazole 30 mg qam.

The patient did not spontaneously report sexual dysfunction; however, he acknowledged such on direct questioning. He desired to maintain his current rational polypharmacy as opposed to potential alternative psychotropics or dose reductions as he focused on his stable psychiatric status. Further, he emphasised adherence to his entire medication regimen, which had remained unchanged over an extended time period.

When an issue arose regarding an inappropriately delayed lamotrigine script refill, the patient was confronted with apparent lamotrigine non-adherence and the potential need to reinstitute lamotrigine titration to avoid Stevens–Johnson syndrome. Only then did he acknowledge non-adherence with lamotrigine secondary to sexual dysfunction. Specifically, with lamotrigine 300 mg total daily dose, he described total sexual dysfunction with lack of libido, impotence, anejaculation and anorgasmia.

When off lamotrigine for 48 h, he described becoming libidinous with difficult intercourse secondary to erectile dysfunction and persistent anejaculation/anorgasmia. When off lamotrigine for 72 h to maximise sexual functioning (decreased erectile dysfunction but persistent anejaculation/anorgasmia), he developed auras without sexual content. His family confirmed the patient's consistent monthly non-adherence for 2–3 days during the past year. Though the treating psychiatrist warned the patient that this non-adherence posed the risk of further seizures and even depressive decompensation, he admitted continuing this periodic non-adherence until instructed to cease by his wife.

## Discussion

Male sexual dysfunction has multiple presentations (decreased libido, lack of libido, erectile dysfunction, impotence, ejaculatory inhibition, anejaculation, delayed orgasm, anorgasmia, priapism, premature ejaculation and retrograde ejaculation)<sup>23,24</sup> with multiple reported aetiologies (medical conditions including, but not limited to, neurologic disorders, hypertension, cardiovascular disease and hormonal disorders; psychiatric disorders including, but not limited to mood, anxiety, trauma-related and substance use disorders; and pharmacotherapies).<sup>16,18–30</sup> This unique case permits discussion of these issues in the context of the patient's comorbid conditions and pharmacotherapies from which a determination of probable aetiology for this patient's lack of libido can be ascertained.<sup>31</sup>

First, the patient had three psychiatric diagnoses: major depression, panic disorder and PTSD. Depression is clearly associated with sexual dysfunction, and decreased libido is a cardinal symptom during a major depressive episode (MDE).<sup>20</sup> Erectile dysfunction is associated with both untreated non-MDE depression<sup>32</sup> and untreated MDE depression.<sup>33</sup> Further, ejaculatory delay has been reported in untreated MDE depression.<sup>33</sup> Though there is literature supporting the interrelationship between anxiety and sexual dysfunction,<sup>24,34</sup> there is limited research addressing panic disorder in men with associated sexual dysfunction with findings suggesting that panic disorder has a small effect after controlling for comorbid conditions and pharmacotherapies.<sup>35</sup> Male military veterans with PTSD have a marked increased prevalence of sexual dysfunctions (including decreased libido, erectile dysfunction and orgasmic difficulties) with recent research addressing the joint neuroendocrine underpinnings of sexual dysfunctions and PTSD.<sup>29,36</sup>

Second, the patient had five comorbid medical diagnoses: complex partial seizures, PNES, hypertension, GERD and hydrocephalus. Significant literature, including animal and pre/post-epilepsy neurosurgery studies, supports increased prevalence of multiple sexual dysfunctions (especially decreased libido, as well as erectile dysfunction and orgasm disturbances) in PWE ranging from 40 to 70% with an emphasis on limbic discharges (complex partial seizures), hormonal status and seizure frequency though these factors are confounded by AED treatment and comorbid mood disorders.<sup>18,19,37,38</sup> In addition to decreased sexual functioning in PWE, sexual auras and ictal hypersexuality have been reported.<sup>39,40</sup> Though prevalence rates for physical and sexual abuse associated with PNES is well-researched,<sup>41,42</sup> there are no prevalence rates reported for sexual dysfunction in patients with PNES. Hypertension has negative effects on vascular function and structure resulting in significant sexual dysfunction (erectile dysfunction and impotence in men) with: (1) approximately two-fold increased prevalence when comparing hypertensive patients with normotensive individuals<sup>26,43</sup> and (2) large epidemiologic studies revealing increased relative risk range for developing erectile dysfunction in hypertension of 1.3–6.9.<sup>43</sup> Sexual dysfunction has been reported with GERD; specifically, untreated patients with GERD have an increased difficulty in obtaining orgasm when compared with healthy individuals.<sup>44</sup> Chronic hydrocephalus may be associated with sexual dysfunction (decreased libido, erectile dysfunction and decreased ejaculation), which in one study markedly improved following shunt placement.<sup>45</sup>

Third, the patient was treated with three psychotropics (escitalopram, mirtazapine and alprazolam), which all have reported treatment-emergent sexual dysfunction. SSRIs, including escitalopram, negatively impact all spheres of sexual functioning in men (libido, erection, ejaculation and orgasm); SSRIs as a class of antidepressants have a significantly increased prevalence of total sexual dysfunction ranging from 25 to 80% of treated patients (escitalopram 37%).<sup>16,46</sup> In a prospective study comparing sexual dysfunction

among 10 antidepressants, mirtazapine had a prevalence rate of 24.5% involving all spheres; however, the prevalence rate and severity of symptoms were less when compared to SSRIs.<sup>47</sup> Though there are limited studies addressing benzodiazepines and alprazolam in particular, one retrospective audit of male veteran PTSD patients treated with benzodiazepines noted significant sexual dysfunction (erectile dysfunction) only with clonazepam, whereas one report of two patients receiving alprazolam in a double-blind protocol noted dose-dependent decreased libido, erectile dysfunction, anejaculation and anorgasmia.<sup>48,49</sup>

Fourth, the patient was also treated with three additional medical condition pharmacotherapies (lamotrigine, enalapril and lansoprazole) which all may be associated with changes in sexual functioning. Lamotrigine, a sodium channel inhibitor with antiglutamatergic properties, is an AED with FDA approval for monotherapy treatment of partial seizures and is used to treat multiple psychiatric disorders including mood disorders.<sup>50</sup> Hepatic cytochrome P450 enzyme inducing AEDs, and even some non-enzyme inducing AEDs, have well-reported multiple sexual dysfunction presentations (decreased libido, erectile dysfunction, impotence, delayed ejaculation, anejaculation and anorgasmia).<sup>19,22,23,51</sup> Lamotrigine does not have enzyme inducing properties and monotherapy lamotrigine treatment was noted to have minimal sexual effects in men but improvement in all spheres in women.<sup>52,53</sup> This finding was supported by a further study comparing Arizona Sexual Experience Scale (ASEX) scores among different AEDs and healthy controls noting improvement in ASEX scores in women but not men treated with lamotrigine.<sup>54</sup> Further, one report of three male patients with epilepsy on AEDs with sexual dysfunction noted improvement in sexual functioning with the addition of lamotrigine;<sup>55</sup> however all three cases were confounded by the discontinuation of gabapentin which has been reported to cause total loss of libido, impotence, anorgasmia and anejaculation at 300 mg total daily dose.<sup>23</sup> Patients receiving antihypertensive agents have an increased prevalence of sexual dysfunction compared with untreated patients with hypertension;<sup>43</sup> however, this depends both on the class of antihypertensive agent utilised and the generation within that class.<sup>56–58</sup> Enalapril is an ACE inhibitor antihypertensive agent; ACE inhibitors are noted to have minimally negative or neutral effect on sexual functioning.<sup>56,57,59</sup> Lansoprazole is a PPI without published reports of sexual dysfunction; however, its potential for causing sexual dysfunction must be considered for it induces testosterone metabolism<sup>60</sup> and omeprazole, another PPI, is associated with decreased libido, erectile dysfunction and impotence.<sup>61,62</sup>

Fifth, key to determining the aetiology of an AE is a time-line incorporating all diagnostic conditions and pharmacotherapies. In this case, all medical and psychiatric conditions had prolonged stability suggesting that these were not immediate factors in the patient's decreased libido. With regard to pharmacotherapies, only lamotrigine was changed with an on/off/on/off protocol determined by the patient's monthly non-adherence. When off lamotrigine for 48 h, he went from no libido to being libidinous. The degree to which the patient's being off lamotrigine for an additional day improved his erectile dysfunction, he describes improved though still difficult sexual performance (decreased erectile dysfunction but persistent anejaculation/anorgasmia), is unclear. Since multiple medical conditions and pharmacotherapies could cause erectile dysfunction, anejaculation and anorgasmia individually or in combination as described above, the determination of probability by the Naranjo Scale will be limited to lamotrigine and lack of libido. By the Naranjo Scale (a 10-item weighted adverse drug effect scale which is used to determine the probability of such AE being definite, probable, possible or doubtful),<sup>31</sup> the decreased libido adverse drug effect is scored as probable.

This report presents lamotrigine-induced decreased libido as a probable treatment-emergent adverse drug effect. The mechanism for such is unknown. Potentially, there may exist pharmacokinetic or pharmacodynamic interactions;<sup>63</sup> however, such interactions impacting sexual functioning and lamotrigine have not been reported. Nonetheless, to better address potential mechanisms, time-sensitive TDM of all pharmacotherapies with sexual hormones would be of benefit.

This case has multiple limitations. (1) As a case report ( $N=1$ ), the findings cannot be generalised. (2) No sexual psychometric scale was used to judge degree of sexual dysfunction on lamotrigine and during the periods of lamotrigine non-adherence. (3) No hormone levels were obtained to verify whether concomitant monthly hormonal variations occurred with lamotrigine non-adherence and increased libido. (4) No electroencephalograms (EEGs) were performed during the periods of lamotrigine non-adherence though the patient denied any sexual content to his auras. (5) Lamotrigine concentration-dependent decreased libido could not be determined in the absence of routine lamotrigine TDM. The patient acknowledged that he was non-adherent with ordered lamotrigine TDM, to a large extent because the insurance mandated laboratory was inconvenient. (6) TDM monitoring and daily pill counts were not obtained to ensure that the patient was adherent with all other medications negatively impacting sexual functioning as such additional non-adherence would have confounded the purported impact of lamotrigine non-adherence. Though possible, this was unlikely for 48–72 h psychotropic non-adherence (escitalopram and/or mirtazapine) would have resulted in discontinuation syndrome symptoms (rebound depression, anxiety, confusion, etc.), which the patient denied. This patient had been advised regarding the significance of non-adherence – for his AED, potential recurrent seizures; and for his psychotropics, potential discontinuation syndrome requiring psychiatric hospitalisation. When queried regarding this point, the patient emphasised his desire to avoid any psychiatric decompensation, but did acknowledge his willingness to even develop auras with lamotrigine non-adherence to permit increased sexual functioning. (7) Though an on/off/on/off case design based on patient's recurrent non-adherence, for ethical reasons the patient could not be requested to redo such non-adherence with additional testing.

Sexual dysfunction is a key AE leading to AED non-adherence which is often not volunteered by the patient. This case describes dose-dependent lamotrigine-induced sexual dysfunction with episodic non-adherence for 12 months. Patient/clinician education regarding AED-induced sexual dysfunction is warranted, as are routine sexual histories to ensure adherence, and optimal treatment.

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