Lamotrigine induced priapism in children: case analysis and literature review

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Abstract
Lamotrigine is an antiepileptic drug that can be used to control many types of seizures as a single-agent or an add-on therapy in patients over 2 years of age. In addition to common adverse reactions, this current case report describes a paediatric male patient with a rare side-effect of persistent penile erectile due to lamotrigine. Previous studies have shown that it can improve sexual function in adult male patients. This patient suffered from refractory epilepsy and pneumonia. He had taken a variety of antiepileptic drugs for a long time and developed priapism after the dosage of lamotrigine had been increased. The priapism improved after drug withdrawal and sedation. Further research is needed to elucidate the mechanism of this rare side-effect.

Keywords
Lamotrigine, priapism, children, case report

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Introduction
Lamotrigine is a broad-spectrum antiepileptic drug (AED) that is effective in controlling many types of seizures except severe myoclonic epilepsy in infancy.1 It can improve cognitive function and learning ability.2 It is commonly used as a single-agent or as an add-on therapy in patients over 2 years old.3,4 Common side-effects of lamotrigine include rash, Stevens–Johnson 1Department of Pharmacy, The First Affiliated Hospital of Air Force Medical University, Xian, Shaanxi Province, China
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syndrome, blurred vision, diplopia and diz-
ness. There have been five case reports of
hypersexuality associated with lamotrigine
in adult men. This current case report
describes priapism in a paediatric patient
induced by lamotrigine.

Case report

In April 2021, an 11-year-old male patient
presented to the Department of Pharmacy,
The First Affiliated Hospital of Air
Force Medical University, Xian, Shaanxi
Province, China with cough and fever.
The patient was diagnosed with epilepsy
3 years previously and then his motor
and language function regressed for
1 year. Hypoxic–ischaemic encephalopathy
was diagnosed after birth and suspected
mucopolysaccharidosis (MPS) when he
was 5 years old. There were no typical
symptoms of MPS during this current hos-
pitalization. The previous medical records
could not be provided by the guardian
and the previous treatment was not clear.
There was insufficient evidence to diagnose
MPS, so genetic testing was recommended.
Recurrent respiratory infections that lasted
for 6 months were frequent. Epilepsy was
diagnosed when the patient was 8 years of
age. The patient presented with different
types of symptoms during his epileptic sei-
Zures: loss of consciousness, binocular gaze,
head-nodding and hand tremor. Sometimes
a state of continuous seizures lasted up to
20 min. Currently, the patient cannot speak
or walk alone.

Prior to the current hospital admission, the
patient had received long-term therapy
for refractory epilepsy with 0.5 g levetirace-
tam oral twice a day, 100 mg lamotrigine
oral twice a day, 50 mg zonisamide oral
twice a day, 50 mg topiramate oral twice a
day and 0.5 mg clonazepam oral twice a
day, but the convulsive seizures still
occurred 3–4 times a day. These seizures
took a variety of forms comprising
binocular gaze and limb stiffness, lasted a
few seconds or minutes, and the electroen-
cephalograph was abnormal, so he was
transferred to the paediatric intensive care
unit for further treatment.

The child suffered from refractory epilep-
sy (suspected Lennox-Gastaut Syndrome)
and pneumonia. He was administered
AEDs and anti-infective agents (cefatriaxone
and azithromycin as described below) at the
same time. He was experiencing at least 3–4
convulsive seizures per day, so his lamotri-
gine dose was increased 150 mg oral twice a
day for 4 days and 2 mg perampanel oral
once a day for 4 days was added on day 5
of hospitalization. He also received 1.7 g
cefatriaxone intravenous drip once a day
for 9 days and 0.3 g azithromycin oral once
da day for 2 days. Four days later, the patient
developed a persistent penile erection. The
published literature on adverse reactions to
lamotrigine and perampanel were reviewed.
It was confirmed that the priapism could be
attributable to lamotrigine according to the
Naranjo Scale. As a consequence, lamotri-
gine was discontinued but other treatments
remained unchanged. The penile erection
lasted for approximately 20 h.

The maximum recommended dose of
lamotrigine is 200 mg in children aged
2–11 years when using it with other drugs
that do not significantly inhibit or induce its
glucuronidation. The dosage of this child
was increased to 300 mg lamotrigine per
day. When priapism occurred, the child was
intermittently given drug withdrawal, treated
with midazolam for sedation and the symp-
toms were relieved. The determination of
drug concentration would have been useful,
but unfortunately it was not undertaken. For
ongoing long-term treatment, 100 mg lamo-
trigine once a day was added back to the
AED regimen and there was no recurrence
of priapism at 1 month follow-up.

The case report received approval for
publication from the Ethics Committee of
The First Affiliated Hospital of Air Force
Medical University, Xian, Shaanxi Province, China (no. KY20222245). Verbal consent was obtained from the patient’s guardian for publication of this case report. All patient details have been de-identified. The reporting of this study conformed to CARE guidelines.9

Discussion

As part of a review of the adverse effects of lamotrigine, the PubMed® and EMBASE databases were searched using the following words: sexual dysfunction, decreased libido, lack of libido, erectile dysfunction, impotence, ejaculatory inhibition, anejaculation, delayed orgasm, anorgasmia, priapism, premature ejaculation, retrograde ejaculatory and hypersexuality. Evidence suggests that lamotrigine improved sexual function in adult male patients.6,7

It is generally believed that sexual dysfunction is very common in patients with epilepsy. The aetiological basis of sexual dysfunction is likely to be multifactorial such as the epilepsy itself, the AEDs and psychosocial factors. A review published in 2017 focused on the role of AEDs in sexual function.10 Most of the AEDs cause sexual dysfunction, but a few can increase libido, which might be associated with their effects on reproductive hormones (testosterone/oestradiol).11,12 This current child was being treated with six AEDs, none of which was expected to lead to a high incidence of sexual dysfunction, such as might be observed with carbamazepine, phenytoin, phenobarbital and sodium valproate.10 There have been some reports about the effects on sexual function in both men and women of the AEDs used in this current patient. For example, levetiracetam has no effect on hormones and its effect on sexual function remains controversial, but it may improve sexual function or decreased libido in men.10 Zonisamide and topiramate were reported to cause erectile dysfunction in case reports of male patients.10 Clonazepam is used as an add-on therapy for adults and children with refractory focal onset or generalized onset epileptic seizures.13 Its common adverse events included sexual dysfunction.14 Perampanel has been approved as an effective and safe drug for the treatment of adults and adolescents with drug-resistant epilepsy and there have been no adverse reactions related to sexual function based on post-marketing surveillance.15,16 Lamotrigine has been primarily reported to improve sexual function, particularly in women.17,18 Little information exists on its effects on sexual function in men. Table 1 presents the key information from three reports that describe the effects of lamotrigine on sexual function in six adult male patients.6,7,19

A previous report described three men treated with lamotrigine for epilepsy.6 A 48-year-old patient that was taking phenobarbital and gabapentin complained of decreased potency and anorgasmia; after the dosage of gabapentin was reduced and lamotrigine was added, anorgasmia improved.6 The second 48-year-old patient complained of impotence while applying different treatment strategies with taking phenytoin and carbamazepine or phenobarbital, valproate and gabapentin.6 After gabapentin was replaced with lamotrigine, impotence improved.6 The third 62-year-old patient was treated with five AEDs and complained of long-standing impotence.6 This was gradually resolved within a few months after lamotrigine was substituted for gabapentin.6 A second report described two patients with epilepsy treated with lamotrigine.7 A 55-year-old patient that had not had sexual intercourse for 7 years started having obsessive thoughts about sexual activity and experienced several erections a day while taking lamotrigine.7 After masturbating several times a day, he found these symptoms hard to accept and
Table 1. Major characteristics of case reports describing the effects of lamotrigine on sexual function in seven male patients.

| Author             | Dosage of lamotrigine | Diseases                                      | Age, years | Combination drug therapy                                                                 | Effect on sexual function                                                                 |
|--------------------|-----------------------|-----------------------------------------------|------------|------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| Current case       | 150 mg twice a day    | Epilepsy, pneumonia                           | 11         | Levetiracetam, zonisamide, topiramate, clonazepam, perampanel, ceftriaxone, azithromycin | Persistent penile erection for 20 h                                                        |
|                    | (300 mg daily)        |                                               |            |                                                                                          |                                                                                            |
| Husain et al. 20006| 500 mg daily          | Epilepsy                                      | 48         | Phenobarbital, gabapentin, clonazepam                                                    | Improved potency and orgasm twice a week                                                 |
|                    | 800 mg daily          | Epilepsy                                      | 48         | Phenytoin                                                                                 | Sexually active 3–4 times a month                                                          |
|                    | –                     | Complex partial seizures                      | 62         | Phenytoin, phenobarbital, carbamazepine, valproate                                        | Impotence gradually resolved                                                              |
| Grabowska-Grzyb et al. 20067 | 50 mg twice a day (100 mg daily) | Temporal lobe epilepsy                        | 55         | Carbamazepine                                                                            | Obsessive thoughts about sexual activity, several erections a day, masturbated several times a day |
|                    | 100 mg daily          | Frontal lobe epilepsy, interictal depression  | 50         | Oxcarbazepine                                                                             | Sex drive improved, several erections per day, improved sex life                          |
|                    |                       | (social disability, permanent anxiety, insomnia) |            |                                                                                          |                                                                                            |
| Kaufman et al. 2017 | 300 mg daily          | Depression, panic disorder, post-traumatic    | 56         | Escitalopram, mirtazapine, alprazolam, enalapril, lansoprazole                             | Became libidinous with decreased erectile dysfunction but persistent anejaculation/ anorgasmia when off lamotrigine for 48 h |
|                    |                       | stress disorder, epilepsy, hypertension,      |            |                                                                                          |                                                                                            |
|                    |                       | gastro-oesophageal reflux disease, hydrocephalus |            |                                                                                          |                                                                                            |
lamotrigine was discontinued. Another 50-year-old patient whose frequency of sexual intercourse had been once every 6 months found an improvement in his sex drive and experienced several erections per day after receiving lamotrigine, so finding this pleasant he continued to use lamotrigine to improve his sex life. The sixth patient was a 56-year-old man that reported that he became libidinous with decreased erectile dysfunction but persistent anejaculation/anorgasmia when he came off lamotrigine for 48 h. As this appears to be the opposite effect, it is thought that it might have been a withdrawal reaction. All of above cases occurred in adult males, whereas this current case report presents an adolescent boy that developed a persistent penile erection. It appears to be a short-term adverse reaction that might have negative consequences in some patients. Researchers found that priapism in children for more than 24 h may cause permanent injury, so it deserves more attention.

The current case was taking six AEDs and antibiotics at the same time. A previous report summarized the interactions between AEDs and between AEDs and other drugs. There have been no reports of ceftriaxone interacting with AEDs. Macrolides such as erythromycin might interact with AEDs, especially carbamazepine. There were no interactions found with azithromycin. Topiramate (≥200 mg/day) and perampanel (≥8 mg/day) have weaker enzyme-inducing properties. Topiramate in combination with zonisamide might increase the risk of kidney stones and metabolic acidosis, as well as impaired cognition. The dosage of drugs in this current case was below the interaction limit and the child had no other symptoms. A study in children with intractable epilepsy found the plasma concentration of clonazepam was reduced when lamotrigine was introduced. The limitation of this current case report was the absence of routine therapeutic drug monitoring of these AEDs, especially lamotrigine. Levetiracetam does not affect plasma concentrations of other AEDs in children with epilepsy. The increase in the dose of lamotrigine in the current patient was rapid (increased to 300 mg lamotrigine per day), which might have had an impact on priapism.

Research shows that priapism, a prolonged penile erection lasting >4 h, is a rare condition in children. Ischaemic priapism is the commonest type and is typically painful, so an assessment should be undertaken as a matter of urgency to avoid permanent cavernosal structural damage. Non-ischaemic priapism may be treated less urgently. Sickle cell disease (65%) is the commonest cause of priapism in children, with drugs accounting for only 5%. Drugs known to be involved include phosphodiesterease-5 inhibitors, hormones, anti-psychotics, anti-depressants, anti-hypertensives, erythropoietin, anaesthetics, alcohol, cocaine and marijuana. This current child had an abnormal erection of the penis but did not complain of pain. No other complications occurred and sedation was effective in the current case. The discomfort disappeared when lamotrigine was stopped and midazolam was injected. There was no recurrence during follow-up. This adverse reaction induced by lamotrigine has not been reported before in children.

In conclusion, this current case report described an adolescent male patient with a persistent penile erection caused by lamotrigine after an increase in dose. In contrast to previous reports of improved sexual function in adult males, this is the first report in a child. More research is required to investigate the concentration of lamotrigine and testosterone levels required to further explain this phenomenon.

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**Author contributions**

J.G. wrote the manuscript and provided data for Table 1. S.S.C. and X.Y.C. conducted the patient review. M.T. and F.M. supervised the work. Y.Q., Y.G. and J.W.W. reviewed the final manuscript.

**Declaration of conflicting interests**

The authors declare that there are no conflicts of interest.

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