

Lamotrigine and nightmares

Introduction

Lamotrigine (Lamictal[®]) is indicated for people of 13 years and older *for the treatment of epilepsy as adjuvant or monotherapy in partial epilepsy and generalized epilepsy including tonic-clonic epilepsy, and in epilepsy associated with Lennox-Gastaut's syndrome as adjuvant therapy or initial antiepileptic drug.* In people of 2 up to and including 12 years, it is indicated as *adjuvant therapy of partial epilepsy and generalized epilepsy including tonic-clonic attacks, and in epilepsy associated with Lennox-Gastaut's syndrome, and as monotherapy in typical absence epilepsy.* Furthermore it is indicated for *bipolar disorder.* For people of 18 years and older it is also indicated for *prevention of depressive episodes in patients with a bipolar I disorder who mainly experience depressive episodes* [1].

Lamotrigine is a voltage-dependent blocker of voltage-sensitive sodium channels. It blocks the constantly repeated firing of neurons and inhibits the release of glutamate (the neurotransmitter that serves a key role in the onset of epileptic seizures). These effects probably contribute to the anticonvulsant properties of lamotrigine. The mechanism of action of lamotrigine in bipolar disorders has not been established yet, although voltage-sensitive sodium channels probably play an important role [1].

Lamictal[®] was granted marketing authorization in the Netherlands on 15 January 1996 [1].

A nightmare is a disturbing dream that awakens the dreamer and is a rapid eye movement (REM) related parasomnia. In a nightmare disorder there is exaggeration of the features of REM sleep [2]. Nightmares are defined by The International Classification of Sleep Disorders II as "recurrent episodes of awakening from sleep with recall of intensely disturbing dream mentation, usually involving fear or anxiety, but also anger, sadness, disgust, and other dysphoric emotions". Nightmares generally occur in the early hours of the morning because REM sleep predominates during the final third of the night [3].

The Dutch SmPC of lamotrigine mentions confusion, hallucinations, somnolence, insomnia and agitation as adverse drug reactions, but does not mention nightmares or abnormal dreams [1]. This observation describes the association between nightmares and the use of lamotrigine.

Reports

On 29 October 2013 the database of the Netherlands Pharmacovigilance Centre Lareb contained three reports concerning nightmares and one of abnormal dreaming associated with the use of lamotrigine.

Case A (120197)

This well documented non-serious spontaneous report from a consumer concerns a female aged 51-60 years, with nightmares, headache, diarrhoea, nausea, blurred vision, pruritus, restlessness and listlessness following administration of lamotrigine for a bipolar affective disorder with a latency of an unknown number of weeks after start. The dose of lamotrigine was reduced from 200mg daily to 50mg daily and the patient recovered from having nightmares. The outcome of the other symptoms was unknown. Concomitant medications were levothyroxine, zuclopentixol,

pantoprazole, levocetirizine, mirtazapine and diazepam with unknown start dates. There was no further reported medical history. The past drug therapy indicated that the patient used lithiumcarbonate in the past.

Case B (126472)

This well documented non-serious spontaneous report from a nurse practitioner concerns a male aged 31-40 years, with nightmares following administration of lamotrigine for epilepsy with a latency of about 15 days after start. A short period after dosage increase from 25 mg daily to 50 mg daily the patient got nightmares. Using 25 mg daily the patient initially had no complaints, however later the patient suffered from nightmares even after dosage reduction to 12.5 mg. The drug lamotrigine was withdrawn, and the patient recovered. Lamotrigine was reintroduced again because of trembling in the foot, which resulted in the immediate return of the nightmares (positive rechallenge). Three days after withdrawal of lamotrigine the nightmares had disappeared again. Concomitant medications were carbamazepine and valproic acid, both used for many years. There was no further reported medical history.

Case C (152031)

This well documented non-serious spontaneous report from a specialist doctor concerns a female aged 31-40 years, with sleep disturbance and nightmares following administration of lamotrigine for bipolar affective disorder with a latency of 3 days after start. Lamotrigine was started at a low dose. The complaints became unbearable, shortly after using a dose of 200 mg daily. Lowering the dose to 50 mg diminished the complaints, but there were still a few disturbing dreams present. Concomitant medication was not reported. The medical history indicated recurrent depressions, and hypomanic episodes under antidepressant therapy. The patient had no known past drug therapy.

Case D (46158)

This moderately documented non-serious report from a pharmacist concerns a female aged 41-50 years, with dreams and nightmares and taking lamotrigine 25 mg two times daily with an unknown exact latency of less than a month after start. The action taken for lamotrigine was unknown. The patient outcome was unknown. The patient described the severity of the complaints as a 4 on a scale from 1 to 5. Concomitant medication was alprazolam, used chronically for at least a year with an unknown start date. The past drug therapy indicated gabapentin.

Other sources of information

SmPC

The Dutch SmPC of lamotrigine mentions confusion, hallucinations, somnolence, insomnia and agitation as adverse drug reactions, but does not mention nightmares or abnormal dreams [1]. The US SmPC of the FDA mentions dream abnormality as an adverse event of lamotrigine in 6% of patients with the use of lamotrigine as monotherapy (100 to 400 mg/day) in bipolar disorder in two double-blind, placebo-controlled trials of 18 months' duration, and greater than 1% and less than 5% in all studies [4].

Literature

Uher *et al* [5,6] described a case of a 42-year-old woman with dose-related visual hallucinations and sleep disturbances within 4 weeks of starting lamotrigine. This

patient had a history of depression and alcohol abuse, but not of hallucinations. Because of depression and hypomania this patient started lamotrigine. After four weeks in which the dose of lamotrigine was gradually increased to 100 mg/day, she experienced disturbed sleep with frequent waking and vivid dream-like experiences without being completely asleep. Later she also experienced hallucinations. The dose of lamotrigine was reduced to 50 mg/day. After a dose increase to 75 mg/day two months later, sleep disturbances and nightmares returned within one week. Further increase to 100 mg/day resulted in hallucinations, both during the day and during the night. After decrease to 75 mg/day the hallucinations disappeared and the hallucinations and nightmares have not recurred despite continued treatment on lamotrigine 75 mg/day. Concomitant medication was citalopram.

The book Meyler's Side Effects of Drugs describes two boys aged 6 and 8 years with sleep difficulties, one case associated with scary dreams, after being stabilized on lamotrigine, 8 mg/kg. After dose reduction the disturbances improved [7,8].

On the other hand an article by Economou *et al* [9], describes a case of a 68-year-old man already suffering from a Rapid eye movement (REM) behavior disorder (RBD). RBD is a parasomnia that is manifested by vivid, often frightening dreams associated with simple or complex motor behavior during REM sleep [10]. In the article of Economou *et al* [9], a patient started using lamotrigine because of a diagnosis of epilepsy. This patient started lamotrigine at 25 mg/day, reached a maximum of 100 mg/day after 2 months and was retained at this dose for 1 more month. During treatment there were no appreciable changes in the frequency and intensity of RBD symptomatology. But, after abrupt *discontinuation* of lamotrigine immediately RBD symptomatology was severely aggravated, with dreams becoming more vivid and frightening and occurring almost every night. Over two months RBD symptomatology gradually subsided, reaching levels comparable to those before lamotrigine.

Databases

On 30 October 2013 the database of the Netherlands Pharmacovigilance Centre Lareb contained three reports of the MedDRA® Preferred Term (PT) Nightmare en one report of Abnormal dreams associated with the use of lamotrigine. The reporting odds ratio (ROR) was 1.6 (95% CI 0.5 – 5.1) for nightmare. The combined ROR of nightmare and abnormal dreams was 1.3 (95% CI 0.5 – 3.5). These were not disproportional.

The WHO database of the Uppsala Monitoring contained 107 reports of Nightmare and 75 reports of Abnormal dreams with the use of lamotrigine (see table 1).

Table 1. Reports of nightmares and abnormal dreams associated with lamotrigine in the WHO database

Drug	MedDRA PT	Number of reports	ROR (95% CI)
Lamotrigine	Nightmare	107	1.4 (1.2 - 1.7)
	Abnormal dreams	75	1.2 (0.9 - 1.5)
	Combined	182	1.3 (1.1 - 1.5)

The reports of nightmares and abnormal dreams for lamotrigine in the Eudravigilance database are given in table 2.

Table 2. Reports of nightmares and abnormal dreams associated with lamotrigine in the Netherlands Bijwerkingen Centrum Lareb
May 2014

Eudravigilance database

Drug	MedDRA PT	Number of reports	ROR (95% CI)
Lamotrigine	Nightmare	35	1.6 (1.1 – 2.2)
	Abnormal dreams	13	1.0 (0.6 – 1.7)
	Combined	48	1.35 (1.02 – 1.80)

Prescription data

The number of patients using lamotrigine in The Netherlands is shown in Table 3.

Table 3. Number of patients using lamotrigine in the Netherlands between 2008 and 2012 [11].

Drug	2008	2009	2010	2011	2012
lamotrigine	16,433	16,720	17,237	17,753	18,517

Mechanism

An article by Foldvary *et al* [12] describes a study where ten adults with focal epilepsy taking or carbamazepine or phenytoin were titrated to a lamotrigine dose of 400 mg/day to study the effect of lamotrigine on sleep. Treatment with lamotrigine was associated, although not reaching statistical significance, with a reduction in arousals and stage shifts and an increase in REM periods. Maybe, because a nightmare is a REM related parasomnia, the increase of REM periods might play a role in the occurrence of nightmares while using lamotrigine. In the article by Foldvary *et al* increase in dreaming was reported by one subject. Insomnia or restlessness were not reported with treatment in the article by Foldvary *et al*. The article did also not mention the occurrence of nightmares.

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received three reports of nightmares and one of abnormal dreams associated with the use of lamotrigine. In the WHO database there are 107 cases present of nightmares and 75 cases of abnormal dreams associated with lamotrigine. In the Lareb database the associations are not disproportionally present. In the WHO- and Eudravigilance database the association between nightmares and lamotrigine, and the combination of nightmares and abnormal dreams and lamotrigine are disproportionally present.

The US SmPC of the FDA mentions dream abnormality as an adverse event of lamotrigine [4].

In the three cases of nightmares from Lareb there were positive dechallenges, after lowering the dose or withdrawal of the drug, the nightmares diminished or disappeared. In one case (case B) it is known that three days after withdrawal of the lamotrigine, the nightmares had disappeared. In case B there was also a clear rechallenge. Case D contained no information on de- and rechallenge.

In case A, B and C a relation is described between the dosage and the severity of the nightmares, what could fit in a type A adverse drug reaction.

Weak aspects of the associations were the differences in latencies of three days to a number of weeks, and an unknown exact latency of less than a month in case D. In case A and D concomitant medications could play a role. In case A the patient used zuclopentixol, mirtazapine and diazepam as concomitant medication with unknown start dates. The Dutch SmPC of zuclopentixol describes nightmare as a uncommon ($\geq 1/1,000$, $<1/100$) occurring adverse reaction [13]. Nightmares are

described as an uncommon ($\geq 1/1,000$, $<1/100$) occurring adverse reaction in the Dutch SmPC of mirtazapine [14]. The Dutch SmPC of diazepam mentions that nightmares were described in the use of benzodiazepines [15]. Whether action was taken for the concomitant medication in case A was unknown. In case D the patient also used alprazolam. Similar to the SmPC of diazepam, the Dutch SmPC of alprazolam also mentions that nightmares were described in the use of benzodiazepines [16].

Although confounding by concomitant medication could not be ruled out, and although there was a variety in latencies, and the association was only slightly disproportionally present in the WHO database, it is supported by the FDA SmPC, literature and positive dechallenges in three cases and in one case also a clear rechallenge. For these reasons, it is suggested that lamotrigine might have a causative role in the occurrence of nightmares.

- Nightmares should be mentioned in the SmPC of lamotrigine

References

1. Dutch SmPC Lamictal[®] 2/5/25/50/100/200 mg, disperseerbare/kauwtabletten. (version date: 26-6-2013, access date: 29-10-2013). <http://db.cbg-meb.nl/IB-teksten/h19115.pdf>
2. UpToDate. (version date: 2012, access date: 29-10-2013). http://www.uptodate.com/contents/classification-of-sleep-disorders?detectedLanguage=en&source=search_result&search=nightmares&selectedTitle=4%7E150&provider=noProvider
3. UpToDate. (version date: 2012, access date: 29-10-2013). http://www.uptodate.com/contents/sleepwalking-and-other-parasomnias-in-children?detectedLanguage=en&source=search_result&search=nightmares&selectedTitle=1%7E150&provider=noProvider
4. FDA SmPC of lamotrigine Lamictal[®]. (access date: 29-10-2013). http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/020241s10s21s25s26s27,020764s3s14s18s19s20lbl.pdf
5. Uher R, Jones HM. Hallucinations during lamotrigine treatment of bipolar disorder. *Am J Psychiatry*. 2006 Apr;163(4):749-50.
6. Micromedex[®] Healthcare Series, (electronic version). Thomson Micromedex, Greenwood Village, Colorado, USA. (access date: 29-10-2013)
7. Aronson J.K. [Edit.], Meyler's Side effects of Drugs, 15th edition 2006, Elsevier
8. Champagne J, Whiting SE. Sleep disturbance on lamotrigine. *Epilepsia* 1999;40(Suppl 7):118-19.
9. Economou NT, Bonakis A, Ghika A, Ferini-Strambi L, Vassilopoulos D, Kyrozis A. Lamotrigine withdrawal may worsen RBD symptoms. *Neurologist*. 2011 Sep;17(5):279-81.
10. Boeve BF. REM sleep behavior disorder: Updated review of the core features, the REM sleep behavior disorder-neurodegenerative disease association, evolving concepts, controversies, and future directions. *Ann N Y Acad Sci*. 2010 Jan;1184:15-54.
11. College for Health Insurances. GIP database. (version date: 9-6-2009, actualized 23-6-2013, access date: 30-10-2013). <http://www.gipdatabank.nl/>
12. Foldvary N, Perry M, Lee J, Dinner D, Morris HH. The effects of lamotrigine on sleep in patients with epilepsy. *Epilepsia*. 2001 Dec;42(12):1569-73.
13. Dutch SmPC Cisordinol[®] 2/10/25 mg filmomhulde tabletten. (version date: 29 november 2012, access date: 30-10-2013). <http://db.cbg-meb.nl/IB-teksten/h04294.pdf>
14. Dutch SmPC Remeron[®] 15 mg tabletten. (version date: 15-2-2011 met laatste herziening 12 maart 2011, access date: 6-11-2013). <http://db.cbg-meb.nl/IB-teksten/h16685.pdf>
15. Dutch SmPC diazepam ratiopharm 2/5/10 mg tabletten. (version date: 05 december 2012, access date: 6-11-2013). <http://db.cbg-meb.nl/IB-teksten/h52640.pdf>
16. Dutch SmPC Xanax[®] 0,25/0,5 mg tabletten, 0,5/1/2 mg tabletten met gereguleerde afgifte. (version date: Jan 2013, laatste wijziging op 25 maart 2013, access date: 30-10-2013). <http://db.cbg-meb.nl/IB-teksten/h14409.pdf>

This signal has been raised on February 2014. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).