CNS Spectrums (2019), **24**, 390–394.
doi:10.1017/S1092852918001049

ORIGINAL RESEARCH

Lamotrigine-induced obsessive-compulsive disorder in patients with bipolar disorder

Verinder Sharma,[1,2]* *and Minakshi Doobay*[2]

[1] Department of Psychiatry and Obstetrics & Gynecology, University of Western Ontario, London, Ontario, Canada
[2] Parkwood Mental Health Building, St. Joseph's Health Care, London, Ontario, Canada

Introduction. Lamotrigine is a commonly used drug in the treatment of bipolar disorder. Although there are reports of its effectiveness in the management of bipolar disorder and comorbid obsessive-compulsive disorder (OCD), lamotrigine has also been associated with obsessionality in patients with bipolar disorder.

Methods. Charts of 8 patients with bipolar disorder who had de novo onset of obsessions and compulsions after the use of lamotrigine were reviewed. The Naranjo scale was used to assess the likelihood of patients developing OCD due to lamotrigine use.

Results. Two to 8 months after the initiation of lamotrigine, patients with no such prior history developed obsessions and compulsions meeting the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) diagnostic criteria for medication-induced OCD. In all except 1 patient, the symptoms resolved within a month of lamotrigine discontinuation.

Conclusions. Some patients with bipolar disorder may develop OCD after initiation of lamotrigine. Due to the inherent limitations of a case series, the findings should be interpreted with caution.

Received 31 August 2017; Accepted 1 May 2018; First published online 8 August 2018

Key words: Antipsychotic, bipolar disorder, comorbidity, lamotrigine, obsessive compulsive disorder.

Introduction

Lamotrigine was first approved by the U.S. Food and Drug Administration in 1994 for treatment of epilepsy. It is indicated in children for partial-onset seizures; primary generalized tonic-clonic seizures, and generalized seizures of Lennox-Gastaut syndrome, and as conversion monotherapy in adults.[1] Lamotrigine is also approved for use in the maintenance treatment of bipolar I disorder to delay the time to recurrence of mood episodes in patients treated with standard therapy.[2] The off-label indications for its use include the acute treatment of bipolar depression and as an augmenting agent in the management of major depressive disorder (MDD), schizophrenia, and obsessive-compulsive disorder (OCD).[3]

Randomized controlled trials have indicated the effectiveness of lamotrigine in patients with treatment-resistant OCD and as adjunctive treatment for patients with OCD[4,5] and comorbid mood and psychotic disorders including schizophrenia and schizoaffective disorder.[6] A meta-analysis also demonstrated its effectiveness in treatment of bipolar disorder.[7] However, there is also literature suggesting that lamotrigine can cause obsessions and compulsions. Kemp *et al*[8] reported 5 patients with bipolar II disorder who experienced the onset of intrusive, repetitive phrases coinciding with lamotrigine treatment. The symptoms abated following the dose reduction or discontinuation of lamotrigine but recurred upon dose escalation or re-challenge of lamotrigine. Unlike symptoms of OCD, the intrusive phrases were not associated with anxiety nor did they appear to neutralize the obsessive thoughts.[8] Kuloglu *et al*[9] reported a case of bipolar II disorder where the patient developed OCD following the addition of lamotrigine to olanzapine and

* Address for correspondence: Dr. Verinder Sharma, Parkwood Institute, Mental Health Care Building, 550 Wellington Road, London, ON N6C 0A7, Canada.
(Email: vsharma@uwo.ca)

The authors would like to thank Christine Baczynski at Parkwood Institute, London, Ontario, Canada for her assistance in manuscript preparation.

citalopram but had symptom abatement 3 days after the discontinuation of lamotrigine.

Case reports in children have noted emergence of tics or Tourette syndrome with lamotrigine.[10–12] One child also developed OCD along with tics.[10] Lamotrigine has also been linked to OCD in patients with schizophrenia or schizoaffective disorder,[13] mood disorders,[14] and epilepsy.[15] In one study, lamotrigine was an independent predictor of OCD diagnosis after adjusting for age and clozapine dosage in patients with schizophrenia or schizoaffective disorder. Among patients treated with lamotrigine, 29.2% had obsessive-compulsive symptoms and 13.8% had OCD.[13]

In this article we describe 8 patients with bipolar disorder who developed OCD for the first time following treatment with lamotrigine. To our knowledge, this is the first case series to report on the association of lamotrigine with OCD diagnosed as per *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5).

Methods

Eight patients who reported first onset of obsessions and compulsions following the initiation of lamotrigine are included in this case series. The patients were assessed by the first author at a specialized mood disorders program in a provincial psychiatric hospital during the period July 2006–May 2017. Prior to the onset of OCD, they had been seen in follow-up by the same psychiatrist for 2–11 years for management of bipolar disorder and comorbid psychiatric disorders.

The patients met the DSM-5 criteria for medication-induced OCD (ie, development of symptoms of OCD after exposure to a medication capable of producing these symptoms), and improvement or remission of symptoms within 4 weeks of discontinuation of the medication. DSM-5 criteria were also applied to confirm a diagnosis of bipolar disorder, or any other comorbid psychiatric disorder.

Charts were reviewed to gather demographic and pertinent clinical information about the patients. Detailed history of medications (both psychotropic and nonpsychotropic) prescribed at our clinic as well as other facilities was obtained. In order to avoid response bias, patients were not informed of the possible association of lamotrigine with OCD at the time lamotrigine was discontinued.

The Naranjo Adverse Drug Reaction Probability Scale was used to ascertain the likelihood of whether the adverse drug reaction (obsessions and compulsions) was actually due to lamotrigine rather than the result of other factors. The scale has 10 questions that are answered as either "Yes," "No," or "Do not know." The total scores range from –4 to + 13. Probability is assigned as definite (a score of ≥ 9), probable (a score of 5 to 8), possible (a score 1 to 4), or doubtful (0 or less).[16] Patients provided informed consent to participate in the case series. Approval for the case series was granted by the Health Science Research Ethics Board at Western University.

Results

Demographic and clinical characteristics of patients are shown in Table 1. The patients were mostly women ($n = 6$), with ages ranging between 29 and 58 years ($M = 45.5$, $SD = 10.81$). All patients met the DSM-5 diagnostic criteria for bipolar disorder: 7 patients had bipolar II disorder, and 1 patient met the criteria for bipolar I disorder. Panic disorder was concurrently present in 5 cases. Only 1 patient (Case 8) had a family history of OCD in a first degree relative. Case 1 had obsessions and compulsions in the past but met the diagnostic criteria of OCD only after the introduction of lamotrigine. The patients were not using any substances (such as cocaine or psychostimulants) or suffering from any medical condition that could account for OCD symptoms. The lamotrigine dose ranged between 50 mg and 300 mg ($M = 168.75$, $SD = 98.88$). The OCD symptoms appeared 2–8 months after patients were first put on lamotrigine.

Scores on the Naranjo scale indicated lamotrigine was a probable cause of OCD. The lag period between initiation of lamotrigine and patients reaching the diagnostic threshold of OCD ranged from 2 to 8 months. Two cases (Case 1 and Case 2) developed OCD when challenged again with lamotrigine. Case 1 first disclosed the OCD symptoms 8 months after being put on lamotrigine; however, upon a rechallenge of lamotrigine the OCD symptoms appeared within 1 month. Similarly, in Case 2 OCD reemerged after only 3 weeks upon a rechallenge of lamotrigine. Interestingly, Case 4 had reemergence of OCD symptoms following the substitution of lamotrigine with carbamazepine 400 mg daily.

In all cases except one, OCD symptoms fully remitted within 1 month of discontinuation of lamotrigine. None of the patients had a recurrence of OCD symptoms during follow-up periods spanning 6 months to 51 months ($M = 17.75$, $SD = 14.58$). The only exception was Case 8, who had a family history of OCD and experienced only abatement of OCD symptoms.

Vignettes of the representative cases are described below.

Case Vignettes

Case 1

Case 1 had had obsessions and compulsions in the past, but these symptoms never interfered with his level of

https://doi.org/10.1017/S1092852918001049 Published online by Cambridge University Press

TABLE 1. Clinical and treatment summary

Case no.	Age/ sex	Diagnosis	Comorbid psychiatric disorders (current)	Lag between the start of LTG and diagnosis of OCD (months)	LTG dose	Concurrent medications	Types of obsessions and compulsions	Naranjo Score	Follow-up (months)
1	56/M	BP II	None	8	225 mg	QUE 700, LI 750 mg	List making, hoarding	8	18
2	47/F	BP I	None	4	50 mg	OLZ 10 mg, FLU 0.5 mg	Checking, safety	8	13
3	58/M	BP II	PD	2.5	50 mg	LI 450 mg, QUE 100 mg, ZOP 10 mg	Checking, cleaning	6	51
4	51/F	BP II	PD	6	150 mg	LI 600 mg, QUE 50 mg	Intrusive sexual thoughts, harm to self and others	7	9
5	34/F	BP II	PD	2	150 mg	LI 600, QUE 50 mg, ZOP 7.5 mg,	Cleaning, handwashing, and contamination	6	24
6	29/F	BP II	PD	5	125 mg	LI 1200 mg, QUE 25 mg	Intrusive sexual thoughts	6	6
7	37/F	BP II	PD	7	300 mg	LI 600 mg, OLZ 5 mg	Checking, seeking reassurance	6	10
8	52/F	BP II	PD	6	300 mg	LI 450 mg, QUE 150 mg, ZOP 15 mg, BUP 300 mg, ESC 10 mg	Checking, touching, skin picking	6	11

Abbreviations: BP I = bipolar I disorder, BP II = bipolar II disorder, BUP = bupropion, ESC = escitalopram, FLU = flupenthixol, LI = lithium, LTG = lamotrigine, OCD = obsessive compulsive disorder, OLZ = olanzapine, PD = panic disorder, QUE = quetiapine, ZOP = zopiclone.

functioning or caused any emotional distress. Following the initiation of lamotrigine, he started making copious notes on a daily basis about actors in television shows he planned to watch that day. The notes included a detailed biography of each actor and information about the television show. He would spend at least 8 hours a day gathering the material online and writing it up.

He also developed a compulsion to write the license plate numbers of all the commercial vehicles he would encounter during the time spent outside his home. He became highly anxious due to his inability to jot down the license plates of all the vehicles and decided to restrict his outdoor activities, resulting in him becoming housebound. During a regular follow-up appointment, he broke down and disclosed the full extent of OCD symptoms, including their "paralyzing" effect on his daily functioning.

Since lamotrigine was the last drug added to the regimen, we decided to taper it off. Within 1 month of lamotrigine discontinuation, he was completely free of OCD symptoms but developed severe depression. We decided to increase his quetiapine dose to 550 mg, but he developed frequent falls. Due to the persistence of depression and concerns regarding his safety, he agreed to retry lamotrigine, albeit in a low dose. Within 1 week of taking lamotrigine 75 mg a day, he had a return of OCD symptoms similar to the ones he had experienced earlier. The symptoms disappeared 3 days after lamotrigine was discontinued and he has remained free of OCD symptoms for 18 months. He is currently taking lithium 750 mg and quetiapine 700 mg daily.

Case 3

Case 3 developed a compulsive need to floss his teeth after lamotrigine was added to lithium 450 mg, quetiapine 100 mg, and zopiclone 10 mg daily. He would floss his teeth at least 20 times a day, spending several minutes each time. This was a major change from before, as he used to floss his teeth every couple of weeks. The frequent and prolonged periods of flossing caused a great deal of distress for him. He would excuse himself several times when sharing meals with his family to go to the washroom to floss his teeth. In between the flossing, he would repeatedly check his teeth to ensure there was no debris. He recognized the senseless nature of his behavior but felt compelled to carry out these activities. The symptoms disappeared within 2 weeks of discontinuation of lamotrigine, and he has not had any symptoms of OCD during the 51-month follow-up.

Discussion

Despite research suggesting lamotrigine as being effective in the treatment of OCD,[4–6] this case series suggests

https://doi.org/10.1017/S1092852918001049 Published online by Cambridge University Press

that lamotrigine may trigger OCD in patients with bipolar disorder. Since OCD is a common comorbidity in the context of bipolar disorder, it can be argued that these patients had spontaneous occurrences of OCD rather than having lamotrigine-induced OCD. Similarly, atypical neuroleptics such as risperidone, olanzapine, and quetiapine have been implicated in the causation of OCD.[17–19] All of our patients were on atypical neuroleptics—2 were on olanzapine and the rest took quetiapine —concurrent to use of lamotrigine. Thus it is possible that atypical neuroleptics may have contributed to the development of OCD symptoms. However, this is highly unlikely because these patients did not have any recurrences of OCD in spite of the continued use of these drugs. OCD can occur any time throughout the lifespan; however, most adults with the disorder report onset in childhood or adolescence.[20,21] None of our patients had onset of symptoms in childhood or adolescence.

Several factors including a close temporal relationship between lamotrigine use and symptom onset, disappearance of symptoms within 1 month of drug discontinuation, re-emergence of symptoms upon rechallenge of the drug, and absence of recurrence of OCD during the follow-up are suggestive of a causative role of lamotrigine. Absence of personal and family history of OCD in all except 1 patient suggests that these patients were not particularly prone to OCD and likely experienced these symptoms after the use of lamotrigine.

Some of our findings are not in accordance with previous reports. Patients in our series met the DSM-5 diagnostic criteria for medication-induced OCD, unlike patients in another case series[4] who were thought to have symptoms distinct from OCD. Notably, the repetitive phrases were not accompanied by anxiety, as is the case with obsessions and compulsions. Kemp *et al*[8] reported onset of OCD symptoms only after lamotrigine was escalated to 200 mg or higher. Only 3 of our patients received doses higher than 200 mg.

It is difficult to comment on the prevalence of lamotrigine-induced OCD in bipolar disorder. Since bipolar disorder is the focus of care in a large number of patients taking lamotrigine, patients (especially those with no prior history of OCD) are rarely asked about obsessions and compulsions. Also, patients with depression may not be sensitized to the symptoms of OCD due to deficits in attention and reasoning,[22] thus delaying the recognition and reporting of obsessions and compulsions. Another important issue is that patients may be reluctant to report these symptoms spontaneously due to feelings of shame and guilt.[23]

Our findings suggest that patients with bipolar disorder should be monitored for emergence of obsessions and compulsions during treatment with lamotrigine. In cases where lamotrigine is thought to have induced OCD, clinicians should consider reducing the lamotrigine dose and monitoring for symptoms of OCD. If there is symptomatic improvement, lamotrigine should be tapered off. Management of bipolar depression comorbid with OCD is particularly challenging and often involves the use of more than one psychotropic drug.[24] Clinicians who are unaware of lamotrigine inducing OCD might be tempted to add drugs to manage OCD rather than discontinue lamotrigine.

The etiology of lamotrigine-induced OCD is unclear. Individuals with OCD have lower glutamate levels in the lower anterior cingulate cortex (ACC),[25,26] and animal models suggest an increase of glutamate within the striatum.[27] It is hypothesized that tonic-phase dysregulation of glutamate in the ACC results in phasic overactivation of the striatum, the outcome of which is OCD symptoms.[21] Lamotrigine acts by inhibiting glutamate by blocking N-methyl-D-aspartate (NMDA) receptors and inhibiting sodium-gated channels.[28,29] Kemp *et al*[8] hypothesized that lamotrigine may disrupt the glutamate balance within the cortico-striato-thalamic-cortical network resulting in the development of OCD. It is also unclear as to why lamotrigine induces OCD in some patients while it ameliorates these symptoms in others. There are examples of this paradoxical effect with other drugs such as atypical antipsychotics, including risperidone, olanzapine, and quetiapine[17–19]; other anticonvulsants such as levetiracetam and topiramate[30,31]; and antidepressants where chronic use can cause tardive dysphoria[32] and treatment resistance[33] in some cases.

Limitations

Selection bias likely played a role in the observed occurrence of lamotrigine-induced OCD in patients with bipolar disorder because there are occasional reports of lamotrigine inducing obsessions and compulsions in patients with other psychiatric disorders. The small number of cases reported and lack of use of a scale to quantify the symptoms are other limitations. Caution should be exercised about generalizing our findings to patients seen in non-tertiary care facilities. Controlled studies exploring lamotrigine-induced OCD might provide useful insights into the etiology of OCD as well as its treatment in patients with comorbid bipolar disorder. Studies are also needed to assess whether patients with lamotrigine-treated epilepsy are at a higher risk of having OCD compared with similar patients on other antiepileptic drugs.

Conclusions

Lamotrigine is a commonly used drug in the treatment of bipolar depression, and there are occasional reports of

https://doi.org/10.1017/S1092852918001049 Published online by Cambridge University Press

its use in the management of OCD. Our case series suggests that lamotrigine use may be associated with first-onset of OCD in some patients with bipolar disorder. Although similar in symptomatology to primary OCD, lamotrigine-induced OCD appears to carry a better prognosis. Hopefully, future studies will shed light on the paradoxical effect of lamotrigine on OCD in individuals with bipolar disorder.

Disclosures

Dr. Sharma has received grant support from, participated on scientific advisory boards for, or served on speakers bureaus of Assurex, Genome Canada, Neurocrine Biosciences, Sage Therapeutics, Stanley Medical Research Institute, and Sunovion Pharmaceuticals. Ms. Doobay has no conflicts of interest to disclose.

REFERENCES:

1. Lamictal [package insert]. Greenville, NC: DSM Pharmaceuticals, Inc; 2009.
2. Yatham LN, Kennedy SH, Parikh SV, *et al*. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. *Bipolar Disord.* 2013; **15**(1): 1–44.
3. Reid JG, Gitlin MJ, Altshuler LL. Lamotrigine in psychiatric disorders. *J Clin Psychiatry*. 2013; **74**(7): 675–684.
4. Bruno A, Mico U, Pandolfo G, *et al*. Lamotrigine augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder: a double-blind, placebo-controlled study. *J Psychopharmacol*. 2012; **26**(11): 1456–1462.
5. Khalkhali M, Aram S, Zarrabi H, Kafie M, Heidarzadeh A. Lamotrigine augmentation versus placebo in serotonin reuptake inhibitors-resistant obsessive-compulsive disorder: a randomized controlled trial. *Iran J Psychiatry*. 2016; **11**(2): 104–114.
6. Poyurovsky M, Glick I, Koran LM. Lamotrigine augmentation in schizophrenia and schizoaffective patients with obsessive-compulsive symptoms. *J Psychopharmacol*. 2010; **24**(6): 861–866.
7. Geddes JR, Calabrese JR, Goodwin GM. Lamotrigine for treatment of bipolar depression: independent meta-analysis and meta-regression of individual patient data from five randomised trials. *Br J Psychiatry*. 2009; **194**(1): 4–9.
8. Kemp DE, Gilmer WS, Fleck J, Dago PL. An association of intrusive, repetitive phrases with lamotrigine treatment in bipolar II disorder. *CNS Spectr*. 2007; **12**(2): 106–111.
9. Kuloglu M, Caykoylu A, Ekinci O, Yilmaz E. Lamotrigine-induced obsessional symptoms in a patient with bipolar II disorder: a case report. *J Psychopharmacol*. 2009; **23**(8): 1001–1003.
10. Lombroso CT. Lamotrigine-induced tourettism. *Neurology*. 1999; **52**(6): 1191–1194.
11. Sotero de Menezes MA, Rho JM, Murphy P, Cheyette S. Lamotrigine-induced tic disorder: report of five pediatric cases. *Epilepsia.* 2000; **41**(7): 862–867.
12. Zaatreh M, Tennison M, D'Cruz O, Beach RL. Anticonvulsants-induced chorea: a role for pharmacodynamics drug interaction? *Seizure.* 2001; **10**(8): 596–599.
13. Szmulewics AG, Valerio MP, Smith JM. Obsessive-compulsive symptoms in adjunctive therapy with lamotrigine in clozapine-medicated patients. *Schizophr Res.* 2015; **166**(1-3): 364–365.
14. Alkın T, Onur E, Özerdem A. Co-occurrence of blepharospasm, tourettism and obsessive–compulsive symptoms during lamotrigine treatment. *Prog. Neuropsychopharmacol. Biol. Psychiatry.* 2007; **31**(6): 1339–1340.
15. Lee SA, Lee HW, Heo K, *et al*. Cognitive and behavioural effects of lamotrigine and carbamazepine monotherapy in patients with newly diagnosed or untreated partial epilepsy. *Seizure.* 2011; **20**(1): 49–54.
16. Naranjo CA, Busto U, Sellers EM, *et al*. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981; **30**(2): 239–245.
17. Lykouras L, Alevizos B, Michalopoulou P, Rabavilas A. Obsessive-compulsive symptoms induced by atypical antipsychotics. A review of the reported cases. *Prog Neuropsychopharmacol Biol Psychiatry*. 2003; **27**(3): 333–346.
18. Stamouli S, Lykouras L. Quetiapine-induced obsessive-compulsive symptoms: a series of five cases. *J Clin Psychopharmacol*. 2006; **26**(4): 396–400.
19. Tranulis C, Potvin S, Gourge M, Leblanc G, Mancici-Marie A, Stip E. The paradox of quetiapine in obsessive-compulsive disorder. *CNS Spectr.* 2005; **10**(5): 356–361.
20. Brakoulias V, Starcevic B, Belloch A, *et al*. Comorbidity, age of onset and suicidality in obsessive-compulsive disorder (OCD): an international collaboration. *Compr Psychiatry.* 2017; **76**: 79–86.
21. Ruscio AM, Stein DJ, Chiu WT, Kessler RC. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. *Mol Psychiatry*. 2010; **15**(1): 53–63.
22. Zaninotto L, Solmi M, Veronese N, *et al*. A meta-analysis of cognitive performance in melancholic versus nonmelancholic unipolar depression. *J Affect Disord*. 2016; **201**: 15–24.
23. Fergus TA, Valentiner DP, McGrath PB, Jencuis S. Shame- and guilt-proneness: relationships with anxiety disorder symptoms in a clinical sample. *J Anxiety Disord*. 2010; **24**(8): 811–815.
24. Amerio A, Stubbs B, Odone A, Tonna M, Marchesi C, Ghaemi SN. The prevalence and predictors of comorbid bipolar disorder and obsessive-compulsive disorder: a systematic review and meta-analysis. *J Affect Disord*. 2015; **186**: 99–109.
25. Rosenberg DR, Mirza Y, Russell A, *et al*. Reduced anterior cingulate glutamatergic concentrations in childhood OCD and major depression versus healthy controls. *J Am Acad Child Adolesc Psychiatry*. 2004; **43**(9): 1146–1153.
26. Yücel M, Wood SJ, Wellard RM, *et al*. Anterior cingulate glutamate–glutamine levels predict symptom severity in women with obsessive-compulsive disorder. *Aust N Z J Psychiatry*. 2008; **42**(6): 467–477.
27. Wu K, Hanna GL, Rosenberg DR, Arnold PD. The role of glutamate signaling in the pathogenesis and treatment of obsessive-compulsive disorder. *Pharmacol Biochem Behav*. 2012; **100**(4): 726–735.
28. Cheung H, Kamp D, Harris E. An in vitro investigation of the action of lamotrigine on neuronal voltage-activated sodium channels. *Epilepsy Res*. 1992; **13**(2): 107–112.
29. Ostadhadi S, Ahangari M, Nikoui V, *et al*. Pharmacological evidence for the involvement of the NMDA receptor and nitric oxide pathway in the antidepressant-like effect of lamotrigine in the mouse forced swimming test. *Biomed Pharmacother*. 2016; **82**: 713–721.
30. Çökmüş FP, Aşçıbaşı K, Öztekin S, Demet MM. Relationship of levetiracetam and obsessive-compulsive disorder: a case report. *Psychiatry and Clinical Psychopharmacology*. 2017; **27**(3): 325–327.
31. Ozkara C, Ozmen M, Erdogan A, Yalug I. Topiramate related obsessive-compulsive disorder. *Eur Psychiatry*. 2005; **20**(1): 78–79.
32. El-Mallakh RS, Gao Y, Jeannie Roberts R. Tardive dysphoria: the role of long term antidepressant use in-inducing chronic depression. *Med Hypotheses*. 2011; **76**(6): 769–773.
33. Sharma V. Treatment resistance in unipolar depression: is it an iatrogenic phenomenon caused by antidepressant treatment of patients with a bipolar diathesis? *Med Hypotheses*. 2006; **67**(5): 1142–1145.

https://doi.org/10.1017/S1092852918001049 Published online by Cambridge University Press