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CPAP-induced mania in bipolar disorder: a case report

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Abstract

Objective—In this case report we present our clinical observations of two patients with bipolar disorder with comorbid obstructive sleep apnea (OSA) who were treated with continuous positive airway pressure (CPAP) for their sleep apnea.

Background—Bipolar disorder is a psychiatric disorder characterized by the presence of one or more episodes of mania and frequent episodes of depression. This disorder affects approximately 0.8% of the adult population, with estimates from community samples ranging between 0.4% and 1.6%. OSA syndrome is a severe sleep disorder with a prevalence of 2–4% in the general population, the risk of which is increased by obesity. The prevalence of OSA is expected to be high in bipolar disorder due to high comorbid obesity. It is expected that improvement in OSA in patients with bipolar disorder with CPAP will improve mood and other symptoms of bipolar disorder. However, there is a relative lack of data examining this aspect.

Results—In both cases of bipolar disorder, CPAP was started after a polysomnographic diagnosis of OSA and CPAP titration study indicating that most of the apneas/hypopneas were eliminated with a significant improvement in oxygen saturation. To our surprise, we noted that in both of these cases initiation of CPAP resulted in manic symptoms.

Conclusions—Clinicians need to monitor patients with bipolar disorder closely for worsening of manic symptoms when they are started on CPAP for underlying OSA.

Keywords

bipolar disorder; continuous positive airway pressure; CPAP; obstructive sleep apnea; OSA

Bipolar disorder is characterized by the presence of one or more episodes of mania, and 90% of patients with bipolar disorder have episodes of depression as well (1). This disorder affects approximately 0.8% of the adult population, with estimates from community samples ranging between 0.4% and 1.6% (2). It is estimated that as many as 60% of people

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diagnosed with bipolar I disorder experience chronic interpersonal or occupational difficulties and subclinical symptoms between acute episodes (3–5).

Patients with untreated bipolar disorder may have more than ten total episodes of mania and depression during their lifetime, with the duration of episodes and inter-episode periods stabilizing after the fourth or fifth episode (6, 7). There is growing evidence that environmental and lifestyle features can have an impact on the severity and course of the illness (8–10). Stressful life events, changes in the sleep–wake schedule, non-compliance with treatment, and current alcohol or substance abuse may affect the course of illness and lengthen the time to recovery (6, 11–15).

Sleep disturbances and sleep disorders are known to increase the risk of mood disorders such as depression, seasonal affective disorder, and bipolar disorder (16, 17). However, here we report two cases that developed mania after correcting their underlying sleep disorder [obstructive sleep apnea (OSA)] with continuous positive airway pressure (CPAP).

Case 1

Mr. H is a 51-year-old married Caucasian man diagnosed with bipolar I disorder and comorbid generalized anxiety disorder, ulcerative colitis, hypertension, and borderline diabetes. He has been followed on a monthly basis in our clinic since January 2006. His first mood episode occurred at the age of 16. Over the past six years, he has typically experienced major depressive episodes in the winter months (November to January) and manic episodes in the summer months (May to July) without any non-seasonal recurrence. His last manic episode was in June 2008, characterized by hypersexuality, racing thoughts, reckless driving, and decreased sleep. In January 2009, he developed a depressive episode with symptoms of depressed mood, anhedonia, decreased concentration, isolation, frequent fatigue, worsening anxiety, and difficulty in maintaining sleep. His symptoms remitted in January 2009 and he was stabilized until March 2010 with lithium (900 mg) and gabapentin (600 mg).

However, in spite of having stable mood, he continued to complain of fatigue and sleepiness during the day, and his wife also reported increased snoring at the same time. Therefore, he was referred for polysomnography (PSG) to evaluate for OSA. PSG revealed 257 obstructive apneas and 19 obstructive hypopneas. The apnea/hypopnea index was 94.6/hour, and his lowest oxygen saturation (SpO_2) was 85% during sleep. His SpO_2 was below 90% for 18.4% of the recording. CPAP titration was performed and revealed that at a pressure of 7 cm H_2O most of the apneas/hypopneas were eliminated, and the minimal SpO_2 during sleep was 93%; therefore, he was started on CPAP at 7 cm H_2O.

Soon after starting the CPAP treatment in February 2011, his sleep improved and he felt more rested; however, his anxiety started worsening. After three weeks of the CPAP treatment, he progressively started experiencing euphoria with increased energy, physical aggression, motor hyperactivity, racing thoughts, decreased sleep, and pressured speech. In addition, he started driving recklessly. He had no concurrent symptoms of depression. Precipitating factors such as psychosocial stressors, recent travel, medication changes, and recent substance or over-the-counter medication use were ruled out clinically. He scored 14

on the Altman Self-rating Mania Scale (a cut-off score ≥ 6 indicates a high probability of mania) and 21 on the Young Mania Rating Scale (a cut-off score of 12 indicates mania) at Week 4 of CPAP. Several tests were conducted to rule out underlying medical causes: (i) his lithium level was 0.6 mEq/L; (ii) measurement of thyroid hormone levels showed no changes; and (iii) no anomalies in blood count, or liver or kidney function were found. Compliance with CPAP was 80%. Due to manic symptoms, lithium was increased to 1,200 mg, resulting in lithium plasma levels of 1.0 mEq/L; gabapentin was increased from 600 to 900 mg; and risperidone was started and titrated up to 3 mg. After two weeks of increased medication, his mood stabilized.

Case 2

Mr. R is a 60-year-old married Caucasian man with bipolar I disorder, hypercholesterolemia, benign prostatic hyperplasia, and status-post colon resection secondary to colon cancer. He has been followed on a monthly basis in our clinic since December 2006. He has a history of multiple inpatient psychiatric hospitalizations and has also received two courses of electroconvulsive treatment in the past during depressive episodes. His first mood episode occurred in his 20s. For the past three to four years, his episodes have had a seasonal pattern: a depressive episode during the fall and winter months and a hypomanic/manic episode during the summer months, without any non-seasonal recurrence. His last manic episode was in June 2010, characterized by decreased sleep, hyper-activity, racing thoughts, pressured speech, and grandiose delusion. His last depressive episode was in September 2010. He continued complaining about significant anxiety during depressive as well as manic episodes. He was taking divalproate (1,500 mg), quetiapine (400 mg), and lamotrigine (200 mg).

Mr. R's wife complained of his severe snoring and restless sleep and subsequently he was referred to our sleep center with a concern of OSA. He underwent an overnight PSG in September 2011 which revealed 0 obstructive apnea and 275 obstructive hypopneas with 29 central apneas. The apnea/hypopnea index was 64.7/hour and his lowest SpO_2 was 88% during sleep. His SpO_2 was below 90% for 16.2% of the recording. CPAP titration was carried out and revealed that at a pressure of 11 cm H_2O most of the apneas/hypopneas were eliminated, and the minimal SpO_2 during sleep improved to 92%. He was started on CPAP at 11 cm H_2O.

Soon after starting the CPAP treatment in November, his sleep improved and he felt more rested, but his anxiety started worsening. Mr. R was continued on divalproate 1,500 mg, quetiapine 400 mg, and lamotrigine 200 mg. After about two to three weeks of the CPAP treatment, he presented to the clinic with pressured speech, euphoric mood, psychomotor agitation, and grandiose delusions. He scored 20 on the Altman Self-Rating Mania Scale at Week 4 of CPAP. Psychosocial stressors and recent substance use were ruled out clinically. Blood tests were repeated to rule out other medical causes. His blood valproate level was 96.8 μg/mL, and no anomalies in blood count, or liver or kidney function were found. Compliance with CPAP was 75%, with an average use of six to seven hours per night. Initially, quetiapine was increased to 800 mg, without any improvement in manic symptoms. As a result, quetiapine was switched to olanzapine, which was gradually increased to 25 mg/

day. However, with olanzapine 25 mg/day, he developed physical restlessness and agitation indicating akathisia. As a result, olanzapine was discontinued and lithium was added to divalproate and lamotrigene. The dose of lithium was gradually titrated to 600 mg/day. His lithium level was 0.6 mg mEq/L after five days of lithium. After two weeks of receiving lithium and valproate (with lamotrigine), his mood stabilized and CPAP was continued.

Discussion

It is well documented that CPAP use in OSA leads to improvement in sleep quality, daytime sleepiness, daily performance, psychosocial adjustment, and psychological symptoms, including improvement in mood (18). However, in these two cases of male patients with bipolar disorder, an improvement in OSA triggered mania. These two cases are not isolated cases of mania associated with CPAP treatment. Three cases of CPAP-induced mania have been previously reported (19–21). In two of these cases, in male patients, there was no prior history of bipolar disorder and they were not being treated with mood stabilizers (19, 20). The third reported case involved a 43-year-old woman with bipolar disorder, who switched from depression to mania after starting on CPAP for OSA (21). However, again, in this case she was not taking mood stabilizers, and her menstrual history was not reported. At the time of initiation of CPAP, she was taking quetiapine, fluvoxamine, and alprazolam for a depressive episode. Our cases are unique, in that both of the patients were taking mood stabilizers and their symptoms resulting from bipolar disorder were well controlled prior to being started on CPAP. Despite the bipolar disorder symptoms being well controlled with mood stabilizers, both patients developed manic episodes with CPAP.

It is possible that various mechanisms may be involved in the precipitation of a manic episode with CPAP correction of underlying OSA in bipolar disorder. Administration of oxygen under pressure has been found to precipitate a manic-like syndrome in professional divers (22). Thus, it is possible that the improvement in SpO_2 with CPAP may have resulted in manic episode in these two cases. Some evidence suggests OSA in men is associated with dysfunction of the pituitary–gonadal axis. The relationship between luteinizing hormone–testosterone profiles and the severity of OSA suggests that sleep fragmentation and, to a lesser extent, hypoxia, in addition to the degree of obesity and aging, may be responsible for the central suppression of testosterone in these patients (23). Correction of OSA with CPAP therapy may revert low serum testosterone levels to normal levels (24). Of interest, both of the cases that we report and also the previously published reports of CPAP-induced mania were in male patients, except for one case in a female patient. Changes in the testosterone level may have contributed to manic episode in these male cases. The episode of mania induced by CPAP in both the cases occurred in the non-summer months, unlike their typical manic episodes. Dysfunction in the circadian clock has been hypothesized as having a causal role in the mood disorders. Antidepressants and mood stabilizers are known to influence the circadian clock (25). Additionally, OSA can cause dysfunction in one of the clock genes (h*Per1*) which regulates mammalian circadian rhythms, and CPAP treatment seems to improve such clock gene dysfunction (26). Thus, it is possible that CPAP use may have influenced the previously set balance of clock gene expression, resulting in a manic episode during the non-summer months in these two cases.

OSA affects 2–4% of the general population, and obesity increases the risk of this condition. Considering that the prevalence of obesity in bipolar disorder is double that in the general population, it is not surprising that patients with bipolar disorder have an increased rate of OSA (27, 28). Thus, it is likely that relatively more patients with bipolar disorder (compared to the general population) will be treated with CPAP for their comorbid OSA. In the literature, many studies have shown an improvement in depressive symptoms with the use of CPAP in patients with OSA (29, 30). Somatic treatments for depression, such as antidepressants and electroconvulsive therapy, have been reported to cause a manic switch (31, 32) in bipolar disorder. Similarly, it is likely that CPAP may precipitate manic episode in patients with bipolar disorder. As indicated by these two cases, there is a possibility that, irrespective of their bipolar symptoms being stable, initiation of CPAP may precipitate a new manic episode. In addition to physicians being aware of such a possibility, appropriate education of patients in this aspect, as well as informing the patient to look out for any early warning signs of manic symptoms, such as a decreased need for sleep, hyperactivity, impulsivity, and worsening anxiety (33), may be useful for better control of such CPAP-induced manic episodes.

Even though CPAP initiation in well-controlled bipolar disorder may precipitate a manic episode, better control of OSA is more beneficial for the overall health, including emotional health, of the patient. It is well known that sleep apnea increases the risk of motor vehicle accidents, hypertension, cardiovascular disorders, and cognitive disturbances (34). Therefore, although clinicians should be watchful when starting a patient with bipolar disorder on CPAP, they should clearly emphasize the importance of being compliant with CPAP for better control of underlying OSA.

Conclusions

The prevalence of OSA in bipolar disorder is expected to be high because of high comorbid obesity. These two cases suggest that clinicians need to monitor patients with bipolar disorder closely for a new manic episode or worsening of manic symptoms when they are started on CPAP for OSA. Future studies are needed to explore further these anecdotal findings and to understand the underlying mechanisms.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4. Washington, DC: APA; 2000. text revision
2. Merikangas KR, Jin R, He JP, et al. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Arch Gen Psychiatry. 2011; 68:241–251. [PubMed: 21383262]
3. Goldberg JF, Harrow M, Grossman LS. Course and outcome in bipolar affective disorder: a longitudinal follow-up study. Am J Psychiatry. 1995; 152:379–384. [PubMed: 7864263]
4. Fagiolini A, Kupfer DJ, Masalehdan A, Scott JA, Houck PR, Frank E. Functional impairment in the remission phase of bipolar disorder. Bipolar Disord. 2005; 7:281–285. [PubMed: 15898966]
5. Judd LL, Schettler PJ, Solomon DA, et al. Psychosocial disability and work role function compared across the long-term course of bipolar I, bipolar II and unipolar major depressive disorders. J Affect Disord. 2008; 108:49–58. [PubMed: 18006071]

6. Judd LL, Akiskal HS, Schettler PJ, et al. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. Arch Gen Psychiatry. 2003; 60:261–269. [PubMed: 12622659]
7. Swann AC, Bowden CL, Calabrese JR, Dilsaver SC, Morris DD. Differential effect of number of previous episodes of affective disorder on response to lithium or divalproex in acute mania. Am J Psychiatry. 1999; 156:1264–1266. [PubMed: 10450271]
8. Leverich GS, McElroy SL, Suppes T. Early physical or sexual abuse and the course of bipolar illness. Biol Psychiatry. 2002; 51:288–297. [PubMed: 11958779]
9. Johnson SL, Miller I. Negative life events and time to recovery from episodes of bipolar disorder. J Abnorm Psychol. 1997; 106:449–457. [PubMed: 9241946]
10. Frank E, Thase ME. Natural history and preventative treatment of recurrent mood disorders. Annu Rev Med. 1999; 50:453–468. [PubMed: 10073289]
11. Ashman SB, Monk TH, Kupfer DJ, et al. Relationship between social rhythms and mood in patients with rapid cycling bipolar disorder. Psychiatry Res. 1999; 86:1–8. [PubMed: 10359478]
12. Colombo C, Benedetti F, Barbini B, Campori E, Smeraldi E. Rate of switch from depression into mania after therapeutic sleep deprivation in bipolar depression. Psychiatry Res. 1999; 86:267–270. [PubMed: 10482346]
13. Goldberg JF, Garno JL, Leon AC, Kocsis JH, Portera L. A history of substance abuse complicates remission from acute mania in bipolar disorder. J Clin Psychiatry. 1999; 60:733–740. [PubMed: 10584760]
14. Leibenluft E, Suppes T. Treating bipolar illness: focus on treatment algorithms and management of the sleep-wake cycle. Am J Psychiatry. 1999; 156:1976–1986. [PubMed: 10588413]
15. Tondo L, Baldessarini RJ, Hennen J, et al. Suicide attempts in major affective disorder patients with comorbid substance use disorders. J Clin Psychiatry. 1999; 60:63–69. [PubMed: 10073390]
16. Okajima I, Komada Y, Normura T, et al. Insomnia as a risk for depression: a longitudinal epidemiologic study on a Japanese rural cohort. J Clin Psychiatry. 2012; 73:377–383. [PubMed: 22053828]
17. Harvey AG. Sleep and circadian rhythms in bipolar disorder: seeking synchrony, harmony, and regulation. Am J Psychiatry. 2008; 165:820–829. [PubMed: 18519522]
18. Lahera FG, Gonzalez AF. Psychotic mania after introduction of continuous positive airway pressure (CPAP) in the treatment of obstructive sleep apnoea. Actas Esp Psiquiatr. 2007; 35:406–407. [PubMed: 18004679]
19. Hilleret H, Jeunet E, Osiek C, Mohr S, Blois R, Bertschy G. Mania resulting from continuous positive airways pressure in a depressed man with sleep apnea syndrome. Neuropsychobiology. 2001; 43:221–224. [PubMed: 11287803]
20. Berge D, Salgado P, Rodriguez A, Bulbena A. Onset of mania after CPAP in a man with obstructive sleep apnea. Psychosomatics. 2008; 49:447–449. [PubMed: 18794515]
21. Trakada GP, Steiropoulos P, Bouros D. Continuous positive airways pressure treatment in a patient with sleep apnea-hypopnea syndrome and coexisting bipolar disorder. Psychopharmacol Bull. 2008; 41:89–92. [PubMed: 18668018]
22. Stoudemire A, Miller J, Schmitt F, et al. Development of an organic affective syndrome during a hyperbaric diving experiment. Am J Psychiatry. 1984; 141:1251–1254. [PubMed: 6435458]
23. Luboshitzky R, Aviv A, Hefetz A, et al. Decreased pituitary-gonadal secretion in men with obstructive sleep apnea. J Clin Endocrinol Metab. 2002; 87:3394–3398. [PubMed: 12107256]
24. Bercea R, Bercea B, Milhaescu T. Association between the serum level of testosterone and other comorbidities in obstructive sleep apnea. Pneumologia. 2012; 61:98–101. [PubMed: 22783600]
25. McCarthy MJ, Welsh DK. Cellular circadian clocks in mood disorders. J Biol Rhythms. 2012; 27:339–352. [PubMed: 23010657]
26. Burioka N, Koyanagi S, Endo M, et al. Clock gene dysfunction in patients with obstructive sleep apnoea syndrome. Eur Respir J. 2008; 32:105–112. [PubMed: 18321934]
27. Goldstein BI, Liu SM, Zivkovic N, Schaffer A, Chien LC, Blanco C. The burden of obesity among adults with bipolar disorder in the United States. Bipolar Disord. 2011; 13:387–395. [PubMed: 21843278]

28. Sharafkhaneh A, Giray N, Richardson P, et al. Association of psychiatric disorders and sleep apnea in a large cohort. Sleep. 2005; 28:1405–1411. [PubMed: 16335330]

29. El-Sherbini AM, Bediwy AS, El-Mitwalli A. Association between obstructive sleep apnea (OSA) and depression and the effect of continuous positive airway pressure (CPAP) treatment. Neuropsychiatr Dis Treat. 2011; 7:15–21. [PubMed: 21750624]

30. Schwartz DJ, Kohler WS, Karatinos G. Symptoms of depression in individuals with obstructive sleep apnea may be amenable to treatment with continuous positive airway pressure. Chest. 2005; 128:1304–1309. [PubMed: 16162722]

31. Goldberg JF, Truman CJ. Antidepressant-induced mania: an overview of current controversies. Bipolar Disord. 2003; 5:407–420. [PubMed: 14636364]

32. Loo C, Katalinic N, Mitchell PB, Greenberg B. Physical treatments for bipolar disorder: a review of electroconvulsive therapy, stereotactic surgery and other brain stimulation techniques. J Affect Disord. 2011; 132:1–13. [PubMed: 20858566]

33. Altman ES, Rea MM, Mintz J, Miklowitz DJ, Goldstein MJ, Hwang S. Prodromal symptoms and signs of bipolar relapse: a report based on prospectively collected data. Psychiatry Res. 1992; 27:245–248.

34. Lurie A. Obstructive sleep apnea in adults: epidemiology, clinical presentation, and treatment options. Adv Cardiol. 2011; 46:1–42. [PubMed: 22005188]