Triple Chronotherapy for Bipolar Depression: A Case Report

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SUMMARY

Bipolar disorder (BD) is a chronic disease with recurrent episodes of mania and depression. There is urgent need for rapid, effective, and safe treatments for bipolar depression which is difficult to treat using the current standard methods. Triple chronotherapy is a combination of sleep deprivation, sleep phase shift, and bright light therapy which has been shown to induce accelerated and sustained remissions in bipolar depression. In this report, we present a case of bipolar depression undergoing triple chronotherapy in addition to the standard treatment and discuss the importance of getting fast and sustained response in these cases.

Keywords: Bipolar disorder, depression, chronotherapy, sleep deprivation

INTRODUCTION

Duration of depressive episodes with subthreshold depressive symptoms in BD is longer than that of other episodes (Kupka et al. 2007). There is definite evidence that the clinical features and treatment methods for bipolar depression are different from those for unipolar depression. Although depression is a long-lasting period that challeges the physician, data on its treatment are not adequate (Akiskal 2005). The depressive episode of bipolar disorder is predominant and is associated with increased mortality related to cognitive, occupational and social impairment, psychiatric comorbidity, suicide and general health problems (Novick et al. 2010).

Treatment options are limited in bipolar depression. Although antidepressant treatment is widespread, there is not enough evidence about its efficacy (Frye et al. 2014). Mood stabilizers such as lithium, valproic acid or lamotrigine are effective in preventing mood episodes but require months to affect depressive symptoms. In addition these treatments generally result in partial remission with significant residual symptoms. The psychopharmacological development providing benefit in this area has been the introduction of atypical antipsychotic drugs such as quetiapine. Quetiapine was shown to be significantly superior to placebo and standard antidepressants in the acute treatment of bipolar depression (Young et al. 2010). Quetiapine was found to be clinically effective despite its marked side effect profile limiting its tolerability and use. These side effects are metabolic changes such as hyperglycemia, diabetes mellitus, weight gain, increased cholesterol levels and heart rhythm disorders that can lead to sudden death (Schneeweiss and Avorn 2009). Hence, the three standard treatment options of bipolar depression suffer from lack of rapid efficiency, limited tolerability, or both and in this regard, urgent clinical need for the development of more effective therapies with no related side-effect burden is emphasized.

Sleep deprivation has been confirmed to have antidepressant activity for more than forty years (Pflug and Tolle 1971). The rapid and often complete remission of depressive symptoms is recorded after one night of complete sleep deprivation. These dramatic remissions are usually temporary and are replaced by relapses after short-term sleepiness or recovery sleep (Sack et al.1988). Recently, a package of triple chronotherapeutic interventions consisting of the first night total sleep deprivation, followed by a three-day sleep phase shift and

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bright light therapy in the morning for three daysproposed by Wu et al. (2009) was reported to provide rapid and permanent remission in bipolar depression. In this article, we present the case of bipolar depression paitent who underwent triple chronotherapy in addition to psychopharmacological treatment. In the light of this case, we aimed to discuss the importance of treatment modalities that provide rapid and permanent response in bipolar depression.

CASE

S.A., a 58-year old university graduate male patient, divorced and unemployed was living with his family. He consulted our outpatient clinic with complaints of low mood, avolition, sleep disorder, introversion, inability to enjoy life and inability to work which had increased over a month after starting three months previously. It was learned that his problem started with depressive symptoms after psychosocial stressors in 1997 when he was put on escitalopram (10 mg/day), quetiapine (200 mg/day) and valproate (1500 mg/day) treatment for about ten months on a regular basis during this period. He had also benefited from trazodone treatment. In 2013, he had symptoms of pressured speech, increased activity, increased money spending, increase in sexual desire, inflated self-esteem and skepticism. It was learned that this period had lasted about one year and was followed by depressive complaints. He had used sertraline (200 mg/day) for a period of about six months in this depressive episode, but having partially benefited from the treatment, he had stopped it with his own desire. He had remained on regular psychiatric follow-up and mood stabilizer treatment for BD since May of 2015. In June 2015, he received inpatient treatment in a psychiatry clinic because of increased depressive symptoms. His drug therapy at the time of consulting us was learned to be started at that time. After discharge, his complaints had partially regressed, but he still had depressed mood.

He had a medical history of hypertension, diabetes and a coronary by-pass operation in 2008. His brother had a history of alcohol use disorder, his sister's son had depression, and his older sister had epilepsy. The patient had no alcohol-substance use except 1 pack/day smoking for 35 years. In his mental state examination, his self-care was decreased, his psychomotor activity was slightly decreased, his speech quantity and speed were decreased, his sleep was irregular and his affect was depressive. Concerns about guilt, worthlessness and death were present in his thought content. At admission as an inpatient, his Hamilton Depression Scale (HAM-D) score was 18. Routine biochemistry analyses, thyroid function tests, complete blood count were within normal limits. His cranial magnetic resonance imaging (MRI) and electroencephalography (EEG) were normal. Escitalopram (10 mg/day), quetiapine (300 mg/day) and valproate (1500 mg/day) were administered. Total sleep deprivation, sleep phase shift and bright light therapy were planned as treatment. The patient was followed up with daily assessments on the HAM-D, the visual analog scale (VAS) and the Epworth Sleepiness Scale (ESS) during the triple chronotherapy.

Complete sleep deprivation was performed from 09.00 am until 18.00 pm of next day (33 hours). The patient was under control by nurses and interns in the clinic during the sleep deprivation night and on the following day. Bright light therapy was started on the morning of sleep deprivation. 10,000 lux power of light was applied for 30 minutes as the light treatment. After scoring 65 points on the self-assessment morningness-eveningness questionnaire, the phototherapy of the patient was planned to start at 05:45 and was applied for a total of 15 times. Sleep phase shift began at the day following the complete sleep deprivation. The bedtime and waking time of the patient were planned as 18.00-02.00 on the first day, 20.00-04.00 on the 2nd day and 22.00-06.00 on the 3rd day respectively. HAM-D score decreased to 8 at the end of the first day after sleep deprivation treatment; and were determined to be 6, 4 and 3 at the following controls. The energy, happiness, depression and stress levels of the patient were evaluated with VAS. Before treatment the VAS values were 3.2 cm for energy, 2 cm for happiness, 8.5 cm for depression and 5.2 cm for stress; and at the end of the first day these values were, respectively, 5.7 cm, 4.9 cm, 3.4 cm and 1.4 cm. and became, respectively 9 cm, 8.5 cm, 1 cm and 2 cm before discharge. Pre-treatment score on the ESS was 8, and became 10 at the end of the first day of treatment, and 5, 5 and 4, respecively, in the following controls. During the treatment there were not any side effects other than a mild headache that disappeared in 2-3 days without need for additional medication and was attributed to the bright light therapy. Blood level of Valproic acid was determined as 72.9 ug/ml. Lamotrigine (25 mg/day; titrated up to 200 mg/day.) was added to the patient's treatment after triple chronotherapy. After 3 weeks of inpatient treatment in our clinic he was in remission, had no complaints and his HAM-D score was 3. He was discharged on maintenance treatment with valproate (1500 mg/day), quetiapine (300 mg/day), escitalopram (10 mg/day) and lamotrigine (200 mg/day). After discharge, the patient was on weekly polyclinic follow-up for one month and thereafter continued with monthly follow-up visits. Recurrence of depressive symptoms was not seen for 4 months during follow-up.

DISCUSSION

The depressive episode of BD is an important component of the disease with high morbidity and mortality rates and increased risk of suicide (Wulsin et al. 1999). Development of a rapidly effective and sustainable treatment has long been

aimed for bipolar depression. The response to traditional treatments usually requires 2-8 weeks, but the risk of suicide and symptoms persists during this time (Machado-Vieira et al. 2008). Melatonin secretion and circadian rhythm abnormalities have been reported in BD (Plante and Winkelman 2008). Regulation of circadian rhythm in mood disorders is known to improve symptoms rapidly (Bunney and Potkin 2008). As suggested in excess of 60 studies involving more than 1700 patients worldwide, sleep deprivation is the most common chronotherapeutic intervention used as it leads to reduction of depressive symptoms 40-60% of the patients within 24-48 hours (Benedetti et al. 2007).

The benefit of adopting chronotherapeutic approaches to the treatment of depression has been the subject of several reviews. Although sleep deprivation response is transient, its effect can be sustained with interventions to circadian rhythm such as bright light and sleep phase shift and with concomitant medications like selective serotonin reuptake inhibitors and lithium (Machado-Vieira et al. 2008, Benedetti et al. 2007). The patient whose case is discussed here had also been on antidepressant treatment for about 10 months. However, we planned triple chronotherapy as his complaints persisted and a quick response was desired.

A rapid antidepressant response with total sleep deprivation was reported in both unipolar and bipolar depression studies (Benedetti et al. 2007, Wirz-Justice et al. 2005). However, clinical use of this technique is limited due to the typical rapid reversal of this response after sleep. Addition of pharmacotherapy, sleep phase shift and bright light therapy to sleep deprivation was shown to be effective in preventing recurrence of depression (Wu et al. 2009, Echizenya et al. 2013). In our treatment protocol we also applied sleep phase shift after complete sleep deprivation and bright light treatment for 15 days. Thus, we prevented the rapid worsening of symptoms with recovery sleep after full sleep deprivation.

A combined total sleep deprivation, sleep phase shift and bright light therapy, called triple chronotherapy, was reported to provide a rapid improvement in depressive symptoms over 9 weeks with concomitant pharmacotherapy (Echizenya et al. 2013). Considering its early encouraging results, triple chronotherapy seems to be a method of inpatient treatment close to ideal with few side effects, easy technique and low cost. Despite the encouraging results, triple chronotherapy method was used in the treatment of patients with high risk of suicidal diseases only in one study. In this study, a slightly different variation of chronotherapy including three-day sleep deprivation and three-day bright light therapy sessions was used in addition to lithium treatment (Benedetti et al. 2014). With sleep deprivation treatment, a rapid improvement in depression is achieved, but the therapeutic effect lasts until the end of the day of sleep deprivation treatment. Relapse occurred in 80% of patients who did not use medication after the following night's sleep or a short sleep (Giedke and Schwarzler 2002). The general lack of interest in sleep deprivation therapy has been reported to be due to relapses occurring after the recovery sleep (Wirz-Justice and van den Hoofdakker 1999). On the other hand, we think that triple chronotherapy instead of sleep deprivation alone as applied in the case of our patient along with psychopharmacological drugs can effectively eliminate this problem.

Previous clinical studies about light therapy had predominantly focused on seasonal affective disorder. However, the place of light therapy is worthwhile in the treatment of mood disorders, especially bipolar depression and major depressive disorder. Complete sleep deprivation or light therapy was combined with the use of psychotropic substances in most studies on the efficacy of light therapy for bipolar depression or major depression (Benedetti et al. 2014). Light therapy was reported to provide a net benefit of 12-35% in non-seasonal depression and application with standard treatments had synergistic effects (Kripke 1998). Yamada et al. (1995) reported that bright light therapy significantly reduced the severity of depression in non-seasonal depression. In addition, using the bright light therapy with 10.000 lux power and its repetition for 15 days eliminated the problem of inadequate treatment in our case.

Bright light therapy was associated with suicidal behavior and manic shift (Praschak-Rieder et al. 1997, Chan et al. 1994). In a meta-analysis evaulating light therapy in bipolar disorder, disease severity was shown to be significantly reduced by a combination of light therapy with drug administration or complete sleep deprivation in bipolar depression. Furthermore, there was a significant decrease in the intensity of symptoms after augmentation of light therapy when compared to treatments without light therapy (Tseng et al. 2016). Sleep deprivation is associated with a higher manic shift incidence in patients with bipolar depression and seasonal mood disorders. However, any symptoms related to hypomania or mania were not observed during the follow-up of the patient discussed here.

The decrease in HAM-D scores of our patient after triple chronotherapy was reflecting the rapid improvement in depression. In conclusion, psychopharmacological treatment combined with triple chronotherapy in bipolar depression may be effective in preventing relapses after sleep deprivation. For those patients requiring early treatment response, triple chronotherapy with fewer side effect profile may be a combination alternative and augmentative treatment option. In our case, we found a significant decrease in depressive symptoms as early as 48 hours after triple chronotherapy. Rapid response to adjuvant chronotherapy is important for the treatment of bipolar depression. Chronotherapy offers a safe and noninvasive method to accelerate, strengthen and maintain the antidepressant response.

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