CASE REPORT

Manic Switch On Mirtazapine: A Case Report

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Abstract

Background: In recent years, more cases of manic switches on Mirtazapine have been reported. In this report, we discuss a case of manic switch in a gentleman who was treated as unipolar depression. A 66-year-old man presented to psychiatry 8 months following a nephrectomy for symptoms of depression. Treatment with Sertraline 50mg daily was initiated and titrated to 150mg, along with Zolpidem and Clonazepam to aid his sleep. Despite these medications he never achieved remission and continued to have persistent anxiety and insomnia. Due to suboptimal control, treatment was changed to Mirtazapine 15mg daily. At day 20 he showed symptoms of mania which included talkativeness, increased goal directed activities, reduced need for sleep and socially disinhibited behavior. Mirtazapine was discontinued, and treatment was changed to Sodium Valproate, optimized to 1000mg daily, augmented with Quetiapine 150mg daily. Remission was achieved after 4 months and he has remained asymptomatic for 2 months. This was his first episode of mania, and a diagnosis of Bipolar I disorder was made.

In conclusion, antidepressant induced manic switches are common, they are relatively under-appreciated and under-reported, especially with the use of sleep-promoting antidepressants. All antidepressants should be considered to be a potential mediator of a switch in view of its pharmacological properties.

Keywords: Mania, Switch, Bipolar, Antidepressants, Mirtazapine, Depression

Introduction

Antidepressants have been long known to induce mania, either alone or in combination. Mirtazapine belongs to noradrenergic and specific serotonergic antagonistic group, with relatively less numbers of reports [1] causing manic switches compared to older groups like TCAs, SSRIs, and Venlafaxine. However, over the last several years, more cases of manic switches caused by mirtazapine have been reported [2-6]. Here, we discuss a case of manic switch after initiation of Mirtazapine in an elderly man who has been treated as unipolar depression.

Case Report

Mr CAL is a 66-year-old married man, who has undergone Right nephrectomy at 58 years old, for renal carcinoma. He was
initially referred to psychiatry by his surgeon, for symptoms suggestive of depression following the nephrectomy. He experienced poor sleep, lethargy, loss of interest, and multiple somatic complaints over a period of 8 months. His main stressor was the nephrectomy and the thought of living with 1 kidney. He exhibited no symptoms of mania, hypomania or ADHD in the past and had no family history of bipolar affective disorder. He was treated as depression and prescribed with Sertraline 50mg daily, which was later titrated up to 150mg daily. Concomitant medications were Zolpidem and Clonazepam to aid his sleep. Despite these medications, he has never achieved remission. Persistent anxiety and insomnia remained as a disabling symptom. Due to long duration of suboptimal control, treatment was changed to Mirtazapine at 15mg daily. At day 20 of Mirtazapine, he became increasingly talkative, easily irritable, and had increased energy level despite reduced amount of sleep. He also exhibited increased goal directed activities and socially disinhibited behaviour. No features of delirium were present. These symptoms continued for 9 days before his clinician was alerted about the switch. Blood parameters were within normal limits with the exception of his creatinine level (144 umol/L). Mirtazapine was discontinued at day 29 of treatment, and sodium valproate was started on 400mg daily. Though Mirtazapine was completely discontinued, Mr CAL took 4 months to achieve remission of manic symptoms. Sodium valproate was optimized to 1000mg daily and augmented with Quetiapine 150mg daily. He remained asymptomatic for 2 months following combination of sodium valproate and quetiapine. This was his first episode of mania, and a diagnosis of Bipolar type I disorder was made.

Discussion

Over the years, studies have shown manic switch while on antidepressants were reported to be higher in the case of tricyclic antidepressants (TCAs) and venlafaxine, with lower risk for selective serotonin inhibitors (SSRIs) and bupropion [7]. In fact, other antidepressants like mirtazapine, trazodone, and agomelatine, were even safe to be use in low dose in bipolar patients for their hypnotic effects [7].

Several studies have attempted to hypothesized the possible underlying process in the development of a manic switch, however it is found that the precise mechanism has yet to be elucidated.

In a review by Salvadore et al [8], it was suggested that the role of the serotonergic, catecholaminergic, noradrenergic, and dopaminergic systems targeted by antidepressants may provide clues to the mechanism of switch process. Based on the review, dopaminergic drugs showed a higher rate of mania, as evidenced by a study done by Murphy and colleagues [9] where 6 out of 7 subjects who were treated with L-dopa developed hypomania. This suggests that the increased functional brain norepinephrine and dopamine may be associated with development of a manic switch. Similarly, stimulants with dopaminergic properties such as amphetamines produced manic like states in animal models with bipolar disorder [10-14]. This is further evidenced by animal models where decreased dopaminergic activity in the mesolimbic cortex and nucleus accumbens lead to depressive like states which were reversed by the use of antidepressants that potentiate dopaminergic activity [15]. Glutaminergic system has also been implicated in the switch phenomenon,
where inhibition of certain glutamic receptors in rodents produced symptoms that resembles mania [16]. Alternatively, many studies have also mentioned the role of sleep deprivation as a significant trigger of manic switches in both bipolar and unipolar depression [17-19]. One possible explanation is by direct regulation of brain dopaminergic receptor sensitivity seen in a study done on the rat limbic system[20]. Discontinuation of an antidepressant may also precipitate a switch, where withdrawal of SSRI have been implicated in a study where they reported 10 out of 19 patients with bipolar depression developed mania after SSRI was discontinued [21]. Several hypotheses were postulated to explain this phenomenon, which includes hyposerotonergic mania, noradrenergic hyperactivity, rapid eye movement rebound, and hyperdopaminergic mania [22-25]. In Mr CAL, the combination of long standing insomnia and the abrupt withdrawal of chronic SSRI use may have contributed to his manic switch. In addition, pharmacological properties of Mirtazapine, namely noradrenergic and serotonergic antagonist may have aided in the switch.

Various risk factors have been identified that may predict a switch during treatment with antidepressants. In a study done by Henry et al [26], 27% of bipolar depressed patients developed switches to hypomania and mania shortly after starting antidepressants. In the study, it was found that gender, age, and diagnosis (Bipolar type I and Bipolar type II) did not affect the risk of switch, however patients who had a hyperthymic temperament was shown to have a greater risk of switching[26]. Other risk factors for mania includes a family history of bipolar disorder, a depressive episode with psychotic,melancholic ,and atypical features, a younger age of onset of depression, and treatment resistant depression [27].

Lower risk of manic switch with mirtazapine and other sleep promoting antidepressants like tradozone, have been found in various clinical trials [7]. One in particular showed the rate of treatment induced manic switch was highest with bupropion (35.7%), followed by venlafaxine (30.6%) and SSRI (30.1%), but no switches were observed for mirtazapine [28]. In a review by Fawcett et al on the safety profile of Mirtazapine, it was found to have lesser anxiety inducing effect compared to placebo, making it a safer option because of its sedating profile [29]. Thus, based on its sedating effect, its treatment of insomnia in bipolar patients may improve the outcome of the disorder, and may even decrease the risk of switching, provided other risk factors for manic switch have been examined, ie; extreme age of onset or family history of bipolar illness and past history of mania [28].

However, despite mirtazapine having less incidence of switches, manic switch have been mentioned in multiple cases [28]. The first was seen in a patient where it was used to augment fluoxetine [30]. In another patient, hypomania was reported after combining with sertraline [31]. In another 2 cases, Liu et al reported a case of manic switch in an elderly woman with hypertension and diabetes mellitus presenting with depression at a later age, and De Leon et al reported a manic switch involving a case of depression with comorbid stroke affecting the frontal lobe [32,33].

**Conclusion**

Although in practice, antidepressant induced manic switches are common, they are relatively under-appreciated and under-reported, especially with the use of sleep promoting antidepressants. It is important to identify risk factors for manic switch,
especially in extreme age population. All antidepressants should be considered to be a potential mediator of a switch in view of its pharmacological properties.

References


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