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Delirium Associated with Bupropion Sustained Release

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Bupropion is a newer antidepressant with the main pharmacological effects of dopamine and norepinephrine reuptake inhibition. The usage of bupropion is relatively safe with minor side effects. In some rare instances, psychosis and delirium may emerge because of its potentiating effects on dopaminergic neurotransmission. Here we presented a case of bupropion SR (300mg/day) related to delirium with concurrent quetiapine (400mg/day) usage. Although there are fewer side effect profiles of bupropion SR, our case revealed acute delirium after administration of a therapeutic dosage of bupropion. Poor cytochrome P450 2D6 (CYP2D6) and cytochrome P450 2B6 (CYP2B6) metabolism and underlying bipolarity may contribute to this adverse effect. Clinicians should be cautioned when prescribing bupropion SR to vulnerable populations.

Key words: bupropion, delirium, bipolar disorder

INTRODUCTION

Bupropion is a newer antidepressant which has the main pharmacological effects of dopamine and norepinephrine reuptake inhibition.[1] The usage of bupropion is relatively safe with minor side effects of headache, insomnia, dry mouth, tremor, nausea, agitaton and restlessness. However, high dosage of bupropion may increase seizure risk.[2] In some rare instances, psychosis[3,4] and delirium[5-8] may emerge because of burpropion's potentiating effects on dopaminergic neurotransmission. Three formulations of bupropion are currently available, including immediate release (IR), sustained release (SR) and extended release (ER). Bupropion SR seems to have better tolerability and fewer side effects compared to bupropion IR.[2] However, delirium associated with bupropion has been reported with the combination of other medications which may interact with bupropion.[5-8] Here we presented a case of bupropion SR related to delirium with concurrent use of quetiapine.

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CASE REPORT

Mr. A, a 23 year old college student, initially visited our outpatient department with the chief problems of a depressed mood, lack of interest and energy, insomnia, poor appetite, poor concentration, negative thoughts of worthlessness and suicidal tendencies for one month. These depressive symptoms also impaired his academic performance and interpersonal relationships. He became social withdrawal and finally dropped out of college. At first, he received fluoxetine 20 mg and zolpidem 10 mg per day. When a suicide attempt by drug overdose occurred, he was admitted to our hospital for 5 days and then followed up in our clinics. However, a manic episode developed after administration of fluoxetine for two weeks with symptoms of an irritable mood, racing thoughts, talkativeness, a decrease in need for sleep, psychomotor agitation, buying sprees, increased reckless behavior and violent tendencies. Antidepressant induced mania was suspected and we revised his diagnosis as bipolar disorder, not otherwise specified. Fluoxetine was stopped and we added valproate 1000 mg per day for his manic symptoms. We slowly added quetiapine to 400 mg per day and decreased valproate to 500 mg for his maintenance treatment. His condition was relatively stable for one year and valproate was gradually stopped. However, he broke up with his girl friend several weeks ago before coming to our clinic. Depressive symptoms of low mood, insomnia, poor appetite, social withdrawal, psychomotor retardation and negative thoughts developed

Table 1 Summary of the cases of bupropion associated delirium (reference from 5-8)

Authors	Journal	Patient and diagnosis	Medication
Liberzon I.et al	Am J Psychiatry 1990;147:1689-90	75 year old male, Parkinsonism and depression	*Bupropion **IR** 450 mg /day* with haloperidol 2mg/day, amantadine 300mg/day, beztropine 2 mg/day
Dager SR. et al	J Clin Psychiatry 1990;51:307-8	48 year old male, bipolar disorder	*Bupropion **IR** 450 mg /day with* lithium 1800 mg /day
Van Putten T. et al	J Clin Psychopharmacol 1990;10:234	41 year old male, major depressive disorder	*Bupropion **IR** 300 mg/day,* previous usage of fluoxetine 60 mg/day
Chan CH. et al	J Clin Psychopharmacol 2006;26:677-9	51 year old male, major depressive disorder	Fluoxetine 40mg/day, *bupropion **SR** 150 mg/day,* bromazepam 3 mg/day, alprazolam 1 mg/day

for one week. We added bupropion SR 300 mg per day for his depressive symptoms under the former treatment of quetiapine 400 mg per day. As a result, he had dizziness and somnolence with subsequent confusion after using bupropion for 3 days. In the 3 days, he also did not regularly take quetiapine because of somnolence. He was sent to our emergency room (ER) and revealed disorientation, psychomotor agitation, and suspicion with incoherent and irrelevant speech. He shouted in the ER and claimed that he was being monitored and watched. Haloperidol 10 mg and lorazepam 4 mg were injected intramuscularly for his agitation. Physical examination and routine laboratory studies, including urine toxicology screening, were all in normal range. Computed tomography (CT) of the brain did not show significant abnormal findings except for cavum septi pellucidi. He was admitted to the acute psychiatric ward under the impression of acute delirium.

At admission, we stopped his medication and set up an intravenous routine for hydration. He became alert and orientated the day after admission and could not recall events from the previous day. He denied any physical discomfort and history of drug or substance misuse. He had appropriate affect, normal speech and behavior. Physical and more detailed laboratory exams, including electroencephalography (EEG), were all normal. We used valproate 1000 mg/day and quetiapine 400 mg/day for him and his affect was stable under this treatment. There were no more episodes of delirium or mood swings during hospitalization. Therefore, he was discharged in stable condition after three weeks of admission. To date, he is regularly following up in the outpatient department and exhibits a euthymic state under his maintenance treatment.

DISCUSSION

The patient demonstrated what we believe to be a case of bupropion related delirium. He had symptoms of disorientation, confusion, disorganized speech and perceptual disturbance. These symptoms emerged after using bupropion 300 mg/day for 3 days and rapidly resolved after discontinuation of bupropion. During the whole course of events, there was no history of seizure attacks and his EEG finding was negative. His delirious symptoms persisted for 2-3 days and postictal confusion was less likely to last for such a long period. We did not re-administer bupropion because of ethical issues and the patient's insistence.

Bupropion is metabolized via CYP2B6 to hydroxybupropion and then further metabolized via CYP2D6.[8,9] Adverse effects may arise because of drug interactions with CYP2B6 or CYP2D6 and individual vulnerability of medication metabolism.[8] Increased dopaminergic activity or acumination of bupropion's active metabolite, hydroxybupropion, may cause delirium symptoms.[8]

There are four case reports in previous studies related bupropion induced delirium. We summarize these articles in Table 1.[5-8] Three of them studied the bupropion immediate release (IR) formulation and one studied the sustained release (SR) formulation. All these cases combined bupropion with dopaminergic agents or medications which may interact with bupropion metabolism. Although our patient took bupropion and quetiapine concurrently, quetiapine is metabolized by cytochrome P450 3A4 (CYP3A4)[10] and does not interact with the metabolism of bupropion. It seems less likely that the cause of delirium arises from the drug interaction of bupropion and quetiapine. Even if bupropion SR has fewer side effect profiles, our case revealed acute delirium after administration of a therapeutic dosage of bupropion for 3 days. In our case, poor CYP2D6 and CYP2B6 metabolism and underlying bipolarity may

have contributed to this adverse effect. However, further studies are warranted to verify this point.

CONCLUSION

Bupropion SR has better tolerability and fewer side effects, however, caution should be taken when prescribing bupropion SR to vulnerable populations.

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