

Complex drug interaction of carbamazepine, fluvoxamine and clozapine in a patient with bipolar depression

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Dear Editor,

In the treatment of bipolar depression, classes of commonly used drugs include lithium, anticonvulsants and antipsychotics. Sometimes antidepressants can also be considered a choice¹. Some of them may induce or inhibit cytochrome P450 isoenzymes and, when combined in clinical use, may not accurately predict the effects of drug interactions. For example, previous studies have shown that carbamazepine (CBZ) can reduce plasma levels of clozapine (CLZ), while fluvoxamine (FVX) can increase plasma levels of CLZ². Additionally, the combined administration of FVX and CBZ may increase plasma concentrations of CBZ³. Here, we report the drug interaction in a patient with bipolar depression with the concomitant use of CBZ, CLZ and FVX.

A 46-year-old man with bipolar II disorder treated with 800 mg quetiapine and 400 mg CBZ controlled release daily. He was admitted to an acute psychiatric ward because of his depressed mood, insomnia, and suicidal thoughts. He maintained a blood CBZ level of 8.86 µg/mL on admission (normal range: 4 to 12 µg/mL). Initially, we added 50 mg of agomelatine for depression and insomnia, but to no avail. Therefore, we administered 100 mg FVX plus 100 mg CLZ in place of quetiapine and agomelatine. The result was wonderful in improving his depressive symptoms and insomnia, with the exception of dizziness that complained of the patient during the day. The blood level of CBZ increased to 13.83 µg/mL after re-verification. We adjusted the dose of CLZ from 100 mg to 50 mg and used fast-acting CBZ instead of controlled release without dose modification. After adjustment, her dizziness improved and also remained effective in cases of depression and insomnia with a CBZ blood level of 10.82 µg/mL.

To our knowledge, this is the first case describing the concomitant use of CBZ, FVX and CLZ. Previous studies had suggested that FVX increased plasma levels of CLZ and CBZ as an inhibitor of

CYP1A2 and 3A4, respectively^{2,3}. In contrast, CBZ decreased the plasma level of CLZ by being a CYP3A4 inducer². The increase in blood levels of CBZ in this patient could be explained mainly by the effect of FVX. Although FVX and CBZ have an opposite effect on CLZ, we have suggested that the effect of FVX on CLZ was much greater than that of CBZ on CLZ, which would reduce the dose of CLZ required in this patient. Formal pharmacokinetic studies examining the potential interaction between these three drugs are needed to confirm this finding. In summary, this case highlights the importance of monitoring plasma concentrations or clinical status when multiple drugs that inhibit or induce CYP450 are combined.

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