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Delirium Associated with Mirtazapine Substituting Duloxetine in a Depressed Patient with Alzheimer's Dementia

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Mirtazapine Related Delirium in a Depressed Alzheimer's Patient

Depression is a common and important comorbidity in dementia, so antidepressants are frequently used for treating depression in dementia [1]. Limited evidence suggests that for certain elderly patients, mirtazapine may be more effective for treatment of depressive patients who have dementia, while it is uncommon for duloxetine to be administered in such cases. Mirtazapine may be tolerable for all ages [2] and taking it alone in overdose is relatively benign and no patients develop delirium. To our knowledge, five cases have been reported in which delirium were caused by miratapine, one was observed in depressed with an early stage of senile dementia of Lewy body type, and two major depressed patients with mild memory impairment or with small lacuna of the left basal ganglion, the last two suffering hyponatremia [3-6]. We reported a case of delirium associated with mirtazapine substituting duloxetine in a depressed patient with Alzheimer's dementia in the absence of hyponatremia. Because one case has been reported in which delirium was observed in an 86-year-old woman with Alzheimer's dementia after taking duloxetine [7].

Ms Z, an 69-year-old woman was hospitalized in our department with depression. She visited mental clinic for backache, waist discomfort and low mood and was diagnosed as major depressive disorder. She had been treated with duloxetine 60 mg per day (maximum 90 mg per day) for 8 months. She stopped treatment for symptoms improvement with residual symptoms including fatigue and palpitation 3 months ago. she had presented with palpitation, insomnia, significant weight loss, decrease in appetite, retardation, dejection, poor memory, feeling of worthlessness and guit, and occasional suicidal ideation for 2 months. After inward, brain CT scan suggested "right basal ganglia ischemic focus or lacunar infarction" as is consistent with cerebrovascular disease (these findings are not considered abnormal in a woman of this age). A diagnosis of major depressive disorder was made. The patient was treated with duloxetine 60 mg daily for 12 days which followed by 90 mg daily. No improvements were observed, instead, the patient felt worsening anxiety and could not sleep. On day 14, duloxetine was reduced to 30 mg and mirtazapine 30 mg per day was started. Duloxetine was withdrawn on day 15. However, severe anxiety was observed. Although, on day 18, mirtazapine was titrated up to 45 mg per day, patient still complained of chest distress, palpitation and insomnia while the blood pressure and heart rate were normal. So lorazepam 2 mg per day or alprazolam 0.8 mg per day was combined respectively of mirtazapine, while clonazepam 1 mg was given by intravenous drip respectively on day 18 and 22. On day 22, the patient's mental status changed markedly and she show apparent disturbance of consciousness. Severe disorientation and visual hallucination became significant at night, Therefore, the patient was diagnosed with drug-induced delirium and mirtazapine was withdrawn. On day 28, brain MRI scan suggested "dual basal ganglia ischemic focus or lacunar infarction" as is roughly consistent with on finding on admission. The patient could not sleep and wandered in ward, so olanzapine 2.5 mg was given at night to improve the delirium [8]. Her delirium was vanished by day 34, while her dementia was recognized for poor memory and visuospatial ability. Her daughter reported that patient had poor memory one year ago in fact. Minimental state examination predicated 18/30 and the subject could not draw clock face components, so diagnosis was revised to dementia, Alzheimer'dementia. Patient complained of palpitation, then venlafaxin 75 mg per day was started to treat her anxiety. On day 42, the patient went home with relieved anxiety. Informed consent was obtained in writing from subject.

According to this subject, mirtazapine and duloxetine which are metabolized in the liver by the cytochrome P450 (CYP) enzyme system directly can contribute to the onset of delirium based on the timing of the onset of delirium and the timing of drugs administered [9]. *In vitro* studies have indicated that CYP2D6 and, to a lesser extent, CYP1A2 are the major isoforms involved in metabolizing mirtazapine, weak inhibitor of

CYP isozymes, which has minimal inhibitory effects on the various CYP isoforms *in vitro* and appears to carry a low risk for drug pharmacokinetic interactions [10]. It is proved that coadministration of fluvoxamine 50 mg per day, potent inhibitor of various CYP isoforms, and mirtazapine 30 mg per day resulted in 3- and 4-fold increases in plasma concentrations of mirtazapine [11]. Thus, the inhibitory effect on the CYP2D6 may mediate metabolism of mirtazapine. Duloxetine is extensively metabolized in the liver primarily by CYP1A2 and has clinically insignificant inhibition on it. Moreover, duloxetine is moderate inhibitors of CYP2D6. The potential of duloxetine to affect other drugs has been evaluated by a number of drug interaction studies, for example that duloxetine 60

mg twice daily for 3 weeks increased the C_{max} and AUC of desipramine [12,13]. According to this case, delirium occurs when dose of duloxetine 30 mg per day was reducing and that of mirtazapine 45 mg per day was administrating. It can be inferred that disposition of duloxetine, a serotonin and norepinephrine re-uptake inhibitor and mirtazapine, a noradrenergic and specific serotonergic antidepressant, result in increasing blood concentrations of mirtazapine, thus enhancing serotonin and norepinephrine reuptake [9]. A central increase of the serotonin and norepinephrine have both been implicated in the pathogenesis of delirium [14], though the exact mechanism by which delirium is induced has not been clarified. There remains possibility that a hyper-responsitivity to the effects of serotonin and norepinephrine in the brain of this patient suffering from Alzheimer's disease could be the reason of development of delirium.

Given the popularity and good tolerability of mirtazapine use in elderly and comorbid depressed patients [2,15], the risk of rare but severe delirious states should be taken into consideration. A relatively low dosage from beginning of the treatment is recommended. In addition, the replacement should be slow to avoid of the drug interactions when mirtazapine substitutes for a potent inhibitor of CYP2D6, e.g., duloxetine, for the patient with physical conditions increasing vulnerability to this side effect.

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