Salib, E. (1997) Elderly suicide and weather conditions: Is there a link? *Int. J. Geriatr. Psychiat.* **12**, 937–941.

Wæhrens, J. (1981) Connection between frequency of suicide and atmospheric pressure. *Ugeskrift Læger* **143**, 2993–2996.

Serotonin Syndrome with Mirtazapine–Fluoxetine Combination

Dear Editor

I would like to describe a depressed woman who developed serotonin syndrome with mirtazapine and fluoxetine. A MEDLINE search (mirtazapine and fluoxetine, mirtazapine and serotonin syndrome) did not find similar reports.

A 75-year-old woman with chronic major depressive disorder had not responded, during the last 2 years, to desipramine, nortriptyline, sertraline and venlafaxine, with lorazepam and chlorpromazine. The last treatment with fluoxetine, 20 mg/day, chlorpromazine, 75 mg/day, and lorazepam, 2.5 mg/day, for 3 months had not been successful. Then, fluoxetine was discontinued and mirtazapine, 30 mg/day, was soon started with lorazepam, 2.5 mg/day, and chlorpromazine, 50 mg/day. A few hours after the first mirtazapine dose she had a severe syndrome with dizziness, headache, nausea, dry mouth, intense anxiety and agitation with suicidal ideas, difficulty walking, marked resting tremor of the hands and insomnia. Theses symptoms worsened during the following 3 days. On day 5 she discontinued mirtazapine. On day 6 she felt better. On day 7 she restarted fluoxetine, 20 mg/day. Dizziness, nausea, headache and agitation disappeared in a few days. Tremor, anxiety, difficulty walking, dry mouth and insomnia improved during the following 10 days. She had not been taking other drugs.

The timing of the symptoms (onset with mirtazapine, disappearance/improvement with mirtazapine discontinuation) suggests a causal link.

In clinical trials versus placebo, insomnia, agitation, vertigo, headache and nausea were not significantly more frequent with mirtazapine, apart from dry mouth (Burrows and Kremer, 1997). In this patient these symptoms were severe, and associated with other severe symptoms, suggesting an interaction with the associated drugs.

Due to its long half-life, fluoxetine would still have been present when she was taking mirtazapine.

Mirtazapine, by alpha-2-adrenoceptor antagonism, enhances serotonergic and noradrenergic transmission. It has low affinity for dopaminergic D1 and D2, muscarinic cholinergic, alpha-1 and serotonergic 5-HT1 receptors. It has high affinity for histamine H1 and serotonergic 5-HT2/5-HT3 receptors (de Boer, 1996). It is metabolized by cytochromes CYP2D6, 1A2, 3A3/4, which it does not inhibit significantly *in vitro*. Its pharmacokinetic is independent of polymorphic CYP2D6 activity *in vivo*, suggesting that fluoxetine, a potent CYP2D6 inhibitor, should not have changed it significantly in this patient (Delbressine and Vos, 1997; Preskorn, 1997). A pharmacodynamic interaction with fluoxetine seems more likely. This patient's syndrome had many symptoms of the serotonin syndrome, which may present with restlessness, resting tremor, difficulty walking, anxiety, agitation, headache, insomnia, nausea, myoclonic jerks, muscular rigidity, confusion, hypomania, sweating, fever, tachycardia, hypertension/hypotension, tachypnea, vomiting, diarrhoea, flushing of the skin, abdominal cramps, seizures and coma. The difference between this syndrome and the adverse effects caused by serotonergic drugs is the clustering of symptoms, their severity and duration (Lane and Baldwin, 1997). The serotonin syndrome is produced most often by the concurrent use of two or more drugs that enhance serotonin activity, and it usually develops shortly after the addition of another serotonergic drug (Lane and Baldwin, 1997). In this patient, the

serotonin syndrome may have been caused by the sum of the serotonergic effects of mirtazapine and fluoxetine. The serotonin syndrome appeared despite the concurrent use of chlopromazine, which, by blocking 5-HT1/5-HT2 receptors, was reported to treat it (Gillman, 1997). The same mirtazapine, by blocking 5-HT2/5-HT3 receptors, was reported to treat the serotonin syndrome (Hoes and Zeijpveld, 1996). This suggests that the mirtazapine–fluoxetine combination potently increased serotonin activity, and/or this patient had a marked sensitivity to serotonin, possibly age-related.

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REFERENCES

Burrows, G. D. and Kremer, C. M. E. (1997) Mirtazapine: Clinical advantages in the treatment of depression. *J. Clin. Psychopharmacol.* **17**(Suppl. 1), 34S–39S.
de Boer, T. (1996) The pharmacologic profile of mirtazapine. *J. Clin. Psychiat.* **57**(Suppl. 4), 19–25.
Delbressine, L. P. C. and Vos, R. M. E. (1997) The clinical relevance of preclinical data: Mirtazapine, a model compound. *J. Clin. Psychopharmacol.* **17**(Suppl. 1), 29S–33S.
Gillman, P. K. (1997) Serotonin syndrome treated with chlorpromazine. *J. Clin. Psychopharmacol.* **17**, 128–129.
Hoes, M. J. and Zeijpveld, J. H. (1996) Mirtazapine as treatment for serotonin syndrome. *Pharmacopsychiat.* **29**, 81.
Lane, R. and Baldwin, D. (1997) Selective serotonin reuptake inhibitor-induced serotonin syndrome: Review. *J. Clin. Psychopharmacol.* **17**, 208–221.
Preskorn, S. H. (1997) Selection of an antidepressant: Mirtazapine. *J. Clin. Psychiat.* **58**(Suppl. 6), 3–8.

'The Use of Selective Serotonin Reuptake Inhibitors for Depression and Psychosis Complicating Dementia'—1997, **12**, 519–527

Dear Editor

I read with interest the report of Burke *et al.* on the use of SSRIs in behaviour disturbances complicating dementia. They make a statement in the journal Vol. 12, 519–525, 1997 that both trazodone and buspirone have not been tested in a double-blind study. This is actually incorrect. We reported the first pilot study of buspirone and trazodone versus placebo in behaviourally disturbed Alzheimer patients in the *International Journal of Geriatric Psychiatry* in 1994, Vol. 9, 55–59, where buspirone had no benefit over placebo although trazodone showed a small but significant clinical improvement over placebo.

The conclusion from our study was that trazodone warranted further study in behavioural disturbances in dementia.

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