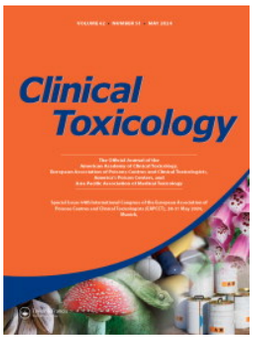

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LETTER

Mirtazepine Overdose and Miosis

To the Editor:

Mirtazepine is a tetracyclic antidepressant that acts by antagonizing presynaptic alpha-2 adrenoceptors, leading to increased noradrenergic neurotransmission. It also antagonises $5HT_2$ and $5HT_3$ receptors, and augments neurotransmission at the $5HT_{1A}$ receptor. There are few reports on its effects in overdose, and data are limited. We describe two cases of mirtazepine overdose.

Case 1. A 34-yr-old female with known depressive illness was admitted ~3 h after ingesting 56 30 mg tablets (1.68 g) of mirtazepine. She had also consumed ~3 units of ethanol. At admission, she was drowsy and unable to hold a conversation. Her Glasgow coma score was 8/15. Cardiac and respiratory function were normal, with a pulse rate of 75 beats per minute, blood pressure 137/75 mmHg, a QTc interval of 411 msec, and a respiratory rate of 10–15 breaths per minute with oxygen saturations of greater than 90% on air. Abdominal examination was unremarkable. Neurological examination revealed bilaterally constricted pupils. The patient was treated with 800 μg of naloxone, without effect on consciousness or pupil size. The patient had recovered completely by 14 h after ingestion, being alert and orientated, with normal pupillary size and reflexes. She declined further psychiatric support and self-discharged the following day.

Case 2. A 42-yr-old female was admitted 1 h after ingestion of eight 30 mg tablets (240 mg) mirtazepine and 100 mg of diazepam. On admission she was incoherent. Over the following 3 h, she became unrousable, with a Glasgow coma score of 5/15. Her pulse rate was 60 beats per minute, and blood pressure 85/46. Respiratory rate was mildly depressed. She had bilateral pinpoint pupils, brisk reflexes, and reduced muscle tone. She was treated with 5 L of crystalloid over the following 24 h to correct her hypotension. A urinary drug of abuse screen was performed, which was negative for opiates. Twenty-four hours after admission she had completely recovered with normal pupils and was discharged with psychiatric follow-up.

Both cases had a benign outcome, strengthening the impression that mirtazepine in overdose is not life-threatening (1,2). However, previous reports of mirtazepine overdose have not documented miosis as a feature. Indeed, one case of mirtazepine ingestion associated with co-ingestion of fluoxetine, tramadol, and sumatriptan led to serotonin syndrome with mydriasis (3).

Mirtazepine antagonizes $5HT_2$ and $5HT_3$ receptors but has only low affinity for the $5HT_1$ receptor. However, the blockade of the $5HT_2$ and $5HT_3$ receptors indirectly enhances $5HT_1$ actions, and this may explain how mirtazepine ingestion causes miosis.

There are serotonergic nerves and serotonin receptors in the iris ciliary body complex in rabbit and human eyes (4,5). Studies using buspirone, a partial $5HT_{1A}$ agonist, suggest that $5HT_{1A}$ agonists cause miosis, probably by inhibiting the sympathetic discharge to the iris dilator smooth muscle (6,7), via interneurons in the locus coeruleus and Edinger-Westphal nucleus. Selective $5HT_2$ antagonists produce a dose-related miosis (8,9), so mirtazepine's action at the $5HT_2$ receptors may augment the effect.

However, mirtazepine also has an alpha-2 antagonistic action. The impact of such antagonism remains uncertain, as some alpha-2 antagonists such as yohimbine cause mydriasis, while others such as mianserin can cause miosis.

In our two cases, mirtazepine overdose caused miosis. The exact mechanism is unknown but probably involves a combination of $5HT_{1A}$ receptor agonism with $5HT_2$ antagonism and possibly alpha-2 adrenoceptor antagonism. Not all patients presenting with reduced

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consciousness and miosis have opiate poisoning; mirtazepine overdose should be considered in the differential diagnosis of miosis.

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