Mr. A., a 55-year-old male with a history of schizoaffective disorder and cannabis abuse, is well known to our treatment team for refractory psychosis with a history of assaultive behavior during decompensation. This year, it seemed Mr. A. was spending more time in hospitals than out of them due to loss to follow up at outpatient clinics and his reluctance to take his medications. He was started on a trial of clozapine in previous years but did not adhere with his treatment, as he stated that it “made him feel like a donkey had kicked him” or “made him feel dead.” This summer he was found by police lying barefoot on a subway platform responding to internal stimuli.

Mr. A. was admitted to the psychiatric unit and restarted on his previous regimen of olanzapine, haloperidone, and benztrapine. However, he continued to demonstrate angry outbursts on a regular basis, necessitating antipsychotic sedation and constant visual observation by staff. Furthermore, Mr. A. complained of severe and constant drooling. He was malodorous as a result, with patches of dried drool on his clothes and a saliva-drenched towel around his neck at all times.

Mr. A. was evaluated by occupational therapy, who, in part, related his drooling habit to poor facial tone and jaw positioning. They provided him with oral exercises to assist him with handling of his profuse saliva. However, Mr. A. did not show any signs of improvement. Over the course of his stay, we tried several agents for psychosis and mood lability, including divalproex and paliperidone, with the goal of sending him home on a paliperidone decanoate. Mr. A.’s paranoia, grandiosity, and religious preoccupation worsened following discontinuation of olanzapine, however. He began to have daily loud outbursts due to persistent critical command auditory hallucinations. In light of his persistent severe and distracting auditory hallucinations, we convinced Mr. A. to give clozapine another try.

Several weeks into his stay, Mr. A. became discouraged, expressing regrets that “the summer was passing him by” while he remained in the hospital. We started him on mirtazapine nightly for depressed mood and poor sleep in hopes the medication would have the added benefit of reducing sialorrhea due to its antihistaminergic and potentially prokinetic muscarinic and serotonergic properties. Mr. A. tolerated the mirtazapine well and demonstrated marked improvement in sialorrhea a few days into treatment. After his mirtazapine was titrated to 45 mg daily, he no longer awoke with pools of saliva on his pillow, nor did he need to carry a towel for persistent daytime drooling.

DISCUSSION
Clozapine is frequently cited as the most effective antipsychotic agent for refractory psychosis, and yet providers remain hesitant to use it for patients with chronic severe mental illness.1 This is due in part to its potentially life-threatening side effects.2

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Disclosure: The authors have no relevant financial relationships to disclose.

doi:10.3928/00485713-20140609-02

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Treatment of Antipsychotic-Induced Sialorrhea

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effects such as agranulocytosis and seizures, as well as more common and unpleasant side effects such as sedation, constipation, and sialorrhea.¹

Although the physiological mechanisms of saliva production continue to remain in question, salivary flow is believed to depend on a balance of parasympathetic and sympathetic input on the salivary glands. The parasympathetic nervous system acts via cholinergic input on M3 receptors resulting in copious watery saliva, whereas the sympathetic nervous system acts via norepinephrine input on alpha receptors resulting in proteinacious saliva. Clozapine may contribute to hypersalivation both by agonism of M4 receptors with antagonism of M3 and M5 receptors as well as by antagonism of alpha-1 and alpha-2 receptors. Of note, alpha-1–receptor antagonism is thought to increase available norepinephrine at synapses resulting in unopposed beta-receptor activation, thereby inducing hypersalivation.²⁻³ This becomes relevant in considering the role of alpha-2 agonists in treatment of clozapine-induced sialorrhea (CIS), as they effectively reduce the amount of norepinephrine available to act on either alpha 1 or beta receptors.² Other researchers have suggested that clozapine may affect hypersalivation by interfering with the patient’s ability to swallow, suggesting a role for promotility agents in treating CIS.⁴

Previous treatment strategies for CIS have attempted to reduce hypersalivation either by anticholinergic or antimuscarinic activity. Current medications in use include alpha-2 agonists such as clonidine and guanafacine; antimuscarinics including benzotropine, atropine drops, glycopyrrolate, and ipratropium bromide drops; as well as antihistamines such as diphenhydramine.²⁻⁵ Botox injections have been considered based on successes in treatment of sialorrhea in patients with cerebral palsy and Parkinson’s disease.² Others have suggested that the combined antimuscarinic and antidiurenergic effects of the tricyclic antidepressant amitriptyline may be of benefit; however, its use is limited due to concerns of worsening of hypotension, sedation, and lowering of seizure threshold when used in combination with clozapine.⁵ Given that Mr. A. developed sleep disturbance and dysphoric affect during his CIS, he presented us with an opportunity to try mirtazapine as a novel approach to sialorrhea.

Mirtazapine is an antidepressant well known for its side effects of sedation and dry mouth due to H1 antihistaminergic (and anticholinergic) properties, as well as increased appetite and weight gain due to its action on the histaminergic and serotoninergic systems.⁶⁻⁷ It is often used as an augmentation strategy with the intention of reversing gastroenterologic side effects of selective serotonin re-uptake inhibitors in depressed patients.⁷ Mirtazapine is an alpha-2 antagonist resulting in increased circulating amounts of norepinephrine. It is a selective blocker of 5HT2A, 5HT2C, and 5HT3 receptors, resulting in an effective increase in available serotonin to act on other serotonin receptors such as 5HT1B receptors (which are thought to contribute to gastrointestinal [GI] motility) and 5HT2B receptors, which regulate stomach contraction in the enteric nervous system.⁸ Furthermore, data suggest that mirtazapine acts as a 5HT1A agonist, which may lead to enhanced esophageal motility as is found with other 5HT1A agonists such as buspirone.⁹⁻¹⁰

In choosing mirtazapine as an antidepressant for Mr. A., we hoped to utilize its advantageous receptor profile to reduce salivation with its anticholinergic effects, and perhaps promote the management of his saliva by enhancing his upper GI motility via the serotoninergic pathway. It is unclear if its alpha-2 blockade would be expected to increase salivation based on increases in the gradient of unopposed alpha-1 blockade compared to unblocked beta receptors or decrease salivation due to flooding both alpha-1 and beta receptors to the extent that alpha-1 antagonism by clozapine was insignificant. We did, however, observe a significant decrease in the patient’s hypersalivation.

CONCLUSION

Although this case demonstrates that there may be an indication for mirtazapine for antipsychotic-in-
duced sialorrhea, further case studies or randomized controlled trials are indicated to determine whether our results can be generalized to larger psychiatric populations. Furthermore, the use of mirtazapine for sialorrhea may be limited by other problematic side effects. Mirtazapine is known to cause both sedation and weight gain, which would likely be an issue in most patients taking clozapine, as they commonly complain of severe sedation—or as Mr. A. would say, “being kicked by a donkey”—and are at significantly higher risk of developing metabolic syndrome. Mr. A.’s improvement in sialorrhea on mirtazapine demonstrates the importance of considering the receptor profiles of the medications we chose to treat psychiatric disease. However, despite our best efforts to control Mr. A.’s symptoms and manage his side effects, Mr. A. promptly discontinued all of his medications upon discharge from the hospital, illustrating how the patient’s subjective experience (including preferences, biases, and limitations) is an essential determinant of clinical outcomes.

REFERENCES