

Psychosis Induced by Smoking Cessation Clinic Administered Anticholinergic Overload

LAURA A. CLARKE, M.D.

Department of Psychiatry, New York University, New York, New York, USA

CURTIS W. CASSIDY, M.D., and GLENN CATALANO, M.D.

Department of Psychiatry and Behavioral Medicine, University of South Florida College of Medicine, Tampa, Florida, USA

MARIA C. CATALANO, D.O.

Psychiatry Service, James A. Haley Veterans' Hospital, Tampa, Florida, USA

KATHLEEN M. CARROLL, M.D.

Psychiatry Service, Bay Pines Veterans' Hospital, St. Petersburg, Florida, USA

Anticholinergic agents have multiple CNS effects, even when used in therapeutic doses. These can include sedation, amnesia, delirium and, in rare cases, psychosis. While there is some symptom overlap between delirium and psychosis, psychotic patients will have a clear sensorium. We present the case of a 59-year-old male who became psychotic and required hospitalization after the administration of a large anticholinergic load from a smoking cessation clinic. We will review the literature regarding previous cases of anticholinergic medication induced psychosis, discuss treatment options and review the clinical effects of anticholinergic medications.

Keywords Anticholinergic agents; Toxicity; Psychosis; Smoking cessation; Delirium.

INTRODUCTION

Anticholinergic medications have long been used in the field of psychiatry to treat the extrapyramidal side effects (EPS) associated with the conventional antipsychotic agents. Psychiatrists are well aware that the use of anticholinergic medications can lead to problematic CNS effects as well. Today, the use of conventional antipsychotics in psychiatry is declining due to the rise in the use of atypical agents, which have a lower EPS burden. In turn, the use of anticholinergic agents is decreasing. However, anticholinergic agents have found greater use in other areas of medicine. In fact, anticholinergic medications have been used in

smoking cessation clinics for rapid treatment of nicotine dependence (1).

Many of the clinics that use anticholinergic medications for smoking cessation refer back to the original pilot study reported by Bachynsky in 1986 (1). In this article, it is theorized that a "tobacco withdrawal syndrome" is caused by the elimination of nicotine blockade at some nicotine-cholinergic synapses. This then leads to rebound acetylcholine stimulation. This acetylcholine excess induces the development of clinical symptoms of nicotine withdrawal such as irritability, concentration difficulties, nervousness and gastrointestinal disturbances (1). Therefore, in theory, it would be possible to use anticholinergic medications to block muscarinic sites in the cerebral cortex to alleviate the clinical symptoms associated with nicotine withdrawal (1). To accomplish this, Bachynsky's protocol was to initially treat his patients with an IM injection that included scopolamine (0.2 mg) and atropine (0.2 mg). If the patient tolerated this

Address correspondence to Glenn Catalano, M.D., University of South Florida Psychiatry Center, 3515 East Fletcher Avenue, Tampa, Florida 33613. E-mail: gcatalan@hsc.usf.edu

injection after 5 minutes, then they received two subcutaneous injections that included atropine (0.2 mg), scopolamine (0.2 mg) and chlorpromazine (10 mg). If that was well tolerated, the patient was given anticholinergic medications to use daily until day 14 of treatment. These included the oral medications trihexiphenidyl or benztropine and scopolamine patches (1).

Cholinergic antagonists are subclassified as antimuscarinic or antinicotinic depending on the type of receptor blocked. Antinicotinics (such as nicotine, trimethaphan, mecamylamine) act on nicotinic receptors of the sympathetic and parasympathetic ganglia. Because antinicotinics block both parasympathetic and sympathetic output, the physiological effects of the ganglionic blockade are unpredictable thus they are rarely used therapeutically (2). In contrast to antinicotinic ganglionic blockers, antimuscarinics have more predictable effects and have a wide range of therapeutic uses.

Through competitive inhibition, antimuscarinics (such as atropine and scopolamine) prevent acetylcholine from binding to parasympathetic postganglionic cholinergic receptors. While parasympathetic actions are blocked, the effects of sympathetic stimulation are left unopposed. The resulting physiological effects include: mydriasis, cycloplegia, bronchodilation, sedation, urinary retention, and relaxation of the gastrointestinal tract (3). Antimuscarinics also block sympathetic neurons that are cholinergic (such as those innervating sweat glands) resulting in xerostomia. The degree of sensitivity to muscarinic blockade is dose-dependent, with the salivary, bronchial, and sweat glands being the most sensitive. Cardiovascular effects are also dose dependent; the heart rate is bradycardic at lower doses and tachycardic at higher doses. The tertiary amines (atropine, scopolamine, and benztropine) are lipid-soluble and are able to penetrate lipid barriers such as the blood-brain barrier and the cornea of the eye (2).

Therapeutically, anticholinergics have many clinical uses involving the gut, urinary bladder, eye, bronchi, and the central nervous system. Therapeutic applications involving the central nervous system include the use of benztropine, biperiden, and trihexiphenidyl to treat Parkinson's disease (4). In the realm of psychiatry, benztropine is commonly used to treat acute dystonias caused by antipsychotic medications (4). Psychotropic drugs with high levels of anticholinergic properties include tertiary tricyclic antidepressants such as amitriptyline and protriptyline (5). Compared to tricyclic antidepressants, serotonin selective reuptake inhibitors (SSRIs) have less anticholinergic properties. Of the SSRIs, paroxetine has the most anticholinergic activity (6). Low potency neuroleptics, such as chlorpromazine and thioridazine, have more anticholinergic effects compared to high potency neuroleptics (4). Of the atypical antipsychotics, clozapine and olanzapine are potent muscarinic antagonists (4). Olanzapine is an antagonist of all the muscarinic receptors (7), while clozapine is an antagonist of M1, M2, M3 and M5

and an agonist of M4 (8). This would explain the siallorrhea commonly encountered during clozapine therapy (8).

Due to the variety of drugs that contain muscarinic blockers, it is important to recognize the clinical signs of anticholinergic toxicity. When used in excessive doses, anticholinergics produce a range of side effects described by the traditional memory aid: "dry as a bone, red as a beet, mad as a hatter, blind as a bat." Blockade of sweating may result in hyperthermia ("atropine fever") and is potentially lethal in infancy (2). Dilation of the cutaneous vessels in the arms, head, neck, and trunk result in "atropine flush." Constipation and blurred vision are common adverse effects. Cardiovascular effects include intraventricular conduction blockade and ventricular arrhythmias (3). Toxic effects on the central nervous system result in restlessness, irritability, convulsions, disorientation, hallucinations, and delirium (3). Central excitation may progress to depression, circulatory collapse, respiratory failure, and death.

Conservative treatment of anticholinergic syndrome involves removal of the offending agent and patient observation. For severe symptoms, physostigmine can be used for both diagnosis and treatment. A cholinesterase inhibitor, physostigmine can cross the blood-brain barrier and reverse central anticholinergic effects (9). The protocol for physostigmine treatment is as follows: the patient is given an initial intramuscular or intravenous dose of 0.5 mg physostigmine and observed for resolution of symptoms. If no clinical change occurs, the dose may be repeated until the total dose equals but does not exceed 4.0 mg in 30 minutes (2.0 mg in children and the elderly) (10). Parenterally administered physostigmine is metabolized within 2 hours, thus repeated doses may be necessary (4). If symptoms of cholinergic toxicity present, the effects of physostigmine can be reversed with intravenous atropine at a dosage of 0.5 mg for each 1.0 mg of physostigmine administered (9,10). Patients treated with physostigmine require continuous cardiac monitoring because the drug may cause arrhythmias and hypotension. Due to its potential harmful side effects, physostigmine should be used cautiously and in only severe cases of anticholinergic toxicity. Relative contraindications to physostigmine include renal hypertension, hyperthyroidism, asthma, diabetes, and coronary artery disease (10). There is another possible new option available to treat anticholinergic delirium. Recently, donepezil, a newer acetylcholinesterase inhibitor, was used to reverse symptoms of an anticholinergic overload (11). It is possible that the newer cholinesterase inhibitors (such as donepezil, galantamine and rivastigmine) may one day be an important option in the treatment of these cases.

Although a common cause of substance-induced delirium (5,12–16), anticholinergic medications have only rarely been associated with substance-induced psychosis. In our review of the literature, only four cases of anticholinergic-induced psychosis were found. These are summarized on Table I. In each case scopolamine was the offending agent.

Table I Previously Reported Cases of Anticholinergic Induced Psychosis

Reference	Age	Gender	Symptoms	Scopolamine dose	Route of administration
17	25	Male	Agitation Auditory hallucinations Paranoia Tactile hallucinations	10.72–33.5 mg	Ophthalmic drops
10	60	Female	Auditory hallucinations Tactile hallucinations Visual hallucinations	3 mg	Transdermal patch
18	71	Female	Agitation Paranoia Visual hallucinations	0.5 mg	Transdermal patch
19	84	Female	Visual hallucinations	0.5 mg	Transdermal patch

The first case described a 25-year-old male who presented to the emergency department (ED) with auditory, visual, and tactile hallucinations after excess use of 1% scopolamine hydrobromide ophthalmic solution (17). Under the assumption that the solution would help his erythematous eyes, the patient placed two to five drops of solution in both eyes eight to ten times over a 12-hour period. The patient received between 10.72 mg and 33.5 mg of scopolamine. The toxic oral dose has been reported to be between 5 mg and 10 mg (17). Family members brought the patient to the ED after he complained of seeing red and blue flashing lights, hearing voices, and feeling ants crawling on his skin. His symptoms resolved 24 hours after the scopolamine was discontinued.

The next three cases describe substance-induced psychosis due to transdermally administered scopolamine patches. The first case described a 60-year-old woman who experienced visual, auditory, and tactile hallucinations accompanied by dizziness, dry mouth, and blurred vision 24 hours after placing a scopolamine patch behind her ear. She described visions of “tiny little old ladies and young people ... flames coming from the door knob.” She also heard voices and felt the sensation of her hair being pulled (10). These patches contain 1.5 mg scopolamine and deliver approximately 0.5 mg/day at a constant rate for 3 days. This patient received approximately 3.0 mg scopolamine over 6 days. Her hallucinations resolved within 18 hours of removing the patch. The second case described a 71-year-old female who experienced paranoid behavior, visual hallucinations, tachycardia, and cycloplegia 3 days after placing a transdermal scopolamine patch behind her ear (18). After the patch was removed the patient was treated with 1 mg intramuscular physostigmine and her symptoms resolved within 3 hours. The fourth case described an 84-year-old woman who developed hallucinations 24 hours after placing a transdermal scopolamine patch behind her ear. Her symptoms resolved promptly after the patch was removed (19).

The following case describes a patient with new onset psychotic symptoms after receiving a large dose of anticholinergics from a smoking cessation clinic.

CASE REPORT

A 59-year-old man was brought to the ED due to a 2-week history of irritability, visual and auditory hallucinations, blurry vision, dizziness, paranoid thoughts, and violent urges. Two weeks prior to admission, the patient went to a smoking cessation clinic. At the clinic, the patient was prescribed anticholinergic medication to help him stop smoking. He was given three injections (one intramuscular and two subcutaneous) of scopolamine and atropine. A transdermal scopolamine patch was placed behind his ear and he was told to replace it with a new patch every 3 days. In addition, he was also given a 2 week prescription of tablets containing phenobarbital (16.2 mg), hyoscyamine sulfate (0.1037 mg), atropine sulfate (0.0194 mg), and scopolamine hydrobromide (0.0065 mg) and was taking these pills three times daily.

Shortly after his visit to the smoking cessation clinic, the patient experienced visual hallucinations, blurry vision, irritability, and dizziness. Due to blurry vision and dizziness, he was unable to concentrate at work. He also developed paranoid delusions after hearing hallucinations of his family members’ voices saying they were going to kill him. These delusions centered around ideas that his family was plotting to kill him so they could steal his “fortune.” As these thoughts became more frequent, he contemplated suicide and expressed homicidal ideations towards his wife for her “betrayal.” Concerned that his symptoms were a possible reaction to his medications, he discontinued the tablets and the transdermal patches after 10 days (4 days prior to his ED evaluation). Collateral information obtained from his son revealed that in the 2 weeks before evaluation, the patient had behavioral changes. He became verbally abusive and physically threatening. However, during this entire episode, he had

never become confused, lethargic or had any alterations in his level of consciousness. Fearing for his family's safety, the patient's son urged him to seek help for his paranoid thoughts and violent urges. He was admitted to the psychiatric unit for safety and stabilization.

The patient's past psychiatric history was notable for a hospitalization 30 years earlier for anxiety. His wife noted that this hospitalization was for "panic attacks." She described these attacks as "shaking episodes" in which the patient would "rock side to side." She denied that there had been any episodes of increased energy, poor judgement, flight of ideas, racing thoughts or decreased need for sleep. She estimated that the hospitalization lasted "less than a week." Aside from that hospitalization, he had never seen a mental health professional nor had he taken psychotropic medications. He denied any substance use. The patient's medical history was significant for hiatal hernia, peptic ulcer disease, gastroesophageal reflux disease, nephrolithiasis, and chronic neck pain. Outpatient medications included ranitidine (150 mg bid), enteric-coated aspirin (325 mg qd), and naproxen as needed for pain. The patient had been using ranitidine for one year without side effects. He had no family history of mental disorders.

At the time of his admission, his temperature was 37.2°C, heart rate 62 beats/min, blood pressure 133/66 mm Hg, and respiratory rate of 18 breaths/min. Physical exam was significant for blurry vision and pinpoint pupils. Mental status exam revealed an agitated patient with mildly pressured speech. His mood was irritable and depressed. Affect was congruent with his mood. He admitted to suicidal ideation with plan and described violent impulses towards his wife. He was extremely delusional upon admission, describing an elaborate "web of deceit" that was "set in motion" by his family to get him "put away." He noted that there may have been "identical doubles" involved in this "plot." While he denied currently experiencing any hallucinations, he was obviously attending to internal stimuli. He demonstrated a clear cognition and was oriented to person, place, time and situation. He scored a 30 out of 30 on the Folstein Mini-Mental Status Examination. Laboratory studies were pertinent for a urine drug screen positive for barbiturates, which was most likely due to the phenobarbital component of his outpatient medication. The patient's urinalysis, comprehensive metabolic panel, and complete blood count were all within normal limits.

Throughout his hospitalization, he remained alert and oriented with a clear thought process. His paranoid thoughts, homicidal ideations and suicidal ideations all disappeared between 24 and 48 hours after admission. He never received any psychotropic medications. The patient received salsalate (500 mg bid) and methocarbamol (750 mg qid) for his chronic neck pain and tolerated the medications without side effect.

The patient was given the diagnosis of substance-induced psychotic disorder secondary to anticholinergic medica-

tions. His anticholinergic medications were not restarted, and he was advised to warn physicians of his adverse reaction to anticholinergics. He returned home with his family, and did well, with no problems noted at follow-up.

DISCUSSION

Our case describes a 59-year-old man who presented to the ED with dizziness, blurry vision, paranoid delusions, and homicidal/suicidal thoughts. Prior to admission, the patient received anticholinergic medications from a smoking cessation clinic. He was given three injections of scopolamine and atropine (two subcutaneous and one intramuscularly), along with a prescription for a 2 week supply of tablets with anticholinergic activity, and a supply of transdermal scopolamine patches. The patient complained of dizziness, blurry vision, irritability, and visual/auditory hallucinations. Convinced that his family was out to harm him, he contemplated hurting himself or his wife. His family brought him to the ED due to his abrupt behavioral change and his symptoms resolved shortly after discontinuation of the anticholinergic medications.

Similar to the previously reported cases of psychosis induced by anticholinergic medications (10, 17–19), our patient developed new onset psychotic symptoms following the use of anticholinergics that quickly abated after discontinuation of the medication. He also experienced paranoid delusions to such an intensity that he contemplated homicide and suicide. The difference in severity of his symptoms may be due to the excessive amount of anticholinergics prescribed to our patient. Although the exact amount of anticholinergics he received is unclear (due to the unknown amount of scopolamine and atropine contained in the intramuscular and subcutaneous injections), it is known that our patient received an excessive dose of anticholinergics over a short period of time.

Given the temporal relationship between the use of the anticholinergic medications and the onset of symptoms, and the symptom relief seen shortly after the discontinuation of these medications, the most likely cause of this patient's psychosis is anticholinergic overload. It is possible that his psychosis could be due to barbiturate withdrawal because the patient discontinued his tablets that contained phenobarbital 4 days prior to admission. However, his symptoms of dizziness, blurry vision, and visual hallucinations better describe anticholinergic side effects rather than barbiturate withdrawal. Furthermore, the onset of symptoms occurred prior to his use of these tablets. Given its propensity for affecting mental status, ranitidine could also have caused his symptoms. However, this is unlikely, as the patient had been on a stable ranitidine dose for a year. An underlying psychotic disorder, such as schizophrenia, is unlikely given the patient's age and lack of history of past psychotic symptoms. Although

anticholinergic medications are a common cause of delirium (5, 12–16), this diagnosis was not included in the differential due to lack of evidence of a delirious process. The patient demonstrated clear cognition, awareness of his environment, and maintained his ability to focus, sustain, and shift attention.

Another possibility is that this patient may have had an anticholinergic medication induced mania. Clinically, however, this is unlikely, as the only manic symptoms noted during this episode were irritability and mildly pressured speech. The most prominent symptoms were psychotic in nature. Still, the adrenergic-cholinergic balance hypothesis postulates that a decrease in central cholinergic activity compared to norepinephrine could induce mania (20, 21). Therefore, a thorough evaluation for manic symptoms was warranted as the patient may have been at increased risk to develop mania due to his massive exposure to anticholinergic agents. Therefore, in theory, anticholinergic agents could be effective in the treatment of depression, but it is felt that those clinical effects are not sufficiently robust to have clinical application (22).

In regards to treatment, it seems that the only prudent pharmacologic intervention is to stop the patient's anticholinergic medications. None of the previously reported cases required treatment with an antipsychotic agent (10, 17–19). Also, physostigmine was used in only one prior case (18). Therefore, our recommendation is that in any case of anticholinergic induced psychosis, the clinician should monitor each patient's condition prior to starting antipsychotic medications, as the effects of the anticholinergic medications may fade rapidly once the offending medications are stopped.

This case demonstrates the importance of prescribing anticholinergic medications in a moderate amount and for the appropriate therapeutic application. This patient received a large amount of anticholinergic medications through a variety of routes over a short period of time. As a result, he became psychotic and contemplated suicide and homicide. Tobacco addiction is a common problem and smoking cessation clinics are seen as a quick way to cure nicotine dependence. These clinics use a variety of methods and medications to overcome addiction. It is important for psychiatrists to be aware of these clinics and the treatments they offer, since these patients may develop a myriad of symptoms easily mistaken for a primary psychiatric condition.

REFERENCES

- Bachynsky N: The use of anticholinergic drugs for smoking cessation: A pilot study. *Int J Addict* 1986; 21:789–805.
- Pappano AJ, Katzung BG: Cholinceptor-blocking drugs. In: Katzung BG, ed. *Basic and clinical pharmacology*, 8th ed. New York: McGraw-Hill; 2001: 107–119.
- Peters, ML: Snipping the thread of life: Antimuscarinic side effects of medications in the elderly. *Arch Intern Med* 1989; 149:2414–2420.
- Meyer JM, Simpson GM: Anticholinergics and Amantadine. In: Sadock BJ, Sadock VA, eds. *Kaplan & Sadock's comprehensive textbook of psychiatry*, 7th ed. Baltimore: Lippincott Williams & Wilkins; 2000: 2276–2282.
- Mintzer J, Burns A: Anticholinergic side-effects of drugs in elderly people. *J R Soc Med* 2000; 93: 457–462.
- Sadock BJ, Sadock VA: *Kaplan and Sadock's synopsis of psychiatry behavioral sciences/clinical psychiatry*, 9th ed. Philadelphia: Lippincott Williams and Wilkins; 2003.
- Silberstein SD, Peres MFP, Hopkins MM, Shechter AL, Young WB, Rozen TD: Olanzapine in the treatment of refractory migraine and chronic daily headache. *Headache* 2002; 42:515–518.
- Zorn SH, Jones SB, Ward KM, Liston DR: Clozapine is a potent and selective muscarinic M4 receptor agonist. *Eur J Pharmacol* 1994; 269:R1–2.
- Nilsson E: Physostigmine treatment in various drug-induced intoxications. *Ann Clin Res* 1982; 14:165–172.
- Ziskind AA: Transdermal scopolamine-induced psychosis. *Postgrad Med* 1988; 84:73–76.
- Noyan MA, Elbi H, Aksu H: Donepezil for anticholinergic drug intoxication: A case report. *Prog Neuro-Psychoph* 2003; 27:885–887.
- MacEwan GW, Remick RA, Noone JA: Psychosis due to transdermally administered scopolamine. *Can Med Assoc J* 1985; 133:431–432.
- Marchlewski MB: Anticholinergic syndrome: Avoiding misdiagnosis. *J Psychosoc Nurs* 1994; 32:22–24.
- Minagar A, Shulman LM, Weiner WJ: Transdermal-induced psychosis in Parkinson's disease. *Neurology* 1999; 53:433–434.
- Patten SB, Williams JV, Petcu R, Oldfield R: Delirium in psychiatric inpatients: a case-control study. *Can J Psychiatry* 2001; 46:162–166.
- Sennhauser FJ, Schwarz HP: Toxic psychosis from transdermal scopolamine in a child. *Lancet* 1986; 2:1033.
- Birkimer LJ, Jacobson PA, Olson J, Goyette DM: Ocular scopolamine-induced psychosis. *J Fam Pract* 1984; 18:464–469.
- Ostherholm, RK, Camoriano JK: Transdermal scopolamine psychosis. *JAMA* 1982; 247:3081.
- Mego DM, Omori DJM, Hanley JF: Transdermal scopolamine as a cause of transient psychosis in two elderly patients. *South Med J* 1988; 81:394–395.
- Janicak PG, Davis JM, Preskorn SH, Ayd FJ: *Principles and practice of psychopharmacotherapy*. Philadelphia: Lippincott Williams & Wilkins; 2001:215–325.
- Janowsky DS, El-Yousef MK, Davis JM, Sekerke HJ: A cholinergic-adrenergic hypothesis of mania and depression. *Lancet* 1972; 2:632–635.
- Thase ME: Mood Disorders: Neurobiology. In: Sadock BJ, Sadock VA, eds. *Kaplan and Sadock's comprehensive textbook of psychiatry*, 7th ed. Philadelphia: Lippincott William & Wilkins; 2000: 1318–1328.

