Managing Anticholinergic Side Effects

Joseph A. Lieberman, III, M.D., M.P.H.

Atypical antipsychotics are associated with a lower risk of extrapyramidal symptoms (EPS) and tardive dyskinesia than the conventional antipsychotics; however, many atypical antipsychotics can cause other potentially harmful side effects such as anticholinergic side effects. Peripheral and central anticholinergic side effects can cause physical and mental impairment. Awareness of the medications that have the potential to cause anticholinergic side effects as well as proper management of these symptoms can aid physicians in treating patients who need antipsychotic therapy.

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While antipsychotics can be effective, they also carry the risk of causing serious complications such as extrapyramidal side effects (EPS) and tardive dyskinesia. One particular pharmacologic action of conventional antipsychotics is the ability to block the muscarinic cholinergic receptors in the brain.[1] The strength of antipsychotics' anticholinergic properties may have a direct relation to their propensity to cause EPS.[1] For example, many conventional antipsychotics have weak anticholinergic properties and thus have a propensity for causing more EPS.[1]

Atypical antipsychotics have varying degrees of anticholinergic effects, but are generally associated with a lower incidence of EPS and tardive dyskinesia than conventional agents.[2] However, the stronger the anticholinergic properties, the more likely a patient is to develop other serious side effects. Anticholinergic side effects may place patients, particularly older patients, in a position to suffer from serious medical complications. Physicians need to be attentive to the potential that some medications have to cause anticholinergic side effects as well as effective treatment strategies if these effects do occur.

TYPES OF ANTICHOLINERGIC SIDE EFFECTS

Anticholinergic side effects can cause physical as well as mental impairment. Often, these side effects may be disregarded as temporary, minor side effects of a medication or a result of a patient's preexisting condition. Taken as a whole, however, anticholinergic side effects can seriously impair a patient. For example, one study[3] reviewed the adverse event reports filed over 4 years by a psychogeriatric open ward. Included in the study were patients with a report of a fall who were 65 years of age or older and had a Mini-Mental State Examination (MMSE) score greater than 27. Of the 34 inpatients who met the criteria, additional characteristics such as age, gender, psychiatric diagnosis, comorbid physical conditions, and medications administered were also studied. Participants were compared with a control group consisting of previous and next admission elderly patients of the same ward. The anticholinergic burden score, which is based on the quantitated anticholinergic effect of each psychotropic compound a subject receives, was calculated. Among the studied participants, the anticholinergic burden score was found to be significantly associated with a higher rate of falls (mean = 3.7 vs. 2.1, $p < .05$) in elderly patients.

Anticholinergic side effects can be divided into 2 types of side effects, peripheral and central. Physicians need to be attuned to the possibility of these side effects in order to effectively treat patients. The potential medical complications of the anticholinergic side effects are appreciable, and in susceptible patients, particularly older patients or patients with a preexisting condition like asthma, these side effects can be debilitating.

Peripheral Side Effects

Peripheral side effects are more physical than central side effects and therefore might be easier to diagnose. Typical symptoms include dry mouth, constipation, urinary retention, bowel obstruction, dilated pupils, blurred vision, increased heart rate, and decreased sweating (Table 1).[4,5]

While the peripheral side effects may not all appear serious, physicians should be wary because these side effects can lead to a plethora of medical complications.

From Jefferson Medical College, Philadelphia, Pa.

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Corresponding author and reprints: Joseph A. Lieberman III, M.D., M.P.H., 2 Aston Circle, Hockessin, DE 19707–2500 (e-mail: jlieberman@jalmd.com).

Table 1. Peripheral Anticholinergic Side Effects of Antipsychotic Agents[a]

Peripheral Effects	Potential Medical Complications
Decreased salivation	Dental caries, ulceration of gums and buccal mucosa
Decreased bronchial secretions	Mucous plugging of small airways in patients with asthma or bronchitis
Decreased sweating	Hyperthermia
Increased pupil size	Photophobia, precipitation of acute narrow angle glaucoma
Inhibition of accommodation	Blurred vision, especially when reading small print
Increased heart rate	Angina, myocardial infarction
Difficulty urinating	Bladder distention, urinary retention
Decreased gastrointestinal motility	Constipation

[a]Based on The American Psychiatric Press Textbook[4] and McEvoy.[5]

Complications can range from ulceration of the gums and respiratory problems to hyperthermia and myocardial infarction (Table 1).[4,5]

Central Side Effects

Impairment in cognitive function has long been recognized as central to the abnormalities in schizophrenia.[6] This preexisting impairment can be exacerbated by the presence of central side effects caused by anticholinergic properties of antipsychotic agents. Central side effects are cerebral and include impaired concentration, confusion, attention deficit, and memory impairment (Table 2).

One study[7] conducted among the elderly found that delirium was associated with higher serum anticholinergic activity. Participants aged 75 years and older and without a high premorbid risk of delirium were included in the study. High premorbid risk was defined as a greater than partial dependency in all activities of daily living scale items, known terminal illness with a life expectancy of less than 6 months, or intensive care unit admission. Among 67 participants, data were collected for a broad range of factors that have been reported to have an association with delirium such as age, residence, comorbidity, functional status, number of medications used, white blood cell count, presence of infection, hematocrit, glucose level, sodium level, blood urea, nitrogen, and creatinine. Also noted was the use of medications that have been proposed as potential iatrogenic agents for delirium such as anticholinergic medications, neuroleptics, narcotics, and benzodiazepines. Delirium was diagnosed using the Confusion Assessment Method and the Delirium Symptom Interview. Delirium occurred in 30% of participants (N = 20). In bivariate and multivariate analyses, high serum anticholinergic activity was associated with delirium ($p = .003$, OR = 1.95; $p = .006$, OR = 2.38, respectively). While this study did not include atypical antipsychotics, the high presence of delirium among patients administered medication with anticholinergic properties

Table 2. Central Anticholinergic Side Effects of Antipsychotic Agents

Impaired concentration
Confusion
Attention deficit
Memory impairment

indicates that physicians need to be attuned to the possibility of central side effects among patients prescribed atypical antipsychotics.

Since schizophrenia inherently carries with it certain mental problems, central side effects must be differentiated from the problems associated with a patient's psychosis. This differentiation can sometimes be difficult. Physicians must thoroughly interview patients suspected to suffer from central side effects and pay close attention to their responses.

CAUSES OF ANTICHOLINERGIC SIDE EFFECTS

Anticholinergic side effects can be caused by a wide range of medications, including some over-the-counter medications.[8] While most anticholinergic drugs prescribed to treat EPS in patients with schizophrenia are cited as the culprits in anticholinergic side effects, antipsychotics may cause varying degrees of anticholinergic side effects as well.[8] Atypical antipsychotics can vary in their anticholinergic strength, resulting in some having a higher propensity for anticholinergic side effects than others.

Tracy et al.[9] observed the anticholinergic burden imposed by clozapine and risperidone and whether this burden produced different cognitive effects. Clozapine is considered to be a highly anticholinergic agent, while risperidone is considered to have minimal anticholinergic effects. Twenty-two inpatients (15 taking clozapine and 7 taking risperidone) with a DSM-IV diagnosis of chronic schizophrenia participated in the study. All participants were free of neurologic and substance use disorders as well as other central nervous system disorders. Treatment doses ranged from 200 to 800 mg/day for clozapine and 1 to 7 mg/day for risperidone. Patients were also free of any other potentially anticholinergic agents or medications that could affect cognition. General cognitive function was measured by the MMSE and anticholinergic levels were measured by 2 blood samples taken a week apart (T1 and T2). Dependent t tests revealed that both clozapine and risperidone maintained statistically identical anticholinergic levels across T1 and T2. Independent t tests indicated that the clozapine and risperidone groups differed in anticholinergic levels at both the T1 ($t = 6.3$, $df = 13.7$, $p < .001$) and T2 ($t = 5.8$, $df = 18.1$, $p < .001$) stages (Table 3). Although the anticholinergic levels were significantly ($p < .001$) higher for the clozapine group at both T1 and T2, the clozapine and risperidone groups did

Table 3. Means and Standard Deviations of Clozapine and Risperidone Groups for Time 1 and 2 Anticholinergic Levels and Mini-Mental State Examination Scores[a]

	Anticholinergic Levels (in pmol/mL) Atropine Equivalent						Mini-Mental State Examination Score		
	Time 1			Time 2					
Medication Group	N	Mean ± SD	(range)	N	Mean ± SD	(range)	N	Mean ± SD	(range)
Clozapine	14	4.35 ± 2.38	(1.7–9.3)[b]	15	4.07 ± 2.22	(1.7–9.7)	15	27.40 ± 2.99	(19–30)
Risperidone	7	0.27 ± 0.28	(0.0–0.81)	7	0.43 ± 0.64	(0.0–1.9)	7	26.70 ± 6.13	(13–30)

[a]Reprinted with permission from Tracy et al.[9]
[b]N = 14 because 1 patient was not available for blood collection at Time 1.

not differ from each other significantly on the MMSE scores, and Pearson correlation data revealed that MMSE scores were not related to anticholinergic levels. It is important to note that while Tracy et al. did not find a correlation between anticholinergic levels and central side effects, they also did not test for peripheral side effects. This study provides evidence of differing anticholinergic levels between atypical antipsychotics while not necessarily ruling out the possibility of differing degrees of side effects.

One 6-week, double-blind, placebo-controlled study[8] measured the efficacy and safety of olanzapine against placebo in patients with dementia. Patients who met the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria for possible or probable Alzheimer's disease and who scored a 3 or higher on any of the agitation/aggression, hallucination, or delusion items of the Neuropsychiatric Inventory-Nursing Home version were randomly assigned to receive placebo or a fixed dose of 5, 10, or 15 mg/day of olanzapine. Anticholinergic effects were assessed using the reported classification terms from the Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART). A total of 206 participants completed the study. No significant difference was found among olanzapine-prescribed patients in regards to anticholinergic effects. However, after the pooling of peripheral anticholinergic items, a significant difference in anticholinergic effects was found between 15 mg/day of olanzapine and placebo (26% and 6.4%, respectively, $p = .008$).

Chengappa and colleagues[10] observed the differences between the antipsychotics olanzapine and clozapine. Twenty-four participants with a DSM-IV diagnosis of chronic schizophrenia, schizoaffective disorder, or bipolar I disorder and who had been prescribed either clozapine or olanzapine for a minimum of 8 weeks were recruited. Participants were required to have been on a stable dose of either medication for at least 4 weeks, the average daily doses being 15 mg/day for olanzapine and 444 mg/day for clozapine. When blood samples were obtained, the olanzapine group had lower serum anticholinergic levels than the clozapine group. Olanzapine-treated patients also had significantly lower scores on anticholinergic items such as constipation, micturition disturbances, palpitations, and tachycardia, while a few clozapine-treated patients scored in the markedly impaired range on items pertaining to constipation, palpitations, and excessive salivation.

Studies[7–9] have shown that atypical antipsychotics do differ in their anticholinergic levels. While the effects of these varying levels have not been completely observed, physicians should be aware of the possibility of anticholinergic side effects, especially with antipsychotics that have higher anticholinergic levels.

MANAGING ANTICHOLINERGIC SIDE EFFECTS

The management of anticholinergic side effects can be simple, although certain situations may arise that deserve special attention. The first step for a physician is to decrease the dose of the antipsychotic. Dose reduction may sometimes ameliorate the anticholinergic effects. Changing to an antipsychotic with a lesser anticholinergic profile can also prevent the continuation of symptoms. While data[9] have demonstrated the differences in vitro among the antipsychotics, whether or not these differences translate to clinical activity is subject to debate.

Another possibility is to eliminate or reduce the doses of other medications known to have anticholinergic side effects. It is not uncommon, especially among elderly patients, for a patient to be prescribed multiple medications. Blazer and colleagues[11] conducted a study of the potential for anticholinergic toxicity among long-term care residents. Participants aged 65 years and older who continuously resided in a nursing home for 1 year were surveyed for drug administration and drug quantity. Of the 5902 nursing home patients, 60% received drugs with anticholinergic properties and 565 patients may have received 3 or more anticholinergic medications. Being aware of what types of medications a patient is taking and eliminating unnecessary medications can help reduce the potential for anticholinergic side effects.

While dose reduction and switching antipsychotics may reduce anticholinergic symptoms, physicians need to be particularly sensitized to specific disorders that may arise as a result of anticholinergic symptoms. These disorders can impair antipsychotic treatment as well as place a patient's health at risk. Narrow-angle glaucoma and pros-

tatic hypertrophy are both contraindications to antipsychotic treatment. These disorders must be properly treated before treatment with anticholinergic medications can begin. Physicians should know a patient's medical history before beginning a treatment to handle potential problems. Bethanechol can also be used to offset obstruction and throughout the course of treatment in patients suffering from prostatic hypertrophy. Anticholinergic delirium, however, constitutes a medical emergency. Symptoms of anticholinergic delirium include hot, dry skin; dry mucous membranes; dilated pupils; absent bowel sounds; and tachycardia. Physicians must first determine and remove the offending agent because patients are at a high risk for cholinergic crisis. Atropine can be used to treat anticholinergic delirium symptoms once the agent has been removed.

CONCLUSION

Since atypical antipsychotics tend to have lower rates of side effects than the conventional agents, they can be invaluable to the treatment of schizophrenia. The risk of side effects does exist, though, and anticholinergic side effects, if left untreated, have the potential to cause serious medical complications. Physicians can help patients avoid these medical complications through awareness of the signs and symptoms of anticholinergic side effects and of effective management of these symptoms.

Drug names: atropine (Atropen), bethanechol (Urecholine), clozapine (Clozaril and others), olanzapine (Zyprexa), risperidone (Risperdal).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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