Anticholinergic Effects of Medication in Elderly Patients

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Anticholinergic toxicity is a common problem in the elderly. It has many effects ranging from dry mouth, constipation, and visual impairments to confusion, delirium, and severe cognitive decline. The toxicity is often the result of the cumulative anticholinergic burden of multiple prescription medications and metabolites rather than of a single compound. The management of elderly patients, particularly those suffering from dementia, should therefore aim to reduce the use of medications with anticholinergic effects. *(J Clin Psychiatry 2001;62[suppl 21]:11–14)*

In frail, elderly patients, particularly those with dementia, anticholinergic toxicity can result in excess morbidity and mortality, behavioral symptoms (including agitation), and delirium. The problem is not new—it is discussed in the writings of Hippocrates and Celsus—but it is becoming more widely recognized. This increased recognition is mainly a result of the aging population and the concomitant dramatic increase in the number of medications that patients are prescribed. In the United States, for example, the average 85-year-old patient may take an average of 8 to 10 prescription medicines. In addition, they may be taking nonprescription substances, such as St. John's wort and *Ginkgo biloba*.

In most instances, it is this accumulation of medicines that gives rise to anticholinergic toxicity. The problem does not occur because patients are overdosing on individual drugs, such as benztropine or biperiden, but rather because the different drugs, both psychiatric and nonpsychiatric, taken by the patient produce a significant anticholinergic burden.

Several published studies have found significant correlations between peripheral serum anticholinergic levels and functional disability, agitation in dementia, and delirium. In this article, data from a number of these clinical investigations are reviewed. Specific recommendations to avoid or replace medications with anticholinergic effects are then discussed.

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DELIRIUM IN PATIENTS WITH DEMENTIA

Delirium and confusional states are common in elderly patients with dementia. They are an important contributor to behavioral symptoms and give rise to significant levels of morbidity and mortality. Delirium has an associated mortality rate of up to 40% and is present in 10% to 25% of elderly inpatients.[1]

In the Commonwealth-Harvard study, Levkoff et al.[2] investigated all geriatric (age > 65 years) admissions to the Beth Israel Hospital, Massachusetts, from either the community or nursing homes. They found that, during 1 year, 24% of admissions who had been living in the community were delirious compared with 64% of patients admitted from the extended-care rehabilitation facility. Rovner et al.[3] examined 454 new admissions to nursing home facilities in the Baltimore, Maryland, area. They found that 17% had significant behavioral problems. The 3 leading causes were delirium, delusions, and depression.

In a separate study, Lerner et al.[4] examined 199 well-defined cases of Alzheimer's disease (AD). They found that 17% of these patients had experienced delirium in the previous 3 years. The primary causes were found to be urinary tract infection, stress, surgery, medical illness, and medications. Importantly, delirious demented patients had more hallucinations and more paranoid delusions for the remainder of their illness than did nondelirious patients; only 19% recovered to baseline levels.

The risk factors for and possible causes of delirium are listed in Table 1.

THE RELATIONSHIP BETWEEN ANTICHOLINERGIC EFFECTS AND DELIRIUM

Why focus on acetylcholine? Acetylcholine is important since it decreases with patient age and is reduced in patients with AD and other dementias. Cholinergic disturbance is also postulated as the central lesion in delirium. There are over 600 known anticholinergic medications, and a dispro-

Table 1. Risk Factors for and Possible Causes of Delirium[a]

Risk factors
Age
Dementia
Drug toxicity
> 5 drugs in the elderly
Anticholinergics
Infection
Electrolyte imbalance
Uremia
Hyponatremia
Alcohol use
Fractures
Hypoxia
Possible causes
Acute illness
Urinary tract infection
Respiratory infection
Chronic illness
Congestive heart failure
Chronic obstructive pulmonary disease causing hypoxia
Renal insufficiency
Anemia
Hypoperfusion states
Recent surgery
Sensory impairment
Cataract
Hearing loss
Iatrogenesis
Anticholinergic effects of many drugs
Recent medication change
Need to rule out withdrawal syndrome (eg, from alcohol or short-acting benzodiazepine)

[a]Data on possible causes from Lipowski.[5,6]

Table 2. Systems Affected by Cholinergic Impairment and Patient Outcomes[a]

System Impairment	Potential Outcome
Vision	Impaired activities of daily living Falls and other accidents
Oral cavity	Decreased nutritional status Increased risk of infection Impaired communication
Gastrointestinal tract	Decreased nutritional status Worsening of disease Anxiety, pain
Cardiovascular system	Worsening of disease Anxiety
Urinary tract	Incontinence Infection Loss of independence
Central nervous system	Cognitive dysfunction Impaired activities of daily living

[a]Reprinted, with permission, from Feinberg.[8]

portionately large number of them (11%) are commonly prescribed to elderly patients.[7]

The morbidity and management issues associated with unwanted anticholinergic activity are underestimated and frequently overlooked.[8] Anticholinergic side effects are common, but are often viewed as "unavoidable" or as a normal part of the aging or disease process. Table 2 provides a summary of body systems affected by anticholinergic side effects and the potential consequences of these effects in elderly patients.

Peripheral anticholinergic effects include decreased secretions, slowed gastrointestinal motility, blurred vision, and increased heart rate. These may be uncomfortable for a younger patient in relatively good health, but in older patients they may be disastrous.[8] The most common side effect, dry mouth, may appear trivial at first sight, but can lead to an increased risk of serious respiratory infection, dental or denture problems, impaired nutritional status, and a reduction in the ability to communicate.

Other peripheral anticholinergic effects include constipation, causing pain, fecal compaction, and increased use of laxatives,[8,9] and urinary retention, resulting in discomfort, urinary tract infections, and an increased need for catheterization. Catterson et al.[10] note the potential for a "vicious circle" of treatment and side effects. Fecal impaction occurs frequently in patients with dementia and can cause agitation because of the associated discomfort. Treating the agitation with an antipsychotic that has anticholinergic properties will worsen the impaction and aggravate the agitation. Finally, visual impairments, such as mydriasis, may increase the risk of accidents and can precipitate narrow-angle glaucoma in patients predisposed to this condition.[8]

Central anticholinergic effects range from sedation, confusion, and inability to concentrate to frank delirium, agitation, hallucinations, and severe cognitive decline.[1,8] Even mild central effects can reduce cognitive function and so increase dependency, resulting in greater caregiver burden, increased health care costs, reduced quality of life, and impaired activities of daily living.[1,8] At the other end of the spectrum, delirium, as mentioned above, has serious consequences in terms of morbidity and mortality.

AD is the most common primary dementia in the elderly. A number of mechanisms have been suggested for the disease process, but a decrease in acetylcholine is a change associated with the condition. It correlates closely both with the characteristic neuropathologic changes and with the severity of the disease.[11] The most successful strategy for the treatment of AD so far is to increase the level of available acetylcholine by inhibiting the enzyme responsible for its metabolism. It is clear that adding a drug with anticholinergic effects is likely to worsen the disease process, and this may account for the cognitive decline seen in patients treated with certain agents.[1,12–14]

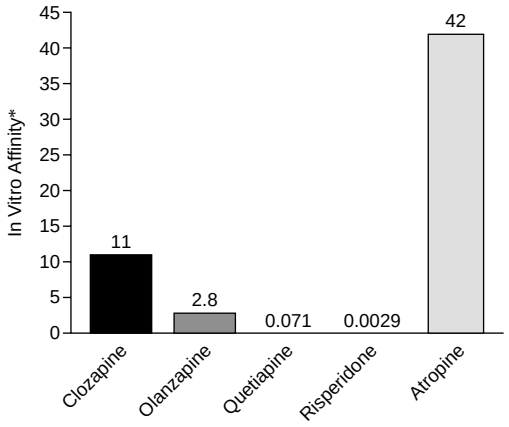
Medications with anticholinergic effects, even mild effects, are an important cause of acute and subacute delirium in the elderly. One of the aims of treatment, therefore, should be to reduce and limit the use of medications with anticholinergic effects. Some of the common anticholinergic medicines are presented in Table 3. Notably, while most psychiatrists would recognize the tricyclic an-

Table 3. Commonly Used Medicines That Have Anticholinergic Effects[a]

Antihistamines	Corticosteroids
Diphenhydramine	Corticosterone
Hydroxyzine	Dexamethasone
Cardiovascular	Hydrocortisone
Captopril	Prednisolone
Chlorthalidone	Gastrointestinal
Digoxin	Atropine
Diltiazem	Cimetidine
Dipyridamole	Ranitidine
Furosemide	Immunosuppression
Hydrochlorathiazide	Azathioprine
Hydralazine	Cyclosporin
Isosorbide mononitrate	Infection
Methyldopa	Ampicillin
Nifedipine	Cefalothin
Triamterene	Cefamandole
Warfarin	Cefoxitin
Central nervous system	Clindamycin
Alprazolam	Cycloserine
Amitriptyline	Gentamicin
Chlordiazepoxide	Piperacillin
Codeine	Tobramycin
Desipramine	Vancomycin
Diazepam	Muscle relaxants
Doxepin	Pancuronium
Flurazepam	Respiratory system
Imipramine	Theophylline
Oxazepam	
Oxycodone	
Phenelzine	
Phenobarbital	

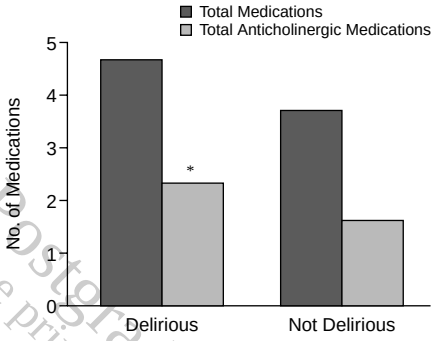
[a]Data from Tune et al.[15]

Figure 1. Relative Anticholinergic Potencies of 4 Atypical Antipsychotics in Comparison With Atropine[a]



[a]Reprinted, with permission, from Richelson.[17]
*Affinity = $10^{-7} \times 1/K_d$, where K_d = equilibrium dissociation constant in molarity.

Figure 2. Number of Anticholinergic Medications Taken by Delirious and Nondelirious Patients[a]



[a]Reprinted, with permission, from Tune and Egeli.[18]
*p < .007 vs. patients who were not delirious.

tidepressants as having anticholinergic properties, fewer would identify the antibiotics tobramycin and clindamycin as having significant anticholinergic effects. Some of the antipsychotics used for the treatment of behavioral and psychological symptoms of dementia also have anticholinergic activity. These include thioridazine, chlorpromazine, loxapine, clozapine, and, to an extent, olanzapine. Indeed, a study by Richelson[16] showed that olanzapine has the greatest M_1 binding affinity of all atypical antipsychotics, and the U.S. package insert for olanzapine clearly lists possible adverse events related to anticholinergic activity. Risperidone, however, has no appreciable anticholinergic properties. The relative anticholinergic potencies of 4 atypical antipsychotics, in comparison with atropine, are shown in Figure 1.

Tune and Egeli[18] examined 91 patients referred to the Emory University Neurobehavioral Unit for "dementia with agitation." Patients were classified as delirious or not on the basis of the Confusion Assessment Method and the Pittsburgh Agitation Scale.[19] A total of 47 patients were categorized as delirious, compared with 44 nondelirious (but agitated and demented) patients. When the patients' medications were compared, it was found that the patients with delirium were receiving significantly more anticholinergic medications than the nondelirious patients ($p < .007$; Figure 2).

EFFECTS OF INTERVENTION TO REDUCE ANTICHOLINERGIC LOAD

In a further study,[7] 34 residents of nursing homes were assessed using psychometric tests, including the Saskatoon Delirium Checklist, the Wechsler Memory Scale (digits), and the Mini-Mental State Examination (MMSE). All patients had been receiving at least one "significant" anticholinergic (commonly thioridazine) for more than 2 weeks. Patients were randomly assigned to intervention or nonintervention groups. The intervention was to reduce the anticholinergic load by 25%. Following this intervention for 2 weeks, the psychometric tests were readministered. Delirium significantly improved in the intervention group compared with the control patients, as did attention span (Wechsler). The MMSE also showed the predicted trend, even in this small group of patients, although the difference

was not statistically significant. Thus, reducing anticholinergic load is an effective intervention.

CONCLUSIONS

Anticholinergic toxicity is an important cause of delirium and confusional states in demented, agitated patients. Importantly, the toxicity arises not from individually powerful drugs, but from an accumulation of anticholinergic burden from a number of different medications. To reduce the morbidity and mortality associated with the anticholinergic burden, patients' medications should be closely monitored. Where possible, medicines with anticholinergic effects should be avoided in elderly patients, particularly those suffering from dementia.

Drug names: alprazolam (Xanax and others), amitriptyline (Elavil and others), benztropine (Cogentin and others), biperiden (Akineton), chlordiazepoxide (Librium and others), cimetidine (Tagamet and others), clozapine (Clozaril and others), desipramine (Norpramin and others), dexamethasone (Decadron and others), diazepam (Valium and others), digoxin (Lanoxin and others), diltiazem (Cardizem and others), diphenhydramine (Benadryl and others), doxepin (Sinequan and others), furosemide (Lasix and others), loxapine (Loxitane and others), methyldopa (Aldomet and others), nifedipine (Adalat, Procardia), olanzapine (Zyprexa), oxazepam (Serax and others), phenelzine (Nardil), quetiapine (Seroquel), ranitidine (Zantac), risperidone (Risperdal), warfarin (Coumadin).

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