



IJPPR

INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals

ISSN 2349-7203




Human Journals

Review Article


November 2019 Vol.:16, Issue:4

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Anticholinergic Drugs Induced Dementia –A Review



IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals



ISSN 2349-7203

Ashmi Samuel*, Abini Daniel M, Jency J, Irene Thomas, Ansa Mathew

Dr. Joseph Mar Thoma Institute of Pharmaceutical Sciences And Research Kattanam, Alappuzha, Kerala

Submission: 25 October 2019
Accepted: 30 October 2019
Published: 30 November 2019

Keywords: Anticholinergic activity, cognitive impairment, dementia

ABSTRACT

Dementia is a diseased condition characterized by a decline in memory, language, solving problem and other thinking skills that affect a person's ability to perform everyday activities. It is caused by damage in the brain cells. This damage interferes with the ability of brain cells to communicate with each other. Studies found that **Anticholinergic medications** used to treat bladder conditions, Parkinson's disease, and depression is associated with an increased risk of dementia. The longer administration of anticholinergic medication increases the risk of developing dementia.



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INTRODUCTION

Dementia is defined as an impairment of higher cortical functions, including memory such as capacity to solve problems of everyday living, the performance of learned perceptual motor skills, the correct use of social skills, and the control of emotional reactions.

There are a number of things that can increase the risk of dementia: age, of course, as well as certain genetic profiles and behaviors such as smoking and drinking. Some of the same things that contribute to heart disease, such as high cholesterol levels and the formation of plaques in the blood vessels, can also boost the chances of developing dementia.

Researchers report another possible factor: a group of drugs known as anticholinergics. These include prescription medications for treating depression, pulmonary disease, and Parkinson's, as well as over-the-counter remedies for allergies. Analyzed data from nearly 59,000 people with dementia as well as people without the condition and found that those who took the most anticholinergic drugs were 49% more likely to have developed dementia compared to those not taking the medications.¹

Cholinergic drugs enhance the effects of acetylcholine, increasing the actions of the parasympathetic nervous system.²

Anticholinergic drugs block effects of acetylcholine, reducing parasympathetic actions and increasing sympathetic ones.

Drugs with anticholinergic properties are frequently prescribed for anxiety, depression, and certain types of pain or purchased over the counter for conditions including allergies or sleep problems.³

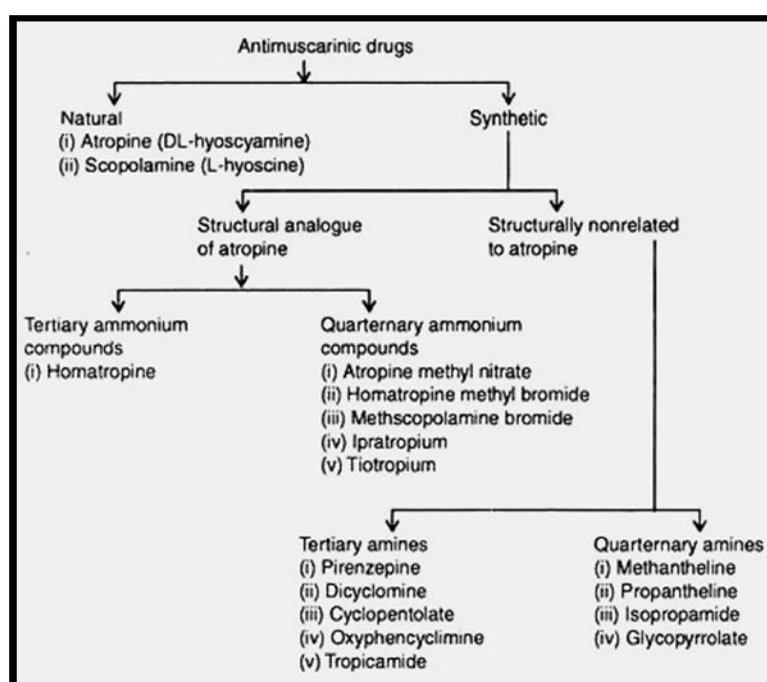
A link between anticholinergic drug use and dementia was recently observed from observational studies on randomized clinical trials. The researchers examined that the use of anticholinergic drugs, they found that people who used these drugs were more likely to have developed dementia as those who didn't use them. Moreover, dementia risk increased along with the cumulative dose.⁴

In 2005, there were more than 36 million Americans aged 65 and older. This population is known to suffer from multiple chronic diseases, require numerous prescribed and over-the-counter medications, and is at a higher risk of developing dementia. It is estimated that 20%–

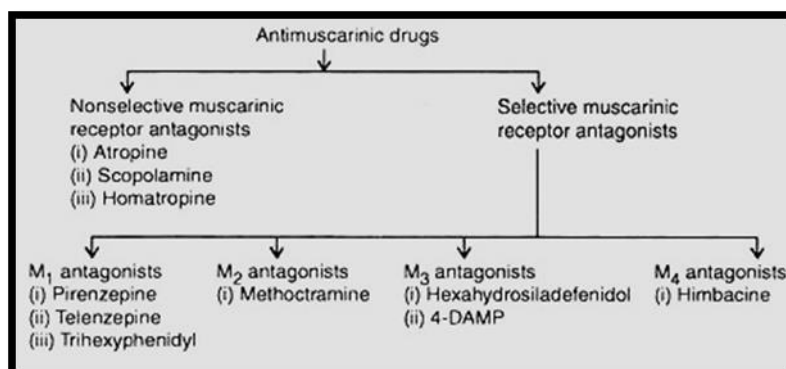
50% of the same cohort, including the four million with dementia, took at least one medication with some anticholinergic activities. The use of drugs with anticholinergic activity has been an integral part of the routine treatment of common conditions such as asthma, urinary incontinence, and various psychiatric disorders. However, the adverse effects of these anticholinergics have been known for a long time including peripheral effects such as dry mouth and constipation, and central nervous system effects such as attention deficits and hallucinations. The central nervous system of older patients is very sensitive to the above adverse anticholinergic effects due to the significant decrease in cholinergic neurons or receptors in the brain of older adults, the reduction in hepatic metabolism and renal excretion of medications, and the increase in blood–brain barrier permeability. Many clinical researchers have recognized the importance of accounting for the risk of medications with central nervous system anticholinergic effects in the medical care of older patients, especially those with pre-existing cognitive disorders. However, there has been no systematic confirmation that acute or chronic prescribing of such medications leads to transient or permanent adverse cognitive outcomes. Thus, we conducted this systematic review of the literature to identify the various methods used to determine the central anticholinergic effects of various medications and evaluate the impact of such activities on cognitive function of older adults.⁵

Classification of Anticholinergic Drugs:

(A) On the Basis of Source:



(B) On the Basis of Mode of Action:



Sources and Chemistry of Anticholinergic Drugs:

Atropine is obtained from *Atropa belladonna* and *Datura stramonium*. Scopolamine is found in the shrub *Hyoscyamus niger* and *Scopolia carniolica*. Atropine consists of equal parts of d- and l-hyoscyamine, but the antimuscarinic activity is almost wholly due to the l-isomer. The active ingredient in scopolamine is l-hyoscyne. Atropine (hyoscyamine) is composed of tropic acid (active) and tropine (tropanol-inactive). Scopolamine (hyoscyne) is the structural combination of tropic acid (active) and scopine (inactive). Homatropine is the combination of mandelic acid and tropine. The intact ester of tropine/scopine and tropic/mandelic acid is essential for the significant anti-muscarinic action of these drugs. The free OH group in the acid portion is also important.

Mechanism of Action:

Atropine and related drugs are competitive antagonists of Ach and other muscarinic agonists. They compete with such agonists for common binding sites on the muscarinic receptor. The receptors affected are those of exocrine glands and smooth and cardiac muscles. These drugs block muscarinic receptors only. That's why it is more appropriate to term them as anti-muscarinic agents. They are also called as atropine-like drugs.

Drug-induced dementias fall under the broad category of pseudodementias, which differentiates them from dementias associated with degenerative neurologic disorders, as well as under the category of reversible dementias, which imply that the manifestations improve following discontinuation of the offending drug. Several drugs can induce dementia, but significant categories are anticholinergic drugs, antiepileptics, antineoplastic drugs, and sedative-hypnotics. People taking anticholinergic drugs were at increased risk of dementia.

Discontinuing anticholinergic treatment was associated with a decreased risk. Physicians should carefully consider prescription of anticholinergic drugs in elderly people especially in the oldest at high genetic risk of cognitive disorder. ⁶

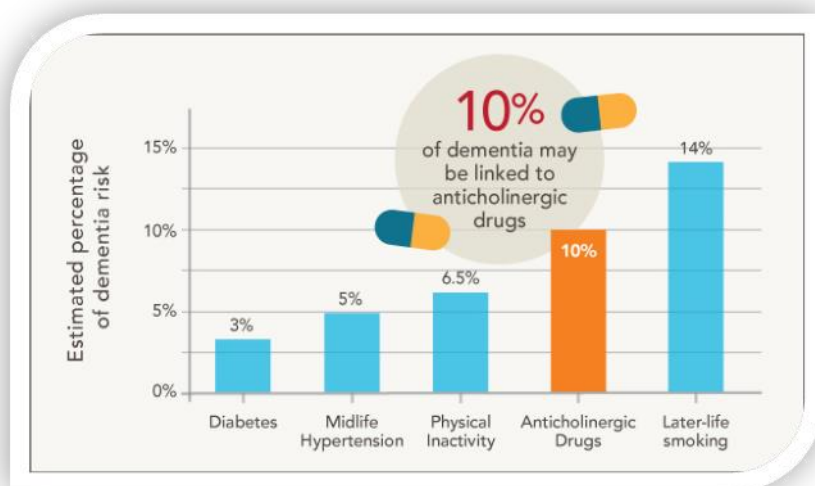


Figure No. 1: A graph of estimated percentage of dementia risk

Anticholinergics are drugs that block the action of acetylcholine. Acetylcholine is a neurotransmitter or a chemical messenger. It transfers signals between certain cells to affect how your body functions. Anticholinergics are known to cause confusion, memory loss, and worsening mental function in people who are older than 65 years. ⁷

An acute illness is uniquely sensitive to the central anticholinergic adverse effects of medications and should be closely monitored for the development of unwanted adverse effects on cognition. Recognizing patients at risk due to exposure of anticholinergics should warrant cognitive evaluation not only in acute care environments but also ambulatory environments when subjective complaints of cognitive impairment supplement clinical suspicion. In clinical practice situations where anticholinergic cognitive adverse effects are suspected, the course of action might be to consider the withdrawal of potentially offending medication(s). Although the expected clinical impact on cognitive deficits with a reduction in anticholinergic burden remains to be sufficiently studied, removal of potentially harmful medications in lieu of equally effective alternatives with lower anticholinergic activity might be a good practice. Certain types of widely prescribed medications have been linked to dementia. Evidence has been building up that anticholinergic medications may negatively affect the brain.

This is particularly concerning to doctors as these are widely prescribed for a multitude of medical conditions. They are used to treat depression, allergies, urinary incontinence, and several other conditions.

For some applications, alternatives exist. For example, Benadryl is a potential risk factor. However, there are many antihistamines that do not affect the brain as much such as Claritin or Allegra.⁸

Mechanism:

Anticholinergic drugs work by blocking a specific neurotransmitter called acetylcholine in the central and peripheral nervous systems. While it's unclear exactly why these medications increase dementia risk, one theory is that some may block the normal activity of acetylcholine in the regions of the brain associated with memory loss and cognition. Since levels of acetylcholine are known to be significantly lower in patients with Alzheimer's disease, this potential blockage could result in memory loss.

Drugs with anticholinergic activity fall across a fairly broad spectrum, and the research indicated that certain anticholinergic drugs posed more risk than others.⁹

Study Methodology, Results

The study authors analyzed data evaluated whether exposure to anticholinergic drugs was associated with dementia risk in 58,769 patients with a diagnosis of dementia and 225,574 controls 55 years or older matched by age, sex, general practice, and calendar time.

Extracting information on prescriptions for 56 drugs with strong anticholinergic properties, they calculated measures of cumulative anticholinergic drug exposure. Data analysis spanned from May 2016 to June 2018. The primary exposure consisted of the total standardized daily doses of anticholinergic drugs prescribed in the one to 11 years before the diagnosis date of dementia or a parallel date in matched controls.

Among the findings, the adjusted odds ratio for dementia rose from 1.06 (95% CI, 1.03-1.09) in the lowest overall anticholinergic exposure category to 1.49 (95% CI, 1.44-1.54) in the highest category, compared with no anticholinergic drug prescriptions in the one to 11 years before the index date.¹⁰

Higher Doses = Higher Risk

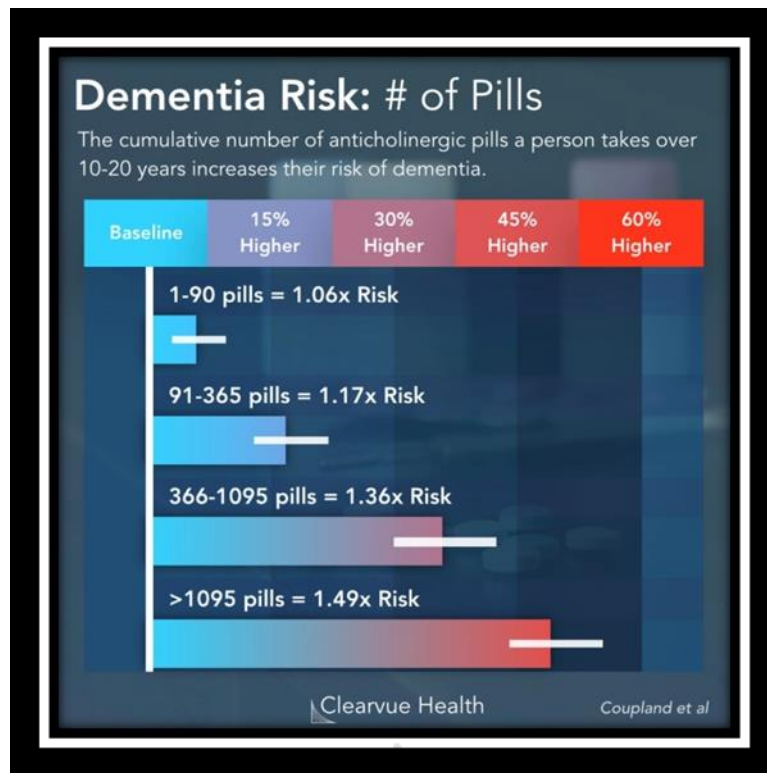


Figure No. 2: Anticholinergics & Dementia Data

The cumulative number of anticholinergic pills a person takes over 10-20 years increases their risk of dementia. The data above was obtained from 284,343 patients. These included cases of dementia and matched controls. Researchers estimated dementia risk at each "amount" of pills taken over a decade.

The more pills you take in a lifetime, the higher your overall risk of developing dementia.

Taking a few Benadryls here and there likely won't affect dementia risk. However, taking them regularly over many years might.

These data were calculated based on cumulative intake over all classes of anticholinergic drugs.

For example, if somebody takes a schizophrenia medication, a urinary incontinence medication, and an antihistamine, they would all be added together for the number of anticholinergic pills.

Dementia Risk for Each Drug Class

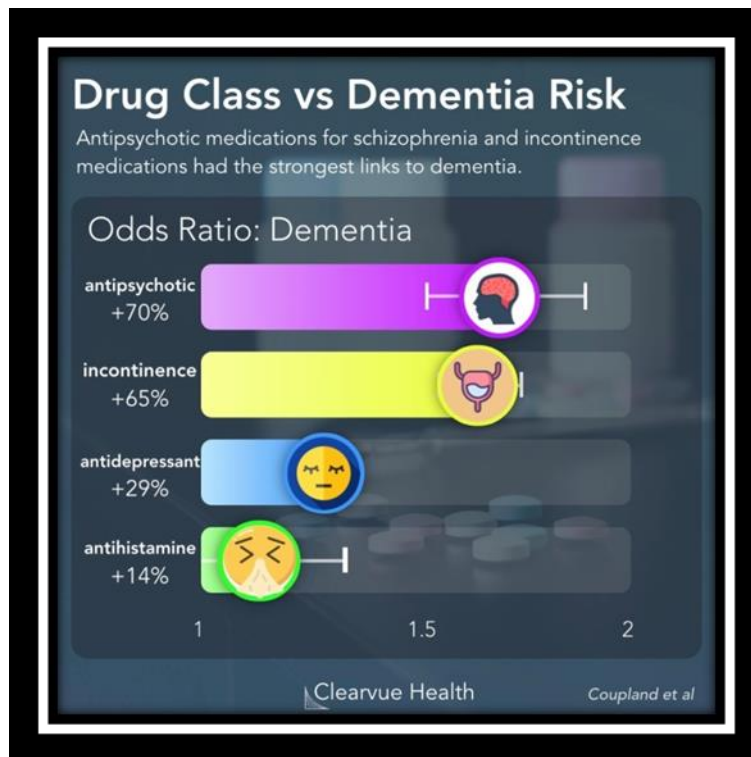


Figure No. 3: Dementia Risk for Antipsychotics

Incontinence Medications, Antidepressants, and Antihistamines. Each bar above is scaled the increase of risk for anticholinergics of each class. Antipsychotic medications lead to the highest estimated increases in risk of dementia. Antihistamines lead to the lowest increases of risk.

Some classes of anticholinergic medication tend to be more dangerous than others. Among the most commonly prescribed types, antipsychotic medications have the strongest link to dementia risk. Antihistamines have the weakest link.

A causal link between anticholinergic medications and dementia is confirmed, changing from an anticholinergic to another drug would be less difficult than many other interventions known to modify dementia risk such as increasing physical activity, controlling diabetes, or decreasing blood pressure.

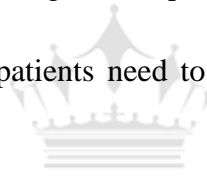
The three research scientists say that the next and definitive step to determine whether anticholinergic drugs cause dementia is to conduct long-term randomized deprescribing trials – decreasing or eliminating use of these very common medications – as they will be doing

later this year, to see if cholinergic neurotransmission in the areas of the brain related to cognitive performance can be improved, ultimately reducing the risk of developing dementia or delaying onset.

Though we learn about potential risk factors through observational studies, the best way to define a causal relationship between anticholinergics and dementia requires a prospective, randomized trial, said commentary lead author and Regenstrief Institute research scientist Dr. Campbell, also a faculty member of Purdue University's College of Pharmacy. In conducting such a trial, we can also learn about the risks and benefits of deprescribing medications, including the impact on symptom control, withdrawal or other adverse events, quality of life, and healthcare utilization.

Other areas for exploration noted in the commentary include whether a critical window of opportunity exists to capture the cognitive benefit of deprescribing anticholinergics, for example, whether deprescribing must be performed while these neurotransmitters are sufficiently healthy to benefit and show signs of improvement in cognition.

Clinicians, health policymakers and patients need to understand the benefits and harms of deprescribing anticholinergics.¹¹



Anticholinergic drugs may increase the risk for dementia in older adults.

The drugs implicated are commonly used, estimated to be taken by about 20% of the older adult population for many conditions. They include popular antihistamines sold over the counter as sleep aids, such as diphenhydramine (Benadryl, McNeil-PPC Inc), or for allergy relief, such as chlorpheniramine; oxybutynin and tolterodine for overactive bladder; and the tricyclic antidepressants, such as doxepin or amitriptyline, even when used at low doses for migraine prevention or neuropathic pain.

It is found that a high anticholinergic burden -- either from one or multiple drugs -- plus two to three months of continuous exposure to that high burden approximately doubled the risk of developing cognitive impairment.¹²

CONCLUSION

Medications with anticholinergic activity negatively affect older adults. **Anticholinergic** medications can cause dry mouth, low blood pressure and also confusion, difficulty concentrating agitation and **memory problems**. These side effects have been assumed to be temporary, but recent studies suggest that long term use of **anticholinergics** elevated risk of dementia.

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