

Anticholinergic drugs and dementia

Anticholinergics are a class of drug used to treat a wide variety of medical conditions. As with any medication, anticholinergics can have many beneficial effects, but these need to be balanced against a number of potential risks. This sheet provides information about how these drugs work as well as the impact that they may have in respect to dementia risk and cognitive functioning.

What are anticholinergics?

Anticholinergics are generally used to inhibit the involuntary movements of muscles or balance the production of various chemicals within the body. They have been used in treating a wide variety of medical conditions including symptoms of psychosis (which can be caused by bipolar disorder and schizophrenia), depression, urinary incontinence (e.g. overactive bladder), gastrointestinal spasms, allergies, respiratory conditions (such as asthma and chronic obstructive pulmonary disease), Parkinson’s disease, conditions concerning muscles in the eye and pupil dilation, nausea, sleep disorders and cardiovascular complaints (slow heart rhythms) (Table 1).^{1,2} Some cold and flu medications that can be purchased over-the-counter also contain anticholinergic properties.³ Anticholinergic medications may be taken as a tablet, inhaled, injected or as eye drops.

Anticholinergic drugs are widely available and may be used by up to 60% of older Australians at some point

in time.⁴ It has been estimated that in Australia, 33% of people over the age of 65 years take enough medications with anticholinergic effects to potentially increase their risk of harm.⁵ The use of anticholinergics is more common in older people because these drugs are prescribed for the symptomatic management of medical conditions that often occur in later life.

How do anticholinergic drugs work?

Anticholinergics are a class of drug that block the action of acetylcholine in the nervous system, a chemical (neurotransmitter) that is used to control messages travelling from one cell to another. They do this by blocking the binding of acetylcholine to its receptor in the nerve cells. In the brain, acetylcholine is involved in learning and memory whereas in the rest of the body, it stimulates muscle contractions.

However, drugs other than pure anticholinergic agents can also produce anticholinergic effects. These include tricyclic antidepressants, antihistamines, and antipsychotic drugs.⁶

Table 1. Medicines with anticholinergic properties^{1-3,7}

Main Use	Generic Name	Brand Name(s)
Psychosis	Chlorpromazine*	Largactil®
	Olanzapine*	APO-Olanzapine®, Auro-Olanzapine®, Chemmart Olanzapine®, Lanzek®, Olanzacor®, Olazapine Generichealth®, Olanzapine Sandoz®, Olanzapine-Synthon®, Ozin®, Stada Olanzapine®, Pharmacy Choice Olanzapine®, Terry White Chemists Olanzapine®, Zylap®, Zypine®, Zyprexa®
	Pericyazine*	Neulactil®

Main Use	Generic Name	Brand Name(s)
Depression	Amitriptyline*	APO-Amitriptyline®, Amitriptyline Alphapharm®, Chemmart Amitriptyline®, Endep®, Entrip®, Terry White Chemists Amitriptyline®
	Clomipramine*	Anafranil®, Chemmart Clomipramine®, GenRx Clomipramine®, Placil®, Terry White Chemists Clomipramine®
	Dothiepin*	Dothep®
	Doxepin*	Deptran®, Sinequan®
	Imipramine*	Tofranil®, Tolerade®
	Nortriptyline*	Allegron®
Urinary Incontinence	Darifenacin†	Enablex®
	Oxybutynin	Ditropan®, Oxybutynin Sandoz®, Oxybutynin Winthrop®, Oxytrol®
	Propantheline	Pro-Banthine®
	Solifenacin†	Vesicare®
	Tolterodine†	Detrusitol®
Allergies (antihistamines)	Brompheniramine*†	Demazin®, Dimetapp®
	Chlorpheniramine*†	APOHealth, Chemists' Own®, Codral®, Demazin®
	Cyproheptadine*	Periactin®
	Diphenhydramine*†	Benadryl®, Chemists' Own®, Difenacol®, Snuzaid®, Unisom®
	Pheniramine*†	Avil®, Naphcon-A®, Visine®
	Promethazine*†	Allersoothe®, Avomine®, Gold Cross®, Phenergen®, Sandoz Fenezal®
Respiratory Conditions	Aclidinium	Bretaris Genuair®
	Glycopyrronium	Seebri®, Ultibro®
	Ipratropium	Aeron®, APO-Ipratropium®, Aproven®, Atrovent®, Chemmart Ipratropium®, GenRx®, Ipratrin®, Ipravent®, Terry White Chemists Ipratropium®
	Tiotropium	Spiolto®, Spiriva®,
	Umeclidinium	Anoro Ellipta®, Incruse Ellipta®
Parkinson's Disease	Amantadine	Symmetrel®
	Benzhexol	Artane®
	Benztropine	Benztrop®, Cogentin®
	Biperiden	Akineton®
Eye Conditions	Atropine	Atropt®, Minims Atropine®
	Cyclopentolate†	Cyclogyl®, Minims Cyclopentolate®
	Homatropine	Isopto®
	Tropicamide†	Minims Tropicamide®, Mydracyl®

Please note that this is not an exhaustive list of all possible medications with anticholinergic properties. Those drugs with significant anticholinergic effects and/or have an anticholinergic mode of action have been included.

* These drugs are not pure anticholinergic agents but do exhibit significant anticholinergic effects.

• † Not listed on the Pharmaceutical Benefits Scheme (PBS).

What side-effects are associated with the use of anticholinergic drugs?

Common anticholinergic side-effects include dry mouth, drowsiness, blurred vision, urinary retention and constipation. At very high doses (including deliberate or unintentional overdose) anticholinergic delirium may occur with enlarged pupils, hot, dry and flushed skin and tachycardia (faster than normal heart rate).^{1, 6}

What are the implications of anticholinergic drugs with respect to dementia risk?

The impact of anticholinergic drugs on people's likelihood of developing dementia has received increasing attention, although the research findings are mixed. In a recent study that followed participants for an average of seven years, higher cumulative anticholinergic use was associated with dementia risk. Specifically, older people in the highest exposure category had a 1.5-fold increased risk of developing dementia compared with non-users. Further, the increased risk for dementia remained consistent across the various types of anticholinergic drugs.⁸ In contrast, other studies have found no link between anticholinergic medication use and dementia risk.⁹ It is unclear whether or not dementia associated with anticholinergic drug use is reversible, even if the medication has been stopped for a number of years.

It is possible that anticholinergic use is associated with an increased risk of mild cognitive impairment (MCI). One study has shown that compared with older adults with no exposure to anticholinergic drugs, the odds for having a diagnosis of MCI may be more than two times greater among older adults who were exposed to at least three possible anticholinergic drugs for at least three months.¹⁰

The mechanism by which anticholinergics may increase risk for dementia is not yet known. Larger studies following participants over longer time periods are necessary to understand the true long-term impact of these drugs on the brain.

What are the impacts of anticholinergic drugs on cognitive functioning?

People may feel drowsy and less attentive after they have taken an anticholinergic medicine, but these are short-term, reversible changes. Older people may be more susceptible to anticholinergic effects such as confusion or delirium, which in turn may increase their risk of falls or hospitalisation.^{11,12} Research has shown that some older people taking anticholinergic medications perform more poorly on tasks involving short-term memory, verbal reasoning, planning, and problem solving compared to those who are not using these drugs,^{13,14} although in one study, no association

was found between anticholinergic drug use and any cognitive measures for people already diagnosed with MCI or Alzheimer's disease.¹⁴

Anticholinergics are believed to impact cognitive function because of its role in blocking the action of acetylcholine in the brain. Acetylcholine is an important neurotransmitter involved in memory processes, particularly short-term memory and attention. Decreasing the action of acetylcholine may, therefore, lead to reduced memory performance.

Do anticholinergic drugs interact with Alzheimer's disease medications?

Cholinesterase inhibitors, such as donepezil and rivastigmine, may offer temporary relief from the symptoms of Alzheimer's disease. Enzymes called cholinesterases break down acetylcholine in the brain and if their action is inhibited, more acetylcholine is available for communication between brain cells. Some people may find improvements in their ability to think clearly, memory, function in daily activities and behavioural and psychological symptoms.

Anticholinergic drugs, which block the transmission of acetylcholine in the brain, have the opposite pharmacological action to cholinesterase inhibitors. Concurrently taking cholinesterase inhibitors and anticholinergic medications may reduce or nullify the effectiveness of both medications.⁷ In order to achieve maximum therapeutic effects, these drugs generally should not be used in combination with each other.

What are the potential interactions with other common drugs?

Giving an anticholinergic drug with other drugs with known anticholinergic effects will not only increase therapeutic impact of the medication but also the risk of any potential adverse effects. Conversely, combining anticholinergics with drugs that increase the concentration of acetylcholine in the brain (e.g. cholinesterase inhibitors) will reduce the anticholinergic effect.¹ Anticholinergics may also interact with other medications. For example, tolterodine (a medication used for treating an overactive bladder) may increase warfarin's anticoagulant (blood thinning) effect and therefore, the risk of bleeding.¹

What are the impacts of taking one or more medicines with anticholinergic properties?

The cumulative, sedative effect of taking one or more medicines with anticholinergic properties is known as the anticholinergic 'load' or 'burden'.³ This may occur from an individual anticholinergic medicine or taking multiple medicines (even at low doses) that have of anticholinergic properties.⁴ As the anticholinergic burden increases, so too does the possibility of

experiencing medication side-effects and cognitive decline.

Anticholinergics should be used with caution in older adults and avoided if possible in people who have dementia. It is generally recommended that for conditions with no therapeutic alternatives, the lowest effective dose of anticholinergic medication should be prescribed.¹ Reducing the number and dose of anticholinergic and sedative medicines may improve cognitive function and reduce the likelihood of adverse events in older people.^{3,15}

What questions should you ask your doctor about any drug being prescribed?

- What are the potential benefits of taking this drug?
- How long before improvement may be noticed?
- What action should be taken if a dose is missed?
- What are the known potential side-effects?
- If there are side-effects, should the dose be reduced or should the drug be stopped?
- If the drug is stopped suddenly, what happens?
- What other drugs (prescription and over-the-counter) might interact with the medication?
- How might this drug affect other medical conditions?
- Are there any changes that should be reported immediately?
- How often will a visit to the doctor be needed?
- Is the drug available at a subsidised rate?

References

1. Australian Medicines Handbook. Adelaide: Australian Medicines Handbook Pty Ltd; 2016 [cited 2016 Apr 27]. Available from: <https://amhonline.amh.net.au/>
2. MIMS Online. MIMS Australia. 2016 [cited 2016 Apr 27]. Available from: <http://www.mimsonline.com.au>
3. Royal Australian College of General Practitioners (RACGP). Anticholinergic and sedative medicines. Prescribing considerations for people with dementia. *Australian Family Practice*. 2012;41(1):45-49.
4. Parkinson L, Magin MJ, Thomson A, Byles JE, Caughey GE, Etherton-Beer C, Gnjjidic D, Hilmer SN, King Tong Lo T, McCowan C, Moorin R, Pond DC. Anticholinergic burden in older women: not seeing the wood for the trees? *Medical Journal of Australia*. 2015;202(2):91-94.
5. Ball PA, Morrissey H, Pilotto LSJ. Anticholinergic burden assessed using general practice electronic records. *Journal of Pharmacy Practice and Research*. 2013;43(3):202–205.
6. Therapeutic Guidelines. eTG Complete. November 2015 [cited 2016 Apr 27]. Available from: <https://tgldcdp.tg.org.au/etgcomplete>

7. Gadzhanova SV, Roughead EE, Robinson M. Use of Medicines with Anticholinergic and Sedative Effect Before and After Initiation of Anti-Demential Medications. *Drugs-Real World Outcomes*. 2015; 2(1):53-60.

8. Gray SL, Anderson ML, Dublin S, Hanlon JT, Hubbard R, Walker R, Yu O, Crane PK, Larson EB. Cumulative use of strong anticholinergics and incident dementia. A prospective cohort study *JAMA Internal Medicine*. 2015;175(3):401-407.

9. Ancelin ML, Artero S, Portet F, Dupuy AM, Touchon J, Rithie K. Non-degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study. *BMJ*. 2006;332(7539):455-459.

10. Cai X, Campbell N, Khan B, Callahan C, Boustani M. Long-term anticholinergic use and the aging brain. *Alzheimer's and Dementia*. 2013;9(4):377-385.

11. Campbell N, Boustani MA, Limbil T. The cognitive impact of anticholinergics: a clinical review. *Clinical Interventions in Aging*. 2009; 4(1):225-233.

12. Kalisch Ellett LM, Pratt NL, Ramsay EN, Barratt JD, Roughead EE. Multiple anticholinergic medication use and risk of hospital admission for confusion or dementia. *Journal of the American Geriatrics Society*, 2014;62:1916-1922.

13. Risacher S, McDonald BC, Tallman EF, West JD, Farlow MR, Unverzagt FW, Gao S, Boustani M, Crane PK, Petersen RC, Jack CR, Jaquist WJ, Aisen PS, Weiner MW, Saykin AJ. Association between anticholinergic medication use and cognition, brain metabolism, and brain atrophy in cognitively normal older adults *JAMA Neurology*. 2016; Published online April 18, 2016. doi:10.1001/jamaneurol.2016.0580.

14. Sittironnarit G, Ames D, Bush AI, Faux N, Flicker L, Foster J, Hilmer S, Lautenschlager NT, Maruff P, Masters CL, Martins RN, Rowe C, Szoek C, Ellis KA, AIBL research group. Effects of anticholinergic drugs on cognitive function in older Australians: Results from the AIBL Study. *Dementia and Geriatric Cognitive Disorders*. 2011; 31:173-178.

15. Salahudeen MS, Duffull SB, Nishtala PS. Impact of anticholinergic discontinuation on cognitive outcomes in older people: A systematic review. *Drugs and Aging*, 2014; 31:185–192.

FURTHER INFORMATION

Dementia Australia offers support, information, education and counselling. Contact the National Dementia Helpline on **1800 100 500**, or visit our website at **dementia.org.au**



For language assistance phone the Translating and Interpreting Service on **131 450**

4 ANTICHOLINERGIC DRUGS