

Association Between Anti-Cholinergic Medication Use and Cognition, Brain Metabolism, and Brain Atrophy in Cognitively Normal Older Adults

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This paper was prepared for the *Alzheimer's Disease Neuroimaging Initiative*.

BACKGROUND FROM DAN MURPHY

Anti-Cholinergic drugs block the neurotransmitter *Acetylcholine*. Many of these drugs are common over-the-counter drugs used to treat colds, flu, hay fever, allergies, and heartburn.

Abbreviations:

AC+	participant taking anti-cholinergic medication with medium or high anticholinergic activity
AC-	participant not taking anticholinergic medication
ADNI	Alzheimer's Disease Neuroimaging Initiative.
CN	Cognitively Normal
IMAS	Indiana Memory and Aging Study

KEY POINTS FROM THIS STUDY

- 1) "The use of anti-cholinergic (AC) medication is linked to cognitive impairment and an increased risk of dementia." **[20 references are cited]**
- 2) This study used 2 cohorts of cognitively normal older adults assessing 451 subjects:
Alzheimer's Disease Neuroimaging Initiative (ADNI)
Indiana Memory and Aging Study (IMAS)
- 3) This is the first study to have examined the effects of regular AC medication use with neuroimaging measures of brain structure and function in cognitively normal (CN) older adults.

- 4) Subjects were assessed using these outcomes:
- Cognitive scores
Memory Scale–Revised Logical Memory Immediate and Delayed
 - Fluorodeoxyglucose F-18 (FDG) uptake with Positron Emission Tomography (FDG-PET)
 - Brain atrophy measures from structural magnetic resonance imaging were compared between AC+ participants and AC– participants after adjusting for potential confounders.
- 5) The total AC burden score was calculated by dose and duration of use.
- 6) The assessment included the total number of medications, the total number of common comorbid conditions, including transient ischemic attack, myocardial infarction, cardiac surgery, hypertension, hyperlipidemia, diabetes, sleep apnea, other vascular disorders, insomnia, depression, anxiety, attention-deficit/hyperactivity disorder, and other psychiatric disorders.
- 7) The AC+ participants showed lower memory and recall scores, lower executive function composite scores, and reduced total cortical volume and cortical thickness. **[Key Point]**
- 8) “The use of AC medication was associated with increased brain atrophy and dysfunction and clinical decline. Thus, use of AC medication among older adults should likely be discouraged if alternative therapies are available.” **[Key Point]**
- 9) Given the importance of the cholinergic system in cognition, researchers speculate that direct impairment of cholinergic neurons by the use of these AC drugs may underlie these deleterious effects.
- 10) This study showed that cognitive performance, brain glucose hypometabolism, structural brain atrophy, and clinical progression to mild cognitive impairment (MCI) and/or Alzheimer disease (AD) were associated with the use of AC medication. **[Key Point]**
- 11) Significant effects of anti-cholinergic (AC) drugs included:
- Reduced cognition, memory, executive function, verbal reasoning, planning, and problem solving.
 - Reduced glucose metabolism on FDG-PET.
 - “A significant effect of AC medication use on brain structure was observed. The AC+ participants demonstrated reduced total cortical volume and larger lateral ventricle and inferior lateral ventricle volumes.”

“Regional effects were also observed in the temporal lobe, with AC+ participants showing a reduced temporal lobe cortical thickness.”

12) “A higher total AC burden score was associated with reduced general cognition and [increased] atrophy.”

13) “A significant association between AC medication use and future progression of ADNI participants to MCI and/or AD was observed.” **[increased risk by 147%]**

14) AC+ participants who are A β positive [genetic markers for increased dementia risk] showed the highest risk of conversion.” **[increased risk by 673%]**

15) Use of medications with medium or high AC effects was “associated with poorer cognition (particularly in immediate memory recall and executive function), reduced glucose metabolism, whole-brain and temporal lobe atrophy, and clinical decline. The effect appeared additive because an increased burden of AC medications was associated with poorer executive function and increased brain atrophy.” **[Key Point]**

16) “These results suggest that medications with AC properties may be detrimental to brain structure and function, as well as cognition.”

17) “The observed findings support previous reports regarding the association between AC medication use and cognitive impairments, with a significant effect of AC medication use on executive and immediate, rather than delayed, memory.” **[16 references are cited]**

18) “We also found that the increased clinical progression from CN to MCI and/or AD was associated with AC medication use.”

19) “We observed that AC+ participants had reduced brain glucose metabolism and increased brain atrophy compared with AC– participants. Furthermore, those with the highest total AC burden scores showed the most atrophy.”

20) “The increased brain atrophy and decreased brain function that we observed may be linked to the central effects of AC medications on cholinergic pathways within the brain.” Cholinergic pathways are “important for cognition.”

21) “AC medication administration leads to an uncoupling between brain structure and cognition in older adults.”

22) “Decreased cholinergic activity due to AC medications may induce synaptic loss and neurodegeneration in regions with significant cholinergic innervation.”

23) “Reduced cholinergic activity has been linked to increased plasma corticosteroid levels, which in turn are linked to increased hippocampal cell death.”

24) “The findings in this study provide a potential biological basis for the reduced cognition associated with the use of AC medications through the functional and structural changes in the brain.”

25) “A significant association between AC use and future progression of participants to mild cognitive impairment and/or Alzheimer disease was observed.”
[by 147%]

26) “These findings highlight the importance of considering the cognitive adverse effects of AC medications before using them to treat older adults at risk for cognitive decline in a clinical setting.”

KEY POINTS FROM AUTHORS

Question:

Is use of anti-cholinergic (AC) medication associated with poorer cognition, brain hypometabolism, brain atrophy, and/or increased risk of clinical decline in cognitively normal older adults?

Findings:

“In this longitudinal study of 2 cohorts of cognitively normal older adults, use of medications with medium or high anti-cholinergic activity was associated with poorer memory and executive function, brain hypometabolism, brain atrophy, and increased risk of clinical conversion to cognitive impairment.”

“This finding was greatest for those taking drugs with the most anti-cholinergic activity”.

“Use of medication with significant anti-cholinergic activity should likely be discouraged in older adults if alternative therapies are available.”

COMMENTS FROM DAN MURPHY

Prior studies on this topic indicate that these effects of anti-cholinergic drugs have been known for about 10 years; weaker anti-cholinergic cause cognitive problems within 90 days; stronger anti-cholinergic drugs can cause cognitive problems when taken continuously for as few as 60 days.

The individual, family, societal, and governmental burden of dealing with dementia is staggering. This topic was deeply explored in the September/October 2015 issue of *The Rand Review*, titled *Costs of Dementia*. The burdens include financial, time, emotional, stress, heartache, etc. My Letter To The Editor pertaining to this article is:

From: Dan Murphy dan@danmurphydc.com

Subject: Costs of Dementia

Date: September 17, 2015 at 10:44 AM

To: letters@rand.org

Dear Editor:

Thank you for your article "Costs of Dementia" in the September/October 2015 Rand Review. The magnitude of the problem and its associated costs are staggering. Simple math indicates that throwing more money at the problem, once diagnosed, is not the answer, which is why I believe your article missed the point. The only workable solution is prevention. This means that lifestyle changes that are known to reduce the risks of dementia should be started much earlier in one's life.

**Dan Murphy, DC
Auburn, CA**

It is stunning that this article indicates that common over-the-counter and prescription anti-cholinergic drugs are partially to blame for this phenomenon. Perhaps my *Letter To The Editor* to the *Rand Review* should have included the avoidance of anti-cholinergic drugs. A list of these drugs is included below.

We encourage all of our patients taking these drugs, and patients wanting to enhance brain function, to also consume acetylcholine-enhancing supplements, specifically:

Complete Brain Charge

Complete Synapse

These products are available through
Nutri-West (800)-443-3333

List of Implicated Anti-Cholinergic Drugs, From *Aging Brain Care*

Drug	Prescribed for / Type of Drug	US Brand Name
Alprazolam	Sedative / Anxiety	Xanax
Aripiprazole	Antipsychotic	Abilify
Asenapine	Schizophrenia	Saphris
Atenolol	Beta Blocker / High Blood Pressure	Tenormin
Amantadine	Antiviral / Flu	Symmetrel
Amitriptyline	Antidepressant	Elavil
Amoxapine	Antidepressant	Asendin
Bupropion	Antidepressant / Quit Smoking	Wellbutrin
Benzotropine	Parkinson's Disease	Cogentin
Brompheniramine	Antihistamine	Dimetapp
Captopril	High Blood Pressure / Heart Failure	Capoten
Cetirizine	Antihistamine	Zyrtec
Chlorthalidone	Diuretic	Diuril
Cimetidine	Stomach Ulcer Gastroesophageal Reflux	Tagamet
Clidinium	Peptic Ulcers	Librax
Clorazepate	Anxiety, Seizures, Alcohol Abuse	Tranxene
Codeine	Opioid Painkiller	Contin
Colchicine	Gout	Colcrys
Carbamazepine	Anticonvulsant / Seizures	Tegretol
Cyclobenzaprine	Musculoskeletal Pain, Injury	Flexeril
Cyproheptadine	Antihistamine	Periactin
Carbinoxamine	Antihistamine	Histex
Chlorpheniramine	Antihistamine	Chlor-Trimeton
Chlorpromazine	Anti-psychotic	Thorazine
Clemastine	Antihistamine	Tavist
Clomipramine	Antidepressant	Anafranil
Clozapine	Antipsychotic	Clozaril
Desloratadine	Antihistamine	Clarinx
Diazepam	Anxiety, Alcohol Abuse, Muscle Spasms	Valium
Digoxin	Heart failure	Lanoxin
Dipyridamole	Prevents Blood Clots	Persantine
Disopyramide	Irregular Heartbeat	Norpace
Darifenacin	Overactive Bladder	Enablex
Desipramine	Antidepressant	Norpramin
Dicyclomine	Irritable Bowel Syndrome	Bentyl
Dimenhydrinate	Anti-Nausea	Dramamine
Diphenhydramine	Antihistamine	Benadryl
Doxepin	Depression, Anxiety	Sinequan
Doxylamine	Antihistamine	Unisom
Fentanyl	Opioid Painkiller	Duragesic
Furosemide	Heart Failure, Liver Disease	Lasix
Fluvoxamine	Antidepressant / Obsessive Compulsive Disorder	Luvox
Fesoterodine	Overactive Bladder	Toviaz
Flavoxate	Bladder Pain, Incontinence	Urispas
Haloperidol	Schizophrenia	Haldol

Hydroxyzine	Antihistamine	Atarax
Hyoscyamine	Muscle Spasms, Stomach and Intestinal Disorders	Anaspaz
Hydralazine	High Blood Pressure	Apresoline
Hydrocortisone	Steroid / Eczema, Psoriasis	Cortef
Iloperidone	Schizophrenia	Fanapt
Isosorbide	Angina	Isordil
Imipramine	Antidepressant	Tofranil
Levocetirizine	Antihistamine	Xyzal
Loperamide	Diarrhea	Immodium
Loratadine	Antihistamine	Claritin
Loxapine	Schizophrenia	Loxitane
Metoprolol	Angina, High Blood Pressure	Lopressor
Morphine	Opioid Painkiller	MS Contin
Meperidine	Opioid Painkiller	Demerol
Methotrimeprazine	Anti-Psychotic	Levoprome
Molindone	Anti-Psychotic	Moban
Meclizine	Nausea, Vomiting, Dizziness	Antivert
Methocarbamol	Muscle Relaxant	Robaxin
Nifedipine	High Blood Pressure, Angina	Procardia
Nefopam	Painkiller	Nefogesic
Nortriptyline	Antidepressant	Pamelor
Oxcarbazepine	Epilepsy, Anti-Convulsant	Trileptal
Paliperidone	Anti-Psychotic	Invega
Prednisone	Anti-Inflammatory	Deltasone
Pimozide	Anti-Psychotic	Orap
Olanzapine	Anti-Psychotic	Zyprexa
Orphenadrine	Muscle Relaxant	Norflex
Oxybutynin	Overactive Bladder	Ditropan
Paroxetine	Antidepressant	Paxil
Perphenazine	Anti-Psychotic	Trilafon
Promethazine	Antihistamine	Phenergan
Propantheline	Reduces stomach Acid	Pro-Banthine
Propiverine	Incontinence	Detrunorm
Quinidine	Heart Rhythm Disorders	Quinaglute
Quetiapine	Anti-Psychotic	Seroquel
Ranitidine	Stomach Ulcers	Zantac
Risperidone	Anti-Psychotic	Risperdal
Scopolamine	Nausea, Vomiting, Motion Sickness	Transderm Scop
Solifenacin	Overactive Bladder	Vesicare
Theophylline	Asthma, Bronchitis, Emphysema	Theo-Dur
Trazodone	Antidepressant	Desyrel
Triamterene	Diuretic	Dyrenium
Thioridazine	Anti-Psychotic	Mellaril
Tolterodine	Urinary Incontinence	Detrol
Trifluoperazine	Anti-Psychotic	Stelazine
Trihexyphenidyl	Parkinson's Disease	Artane
Trimipramine	Depression	Surmontil
Trospium	Overactive Bladder	Sanctura
Venlafaxine	Antidepressant	Effexor
Warfarin	Prevents Blood Clot Formation	Coumadin

