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Drug Therapies for Chronic Conditions and Risk of Alzheimer's Disease and Related Dementias: A Scoping Review

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Abstract

INTRODUCTION: Most older Americans use drug therapies for chronic conditions. Several are associated with Alzheimer's disease and related dementias (ADRD) risk.

METHODS: A scoping review was used to identify drug classes associated with increasing or decreasing ADRD risk. We analyzed size, type, and findings of the evidence.

RESULTS: We identified 29 drug classes across 11 therapeutic areas, and 404 human studies. Most common were studies on drugs for hypertension (93) or hyperlipidemia (81). Fewer than five studies were identified for several anti-diabetic and anti-inflammatory drugs. Evidence was observational only for beta blockers, proton pump inhibitors (PPIs), benzodiazepines (BZDs), disease-modifying anti-rheumatic drugs (DMARDs). For 13 drug classes, 50% or more of the studies reported consistent direction of effect on ADRD risk.

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DISCUSSION: Future research targeting drug classes with limited/non-robust evidence, examining sex, racial heterogeneity, and separating classes by molecule will facilitate understanding of associated risk, and inform clinical and policy efforts to alleviate the growing impact of ADRD.

Keywords

Alzheimer's disease; dementia; drug therapies

Introduction

The looming public health and public finance crisis from a growing population with Alzheimer's disease and related dementias (ADRD) was identified by researchers decades ago yet the social, health and economic consequences of the disease continues to strain families and healthcare systems in the U.S. [1] The urgency to prevent and treat ADRD is escalating as an estimated 5.8 million Americans have Alzheimer's disease (AD) alone and 6.5 million Americans aged 65 years and older have ADRD, which is projected to reach about 14 million by 2050. [2–4] This is not a unique challenge to the U.S. Societies across the globe are ageing, and ADRD is straining the health care systems of them all.[5]

Clinical trials for new drugs to prevent or treat ADRD have been disappointing, but commitment to developing effective therapies that affect the underlying disease process is advancing.[4,6] Risk reduction strategies today could complement the traditional drug discovery approach. Several chronic conditions common in the older population, such as hypertension and diabetes, are associated with greater risk of developing ADRD, and these conditions are modifiable through both lifestyle approaches and drug treatments. [7] Many drug therapies commonly used by older adults have been associated with impacting ADRD risk. Some drugs, for example, antihypertensives may reduce ADRD risk by treating the target condition, hypertension. They may also interact with ADRD-related pathophysiological pathways by way of mechanisms unrelated to their original therapeutic indication. On the other hand, drugs such as benzodiazepines for anxiety or antispasmodics for overactive bladder, have been associated with increased risk of ADRD.

The study reports the result of a comprehensive scoping review on drug classes that have been associated with ADRD risk. [8] We assessed the size and scope of the research literature on pharmaceuticals approved for non-ADRD indications that are associated with ADRD risk. We did not, however, assess the strength of the evidence within a drug class, thus scholars should refer to the source study to assess a its rigor. We compiled the following evidence with the aim of informing future studies and identifying knowledge gaps: (1) the numbers and types of pharmaceuticals approved for non-ADRD indications associated with decreased and increased ADRD risk; (2) prevalence of drug use by drug class in the older US population; (3) number and type of study design that have examined them; (4) summary findings of the studies. Finally, we provided a public tool for customized searches and bibliographies of the studies presented here to support future research in this area.

The study goal was a mapping of human studies that inform prevention and risk reduction opportunities for ADRD, not solely through repurposing, but potentially achievable by

distinguishing differences across drug classes used to treat a common condition, initiating/achieving better adherence to treatments that reduce risk and by reducing use of drugs associated with increased risk of ADRD. Given the high prevalence of chronic conditions and use of drugs to treat them in the older U.S. population, improved understanding of which drug classes have been associated with risk of ADRD, and the size and type of evidence base provides valuable information for targeting more specific questions about the relationships and facilitate better research on drugs that can increase or decrease risk of ADRD. These new studies can inform both clinical and policy efforts to alleviate the growing impact of the disease.

Methodology

The development of the methodological framework was guided by Arksey and O'Malley's *Scoping studies: towards a methodological framework*.[9] The research team developed a protocol a priori that established: research questions; inclusion and exclusion criteria; search strategies; study appraisal method; and data collection and synthesis. Two independent researchers then undertook a systematic search using PubMed, SCOPUS and Cochrane Central Register of Controlled Trials (CENTRAL) databases for all published studies on humans from January 2008 to August 2018 associated with each of the identified drug classes and Alzheimer's disease, dementia or cognitive outcomes. Grey literature was excluded from our search. The total number of papers returned was 15,473. Papers were excluded, included or added through an iterative process reviewed by both researchers and resulted in a total of 404 unique papers. Papers that studied more than one drug were listed under each drug class thus the total count was 534 drug studies. We followed reporting guidelines in the PRISMA extension for scoping reviews, compiling data from the papers on each drug class to identify type of study, primary outcome, and main results. Details on study methodology are available in the Methods Appendix including: flow diagram, sample search strategy and data charting.

Results

We list the therapeutic area and then number of classes in parentheses, e.g. Type II diabetes (six). Type II diabetes is the therapeutic area and six is the number of classes. The therapeutic areas (number of drug classes) were: Type II diabetes (6), depression (6), hypertension (5), insomnia (3), atrial fibrillation (2), chronic inflammation (2), hyperlipidemia (1), bipolar disorder (1), gastroesophageal reflux (1), allergies (1), and incontinence (1). Table 1, Appendix, lists drug classes and prevalence of medication use by drug class, among Medicare claims Part D beneficiaries in 2016. Antihypertensive medications were the most prevalent, with 14.7 million beneficiaries filling a prescription for a beta blockers, and 13.8 million and 12.2 million for diuretics and ACEIs, respectively. The second most prevalent drugs were statins – over 21 million beneficiaries filled a prescription for a statin in 2016.

Drug Abbreviations			
calcium channel blockers	CCBs	monoamine oxidase inhibitors	MAOIs
angiotensin- converting enzyme inhibitors	ACEIs	dipeptidyl peptidase-4 inhibitors	DPP-4s
angiotensin II receptor blockers	ARBs	glucagon-like peptide 1 receptor agonists	GLP-1s
selective serotonin reuptake inhibitors	SSRIs	thiazolidinediones	TZDs
serotonin-norepinephrine reuptake inhibitors	SNRIs	proton pump inhibitors	PPIs
serotonin antagonist and reuptake inhibitors	SARIs	benzodiazepines	BZDs
tricyclics	TCAs	non-steroidal anti-inflammatory drugs	NSAIDs
tetracyclics	TeCAs	disease-modifying anti-rheumatic drugs	DMARDs

Table 1 summarizes the number of studies by: (1) drug class/subclass; (2) study type (randomized control trial (RCT), observational, literature review/meta-analysis); (3) outcome (Alzheimer's disease, dementia, cognition); (4) result/conclusion excluding literature review/meta-analysis in the counts. Results were classified as increasing or decreasing risk of ADRD or no/weak relationship, which was signified by a statistically significant estimate ($p<0.05$) in the main analyses. A full description of our classification methods is included in the Methods Appendix. Of the 534 papers on 29 drug classes, almost half (46%) investigated antihypertensive drug classes and statins. Seventy-one were RCTs, 326 were observational and 137 were literature reviews or meta-analyses. Seventy-six RCTs and observational studies examined outcomes related to Alzheimer's disease (incidence, diagnosis, and pathology), 170 included dementia outcomes and 151 measured cognition or cognitive decline. We reported authors' stated conclusions on the primary outcome and population.

A detailed discussion of results from each of the 29 drug classes and citations for the 404 unique papers are in the Appendix. In this material, we described each drug class' hypothesized mechanism of action on risk of ADRD, such as reducing Aβ, tau pathology, or neuroinflammation. We then summarized the literature on each class or subclass. We encourage readers with interest in a specific drug class or classes to read the full text in the online supplementary materials. The following is a *brief* summary of highlighted results.

Antihypertensives (CCBs, diuretics, beta blockers, ACEIs, ARBs):

Antihypertensives reduce ADRD risk by reducing blood pressure, however, other pathways specific to a subtype, have been hypothesized. Specifically, drugs that act on the renin-angiotensin system, ACEIs and ARBs, are thought to be more protective against dementia risk than other antihypertensives (AHTs).[10] The 161 studies of five drug classes generally found that AHTs were protective against ADRD risk and cognitive impairment. ACEIs and ARBs were studied the most. Two studies rank ordered the classes and both reported ARBs were the most effective in reducing risk of ADRD but the remaining order differed.

Statins:

Research indicates hyperlipidemia promotes AD pathology. Independent of their cholesterol-lowering effects, statins may directly alleviate AD pathology by suppressing Aβ

formation and inflammation in the brain.[11] Among the 84 studies, eleven RCTs and some cross-sectional studies found no effect. Longitudinal observational studies generally found protective effects, and reported variation by sex and race/ethnicity.

Antidepressants (SSRIs, SNRIs, SARIs, TCAs, TeCAs, MAOIs):

Epidemiological studies have found a strong association between depression and development of AD.[12] Treating depression is hypothesized to reduce risk, with variation in mechanisms of action across subtypes. For example, TCAs and SSRIs have anticholinergic properties and may increase risk of dementia, but some SSRIs have also been shown to reduce Aβ burden and tau pathology. Evidence from the 71 studies was mixed. SSRIs (30) and tricyclics (14) were the most highly studied classes. Grouping together multiple classes was common, particularly among observational studies. Only 14 of the 71 studies examined the effect a single antidepressant, 13 of which analyzed SSRIs.

Antidiabetic (biguanides, sulfonylureas, insulin, DDP-4s, GLP-1s, TZDs):

Diabetes is a significant risk factor for ADRD and managing glucose levels reduces risk. Some drug treatments for diabetes may provide further protection against AD risk – for example, biguanides have been shown to decrease phosphorylated tau.[13] The majority of the 65 studies analyzed biguanides (16), insulin (19) and TZDs (21), generally finding they reduced ADRD risk and cognitive decline. There were few studies on sulfonylureas (6), DPP-4s (2), and GLP-1s (1) and evidence was mixed.

Proton pump inhibitors (PPIs):

PPIs have been shown to affect the metabolism of Aβ and lead to vitamin B12 deficiency, which increases AD risk.[14,15] Twelve observational and 4 review studies examined PPIs and findings were mixed. Five of the 12 found increased risk or cognitive decline, two reported neuroprotective benefits, and five were inconclusive.

Benzodiazepines (BZDs) and Z-drugs:

BZDs and Z-drugs have short-term cognitive effects, but hypothesized mechanisms related to longer-term ADRD risk act in both directions, none of which have been confirmed in experimental studies.[16] The 36 studies on BZDs (28), non-BZD hypnotics/Z-drugs (2) and atypical antipsychotics (6) generally found increased ADRD risk and cognitive decline. Fifteen of the observational studies on BZDs reported increased risk of ADRD and 8 found inconclusive evidence/no effect.

Anti-inflammatories (NSAIDs, DMARDs):

Inflammation has been implicated in AD pathogenesis and some anti-inflammatories (e.g. NSAIDs) have been shown to reduce risk or slow AD progression by reducing amyloid deposits and accumulation, for example.[17] Research on anti-inflammatory drugs was on NSAIDs (38), with few studies on DMARDs (2). The majority of NSAID studies reported neuroprotective effects; however, seven of 24 found detrimental effects and six, no relationship.

Anticoagulants/Vitamin K antagonists:

Complications arising from atrial fibrillation (AF), particularly reduced cardiac output and chronic microemboli, have been associated with increased risk of dementia and treating AF may reduce risk.[18] There were eight observational, one RCT and two review studies on anticoagulants. Six of nine found protective effects and two found no effect.

Antiplatelets (PDE3):

Cerebral ischemia and the accumulation of amyloid beta are both associated with developing ADRD. Antiplatelets have been shown to directly reduce risk, but some (e.g. cilostazol) further protect against AD by decreasing Aβ accumulation and reducing cerebrovascular blood flow.[19] All five studies reported protective effects, particularly among those with mild dementia or MCI. The beneficial effect increased with higher doses.

Antispasmodics:

Some antispasmodics have been shown to increase risk by targeting muscarinic M_1 receptors, which promote healthy cognitive functioning.[20] One drug (oxybutynin) has anticholinergic properties which have been linked to dementia. There were 14 studies on antispasmodics, primarily grouped with other drugs with anticholinergic properties (9 of 14). Nine of the 11 RCTs and observational studies reported antispasmodics increased the likelihood of dementia/cognitive impairment.

Antihistamines:

Some antihistamines exhibit anticholinergic properties and, thus, have been implicated in dementia risk, but one drug (latrepirdine) has been shown to boost learning in animal models.[21] Five of seven studies on antihistamines grouped them with other drugs with anticholinergic properties. They reported elevated risk of cognitive impairment or dementia, an exception was the one RCT that examined antihistamines alone and reported improvement in cognition.

Antimanics (lithium):

Among several other neuroprotective mechanisms, lithium has been shown to stimulate neuroplasticity and inhibit the formation of both Aβ and hyper phosphorylated tau protein in cellular and animal models.[22] Seventy percent of the 24 studies reported neuroprotective effects. Eighteen studies, including RCTs, observational studies and meta-analyses, concluded lithium reduced risk of dementia. Recent studies found microdoses were associated with reduced ADRD risk.

Discussion

Most older Americans have at least one chronic condition, and an estimated 80% have two or more. The number of older Americans ages 65 and older is rapidly rising from 55 million today to 86 million by 2050 and including significant increases in the population ages 85 and older who are at high risk of ADRD.[23] Given the high prevalence of chronic conditions and use of drugs to treat them, as well as the growth in the population most at risk of ADRD,

understanding which of these treatments have been associated with either increased or decreased risk of ADRD, and the size and type of evidence base underlying it can provide valuable information for identifying knowledge gaps, targeting more specific questions and informing future research.

This comprehensive scoping review elucidated the current state of knowledge on the impact of drugs commonly used to treat non-ADRD diseases and conditions on the risk ADRD or cognitive impairment. We assessed the size and scope of the available evidence through group judgment process, and systematic database search. We compiled evidence on the number and types of pharmaceuticals approved for non-ADRD indications associated with decreased and increased ADRD risk, prevalence of their use in the Medicare population, and the number and type of study designs that have examined them. We summarized the conclusions of the studies.

This scoping review is the most comprehensive synthesis to date of the vast set of studies on human subjects identifying 29 drugs classes across 11 therapeutic areas. We found that studies assessing ADRD risk associated with pharmaceutical treatment for hypertension and hyperlipidemia were the most common, with 93 and 81 unique papers included in our review, respectively. Several drug classes associated with pharmaceutical treatment for diabetes, inflammation and depression were characterized by both significant numbers of studies for some drug classes and few studies for others. For example, there were 21 and 19 studies on TZDs and insulin (antidiabetics) respectively, 38 studies on NSAIDs (anti-inflammatories) and 30 studies on SSRIs (antidepressants), while GLP1s and DPP4s (antidiabetic), DMARDs (anti-inflammatory), SNRIs, SARIs, MAOIs and tetracyclics (antidepressants) all had fewer than 5 studies that met the criteria for this review. We also found relatively few studies on treatments for stroke (4), allergies (10) and incontinence (16) although there is growing interest in the latter two classes due to the anticholinergic properties of some molecules.

There was variation by type of study across drugs classes. Evidence on several drug classes relied solely on observational studies, including beta blockers, MAOIs, PPIs, BZDs, and DMARDs. For some classes RCTs may be infeasible due to their potential harmfulness. Both PPIs and BZDs meet the Beers Criteria for potentially inappropriate use in older adults.[24] There may be, however, opportunity to study the relationship among beta blockers, MAOIs, DMARDs and dementia risk in clinical trial settings as well as through observational studies. Literature reviews and/or meta-analyses synthesized the evidence in 20 of the 29 drug classes. There were no reviews on SNRIs, tetracyclics, MAOIs, DPP-4s, GLP-1s, Z-drugs, atypical antipsychotics, DMARDs or antiplatelets, generally reflecting the paucity of studies of these classes.

This study is a scoping review; thus, we did not perform an assessment of methodological limitations or bias of evidence. By mapping the evidence however, we identified broad categories of limitations that point to critical future pathways for research on pharmaceutical treatments for non-ADRD conditions and risk or progression of ADRD. One limitation of the current set of review studies and meta-analyses [14,25–27] was the analysis of a myriad of studies with small sample sizes that in large part resulted in findings of mixed evidence.

These types of studies limit our ability to draw conclusions about subpopulations. Recently, there was an increase in the number of studies using large sample sizes broadly representative of the health and demographic composition of the population (e.g. antihypertensives [10,28] and statins [29,30]). Although limitations of unobserved confounding factors in observational studies are well-known, biases can be minimized or possibly avoided with appropriate study design and analysis tools. By way of example, results from observational studies on statins using longitudinal data of large representative samples found reduced risk associated with statin use, in contrast to much of the RCT evidence that found no effect. Differences in results of RCTs and observational studies, have led to inconclusive evidence. In the case of statins, a new, large trial enrolling 20,000 older adults assigned to a statin or a placebo was designed to answer broad questions about statin use and dementia in 'real world settings.'

Another broad category of limitations that this scoping study identified was that grouping many molecules together obscured opportunity to study and better understand different direct and pleiotropic mechanisms of action. In particular, studies on antihypertensives, antidepressants, statins and drugs with anticholinergic properties often grouped numerous subclasses of drugs together. Among the studies of drugs with anticholinergic properties, the evidence found higher anticholinergic burden increased risk. However, individual drugs or classes within the group may lower risk. For example, SSRIs may improve cognition by increasing the amount of serotonin in the brain, but SSRIs with anticholinergic properties may have the opposite effect. This study identified seven studies on SSRIs reporting decreased risk, while 10 reported an increased risk. Many of the studies that found increased risk of ADRD grouped SSRIs with other drugs with anticholinergic properties, while many of the studies that found reduced risk compared SSRIs to other antidepressants.

This study identified several drug classes that have limited representation in the current literature, but strong hypothesized mechanisms of action and, thus an important future research avenue. For example, experts [31] recently highlighted evidence that brain glucose metabolism contributed to dementia pathology, suggesting that treating type 2 diabetes would modify AD/dementia risk or prevent cognitive decline. Indeed, another recent study [32] found untreated type II diabetes led to higher levels of disease biomarkers relative to treated persons and persons without diabetes. Enthusiasm for this potential prevention mechanism was evident by the number of studies on insulin and metformin and by current clinical trials investigating insulin and metformin. Yet, newer classes such as GLP-1s and DPP-4s are increasingly prescribed to treat diabetes and little is known about their effectiveness in reducing dementia risk, alone or in combination with other anti-diabetic drugs. Antimanics (lithium) was another drug class with only 3 RCT and 10 observational studies but with strength of evidence of proposed mechanisms of action. [22,33] Additionally, multiple drug classes are often used together and there is limited evidence on simultaneous use of different drug classes and ADRD risk.[34]

This study identified several drug classes used to treat conditions that may be prodromal symptoms of ADRD. Depression and insomnia are prodromal symptoms of dementia and may occur decades before disease onset [35,36] thereby further complicating an analysis of the relationship between drug therapies for these conditions and ADRD risk. For BZDs, several

recent studies attempted to address this issue through study design, incorporating a washout period between drug use and ADRD risk; [37,38] however, this has generally not been the case among the studies on other pharmaceutical treatments for depression, anxiety and insomnia.

Finally, although there are some exceptions, the vast majority of these studies used data from western countries, and within those countries, the populations studied typically did not represent the demographic composition of the population. A handful of studies were based on study participants in Japan, [39–41] Taiwan [42–44] and Korea, [45] but there were no studies of populations in other Eastern countries, Central and South America, or Africa. Examining these effects in biologically and geographically diverse populations may shed new and critical light on mechanisms of action, and is critical to preventing disease or slowing progression in populations globally.

Scoping review studies are intended to map the evidence in a given field. Although we included a discussion of the type and size of studies in each drug class and, when relevant, identified which types of studies find conflicting evidence (e.g. large versus small, RCTs versus observational), we did not perform an assessment of the methodological limitations or rigor of an individual study or a set of studies within a drug class. Thus, this review should not be viewed as an analysis of the strength of the evidence in any drug class. We encourage readers to refer to the source studies for information on a specific drug class.

Decades of research into a cure for Alzheimer's disease and related dementias without success has renewed calls for new approaches. Strategies that reduce risk or delay onset of dementia or decrease the costs to persons living with dementia, their families and caregivers can address the health and economic impacts of dementia now. [46–49]

This study focused on current drug treatments for common chronic conditions as pathways to decrease the prevalence of disease and/or the duration of disease. Evidence is also building in support of lifestyle modifications and behavioral interventions for reducing burden of dementia. For example, multidomain interventions (diet, exercise, cognitive training and vascular risk monitoring) were found to reduce risk and improve cognition among older persons with at least one study reporting effectiveness across economically and socio-demographically diverse populations.[50–52] Other pathways to reduce the impact of dementia may include better identification of individuals who are at high risk of cognitive impairment and dementia and improved access to early intervention strategies. Detection at earlier stages of disease may allow for timely provision of symptomatic treatments, and avoidance of medications that may worsen symptoms and prolong cognitive and physical disability. [53,54]

To the extent these goals of detection, delay and risk reduction can be achieved, prevalence and disease burden will be greatly reduced. A relatively small reduction in risk of dementia can have large population impacts. A two year delay in onset can reduce the population with dementia by over two million persons by 2040, while a longer, five-year delay would lower prevalence in 2050 by 41% and health care and unpaid caregiving costs by over $600 billion. [2] We do not need a cure to reduce the health and economic impacts of dementia. Incremental progress can have large impacts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Number of Studies by Study Type, Outcome, Finding, for Each Drug Class.

Drug Class	Total RCT & Obs	Study Type			Outcome (RCT & Obs)			Finding (RCT & Obs)		
		RCT	Obs	LR/MA	AD	Dem	Cog	Dec	Inc	No/Weak
All antihypertensives	6	0	6	5	3	1	2	5	1	0
ACE/ARB	55	9	46	13	12	25	18	36	1	18
Beta blockers	16	0	16	6	3	8	5	7	2	7
CCBs	22	2	20	11	3	11	8	14	0	8
Diuretics	19	3	16	8	3	10	6	9	1	9
Statins	57	11	46	27	18	21	18	32	3	21
All antidepressants	11	0	11	1	1	4	6	2	4	5
SSRIs	26	8	18	4	2	11	13	7	10	9
SNRIs	5	1	4	0	0	4	1	1	2	2
SARIs	3	1	2	1	0	1	2	0	2	1
Tricyclics *	12	1	11	2	0	8	4	4	4	4
Tetracyclics *	4	1	3	0	0	3	1	1	1	2
MAOIs	2	0	2	0	0	2	0	0	2	0
Biguanides	13	2	11	3	2	5	6	7	3	3
Sulfonylureas	5	0	5	1	2	3	0	1	1	3
Insulin	11	8	3	8	5	0	6	8	1	2
DPP-4s	2	0	2	0	0	0	2	2	0	0
GLP-1s	1	1	0	0	1	0	0	0	0	1
TZDs	14	7	7	7	2	4	8	6	1	7
Proton Pump Inhibitors *	12	0	12	4	2	7	3	2	5	5
BZDs	24	0	24	4	5	11	8	1	15	8
Non-BZD hypnotics	2	0	2	0	0	1	1	0	1	1
Atypical antipsychotics	6	2	4	0	0	1	5	1	3	2
NSAIDs	24	6	18	14	9	8	7	11	7	6
DMARDs	2	0	2	0	0	2	0	1	1	0

Drug Class	Total RCT & Obs	Study Type			Outcome (RCT & Obs)			Finding (RCT & Obs)		
		RCT	Obs	LR/MA	AD	Dem	Cog	Dec	Inc	No/Weak
Anticoagulants	9	1	8	2	0	5	4	6	1	2
Antiplatelets	5	2	3	0	0	2	3	5	0	0
Antispasmodics*	11	1	10	3	0	3	8	0	8	3
Antihistamines*	5	1	4	2	0	2	3	1	3	1
Antimanics (lithium)	13	3	10	11	3	7	3	9	1	3
Total	397	71	326	137	76	170	151	179	84	133

Abbreviations

RCT Randomized controlled trial

Obs Observational, including prospective, retrospective, and postmortem

LR/MA Literature reviews and meta analyses.

AD Alzheimer's disease incidence/diagnosis outcomes and AD pathology

Dem Dementia incidence/diagnosis outcomes

Cog Cognition outcomes - performance or change in performance on cognitive tests (e.g. MMSE)

Dec Drug decreases risk of AD/dementia and reduced or lower cognition - neuroprotective

Inc Drug increases risk of AD/dementia and reduced or lower cognition

No/Weak No or weak relationship between drug and any cognitive outcome.

Notes:

*hypothesized to increase risk

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