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Medication profiles of patients with cognitive impairment and high anticholinergic burden

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Abstract

Background—Drugs with anticholinergic properties are considered potentially inappropriate in patients with cognitive impairment because harms – including delirium, falls and fractures – may outweigh benefits.

Objective—To highlight opportunities to improve clinical decision making and care for patients with cognitive impairment and multiple chronic conditions, we identified distinct subgroups of patients with mild cognitive impairment (MCI) and dementia who had high cumulative anticholinergic burden and specific patterns of anticholinergic use.

Patients and Methods—Retrospective cohort study in a not-for-profit, integrated delivery system. Participants included **community**-dwelling adults aged 65 and older (N=13,627) with MCI or dementia and at least 2 other chronic diseases. We calculated the Anticholinergic Cognitive Burden (ACB) score for each participant from pharmacy and electronic health record (EHR) data. Among individuals with a mean 12 month ACB score ≥ 2 , we used agglomerative hierarchical clustering to identify groups, or clusters, of individuals with similar anticholinergic prescription patterns.

Results—3,257 (24%;) had high anticholinergic burden, defined as an ACB score ≥ 2 . Clinically meaningful clusters based upon anchoring medications or drug classes included: a cluster of cardiovascular medications (n = 1497; 46%); two clusters of antidepressant medications (n = 633;

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7. Compliance with Ethical Standards

Conflicts of Interest: Dr. Boyd writes a chapter on multimorbidity for UpToDate, for which she receives a royalty. The other authors declare that they have no conflicts of interest relevant to the content of this study.

20%); and a cluster based on use of bladder antimuscarinics (n = 431; 13%). Several clusters were comprised of multiple central nervous system-active drugs.

Conclusions—Cardiovascular and central nervous system-active medications comprise a substantial portion of anticholinergic burden in people with cognitive impairment and multiple chronic conditions. Antidepressants were highly prevalent. Clinical profiles elucidated by these clusters of anticholinergic medications can inform targeted approaches to care.

1. Introduction

One in 10 people age 65 and older has Alzheimer's disease,[1] and the prevalence of dementia in the U.S. is expected to reach 16 million by 2050.[2] Mild cognitive impairment (MCI), often a precursor to dementia, may be present in up to 20% of people age 65 or older, though prevalence estimates vary widely.[3] The vast majority of people with MCI and dementia have multiple chronic conditions (MCC).[4] Providing optimal health care to older adults with MCC is challenging,[5] and cognitive impairment vastly compounds this difficulty.[6] The combination of MCI and dementia with other conditions leads to more medication use and is associated with greater risk of adverse drug events, hospitalization and mortality.[7, 8]

Drugs with anticholinergic effects are prescribed to older adults for a wide variety of indications, including urinary incontinence, depression, pain and insomnia. It is well-recognized that cumulative anticholinergic burden arising from the use of multiple medicines with anticholinergic properties is associated with increased risk of adverse cognitive effects, falls, fractures, and death.[9, 10] Older adults with cognitive impairment are particularly vulnerable to anticholinergic side effects.[11] Higher cumulative use of medications with anticholinergic effects has been associated with increased risk of incident dementia in some studies,[12] though not others,[13] suggesting that anticholinergic burden could be a modifiable risk factor for dementia among individuals with MCI.[14]

Our objective was to describe the prevalence of cumulative anticholinergic burden in a population with dementia or MCI and MCC. We sought to identify distinct subgroups of patients who had high anticholinergic burden based on specific clusters of anticholinergic medications. Such profiles may suggest opportunities for targeted interventions to improve clinical decision making and care for patients with cognitive impairment and MCC.

2. Methods

2.1 Study Design and Population

This was a retrospective cohort study of older adult members of Kaiser Permanente Colorado (KPCO) – a non-profit, integrated delivery system that provides a coordinated continuum of services designed to meet all the health care needs of its members. The non-profit health plan serves approximately 670,000 members in 29 medical offices throughout Colorado. The KPCO Virtual Data Warehouse (VDW) was used to define a cohort of cognitively impaired individuals. The VDW is a standardized and quality controlled secondary observational database that incorporates data from the electronic health record (EHR), pharmacy fills, claims, membership, and administrative systems.

The study population consisted of KPCO members age 65 or older with a diagnosis of dementia or MCI, as well as 2 or more additional chronic medical conditions out of 185, between May 1, 2014 and May 1, 2016.[16] We required that members have at least 2 years of enrollment in a plan that includes benefits for preventative care and medications (eg, original Medicare, Medicare HMO, HMO Plus, deductible/coinsurance, high deductible, Medicaid) prior to May 1, 2016. Alzheimer's disease, related dementias and MCI were identified with a literature-based comprehensive list of ICD-9 and ICD-10 codes (Online Resource 1).[17] We assessed anticholinergic drug exposure in the 12 months prior to October 31, 2016. This time frame ensured that all cohort members had a minimum of 6 months to experience medication exposure and a 24-month period to capture a claims-based diagnosis.

2.2 Assessment of Anticholinergic Use

Anticholinergic burden, as defined by the Anticholinergic Cognitive Burden (ACB) scale, was the primary variable of interest.[15] The ACB scale is one of several tools for quantifying the cumulative effect of individual drugs with anticholinergic properties. There is not yet data about which anticholinergic scale best predicts risk of adverse outcomes, particularly among those with MCI or dementia.[18, 19] We chose the ACB because it is most sensitive for identifying people with possible anticholinergic burden and has been externally validated.[15, 20, 21] On the ACB scale, each medicine is rated from 1–3. Medications with an ACB rating of 1 have serum anticholinergic activity, but their clinical impact on cognition is uncertain. Medications with an ACB rating of 2 or 3 have established, clinically relevant cognitive anticholinergic effects. The total score is the sum of ACB ratings of all medications taken by a person. We used pharmacy fill data to identify ACB medications dispensed between November 1, 2015 and October 31, 2016; this list did not include over-the-counter (OTC) medications. We did not include dispensed topical or inhaled products in this analysis.[21] Medication use was only assessed following the documented diagnosis of MCI or dementia. We calculated cumulative exposure to anticholinergics during a 12 month period as the average total daily ACB score for each patient.[21] The ACB score calculation incorporates duration of use in addition to anticholinergic burden of each drug. We included all prescriptions for anticholinergic drugs in calculating ACB scores for the cohort, however drugs prescribed for short periods of time had little effect on the high ACB scores in the analytic cohort. The numerator was the number of days during the study period that a person was supplied an anticholinergic medication multiplied by its ACB score; then summed across all ACB medications for that person. The denominator was the number of days that the person met eligibility criteria for the cohort in a 12 month period, beginning on November 1, 2015 or the date of the first MCI or dementia diagnosis, whichever came last, and ending on the date of death, disenrollment or October 31, 2016, whichever came first (Figure 1). Average ACB scores can range from zero to high positive values; a continuous ACB score was used in calculating means and an ACB score rounded to the nearest integer was used in categorizing the cohort into low/no ACB use versus high ACB use.

2.3 Descriptive Analysis

We estimated the frequency and proportion of individuals with each characteristic for categorical variables and the mean, standard deviation and median for continuous variables. Demographic and clinical characteristics were summarized overall and by dementia status. We used a two-sided alpha of $p < 0.05$ for chi-square and t-tests in comparing dementia and MCI groups.

2.4 Analysis

Research to identify these populations of patients who are more likely to receive anticholinergic medicines have typically used multivariable regression to identify patient-level characteristics, such as demographics and diseases, that predict anticholinergic use.[22, 23] In contrast to multivariable regression, cluster analysis can be used to identify groups, or “clusters,” of patients with similar patterns of medication use.[24–26] Such patient profiles and medication patterns can be useful clinically for tailoring care to meaningful subpopulations.

Among individuals with a rounded mean 12 month ACB score ≥ 2 , we used agglomerative hierarchical clustering to identify groups of individuals with similar anticholinergic prescription patterns (Online Resource 2). In this method, each individual starts as a unique cluster, and the most similar individuals are joined in a stepwise fashion until there is only one cluster containing all observations. Individuals were clustered on the combination of anticholinergic drugs prescribed over a 12-month period. For each of the 68 ACB drugs present in our cohort, individuals were assigned a value of 1 if they were prescribed the drug and 0 if they were not. Since initial cluster solutions based on the 68 anticholinergic drugs did not produce homogenous and easy to interpret clusters, we underwent a variable simplification process. We grouped drugs together if they had similar therapeutic use and were generally not co-prescribed in the same individual (eg, antipsychotics were grouped together, as were antidepressants). We explored the data and found that, contrary to our expectation, certain medications were often co-prescribed (eg, trazodone and other antidepressants; quetiapine and other antipsychotics), so we kept these drugs separate from the others in their class. This variable simplification process resulted in 32 drug variables, on which we created a distance matrix and performed the final version of hierarchical clustering (Table 2). Analyses were performed using SAS version 9.4.1 (SAS Institute, Inc., Cary, NC). The study was reviewed and approved by the Kaiser Permanente Colorado Institutional Review Board.

3. Results

The cohort consisted of 13627 people (14%) with either dementia or MCI as well as at least two of 185 other chronic conditions (Figure 2). MCI and dementia were first coded between 1998 and 2016. The mean age was 80 ($SD \pm 8$), 8090 (59%) were women and the majority (81%; 11080) were Caucasian. In total, 8083 (59%) people had dementia and 5544 (41%) had MCI (Table 1). Sixty-seven percent of people with dementia and 73% of people with MCI were prescribed ≥ 5 unique medicines during the following 12-month observation period.

Nineteen percent of patients took at least one definite anticholinergic (ACB Level 2 or 3) during the 12-month cohort observation period. Fifty percent of the population had a mean total daily ACB score of 0; 26% had a mean total daily ACB score of 1; 12% had a mean total daily ACB score of 2; 7% had a mean total daily ACB score of 3, and 5% had a mean total daily ACB score of 4 or more.

3.1 Anticholinergic Drug Clusters

We defined a sub-cohort of individuals with high ACB scores as those having mean total daily ACB scores ≥ 2 (approximately the top quartile for all 13627 patients – 24%, 3257 patients). Among people with high ACB scores, cardiovascular medications were the main contributors to anticholinergic burden (Table 2).

The cluster analysis on the high ACB subcohort yielded a 13-cluster solution. We identified several clinically meaningful clusters of anticholinergic medications co-prescribed during the 12-month observation period, as shown in Table 3. In the most common cluster (1497 patients; 46% of those with ACB scores ≥ 2), 98% of individuals were taking cardiovascular medications – beta-blockers (1197 patients; 80% of those in the cluster), diuretics (917 patients; 61%) and warfarin (846 patients; 57%). If taken simultaneously for the whole year, these three cardiovascular drugs would cumulatively result in an ACB score of 3. Individuals prescribed other drugs with anticholinergic properties often also took these common cardiovascular agents as well. For example, all of the 431 people in Cluster 2 had been prescribed bladder antimuscarinics (ACB Level 3) and many were also taking beta-blockers (172 patients; 40%), diuretics (90 patients; 21%) and warfarin (80 patients; 19%). All of the 311 patients in Cluster 4, which comprised 10% of the cohort, were taking antidepressants. Many of these patients were also taking beta-blockers, diuretics and warfarin.

Several clusters were comprised of multiple central nervous system-active drugs. For example, virtually all of patients in Cluster 7 were taking bupropion and many were also taking trazodone, tricyclic antidepressants, other antidepressants, opioids/muscle relaxants and benzodiazepines. All of the 198 patients in Cluster 5 were taking quetiapine and 36 patients (18%) were also taking other antipsychotics.

4. Discussion

Medications for many common chronic conditions contribute to high cumulative anticholinergic exposure. This is particularly relevant for individuals with impaired cognition plus common chronic medical conditions who are prescribed multiple medications and are vulnerable to anticholinergic side effects. Clinical profiles of patients at risk include those with dementia plus cardiovascular disease, depression, incontinence, and/or chronic pain. Increased attention to the anticholinergic medication burden of patients with these common clinical profiles may improve health outcomes for patients with impaired cognition.

Medications commonly used to treat cardiovascular conditions contributed substantially to anticholinergic burden in this population of older adults with cognitive impairment and MCC. This finding is consistent with previous research[27, 28]; however, our study is one of the few to focus on patients with MCI or dementia and MCC in a large, community-dwelling

U.S. cohort.. Multiple common cardiovascular drugs, such as furosemide, metoprolol, captopril and digoxin, have anticholinergic properties. These are widely used to improve symptoms, prevent hospitalization and prolong survival in patients with heart failure, including those with cognitive impairment.[27] These medications individually have low ACB scores, but were frequently co-prescribed, resulting in ACB scores of 3 or greater. A large portion of anticholinergic burden may result from exposure to multiple ACB Level 1 drugs and cumulative anticholinergic exposure from cardiovascular medicines may be an important contributor to the increased prevalence of cognitive impairment in people with heart failure.[27] [29]

We also found that patients with MCI and dementia were frequently exposed to multiple CNS-active drugs, including tricyclic antidepressants, selective serotonin reuptake inhibitors, benzodiazepines, anti-psychotics and opioids. Depression, irritability and sleep problems are common in people with dementia with prevalence rates from 25% to 45%, and there has been an increase in CNS-active prescribing among older adults. [30, 31] However, the evidence for effectiveness of antidepressant pharmacotherapy in people with dementia is weak, and psychotropic medications may result in faster cognitive and functional decline in people with dementia.[32, 33] [34] This risk may be exacerbated by co-prescribing medications for other chronic conditions that contribute to anticholinergic burden (eg, beta-blockers, diuretics and warfarin).

Our findings also highlight potential prescribing cascades that increase the risk of harm for people with dementia. For example, many patients were taking both diuretics and bladder antimuscarinics. Others were prescribed oral steroids, which may precipitate delirium or psychosis, together with antipsychotic medications such as quetiapine and sedating medications such as trazodone. Chronic pain, depression and mobility impairments may lead to functional incontinence in patients with dementia, and this may be exacerbated by diuretic use. Incontinence may, in turn, lead to worsening depression. Bladder antimuscarinics used to treat incontinence may exacerbate balance problems and falls.

A strength of our study is the use of cluster analysis to identify distinct subgroups of patients with specific, clinically relevant combinations of medications, shedding light on prescribing patterns and coexisting conditions that require targeted approaches to care. Another strength of our study is the large sample of community-dwelling older adults with MCI and dementia. Previous research has documented high cumulative anticholinergic burden among people with dementia in nursing homes,[23, 35, 36] but less is known about anticholinergic prescribing practices among patients with impaired cognition (MCI and dementia) in non-institutional settings.[22] We found that 19% of community-dwelling older adults with MCI or dementia took at least one ACB Level 2 or 3 anticholinergic medication, which is consistent with other studies of older adults with impaired cognition.[22, 37, 23, 35] Our analysis was based on EHR data on pharmacy fills, which likely capture patients' use of medication better than prescription data or patient self-report.[38]

Our study also has some limitations. Prescribing patterns in an integrated healthcare delivery system with a shared electronic health record may not be representative of prescribing patterns in other settings. Our findings reflect the KPCO formulary and the existing best

practice advisories for prescribing to older adults embedded in the electronic health record. Over-the-counter drugs, such as diphenhydramine (a Level 3 anticholinergic), could not be identified using our methods. We chose to use the ACB scale, though there is no gold standard for defining medications with anticholinergic effects, and the ACB does not account for dose. Our ability to distinguish between MCI and dementia using claims data was limited, and both may be underreported within claims data.[39] However, the prevalence of MCI and dementia (6% and 9%, respectively) in our cohort was similar to studies in other populations.[40–42]

Multiple factors likely contribute to prescribing practices that increase anticholinergic burden. These include the desire to help patients with dementia and the dearth of effective treatment options, insufficient access to community-based long-term care services and caregiver burden in the face of behavioral symptoms of dementia, and fragmented prescribing by multiple clinicians. [6, 43, 44] Communication between healthcare providers is crucial to ensure that patients – particularly vulnerable older adults with dementia or MCI – receive medicines that will help them achieve their goals, but not medicines that are either likely to be harmful or unhelpful.

5. Conclusion

Decisions about whether medicines to treat chronic conditions are truly “essential” in patients with dementia and MCI should continually be re-addressed, eliciting and respecting patient and family goals of care as cognitive changes occur. Clinicians should bear in mind that both MCI and dementia are independently associated with shortened life expectancy, [45] affecting decisions about therapies or tests with long lag times to benefit.[46] Once dementia is diagnosed, guideline-driven care of chronic conditions may be harmful, burdensome, or no longer concordant with patient and family goals. As a result of tools such as the Beers criteria,[11] clinicians may already be aware that highly anticholinergic drugs, such as oxybutynin, should be avoided in older adults with cognitive impairment. Future studies should investigate whether cumulative anticholinergic burden arising from low-level anticholinergic medicines is associated with adverse health outcomes in people with MCI and dementia. In the meantime, prescribers should be aware that many drugs prescribed to treat co-existing conditions in patients with cognitive impairment have secondary, unintentional anticholinergic effects. If used concurrently, these drugs might lead to clinically significant anticholinergic effects, negatively impacting the well-being of this vulnerable population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. *Neurology*. 2013; 80(19):1778–83. DOI: 10.1212/WNL.0b013e31828726f5 [PubMed: 23390181]
2. Campbell NL, Boustani MA. Adverse cognitive effects of medications: turning attention to reversibility. *JAMA Intern Med*. 2015; 175(3):408–9. DOI: 10.1001/jamainternmed.2014.7667 [PubMed: 25622111]
3. Alzheimer's Association. 2017 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2017; 13(4):325–73. doi:<http://dx.doi.org/10.1016/j.jalz.2017.02.001>.
4. Lin PJ, Zhong Y, Fillit HM, Chen E, Neumann PJ. Medicare Expenditures of Individuals with Alzheimer's Disease and Related Dementias or Mild Cognitive Impairment Before and After Diagnosis. *J Am Geriatr Soc*. 2016; 64(8):1549–57. DOI: 10.1111/jgs.14227 [PubMed: 27295430]
5. Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. *JAMA*. 2005; 294(6):716–24. DOI: 10.1001/jama.294.6.716 [PubMed: 16091574]
6. Hinton L, Franz CE, Reddy G, Flores Y, Kravitz RL, Barker JC. Practice constraints, behavioral problems, and dementia care: primary care physicians' perspectives. *Journal of general internal medicine*. 2007; 22(11):1487–92. DOI: 10.1007/s11606-007-0317-y [PubMed: 17823840]
7. Lin P-J, Zhong Y, Fillit HM, Chen E, Neumann PJ. Medicare Expenditures of Individuals with Alzheimer's Disease and Related Dementias or Mild Cognitive Impairment Before and After Diagnosis. *J Am Geriatr Soc*. 2016; 64(8):1549–57. DOI: 10.1111/jgs.14227 [PubMed: 27295430]
8. Lin PJ, Fillit HM, Cohen JT, Neumann PJ. Potentially avoidable hospitalizations among Medicare beneficiaries with Alzheimer's disease and related disorders. *Alzheimers Dement*. 2013; 9(1):30–8. DOI: 10.1016/j.jalz.2012.11.002 [PubMed: 23305822]
9. Chatterjee S, Bali V, Carnahan RM, Chen H, Johnson ML, Aparasu RR. Risk of Mortality Associated with Anticholinergic Use in Elderly Nursing Home Residents with Depression. *Drugs Aging*. 2017; doi: 10.1007/s40266-017-0475-5
10. Chatterjee S, Bali V, Carnahan RM, Chen H, Johnson ML, Aparasu RR. Anticholinergic Medication Use and Risk of Fracture in Elderly Adults with Depression. *J Am Geriatr Soc*. 2016; 64(7):1492–7. DOI: 10.1111/jgs.14182 [PubMed: 27294403]
11. American Geriatrics Society. 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc*. 2015; 63(11):2227–46. DOI: 10.1111/jgs.13702 [PubMed: 26446832]
12. Gray SL, Anderson ML, Dublin S, Hanlon JT, Hubbard R, Walker R, et al. Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. *JAMA Intern Med*. 2015; 175(3):401–7. DOI: 10.1001/jamainternmed.2014.7663 [PubMed: 25621434]
13. Ancelin ML, Artero S, Portet F, Dupuy AM, Touchon J, Ritchie K. Non-degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study. *BMJ*. 2006; 332(7539):455–9. DOI: 10.1136/bmj.38740.439664.DE [PubMed: 16452102]
14. Campbell NL, Unverzagt F, LaMantia MA, Khan BA, Boustani MA. Risk factors for the progression of mild cognitive impairment to dementia. *Clin Geriatr Med*. 2013; 29(4):873–93. DOI: 10.1016/j.cger.2013.07.009 [PubMed: 24094301]
15. Campbell N, Boustani M, Limbil T, Ott C, Fox C, Maidment I, et al. The cognitive impact of anticholinergics: a clinical review. *Clin Interv Aging*. 2009; 4:225–33. [PubMed: 19554093]
16. Agency for Healthcare Research and Quality. [Accessed August 14, 2017] Chronic Condition Classification. 2017. <http://www.icpsr.umich.edu/icpsrweb/content/AHRQMCC/shared-code.html>
17. Amjad H, Carmichael D, Austin AM, Chang CH, Bynum JP. Continuity of Care and Health Care Utilization in Older Adults With Dementia in Fee-for-Service Medicare. *JAMA Intern Med*. 2016; 176(9):1371–8. DOI: 10.1001/jamainternmed.2016.3553 [PubMed: 27454945]
18. Cardwell K, Hughes CM, Ryan C. The Association Between Anticholinergic Medication Burden and Health Related Outcomes in the 'Oldest Old': A Systematic Review of the Literature. *Drugs Aging*. 2015; 32(10):835–48. DOI: 10.1007/s40266-015-0310-9 [PubMed: 26442862]

19. Salahudeen MS, Hilmer SN, Nishtala PS. Comparison of anticholinergic risk scales and associations with adverse health outcomes in older people. *J Am Geriatr Soc.* 2015; 63(1):85–90. DOI: 10.1111/jgs.13206 [PubMed: 25597560]
20. Campbell NL, Boustani MA, Lane KA, Gao S, Hendrie H, Khan BA, et al. Use of anticholinergics and the risk of cognitive impairment in an African American population. *Neurology.* 2010; 75(2): 152–9. DOI: 10.1212/WNL.0b013e3181e7f2ab [PubMed: 20625168]
21. Campbell NL, Perkins AJ, Bradt P, Perk S, Wielage RC, Boustani MA, et al. Association of Anticholinergic Burden with Cognitive Impairment and Health Care Utilization Among a Diverse Ambulatory Older Adult Population. *Pharmacotherapy.* 2016; 36(11):1123–31. DOI: 10.1002/phar.1843 [PubMed: 27711982]
22. Bhattacharya R, Chatterjee S, Carnahan RM, Aparasu RR. Prevalence and predictors of anticholinergic agents in elderly outpatients with dementia. *Am J Geriatr Pharmacother.* 2011; 9(6):434–41. DOI: 10.1016/j.amjopharm.2011.10.001 [PubMed: 22030114]
23. Chatterjee S, Mehta S, Sherer JT, Aparasu RR. Prevalence and predictors of anticholinergic medication use in elderly nursing home residents with dementia: analysis of data from the 2004 National Nursing Home Survey. *Drugs Aging.* 2010; 27(12):987–97. DOI: 10.2165/11584430-000000000-00000 [PubMed: 21087068]
24. Marengoni A, Rizzuto D, Wang HX, Winblad B, Fratiglioni L. Patterns of chronic multimorbidity in the elderly population. *J Am Geriatr Soc.* 2009; 57(2):225–30. DOI: 10.1111/j.1532-5415.2008.02109.x [PubMed: 19207138]
25. Goldstein G, Luther JF, Jacoby AM, Haas GL, Gordon AJ. A Taxonomy of medical comorbidity for veterans who are homeless. *J Health Care Poor Underserved.* 2008; 19(3):991–1005. DOI: 10.1353/hpu.0.0040 [PubMed: 18677085]
26. Newcomer SR, Steiner JF, Bayliss EA. Identifying subgroups of complex patients with cluster analysis. *Am J Manag Care.* 2011; 17(8):e324–32. [PubMed: 21851140]
27. Shaikat A, Habib A, Lane KA, Shen C, Khan S, Hellman YM, et al. Anticholinergic medications: an additional contributor to cognitive impairment in the heart failure population? *Drugs Aging.* 2014; 31(10):749–54. DOI: 10.1007/s40266-014-0204-2 [PubMed: 25142050]
28. Parkinson L, Magin PJ, Thomson A, Byles JE, Caughey GE, Etherton-Beer C, et al. Anticholinergic burden in older women: not seeing the wood for the trees? *Med J Aust.* 2015; 202(2):91–4. [PubMed: 25627741]
29. Green AR, Oh E, Hilson L, Tian J, Boyd CM. Anticholinergic Burden in Older Adults with Mild Cognitive Impairment. *J Am Geriatr Soc.* 2016; 64(12):e313–e4. DOI: 10.1111/jgs.14554 [PubMed: 27879986]
30. Gerlach LB, Olfson M, Kales HC, Maust DT. Opioids and Other Central Nervous System–Active Polypharmacy in Older Adults in the United States. *J Am Geriatr Soc.*
31. Bhattacharjee S, Oh YM, Reiman EM, Burke WJ. Prevalence, Patterns, and Predictors of Depression Treatment among Community-Dwelling Elderly Individuals with Dementia in the United States. *Am J Geriatr Psychiatry.* 2017; 25(7):803–13. DOI: 10.1016/j.jagp.2017.03.003 [PubMed: 28392190]
32. Rosenberg PB, Mielke MM, Han D, Leoutsakos JS, Lyketsos CG, Rabins PV, et al. The association of psychotropic medication use with the cognitive, functional, and neuropsychiatric trajectory of Alzheimer's disease. *Int J Geriatr Psychiatry.* 2012; 27(12):1248–57. DOI: 10.1002/gps.3769 [PubMed: 22374884]
33. Orgeta V, Qazi A, Spector AE, Orrell M. Psychological treatments for depression and anxiety in dementia and mild cognitive impairment. *Cochrane Database Syst Rev.* 2014; (1):CD009125.doi: 10.1002/14651858.CD009125.pub2 [PubMed: 24449085]
34. Nelson JC, Devanand DP. A systematic review and meta-analysis of placebo-controlled antidepressant studies in people with depression and dementia. *J Am Geriatr Soc.* 2011; 59(4): 577–85. DOI: 10.1111/j.1532-5415.2011.03355.x [PubMed: 21453380]
35. Palmer JB, Albrecht JS, Park Y, Dutcher S, Rattinger GB, Simoni-Wastila L, et al. Use of drugs with anticholinergic properties among nursing home residents with dementia: a national analysis of Medicare beneficiaries from 2007 to 2008. *Drugs Aging.* 2015; 32(1):79–86. DOI: 10.1007/s40266-014-0227-8 [PubMed: 25491558]

36. Kolanowski A, Fick DM, Campbell J, Litaker M, Boustani M. A preliminary study of anticholinergic burden and relationship to a quality of life indicator, engagement in activities, in nursing home residents with dementia. *J Am Med Dir Assoc.* 2009; 10(4):252–7. DOI: 10.1016/j.jamda.2008.11.005 [PubMed: 19426941]
37. Carnahan RM, Lund BC, Perry PJ, Pollock BG, Culp KR. The Anticholinergic Drug Scale as a measure of drug-related anticholinergic burden: associations with serum anticholinergic activity. *J Clin Pharmacol.* 2006; 46(12):1481–6. DOI: 10.1177/0091270006292126 [PubMed: 17101747]
38. Sattler EL, Lee JS, Perri M 3rd. Medication (re)fill adherence measures derived from pharmacy claims data in older Americans: a review of the literature. *Drugs Aging.* 2013; 30(6):383–99. DOI: 10.1007/s40266-013-0074-z [PubMed: 23553512]
39. Ostbye T, Taylor DH Jr, Clipp EC, Scoyoc LV, Plassman BL. Identification of dementia: agreement among national survey data, medicare claims, and death certificates. *Health Serv Res.* 2008; 43(1 Pt 1):313–26. DOI: 10.1111/j.1475-6773.2007.00748.x [PubMed: 18211532]
40. Sachdev PS, Lipnicki DM, Kochan NA, Crawford JD, Thalamuthu A, Andrews G, et al. The Prevalence of Mild Cognitive Impairment in Diverse Geographical and Ethnocultural Regions: The COSMIC Collaboration. *PLoS One.* 2015; 10(11):e0142388.doi: 10.1371/journal.pone.0142388 [PubMed: 26539987]
41. Ward A, Arrighi HM, Michels S, Cedarbaum JM. Mild cognitive impairment: disparity of incidence and prevalence estimates. *Alzheimers Dement.* 2012; 8(1):14–21. DOI: 10.1016/j.jalz.2011.01.002 [PubMed: 22265588]
42. Langa KM, Larson EB, Crimmins EM, Faul JD, Levine DA, Kabeto MU, et al. A Comparison of the Prevalence of Dementia in the United States in 2000 and 2012. *JAMA Intern Med.* 2017; 177(1):51–8. DOI: 10.1001/jamainternmed.2016.6807 [PubMed: 27893041]
43. Matlow JN, Bronskill SE, Gruneir A, Bell CM, Stall NM, Herrmann N, et al. Use of Medications of Questionable Benefit at the End of Life in Nursing Home Residents with Advanced Dementia. 2017 Jul; 65(7):1535–1542. DOI: 10.1111/jgs.14844
44. Reppas-Rindlisbacher CE, Fischer HD, Fung K, Gill SS, Seitz D, Tannenbaum C, et al. Anticholinergic Drug Burden in Persons with Dementia Taking a Cholinesterase Inhibitor: The Effect of Multiple Physicians. *J Am Geriatr Soc.* 2016; 64(3):492–500. DOI: 10.1111/jgs.14034 [PubMed: 27000323]
45. Sachs GA, Carter R, Holtz LR, Smith F, Stump TE, Tu W, et al. Cognitive impairment: an independent predictor of excess mortality: a cohort study. *Ann Intern Med.* 2011; 155(5):300–8. DOI: 10.7326/0003-4819-155-5-201109060-00007 [PubMed: 21893623]
46. Holmes HM, Min LC, Yee M, Varadhan R, Basran J, Dale W, et al. Rationalizing Prescribing for Older Patients with Multimorbidity: Considering Time to Benefit. *Drugs Aging.* 2013; 30(9):655–66. [PubMed: 23749475]
47. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care.* 2005; 43(11):1130–9. [PubMed: 16224307]

Key Points

1. Common cardiovascular medications contribute substantially to anticholinergic burden in patients with cognitive impairment and multiple chronic conditions.
2. Patients with cognitive impairment and multiple chronic conditions are frequently exposed to multiple CNS-active drugs.
3. Clinical profiles of patients at risk of anticholinergic side effects include those with cognitive impairment plus cardiovascular disease, depression, incontinence, and/or chronic pain.

Figure 1. Timeline for study

We assessed anticholinergic drug exposure in the 12 months prior to October 31, 2016 in a cohort of individuals who had a claims-based diagnosis for dementia or MCI, as well as 2 or more additional chronic medical conditions out of 185, anytime between May 1, 2014 and May 1, 2016. Medication use was only assessed following the documented diagnosis. This time frame ensured that all cohort members had a minimum of 6 months to experience medication exposure and a 24-month period to capture a claims-based diagnosis.

Figure 2. Overview of cohort selection

^a KPCO = Kaiser Permanente Colorado

Table 1

Demographic and clinical characteristics of cohort

Characteristic	Overall cohort	MCI ^b	Dementia	p-value
Age ^a , mean (SD)	79.5 (8.05)	76.9 (7.6)	81.3 (7.91)	<.001
Female sex, n (%)	8090 (59.4)	3187 (57.5)	4903 (60.7)	<.001
Race				.015
Asian	194 (1.4)	71 (1.3)	123 (1.5)	
Black	494 (3.6)	176 (3.2)	318 (3.9)	
White	11080 (81.3)	4534 (81.8)	6546 (81.0)	
Other, 1 race or not reported	1859 (13.6)	763 (5.6)	1096 (8.0)	
Hispanic ethnicity	1292 (9.5)	557 (10.0)	735 (9.1)	.028
Use of 5 unique medicines, n (%)	9441 (69.3)	4020 (72.5)	5421 (67.1)	<.001
Charlson Comorbidity Index, mean (SD) ^[47]	3.4 (2.6)	2.9 (2.6)	3.8 (2.6)	<.001

^a As of January 1, 2016^b MCI = mild cognitive impairment

Table 2

Twenty most commonly prescribed anticholinergic drug classes among people with MCI^a/dementia and ACB^b score ≥ 2

Drug	Frequency	Percent ^c	Percent fills per total number of prescriptions ^d
Beta-blockers ^e	1773	54.4	18.6
Diuretics ^f	1360	41.8	12.8
Warfarin	1067	32.8	10.4
Oral steroids ^g	746	22.9	6.9
Bladder antimuscarinics ^h	636	19.5	5.3
Tricyclic antidepressants ⁱ	573	17.6	5.5
Trazodone	561	17.2	5.5
Antidepressants ^j	491	15.1	5.4
Digoxin	356	10.9	3.6
Histamine (H2) receptor antagonists ^k	306	9.4	2.6
Quetiapine	305	9.4	3.2
Opioids/muscle relaxants ^l	290	8.9	2.5
Bupropion	251	7.7	2.6
Isosorbide	196	6.0	1.9
Morphine	193	5.9	4.2
Antipsychotics ^m	193	5.9	2.3
Antispasmodics ⁿ	148	4.5	1.0
Cardiac ^o	138	4.2	1.4
Anticonvulsants ^p	118	3.6	1.3
Benzodiazepines ^q	114	3.5	1.5

^a MCI = mild cognitive impairment

^b ACB = Anticholinergic Cognitive Burden scale

^c Total number of people with ACB ≥ 2 = 3,257

^d Total number of prescriptions among individuals with ACB ≥ 2 = 41,265

^e Includes metoprolol, atenolol

^f Includes furosemide, triamterene

^g Includes prednisone, hydrocortisone

^h Includes trospium, oxybutynin, tolterodine, solifenacin, darifenacin, fesoterodine

ⁱ Includes nortriptyline, amitriptyline, doxepin, imipramine, desipramine, clomipramine

^j Includes venlafaxine, paroxetine, fluvoxamine

^k Includes ranitidine, cimetidine

^{*l*}Includes codeine, fentanyl, cyclobenzaprine

^{*m*}Includes perphenazine, thioridazine, chlorpromazine, trifluoperazine, clozapine, haloperidol, risperidone, olanzapine, aripiprazole, paliperidone, loxapine

^{*n*}Includes dicyclomine, atropine

^{*o*}Includes hydralazine, captopril

^{*p*}Includes carbamazepine, oxcarbazepine

^{*q*}Includes alprazolam, diazepam, clorazepate

Table 3

Clusters of co-prescribed anticholinergic medications among people with MCI^a or dementia and high ACB^b scores

Anchoring medications/drug class	Percent of patients in cluster							
	Cluster 1: Cardiovascular	Cluster 2: Bladder antimuscarinics	Cluster 3: Tricyclic antidepressants	Cluster 4: Other antidepressants	Cluster 5: Quetiapine	Cluster 6: Oral corticosteroids	Cluster 7: Antidepressants and opioids	Cluster 8: Other antipsychotics
Number of members (% of total cohort) ^c	1497 (46%)	431 (13%)	322 (10%)	311 (10%)	198 (6%)	161 (5%)	113 (3%)	79 (2%)
Beta-blockers ^d	80	40	37	49	21	1	37	28
Diuretics ^e	61	21	24	33	12	68	15	0
Warfarin	57	19	8	21	3	14	1	0
Bladder antimuscarinics ^f	4	100	4	4	9	39	14	3
Antidepressants ^g	4	8	5	100	6	6	27	24
Bupropion	5	3	2	3	9	5	98	11
Oral corticosteroids ^h	25	9	15	27	12	82	23	10
Trazodone	16	14	14	22	13	18	40	24
Quetiapine	3	4	1	5	100	8	0	0
Opioids/muscle relaxants ⁱ	8	4	9	13	2	29	16	4
Morphine	6	3	4	14	2	14	6	0
Tricyclic antidepressants ^j	7	7	100	13	8	8	27	9
Benzodiazepines ^k	3	1	6	3	2	5	7	0
Antipsychotics ^l	3	3	2	2	18	4	3	98
Mean ACB score (SD)	2.5 (1.1)	3.1 (1.2)	3.2 (1.1)	3.0 (1.4)	3.2 (1.4)	2.7 (1.3)	2.8 (1.3)	3.4 (1.4)

^aMCI = mild cognitive impairment

^bACB = Anticholinergic Cognitive Burden Score

^cTotal number of people with ACB 2 = 3,257

^dIncludes metoprolol, atenolol

^eIncludes furosemide, triamterene

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- f* Includes trospium, oxybutynin, tolterodine, solifenacin, darifenacin, fesoterodine
- g* Includes venlafaxine, paroxetine, fluvoxamine
- h* Includes prednisone, hydrocortisone
- i* Includes codeine, fentanyl, cyclobenzaprine
- j* Includes nortriptyline, amitriptyline, doxepin, imipramine, desipramine, clomipramine
- k* Includes alprazolam, diazepam, clorazepate
- l* Includes perphenazine, thioridazine, chlorpromazine, trifluoperazine, clozapine, haloperidol, risperidone, olanzapine, aripiprazole, paliperidone, loxapine