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Exploration of 100 commonly used drugs and supplements on cognition in older adults

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Abstract

Background—There are conflicting reports and a lack of evidence-based data regarding effects of medications on cognition in cognitively normal older adults. We explored whether use of 100 common medications taken by older adults is associated with longitudinal cognitive performance.

Methods—A longitudinal observational cohort was used with analysis of data collected September 2005 through May 2011 and maintained in the National Alzheimer's Coordinating Center (NACC) Uniform Data Set. Participants were aged 50 years or older and cognitively normal (N=4414). Composite scores were constructed from 10 psychometric tests. Scores for each participant reflecting change in the psychometric composite score from the baseline clinical assessment to the next assessment were calculated. General linear models were used to test whether the mean composite change score differed for participants who reported starting, stopping, continuing, or not taking each of the 100 most frequently-used medications in the NACC sample.

Results—The average time between assessments was 1.2 years (SD=0.42). Nine medications showed a difference ($p<0.05$) across the four participant groups in mean psychometric change scores from the first to the second assessment. Medications associated with improved psychometric performance were: naproxen, calcium-vitamin D, ferrous sulfate, potassium chloride, flax, and sertraline. Medications associated with declining psychometric performance were: bupropion, oxybutynin, and furosemide.

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The authors report no competing interests.

Conclusions—Reported use of common medications is associated with cognitive performance in older adults, but studies are needed to investigate the mechanisms underlying these effects.

Keywords

cognition; medications; psychometric tests; National Alzheimer's Coordinating Center

1. Background

There are conflicting reports and a lack of evidence-based data regarding effects of medications on cognition in cognitively normal older adults. Discrepancies between some studies are likely due to differences in methodology and definitions of the cognitive outcome.[1] The older adult population accounts for the largest percentage of medication use in the United States, but is often excluded from drug trials due to greater disease burden and differences in pharmacodynamics and pharmacokinetics.[2]

Almost every medication has the potential to influence cognition, and older adults may be especially vulnerable to central nervous system (CNS) effects.[3] While some drugs have detrimental effects on cognitive performance, others may improve performance or show a protective effect. Further, a drug's indication should not be overlooked, as an associated cognitive benefit or detriment of a drug may relate to discomfort, deficiency status, or another medical factor that is resolved or worsened by the drug.

A number of pharmacoepidemiology studies have examined medication use and risk of dementia.[4–6] However, few studies assess the effects of drugs on psychometric performance in cognitively normal older adults. Although not all drugs have an equal potential to interfere with cognitive processes, there is no "gold-standard" list of drugs that affect cognition.[7] Due to this uncertainty, physicians and pharmacists commonly turn to prescribing guides such as the Beers criteria,[8] which lists drugs thought to have high rates of CNS effects in older adults. These criteria are consensus based and lack supporting data.[9]

Due to inadequate literature, it is unknown whether medications commonly taken by cognitively normal older adults are associated with increased or decreased cognitive performance. As a first step in addressing this lack of knowledge, we explored the longitudinal effects on cognition of the top 100 medications reportedly used by cognitively normal participants in the National Alzheimer's Coordinating Center (NACC) database. The purpose was to determine whether use of common medications by older adults is associated with increased or decreased performance on psychometric tests.

2. Methods

Archival data from September 2005 through May 2011 were used from the NACC Uniform Data Set (UDS), supported by the National Institute on Aging. Details about recruitment and assessment of participants have been published elsewhere.[10] Briefly, the UDS contains demographic and clinical data from participants with and without cognitive impairment who are assessed longitudinally in each of the 30 National Institute on Aging-funded Alzheimer's Disease Centers (ADCs) in the United States. Each participant has an informant, or collateral source, typically a family member or close friend, who serves as the study partner during the ADC assessments.[10] Data from these individuals have been used previously in other publications, and written informed consent was obtained from each participant and informant.

Inclusion criteria for participants were (1) age 50 years or older at their first assessment following introduction of the UDS, (2) normal cognition (defined as a Clinical Dementia

Rating[11,12] [CDR]=0) at their first UDS assessment, (3) and at least one additional assessment following the index assessment (assessments are to be obtained annually).

The standard clinical assessment procedures administered by the ADCs has been previously described.[10] Research-trained clinicians from each center follow a uniform protocol to collect data from both the participant and the participant's informant during ADC assessments to determine whether the participant is functioning at their usual level or whether there has been cognitive decline.[13] Data collected include demographic information, health history, medication use, depression and neuropsychiatric inventories, functional status, and cognitive status.[10]

The brief neuropsychological test battery was designed to measure attention, processing speed, executive function, episodic memory, and language.[14] The test battery was administered at each assessment, which was scheduled annually. The battery includes the following psychometric tests: Wechsler Memory Scale-Revised (WMS-R) Logical Memory,[15] WMS-R Digit Span Backward,[15] WMS-R Digit Span Forward,[15] WMS-R Logical Memory Delayed,[15] Category Fluency,[16] Trailmaking A and B,[17] Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Symbol,[18] and Boston Naming Test.[19] Another test included in the battery is the Mini-Mental State Examination (MMSE),[20] which was not used in this study since ceiling effects are found on the MMSE among cognitively normal individuals.

Research-trained clinicians at each ADC use a standardized form to collect medication data, which are linked to drug identification codes from both the participant and their informant. Prescription and non-prescription drugs and vitamins/supplements taken by the participant within the past two weeks of each assessment are captured. For this study, we obtained a list of the most-commonly-used drugs in the NACC data set for all participants who were age 50 or older with normal cognition (CDR=0) and who contributed data for at least one assessment between September 2005 and May 2011 (N=7,472). A frequency table lists in descending order the 100 most commonly used drugs reported by the participant and their informants at each assessment (each medication used by each participant was counted only once) (Table 1).

The sample used to test associations of the 100 medications with changes in cognition was similar to the sample of participants used in constructing the table, except participants must have had at least 2 post-UDS assessments and non-missing data for at least 8 of the 10 psychometric tests. We examined change in cognition from visit 1 to visit 2 as it related to changes in or maintenance of the use of each medication across the same time period. Therefore, we examined longitudinal change in cognition with each participant serving as his or her own control. Due to the self-reporting nature of medication use by the participant and/or the informant, participants with informants considered to have questionable reliability as determined by ADCs' clinicians were excluded from the study. For each of the 100 medications, participants were categorized into 1 of 4 groups: (1) initiated the drug (were not taking the drug at visit 1 but were taking the drug at visit 2), (2) discontinued the drug (were taking the drug at visit 1 but not taking the drug at visit 2), (3) did not take the drug (were not taking the drug at visit 1 or visit 2), and (4) continued the drug (were taking the drug at both visit 1 and visit 2).

A psychometric composite score for each participant was constructed by converting each of the psychometric raw scores to z-scores, and then taking the mean of the 10 standardized scores. Composite change scores were computed by subtracting the composite score at visit 2 from the composite score at visit 1, and dividing by the time between those visits. Because z-scores were used, differences across time in change scores were very small. To make the

change scores easier to work with, the scores were linearly transformed by multiplying by 100,000. General linear models adjusting for age, sex, race, and education were used to test whether the mean change score differed for the 4 groups of participants: those (1) initiating, (2) discontinuing, (3) not taking, or (4) continuing each of the top 100 medications.

An attention and processing speed subscale was developed using Trailmaking A and B[17] and Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Symbol,[18] and the WMS-R Logical Memory Delayed[15] was used as a subscale reflecting episodic memory. These subscales were separately evaluated because changes in attention and processing speed may be due to the normal aging process.

These analyses controlled for reported history of hypertension, hypercholesterolemia, diabetes, vitamin B12 deficiency, thyroid disease, and alcohol abuse (disease states that may interfere with cognition). They also were controlled for Geriatric Depression Scale score.[21] For the medications found to be significantly associated with changes in cognition, we adjusted for additional relevant covariates (if possible) and re-ran the analyses.

3. Results

Participants reported taking an average of 4.3 (SD=3.5) medications at their initial assessment. The average time between visit 1 and visit 2 was 1.2 years (SD=0.42). Of the 3023 participants with APOE genotype data available, 870 (28.8%) had one or more APOE ε4 allele. Demographic characteristics of the 4414 individuals who met inclusion criteria for this study are shown in Table 2. Nine drugs were associated with a statistically significant difference ($p<0.05$) between at least two of the four study groups in mean psychometric change scores from visit 1 to visit 2 (Table 3). There was a greater association between the use of drugs and changes in attention and processing speed than with episodic memory (Appendices 1 and 2). Below we discuss the significant pairwise differences between the groups.

3.1. Medications associated with increased psychometric performance

Naproxen—The largest increase in change scores was in the group that began taking naproxen. The increase was significantly larger than for those who stopped taking the medication ($p=0.0008$), those that were not taking the medication ($p=0.0004$), or those that stayed on the medication ($p=0.0155$).

Calcium-vitamin D—Composite scores increased in all four groups from visit 1 to visit 2, with the largest increase in the group that began taking calcium-vitamin D. The increase was a significantly larger improvement than for those who stopped taking the medication ($p=0.0022$) or who never took the medication ($p=0.0010$).

Ferrous sulfate—There was a large improvement in change scores in the group that began taking ferrous sulfate. This was larger than those who stopped taking the medication ($p<0.0001$), those that were not taking the medication ($p<0.0001$), or those that stayed on the medication ($p=0.0001$). The group that stopped taking ferrous sulfate had a slight absolute decrease in change scores.

Potassium chloride—Participants who stopped taking potassium showed a decline in change scores, whereas those who continued use of potassium showed an overall increase in change scores ($p=0.0309$). Participants taking potassium at both visits had a larger increase in performance than the group not taking potassium ($p=0.0465$). The group that started potassium had a significantly larger increase in change scores compared to those not taking it ($p=0.0017$).

Flax—All 4 groups had an absolute increase in change scores from visit 1 to visit 2. The largest increase was in the group that began flax, and this increase was significantly larger than those not taking flax at either visit (p=0.0116).

Sertraline—The group that started sertraline had an increase in change scores compared to the group that stopped taking the drug (p=0.0241). The group that stopped taking sertraline had a greater decrease in change scores than did the group not taking the drug (p=0.0145). These analyses controlled for Geriatric Depression Scale score, but in separate analyses adding self-reported episodes of depression to the model these group differences were no longer significant (p=0.0752).

3.2. Medications associated with decreased psychometric performance

Bupropion—The group not taking the drug had increased change scores from visit 1 to visit 2, a significantly different result from the group that continued taking (p=0.0027), bupropion. The group that continued bupropion showed an absolute decrease in change scores. These analyses controlled for Geriatric Depression Scale score, but in separate analyses adding self-reported episodes of depression to the model these group differences were no longer significant (p=0.0540).

Oxybutynin—The group that did not take oxybutynin had increased change scores with time compared to the group that began the drug (p=0.0033) and the group that stayed on the drug (p=0.0337), both of which showed declining psychometric composites. These findings remained significant after adjusting for the reported history of neurologic conditions of stroke, transient ischemic attack, Parkinson's disease, seizures, traumatic brain injury, and urinary incontinence.

Furosemide—The group that began the drug had a significant decrease in change scores compared to the group that stayed on the drug (p=0.0376). The group that stopped the drug had a significant decrease in change scores compared to the groups who were not taking the drug (p=0.0161) or stayed on the drug (p=0.0052), both of which increased change scores. These results remained significant after adding the additional covariate of congestive heart failure.

4. Discussion

In this exploratory analysis, almost 10% of the 100 most-commonly-used drugs among cognitively normal older adults in our sample were associated with longitudinal changes in cognition. On the psychometric subscales, ferrous sulfate was associated with changes in both attention and processing speed and episodic memory, while the other eight medications were predominantly associated with changes in attention and processing speed. We examined only associations between drug use and changing cognition, and some associations could be due to correction of a deficiency rather than an intrinsic effect on cognitive processes. Two of the associations were not robust to further adjustment for confounding, as described below. Although we have no mechanistic data, below we discuss properties for each medication that may be relevant to changes in cognition as well as previous research regarding the cognitive effects of these drugs. However, because we selected medications of interest based on their frequency of use, we found some associations between medication use among older adults and cognition that appear to have been previously unexplored. Specifically, we could find no previous reports exploring relationships between iron, potassium, and flax supplement use and cognition among older adults.

Naproxen

Initiation of naproxen was associated with an increase in change scores. Naproxen, a nonsteroidal anti-inflammatory drug (NSAID), is used primarily for the treatment of pain and/or inflammation. Previous literature regarding the effects of NSAIDs on cognition in older adults is conflicting.[22–26] A review on the effect of pain on cognitive function suggests pain is associated with decreased performance on psychometric tests, and relief of pain may improve performance,[27] which may be why an association was found in our study.

Calcium-vitamin D

Initiation of calcium-vitamin D was associated with increasing change scores. Calcium-vitamin D is a nutritional supplement commonly taken by older adults to treat or prevent osteoporosis. Because vitamin D deficiency has been previously associated with decreased cognitive performance in older adults,[28–31] it is possible that correction of vitamin D deficiency led to a positive association in our study.

Ferrous sulfate

Beginning ferrous sulfate resulted in the largest absolute increase in change scores for any drug and any group studied. Ferrous sulfate is an iron salt used in the treatment or prevention of iron-deficiency anemia. Anemia is common in the elderly.[32] Iron supplementation increases cognitive performance, regardless of baseline iron status, in randomized controlled trials of women and adolescents, but studies in older adults are lacking.[33] It is possible that correcting an iron-deficiency anemia led to a positive association in our study, suggesting that future studies should determine the effects of iron on cognitive performance in older adults. However, over-supplementation of iron raises concerns for toxicity, and thus use of ferrous sulfate should be monitored carefully.

Potassium chloride

Potassium chloride is used to treat or prevent hypokalemia, which can lead to confusion, delirium, and cognitive dysfunction. Data are lacking on the effects of potassium supplements on cognition in older adults. In our study, participants beginning potassium increased in change scores compared to those not taking the supplement. Participants who stopped taking potassium showed a decline in change scores compared to those who reported continued use. Further, participants taking potassium at both visits showed a greater improvement in change scores compared to participants not taking potassium. This suggests an association between potassium supplements and cognition that should be further investigated.

Flax

Flax seed is a nutritional supplement containing dietary fiber, omega-3 fatty acids, and micronutrients such as magnesium, calcium, iron, and B vitamins.[34] We are unaware of any studies showing an association between flax and increased performance on psychometric cognitive tests in older adults. It is puzzling why flax was associated with increased change scores while the omega-3 fatty acid supplement on the Top 100 list was not. Interestingly, participants taking flax also tended to take calcium-vitamin D at both the first (chi-square, $p<0.0001$) and second (chi-square, $p=0.0058$) clinical assessments. At the first clinical assessment, 17 of 30 (56.7%) participants taking flax were also taking calcium-vitamin D. At the second assessment, 28 of 71 (39.4%) participants who took flax also took calcium-vitamin D. This suggests that individuals who take flax are likely to also take other medications or supplements that may be associated with increased cognition. Another possible explanation involves other micronutrients associated with improved cognitive

performance found in flax that are not found in pure omega-3 fatty acid supplements. For example, flax contains 44% of the adult U.S. recommended daily value of iron.[34]

Sertraline

Sertraline is selective serotonin reuptake inhibitor (SSRI) antidepressant that potentiates serotonin in the CNS. Previous studies in older adults show SSRIs have a superior cognitive profile compared with tricyclic antidepressants,[35] and may improve cognitive function by a mechanism different from their antidepressant effect.[36] Sertraline has been shown to improve immediate and delayed verbal recall in older adults when compared with paroxetine,[37] and other studies show sertraline to have a better effect on cognition compared to other SSRIs.[38] The analyses controlled for Geriatric Depression Scale score, but when self-reported episodes of depression were added to the model, sertraline no longer had an effect on cognition. This suggests that even a history of past depression episodes may be associated with psychometric performance in our dataset. More studies are needed to compare effects of SSRIs on cognitive performance in older adults.

Bupropion

Bupropion is an antidepressant that uniquely and selectively inhibits reuptake of dopamine and blocks norepinephrine reuptake in neurons. We found that continuous use of bupropion was associated with a decrease in change scores when compared to non-use of the drug. Bupropion has not been previously associated with negative effects on cognition in older adults. Studies with younger individuals show no effects of bupropion on attention, memory, or psychomotor speed.[39–41] The analyses controlled for Geriatric Depression Scale score, but when self-reported episodes of depression were added to the model, bupropion was no longer associated with cognition.

Oxybutynin

Change scores declined for individuals who initiated or continued taking oxybutynin, an anticholinergic agent used to treat overactive bladder. Overactive bladder is frequently associated with neurologic conditions that may interfere with cognition, so we adjusted for the additional covariates of cerebrovascular disease, Parkinson's disease, seizures, traumatic brain injury, and incontinence. After these adjustments to the model, oxybutynin continued to be negatively associated with cognition. Previous studies have shown a decrease in cognitive performance on various tests of attention and memory associated with highly anticholinergic drugs.[42–46]

Furosemide

Furosemide is a sulfonamide-derived loop diuretic commonly used in the management of edema, heart failure, renal insufficiency, and hypertension. Furosemide may be associated with impaired cognition due to the medication's effect of depleting electrolytes such as potassium and magnesium. However, our study also showed participants stopping furosemide had a decrease in change scores compared to participants who stayed on the drug or were not taking the drug. This finding does not support the electrolyte depletion hypothesis. To evaluate whether the furosemide finding represents confounding by indication, we adjusted for heart failure and uncontrolled blood pressure, (as these have independently been associated with cognitive decline[47,48]) and found that furosemide was still associated with a decrease in change scores.

Conclusions

Although the effects may be subtle, our results suggest medications commonly used by older adults may be associated with cognitive changes. Older adults who take dietary supplements may be more health conscious and have better overall health, which may have led to the associations between dietary supplements and improved cognitive performance. However, not all supplements showed an association.

The strengths of our study include quantitative cognitive assessments and a large, carefully-characterized sample that allowed us to look at many drugs simultaneously within the same population.

However, there are also limitations to our study, including reliance on self-report of medication use. Verification of medication adherence from pharmacy records was not available. Also, the UDS does not capture dose or duration of the medications, both of which may play an important role in the ability of drugs to affect cognition. We conducted multiple statistical tests, so some statistically significant differences reported here may be due to chance. However, five of the drugs (naproxen, calcium-vitamin D, ferrous sulfate, potassium chloride, and oxybutynin) have p-values <0.005, and p-values of this magnitude reduce the chance that the finding is spurious. Confounding by indication is possible due to our use of an observational design. Older adults commonly suffer from deficiencies known to interfere with cognitive performance such as anemia, hypokalemia, and vitamin D deficiency, which are likely to be treated with drugs and supplements. There were a limited number of disease states captured by the UDS so we were unable to control for all relevant variables. For example, pain is associated with decreased performance on psychometric tests, and effective management of pain (which is not assessed in the UDS) may alleviate the associated cognitive impairment.[27] Participants in this study are cognitively normal volunteers who participated in research at NIA-funded centers, so generalizability to all older adults should not be assumed.

To our knowledge, the clinical meaningfulness of the change scores has not been characterized. We used the change score as a less cumbersome approach to identifying a global psychometric composite change rather than looking at each psychometric test individually. Using regression analysis, we found a significant linear association between the composite and MMSE change scores ($p<0.0001$). However, to examine how average magnitude of change on the composites is reflected in average change on the MMSE does not validly reflect the clinical meaningfulness of the composite change score, since ceiling effects are found on the MMSE. In this sample, 46.2% of participants scored perfectly on the MMSE (i.e., received a score of 30) at the second visit. Therefore, the actual clinical significance of the comprehensive change score is larger than that reflected by the change in MMSE scores. Other indices of cognitive change available in the NACC database (e.g., global Clinical Dementia Ratings) also show ceiling effects among cognitively-normal individuals. It was for that reason that we used a composite of the psychometric scores, which should be free of ceiling and floor effects.

Prescribers should be reminded that commonly used drugs and supplements may affect cognitive performance in older adults, and drug choices should be made carefully.

Additional studies investigating medication use and cognitive performance in older adults are imperative because the rapidly-growing older adult population is the largest consumer of drugs and supplements in the United States. Future studies are needed to determine whether certain drugs may impair cognition enough to lower the threshold for a dementia diagnosis. Future studies may also determine if drugs associated with improved cognitive performance

in cognitively normal adults show a protective effect and delay the onset of incident dementia.

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Abbreviations

NACC	National Alzheimer's Coordinating Center
CNS	central nervous system
UDS	Uniform Data Set
ADCs	Alzheimer's Disease Centers
CDR	Clinical Dementia Rating
WMS-R	Wechsler Memory Scale-Revised
WAIS-R	Wechsler Adult Intelligence Scale-Revised
MMSE	Mini-Mental State Examination
NSAID	nonsteroidal anti-inflammatory drug
SSRI	selective serotonin reuptake inhibitor

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Appendix

Appendix 1

Attention and processing speed subscales- Medications associated with significant differences in psychometric change scores * across the groups

		Mean psychometric change scores			
Drug Name	**P-value†**	**Group 1 Started drug**	**Group 2 Stopped drug**	**Group 3 Did not take**	**Group 4 Continued taking**
Naproxen	0.0030	51.96 (15.26)	0.55 (13.35)	7.95 (9.39)	8.83 (16.57)
Calcium-vitamin D	0.0009	36.99 (12.24)	7.86 (10.01)	7.82 (9.40)	19.50 (11.30)
Ferrous sulfate	< 0.0001	158.24 (25.61)	1.59 (13.20)	8.99 (9.36)	29.27 (26.54)
Potassium chloride	0.0031	45.68 (15.42)	1.95 (12.12)	7.24 (9.39)	21.93 (11.90)
Flax	0.0786	61.49 (25.46)	14.54 (16.17)	7.48 (9.39)	33.85 (23.79)
Sertraline	0.0830	25.07 (19.65)	−27.97 (18.97)	9.01 (9.40)	−1.09 (13.61)
Bupropion	0.0260	−6.91 (18.88)	−2.43 (18.08)	9.15 (9.40)	−21.62 (14.13)
Oxybutynin	0.0006	−53.77 (18.65)	−2.31 (18.72)	7.91 (9.38)	−12.27 (15.40)
Furosemide	0.0105	−7.51 (17.04)	−21.98 (13.49)	7.90 (9.39)	12.09 (11.74)

Note: Numbers in parentheses represent standard error

*Positive change scores indicate that cognition improved between visit 1 and visit 2. Negative change scores indicate that cognition declined between visit 1 and visit 2.

†P-value testing for any difference across the groups

Appendix

Appendix 2

Episodic memory subscales- Medications associated with significant differences in psychometric change scores * across the groups

		Mean psychometric change scores			
Drug Name	**P-value†**	**Group 1 Started drug**	**Group 2 Stopped drug**	**Group 3 Did not take**	**Group 4 Continued taking**
Naproxen	0.4552	63.95 (41.11)	36.10 (36.13)	26.00 (25.49)	−11.89 (44.50)
Calcium-vitamin D	0.1612	46.93 (33.30)	40.86 (27.17)	22.69 (25.54)	49.00 (30.71)
Ferrous sulfate	0.0007	316.43 (75.92)	41.49 (35.40)	26.87 (25.46)	63.70 (75.51)
Potassium chloride	0.5571	66.47 (41.17)	25.99 (32.62)	24.94 (25.51)	39.40 (31.99)
Flax	0.4473	109.98 (66.46)	54.57 (44.23)	25.03 (25.49)	47.55 (64.47)
Sertraline	0.4920	28.88 (54.38)	−35.05 (50.40)	27.84 (25.53)	9.78 (36.59)
Bupropion	0.2068	54.55 (51.81)	83.72 (47.77)	25.97 (25.50)	−15.55 (38.03)
Oxybutynin	0.4453	20.39 (49.03)	−33.41 (50.91)	25.35 (25.49)	−5.50 (41.46)
Furosemide	0.0455	−56.28 (45.71)	10.37 (36.47)	25.58 (25.47)	56.05 (31.41)

Note: Numbers in parentheses represent standard error

*Positive change scores indicate that cognition improved between visit 1 and visit 2. Negative changescores indicate that cognition declined between visit 1 and visit 2.

†P-value testing for any difference across the groups

Our study examined the association between many drugs and performance on psychometric tests in such a large sample. Previous studies typically examine a specific class of drugs such as NSAIDs in a smaller sample size. The advantage to our study is that it may identify other medications for which future studies can investigate possible mechanisms related to these medications.

Studies investigating medication use and cognitive performance in older adults are imperative because the rapidly growing older adult population is the largest consumer of drugs and supplements in the United States. Future studies are needed to determine whether certain drugs may impair cognition enough to lower the threshold for a dementia diagnosis. Future studies may also determine if drugs associated with improved cognitive performance in cognitively normal adults show a protective effect and delay the onset of incident dementia.

Table 1

Frequency table of most commonly-used medications in NACC UDS subjects with normal cognition (N=7,472)

	Participants taking each drug	
Medication	**N**	**%**
Aspirin	3451	46.2
Multivitamin	3190	42.7
Calcium-Vitamin D	2235	29.9
Omega-3 polyunsaturated fatty acids	2109	28.2
Multivitamin with minerals	1911	25.6
Levothyroxine	1497	20.0
Simvastatin	1475	19.7
Ascorbic acid	1373	18.4
Hydrochlorothiazide	1289	17.3
Lisinopril	1255	16.8
Ergocalciferol	1210	16.2
Atorvastatin	1180	15.8
Metoprolol	1017	13.6
Omeprazole	1002	13.4
Calcium carbonate	984	13.2
Vitamin E	981	13.1
Alendronate	945	12.6
Glucosamine	882	11.8
Cyanocobalamin	823	11.0
Amlodipine	805	10.8
Atenolol	770	10.3
Acetaminophen	704	9.4
Folic acid	569	7.6
Potassium chloride	569	7.6
Furosemide	557	7.5
Metformin	544	7.3
Ibuprofen	505	6.8
Warfarin	465	6.2
Clopidogrel	455	6.1
Naproxen	416	5.6
Valsartan	387	5.2
Hydrochlorothiazide-triamterene	380	5.1
Ubiquinone	379	5.1
Lovastatin	377	5.0
Albuterol	360	4.8
Esomeprazole	355	4.8
Zolpidem	354	4.7

	Participants taking each drug	
Medication	**N**	**%**
Tamsulosin	346	4.6
Losartan	335	4.5
Risedronate	312	4.2
Rosuvastatin	312	4.2
Diltiazem	311	4.2
Conjugated estrogens	310	4.1
Calcium acetate	305	4.1
Gabapentin	303	4.1
Ezetimibe	303	4.1
Loratadine	297	4.0
Pravastatin	295	3.9
Ranitidine	283	3.8
Estradiol	281	3.8
Fluticasone-salmeterol	280	3.7
Chondroitin-glucosamine	279	3.7
Celecoxib	277	3.7
Niacin	272	3.6
Pantoprazole	266	3.6
Latanoprost ophthalmic	264	3.5
Fluticasone nasal	259	3.5
Sertraline	255	3.4
Ferrous sulfate	254	3.4
Ezetimibe-simvastatin	247	3.3
Escitalopram	243	3.3
Digoxin	238	3.2
Citalopram	238	3.2
Finasteride	225	3.0
Bupropion	218	2.9
Fexofenadine	218	2.9
Fluoxetine	214	2.9
Docusate	214	2.9
Lansoprazole	213	2.9
Triamterene	201	2.7
Acetaminophen-hydrocodone	201	2.7
Montelukast	201	2.7
Raloxifene	199	2.7
Trazodone	197	2.6
Cetirizine	195	2.6
Oxybutynin	192	2.6
Tramadol	188	2.5
Terazosin	184	2.5

	Participants taking each drug	
Medication	**N**	**%**
Pyridoxine	184	2.5
Nifedipine	179	2.4
Glipizide	179	2.4
Lorazepam	175	2.3
Flax	175	2.3
Ibandronate	174	2.3
Carvedilol	172	2.3
Olmesartan	171	2.3
Nitroglycerin	170	2.3
Tolterodine	170	2.3
Enalapril	169	2.3
Prednisone	168	2.2
Allopurinol	167	2.2
Psyllium	161	2.2
Alprazolam	160	2.1
Verapamil	156	2.1
Meloxicam	153	2.0
Selenium	148	2.0
Venlafaxine	147	2.0
Clonazepam	145	1.9
Paroxetine	144	1.9
Ramipril	142	1.9

Table 2

Baseline Demographics (N = 4414)

	N/Mean	%/SD
Age, y	74.4	9.2
Sex		
Male	1443	32.7%
Female	2971	67.3%
Race		
White	3655	82.8%
African American	638	14.4%
Other	121	2.7%
Education, y	15.5	3.0
MMSE*	28.9	1.5
GDS†	1.2	1.8
Total medications‡	4.3	3.5

*MMSE=Mini-Mental State Examination (worst possible score=0, best possible score=30).

†GDS=Geriatric Depression Scale (minimum possible score=0 [least depression], maximum possible score=15 [most depression]).

‡Total number of medications reported on the first assessment.

Table 3

Medications associated with significant differences in psychometric change scores* across the groups

		Mean psychometric change scores											
		Group 1 Started drug			Group 2 Stopped drug			Group 3 Did not take			Group 4 Continued taking		
Drug Name	**P-value†**	**Mean CS**	**SE**	**N**	**Mean CS**	**SE**	**N**	**Mean CS**	**SE**	**N**	**Mean CS**	**SE**	**N**
Naproxen	0.0040	50.30	(15.68)	[43]	−2.31	(13.70)	[69]	6.91	(9.71)	[4268]	5.54	(16.85)	[34]
Calcium-vitamin D	0.0031	33.58	(12.64)	[103]	6.54	(10.36)	[448]	6.85	(9.74)	[3701]	19.00	(11.67)	[162]
Ferrous sulfate	< 0.0001	197.06	(28.62)	[9]	−0.15	(13.44)	[73]	8.16	(9.67)	[4324]	9.83	(30.00)	[8]
Potassium chloride	0.0019	45.14	(15.72)	[43]	−1.62	(12.46)	[110]	6.07	(9.72)	[4148]	21.72	(12.23)	[113]
Flax	0.0461	65.28	(25.14)	[12]	14.94	(16.92)	[34]	6.37	(9.72)	[4355]	32.20	(24.39)	[13]
Sertraline	0.0460	22.93	(20.99)	[19]	−34.12	(19.39)	[22]	8.28	(9.74)	[4305]	−3.57	(13.90)	[68]
Bupropion	0.0221	−5.77	(19.31)	[23]	4.35	(18.10)	[28]	8.05	(9.73)	[4307]	−24.80	(14.40)	[56]
Oxybutynin	0.0040	−41.77	(19.13)	[24]	−3.86	(19.26)	[24]	6.82	(9.71)	[4322]	−19.21	(15.72)	[44]
Furosemide	0.0144	−16.95	(17.33)	[32]	−17.12	(13.90)	[70]	6.66	(9.72)	[4174]	15.92	(12.04)	[138]

Abbreviations: CS = change score, SE = standard error

*Positive change scores indicate that cognition improved between visit 1 and visit 2. Negative change scores indicate that cognition declined between visit 1 and visit 2.

†P-value testing for any difference across the groups.

Numbers in brackets indicate the number of people in each group.