Published in final edited form as:
Int J Geriatr Psychiatry. 2012 December ; 27(12): 1248–1257. doi:10.1002/gps.3769.

The association of psychotropic medication use with the cognitive, functional, and neuropsychiatric trajectory of Alzheimer's disease

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Author contributions
The original concept for the paper came from Drs. Rosenberg, Mielke, Lyketsos, and Tschanz. The data were collected by Drs. Lyketsos, Rabins, Breitner, Norton, Welsh-Bohmer, Green, Corcoran, and Tschanz. Data analyses were performed by Drs. Leoutsakos, Mielke, Rosenberg, and Han. All authors participated in drafting and revising the manuscript.

Conflict of interest
Dr. Rosenberg has received research support from Merck, Pfizer, Lilly, Elan, and Jannsen, and is funded by NIH grants 5R01AG033032-02 and 5K08AG029157-03, and received research support from the American Federation for Aging Research.
Dr. Mielke is funded by NIH grants U01AG037526-01, R03AG032427-01A1, and R01 AG21136.
Dr. Leoutsakos is funded by NIH grants RAG031348-02S1, R01MH085740-01A2, R01 MH086881, R21AG033769, and 09CRP2250944, as well as by the American Heart Association.
Dr. Lyketsos has received grant support from NIMH, NIA, Associated Jewish Federation of Baltimore, Weinberg Foundation, Forest, GlaxoSmithKline, Eisai, Pfizer, AstraZeneca, Lilly, Ortho–McNeil, Bristol–Myers, Novartis, National Football League, and Elan. He has served as a paid consultant/advisor to AstraZeneca, GlaxoSmithKline, Eisai, Novartis, Forest, Supernus, Adlyfe, Takeda, Wyeth, Lundbeck, Merz, Lilly, Pfizer, Genentech, Elan, NFL Players Association, and NFL Benefits Office. He has received honoraria or travel support from Pfizer, Forest, GlaxoSmithKline, and Health Monitor.
Dr. Rabins has provided legal testimony for Janssen Pharmaceutica. He is funded by NIH grants P30AAG021334, E1A6031348, and AG021136.
Dr. Zandi is funded by NIH grants R01 MH083738, BJ18-JHU-ARRA, R01 MH076953, R37 AA12303, R37 DA011796, R01 MH085018-01A2, R01 MH087979, and U01 GM092654.
Dr. Breitner is funded by NIH grant U01AG15477 and has received research support from Pfizer Canada, McGill University, and the Douglas Mental Health University Institute Foundation.
Dr. Norton is funded by NIH grants R01AG11380, R01AG31272, and R01AG21136.
Dr. Welsh-Bohmer receives support from Zinfandel Pharmaceuticals and from Takeda for sponsored research projects for which she is the primary investigator. She has received honoraria as a speaker and scientific advisory board member to Medivation. She is funded by NIH grants AG11380 and AG028377.
Dr. Zuckerman is supported by grants and contracts from Phillips Healthcare, GlaxoSmithKline, Abt Associates, and American Cancer Society and the NCI.
Dr. Rattinger has received research support from Novartis, Elan and Jannsen, the American Foundation of Pharmaceutical Education and is funded by NIH grant 5K12HD043489-08.
Dr. Green is funded by NIH grant AG027841.
Dr. Corcoran is funded by NIH grants R01 ES 016669, U01 DD 000698, R15 AG037392, R01 AG 31272, and R01 AG 21136.
Dr. Tschanz is funded by NIH grants R01 AG21136 and R01 AG031272
Dr. Han has no disclosures.

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Abstract

Objective—The use of psychotropic medications in Alzheimer's disease (AD) has been associated with both deleterious and potentially beneficial outcomes. We examined the longitudinal association of psychotropic medication use with cognitive, functional, and neuropsychiatric symptom (NPS) trajectories among community-ascertained incident AD cases from the Cache County Dementia Progression Study.

Methods—A total of 230 participants were followed for a mean of 3.7 years. Persistency index (PI) was calculated for all antidepressants, selective serotonin reuptake inhibitors (SSRIs), antipsychotics (atypical and typical), and benzodiazepines as the proportion of observed time of medication exposure. Mixed-effects models were used to examine the association between PI for each medication class and Mini-Mental State Exam (MMSE), Clinical Dementia Rating Sum of Boxes (CDR-Sum), and Neuropsychiatric Inventory – Total (NPI-Total) trajectories, controlling for appropriate demographic and clinical covariates.

Results—At baseline, psychotropic medication use was associated with greater severity of dementia and poorer medical status. Higher PI for all medication classes was associated with a more rapid decline in MMSE. For antidepressant, SSRI, benzodiazepine, and typical antipsychotic use, a higher PI was associated with a more rapid increase in CDR-Sum. For SSRIs, antipsychotics, and typical antipsychotics, a higher PI was associated with more rapid increase in NPI-Total.

Conclusions—Psychotropic medication use was associated with more rapid cognitive and functional decline in AD, and not with improved NPS. Clinicians may tend to prescribe psychotropic medications to AD patients at risk of poorer outcomes, but one cannot rule out the possibility of poorer outcomes being caused by psychotropic medications.

Keywords

Alzheimer's disease; antidepressants; antipsychotics; SSRI; cognition; psychosocial function; neuropsychiatric symptoms; epidemiology; pharmacoepidemiology

Background

Neuropsychiatric symptoms (NPS) are prevalent in Alzheimer's disease (AD) (Steinberg *et al.*, 2008), and psychotropic medications are widely used to treat them, with up to one-third of patients with AD taking antidepressants or antipsychotics (Gruber-Baldini *et al.*, 2007; Kamble *et al.*, 2009). These medications are widely used despite doubts as to their safety and effectiveness (Sink *et al.*, 2005; Drye *et al.*, 2010; Rosenberg *et al.*, 2010; Weintraub *et al.*, 2010). Previous studies of psychotropic medication in AD have identified potential benefits and harms. The loss of serotonergic (Liu *et al.*, 2008) and noradrenergic (Weinshenker, 2008) innervation suggests that antidepressants that increase the availability or enhance the action of these neurotransmitters might be beneficial in slowing disease progression (Nelson *et al.*, 2007; Lauterbach *et al.*, 2010). There is evidence for antidepressants improving several domains of NPS in dementia including depression (DIADS-2 Rosenberg) and agitation (Pollock, 2002). Given that depression is associated with cognitive deficits in older persons (Murphy and Alexopoulos, 2004), it is possible that antidepressant treatment might improve cognition in depressed demented persons. There is also evidence for antidepressants increasing hippocampal neurogenesis with similar potential benefits (Malberg, 2004). Conversely, antipsychotic medication use has been associated with increased mortality (Schneider *et al.*, 2005; Wang *et al.*, 2005; Simoni-Wastila *et al.*, 2009) and poorer cognition (CATIE-AD paper), antidepressant use with increased risk of hip fracture (Ensrud *et al.*, 2003), and use of all major classes of psychotropic medications with increased risk of falls (Woolcott *et al.*, 2009). Given this mixture of possible beneficial and harmful effects of psychotropic medication use in AD, and in the absence of long-term randomized controlled trials for efficacy and safety, it is important to examine whether use of these medications is associated with differential outcomes in population studies. Three prior studies have addressed this question. ElluI and colleagues reported that use of antipsychotics and sedatives (including benzodiazepines) but not antidepressants in 224 community-dwelling persons with AD was associated with more than a two-fold increase in the risk of functional deterioration (Ellul *et al.*, 2007). A similar study found no effect of antipsychotic use on the rate of change of the Severe Impairment Battery (Livingston *et al.*, 2007). In a longitudinal study of 179 AD participants followed for a mean of 4 years, sedative use (including benzodiazepines) was associated with a twofold increase in mortality risk and antipsychotic use with a twofold increase in the risk of functional deterioration, but antidepressant use was not associated with either outcome (Lopez *et al.*, 1999).

A limitation of these studies is that they enrolled participants with prevalent rather than incident dementia. Additionally, two of the three studies had a follow-up duration of 12 months or less, and none evaluated the association of medication use with change in NPS. We, therefore, sought to examine the association of psychotropic medication use with cognitive, functional, and NPS trajectories in a longitudinal population-based study of incident AD participants enrolled in the Cache County Dementia Progression Study [DPS] (Tschanz *et al.*, 2011). We hypothesized that greater exposure to antipsychotic and benzodiazepine use would be associated with more rapid decline in cognition and function, and that antidepressant use would be associated with improvement in NPS (i.e. fewer symptoms) and cognition.

Methods

Participants and dementia diagnosis

The DPS originated from the longitudinal, population-based Cache County Study on Memory in Aging (CCSMA), which examined the prevalence, incidence, and risk factors of dementia in a US county recognized for its residents' longevity. In its first wave, the

CCSMA enrolled 90% of 5677 county residents aged 65 years or older. Three triennial incidence waves were subsequently completed, and incident cases were referred for prospective follow-up by the DPS. The interval between follow-up visits varied from 6 to 18 months.

Methods of identification and diagnosis of Cache County residents with dementia have been described (Tschanz *et al.*, 2011). These methods resulted in preliminary diagnoses of dementia according to DSM-III-R criteria. Dementia severity was rated on the Clinical Dementia Rating (CDR) (Morris, 1993) and health status according to the General Medical Health Rating (GMHR) (Lyketsos *et al.*, 1999). A consensus panel of experts consisting of neurologists, geropsychiatrists, neuropsychologists, and a cognitive neuroscientist then reviewed all available clinical information and (when available) neuropathologic data, assigning diagnoses of Possible or Probable AD according to NINCDS-ADRDA criteria (McKhann *et al.*, 1984) and estimating age of dementia onset. Study procedures were approved by institutional review boards at Utah State, Duke, and the Johns Hopkins Universities.

Measures of dementia progression

Mini-Mental State Exam (MMSE) (Folstein et al., 1975)—The MMSE is a global measure of cognition used widely in AD research. As previously reported (Mielke *et al.*, 2007; Tschanz *et al.*, 2011), an adjusted MMSE score was calculated by discarding items missed because of sensory/motor impairment (e.g. severe vision or hearing loss, motor weakness, tremor), calculating the percent correct of the remaining items, and rescaling the final score on a 30-point scale.

Clinical Dementia Rating (Morris, 1993)—The CDR is a semi-structured interview to assess dementia severity in six functional domains and has excellent reliability and validity (Morris *et al.*, 1997; Morris, 1997). The sum of the six domain scores (CDR-Sum) was chosen here in preference to the composite CDR score because of its greater range and sensitivity to change in mild cognitive impairment and AD (Pavlik *et al.*, 2006).

Neuropsychiatric inventory-Clinician Rating (NPI-10) (Cummings et al., 1994)—The NPI assesses type and severity of behavioral disturbances in dementia. NPI-10 evaluates 10 domains of NPS and records the frequency and severity for each domain. The total score for each domain is calculated as the product of frequency★severity for that domain, and NPI-Total is calculated as the sum of frequency★severity for all 10 domains. The NPI has been widely used for quantifying neuropsychiatric symptoms in AD in observational studies (Palmer *et al.*, 2010) and in recent clinical trials (Porsteinsson *et al.*, 2008). Severity ratings for delusions, hallucinations, or agitation/aggression allowed the rater to consider the use of PRN medications to control the behaviors to indicate “marked” severity, similar to methods used in recent AD trials (Rosenberg *et al.*, 2010).

Medication ascertainment and calculation of persistency index

Ascertainment of medication use relied on visual inspection of all available medication vials at each follow-up (Zandi *et al.*, 2002). When the participants were institutionalized, this information was obtained from nursing home records. We classified current medication use as regular if a medication from a particular psychotropic class was used ≥4 times per week. Psychotropic medication classes were categorized and examined using the following classes: all antidepressants, as well as a subset of these classified as selective serotonin reuptake inhibitors (fluoxetine, sertraline, paroxetine, citalopram, fluvoxamine); all antipsychotics, as well as a subset of these classed as atypical agents (olanzapine, risperidone, quetiapine,

ziprasidone, and aripiprazole) and typical agents (all other antipsychotics); and benzodiazepines.

Given the wide variety of possible patterns of medication exposure, we sought a summary measure to quantify medication exposure. The Persistency Index (PI) (Rountree *et al.*, 2009) represents years of drug use divided by years of observation following AD diagnosis. It can, therefore, range from 0 to 1, the latter indicating that the person has been taking a medication from a psychotropic drug class over the entire study duration. Similarly, a PI of 0.5 indicates that the person was taking it over only half the study duration. Medication use could be at any visit, and patients could have a PI >0 even if not taking medication at baseline, so long as they were taking medication at least one follow-up visit. As we did not have information on medication use between visits, if a person was taking a medication at consecutive visits, we assumed s/he was taking it over the whole time-period between these visits. If an individual was taking the medication at one visit but not at the next consecutive visit, we estimated the time of drug use was half the time between visits. A PI was calculated separately for each psychotropic medication class.

Statistical analyses

Group differences in baseline demographic and health-related characteristics were examined using Fisher's exact test for categorical variables and *t*-tests or analysis of variance with post-hoc *t*-tests for continuous variables. For descriptive purposes, the PI was subdivided into three categories: PI = 0 (no use), $0.01 < PI \leq 0.5$ (use half the time or less), $PI \geq 0.5$ (use more than half the time). For the regression analyses described below, PI was treated as a continuous variable.

To model effects of PI on dementia progression, we examined average change in MMSE, CDR-Sum, and NPI-Total from the visit at which dementia was first diagnosed, using linear mixed effects models, treating subject-specific intercepts and linear change with time as random effects. Because our analysis revealed significant non-linear time effects for both the MMSE and CDR-Sum, and as we have carried out before in similar analyses (Tschanz *et al.*, 2011), we included a quadratic term ($time^2$) and appropriate $time^2$ terms in all examined interactions. The following covariates were included in all models, based on the literature and previous analyses with this dataset: baseline age, sex, education, estimated duration of dementia prior to baseline visit, GMHR, and presence of one or two *APOE* ε4 alleles. Additionally, models with MMSE and CDR-Sum as outcomes included baseline NPI-Total as a covariate to account for the possibility that persons with higher NPI scores would be more likely to be prescribed psychotropic medications. Education, sex, and *APOE* genotype were determined at Wave 1 of the CCSMA. *APOE* genotype was determined from buccal DNA using a standard protocol (Breitner *et al.*, 1999). $P < 0.05$ was used as the threshold for statistical significance. All analyses were conducted using STATA Version 11.0 (StataCorp, College Station, TX, USA).

Results

Demographics and clinical variables (Table 1)

A total of 335 participants were diagnosed with incident AD and enrolled in DPS, of whom 230 had at least one follow-up visit. The participants lacking follow-up were older, had lower MMSE, higher CDR-Sum, and were less likely to be taking acetylcholinesterase inhibitors. The median number of follow-up visits was one and the maximum 12, with mean [SD] duration of follow-up 3.7[2.49] years and range 0.70–12.3 years. On average, the participants were in their mid-80s, had one year of college, were more likely to be female, and were diagnosed within 2 years of estimated AD onset.

Persistency index

The PIs for each medication class are presented in Table 2. The prevalence of all-type antidepressant use and of SSRI use was quite high, with 47.8% of participants taking an antidepressant at some point during the study, 90% of which was SSRI use. The majority of PIs for antidepressants and SSRIs were ≥0.5. We observed a lower prevalence of antipsychotic use (29%) divided about equally between atypical and typical antipsychotics, and with the majority of PIs being calculated as ≤0.5. About a quarter of the participants had used benzodiazepines, with the majority of PIs being ≤0.5.

Most participants who took psychotropic medications were taking medications from more than one psychotropic class. Among 82 participants taking an antidepressant at baseline, only six (7%) did not take any other medication from another psychotropic class throughout the study. Among 18 participants taking an antipsychotic at baseline, 14 (78%) were also taking an antidepressant and seven (39%) a benzodiazepine; all participants also took at least one medication from another psychotropic class throughout the study. Among 24 participants taking a benzodiazepine at baseline, 15 (63%) were also taking an antidepressant and seven (29%) an antipsychotic; all participants also took at least one medication from another psychotropic class throughout the study. Six participants (2.6% of total) were taking an antidepressant, antipsychotic, and benzodiazepine at baseline.

There were specific baseline demographic and clinical variables associated with PI. Comparing participants with PI >0.5 (“persistent” use) versus those with PI = 0 (no use), persistent antidepressant use was associated with longer estimated duration of dementia prior to diagnosis (mean[SD] 2[1.4] vs 1.5[1.2]) years, $F_{1,2} = 3.23$, $p = 0.042$), female gender (81.2% vs 50.8%, $p < 0.001$, Fisher’s exact test), higher CDR-Sum (6.5 [3.1] vs 4.9 [2.5], $F_{1,2} = 6.72$, $p = 0.002$), higher NPI total (6.5[9.7] vs 2.9[5.7], $F_{1,2} = 6.14$, $p = 0.003$), and lower GMHR (2.6[0.6] vs 2.9[0.6], $F_{1,2} = 8.3$, $p = 0.003$). Persistent SSRI use was associated with younger age (83.2[6] vs 86.2[6.2] years, $F_{1,2} = 5.00$, $p = 0.008$), female gender (78% vs 54.5%, $p = 0.006$, Fisher’s exact test), higher CDR-Sum (6.6[3.1] vs 4.8[2.5], $F_{1,2} = 9.54$, $p < 0.000$), higher NPI total (6.3[9.3] vs 3.2[6.5], $F_{1,2} = 4.24$, $p = 0.016$), and lower GMHR (2.6[0.6] vs 2.9[0.6], $F_{1,2} = 4.99$, $p = 0.008$). Persistent antipsychotic use was associated with female gender (93.3% vs 58.3%, $p = 0.010$, Fisher’s exact test), presence of at least one APOE ε4 allele (73.3% vs 40.7%, $p = 0.026$ Fisher’s exact test), and higher CDR-Sum (7.4[3.7] vs 6.4[3.6], $F_{1,2} = 1.35$, $p = 0.001$). Persistent atypical antipsychotic use was associated with higher CDR-Sum (9.1[4.4] vs 6.2[2.3], $F_{1,2} = 7.19$, $p = 0.001$). Persistent use of typical antipsychotics and benzodiazepines was not significantly associated with any clinical variables examined.

Associations of PI with trajectory of MMSE, CDR-sum, and NPI-total

The associations between PI and each individual outcome were examined with linear mixed-effects models, controlling for baseline age, gender, education, estimated duration of dementia prior to baseline visit, the presence of at least one APOE4 allele, and GMHR (Table 3). For all medication classes and for co-use of antipsychotics and antidepressants, a higher PI was associated with a more rapid decline on the MMSE (graphically illustrated in Figure 1 for antipsychotic use). Similarly, higher PIs for anti-depressant, SSRI, benzodiazepine, and typical antipsychotics were associated with a more rapid increase in CDR-Sum. None of the PIs for any medication class were associated with a decrease in NPI-Total, and higher PIs for SSRIs, antipsychotics, and typical antipsychotics were associated with more rapid increase in NPI-Total. In all models, the coefficient for PI*time^2 was opposite in sign to that for PI*time, indicating that the rate of change decreased over time.

Discussion

In this population-based sample of incident AD dementia, we observed that longer duration of exposure to all major classes of psychotropic medications (quantified by PI) was associated with a more rapid rate of decline in general cognition (MMSE), and several classes of medicines were associated with more rapid increase in dementia severity (CDR-Sum) and NPS (NPI). These results strengthen prior reported associations of poorer outcomes with exposure to antipsychotics and benzodiazepines and extend these observations to antidepressants, including SSRIs, and to both typical and atypical antipsychotics. The association of greater benzodiazepine PI with more rapid cognitive and functional decline adds to a substantial literature implicating benzodiazepines with adverse outcomes in AD and indeed in older persons in general. Figure 1 depicts a consistent result of our modeling that the rate of decline itself declines over time, that is, the rates of change in outcomes tend to decelerate over time.

All classes of psychotropic medication were widely used over the study duration (ranging from 15 to 48%) with close to half of the participants using antidepressants and one-quarter using antipsychotics and benzodiazepines over the course of the study. The duration of exposure differed by medication classes, with antipsychotics and benzodiazepines generally being taken less than half the time and antidepressants (mostly SSRIs) more than half the time. The data at enrollment provide strong evidence that psychotropic medications were being prescribed to participants who had greater symptom severity (Lopez *et al.*, 2010; Tschanz *et al.*, 2011). Greater baseline functional impairment (CDR-Sum) was associated with more use of all medication classes except typical antipsychotics. Antidepressants, including SSRIs, were used more by those with greater initial severity of NPS as evidenced by NPI-Total. Female gender and younger age also were associated with greater PI for all classes except atypical antipsychotics and benzodiazepines. Polypharmacy of psychotropic medications was common. The strength of the associations may diminish over long periods of time (10 years) as illustrated in Figure 1, but it is important to note that these are models whose validity over long periods of time should be interpreted with caution.

These results support two plausible explanations: Psychotropic medications are prescribed to AD participants who were already at risk of poorer outcomes, and their use is associated with more rapid decline. These data cannot, however, determine whether the more rapid decline is causally related to the medications or whether an underlying feature of the pathobiology of a specific aspect of the disease causes more severe dementia, more NPS, and worse medical health and is, therefore, the cause of the more rapid decline. Psychotropic medication exposure was also associated with younger age, which has been reported to be a risk factor for more rapid cognitive and functional decline in AD (Lopez *et al.*, 2010).

These results do not support a long term benefit from the use of any class of psychotropic drug, but it is possible that decline would have been more rapid had these drugs not been used. A recent randomized controlled trial of antipsychotics for psychosis in AD lessens concern that participants' use of the treatments was a reflection of their need for such medicines (e.g., because of greater severity of illness at enrollment), but it did not demonstrate long-term benefit either (Sultzer *et al.*, 2008). Taken together, these results support current practice of attempting to use non-pharmacologic treatments, first unless the risk of harm or distress is high, and of recommendations that trials off drug are indicated in most cases.

Strengths of this study include its examination of persons with incident AD who were ascertained from a population-based sample. Most prior reports have relied on clinical or convenience samples. Second, the diagnoses of AD were established by an interdisciplinary

geropsychiatric team that had the benefit of multiple forms of information, including longitudinal observations in most instances and neuropathologic confirmation in a sample. Third, the mean duration of follow-up averaged 3.7 years, longer than any clinical trial and most observational studies. Fourth, ascertainment of medication use was by direct observation on home visits rather than self-report or pharmacy records, a method that is likely to maximize reliability of medicine use data.

The primary limitation of the study is its observational design that cannot exclude confounding by indication, that is, that the observed association is a reflection of some other shared attribute such as symptom or illness severity. Conversely, it is also possible that participants with improvement in NPI may have discontinued these medications, biasing the NPI outcomes toward a negative association with medication use. Further limitations include the following: (i) modifications to the wording of specific NPI domains may have served to bias NPI scores upward; (ii) the NPI total is the sum of 10 domains and may not have sufficient range or sensitivity to detect change in one domain from a single drug class; (iii) we lacked information about the duration of psychotropic medication use prior to baseline, which may have influenced the outcomes; (iv) the PI is a calculated variable that summarizes duration of medication exposure, but in summarizing does not incorporate the details of when medications were stopped and started. There are several types of associations that cannot be captured with such a summary variable, such as delayed or transient effects of medication exposure. Additionally, “confound by indication” can include the possibility that medication discontinuation was associated with improvement in symptoms (particularly NPI), which would tend to bias the associations in the directions we observed; and (v) although the associations present a relatively consistent pattern, certain associations (particularly associations of medication use with NPI trajectory) would not be significant after adjustment for multiple comparisons. Finally, the study would inevitably have benefited from a larger sample size, increased duration of follow-up, and use of a more elaborate summary measure of cognition than the MMSE.

We suggest that the most likely explanation of our findings is that psychotropic medications are preferentially prescribed to AD patients whose clinical characteristics are associated with poorer prognosis including neuropsychiatric symptoms and problem behaviors. We base this suggestion on the observation that virtually all classes of psychotropic medications were associated with poorer outcomes, suggesting that this is an effect of prescribing practices rather than specific effects of individual medications. However, given the prevalence of polypharmacy, this study has limited power to distinguish effects of individual medications. Given these caveats, we cannot rule out the possibility that psychotropic medications have a deleterious effect on the clinical course of AD. To some extent this sort of question can be resolved by larger observational data sets with more elaborate data collection routines and longer follow-up intervals. More likely, however, the ultimate answer to these questions is better left to randomized trials.

Acknowledgments

The study was supported by NIA grants R01AG21136, R01AG11380.

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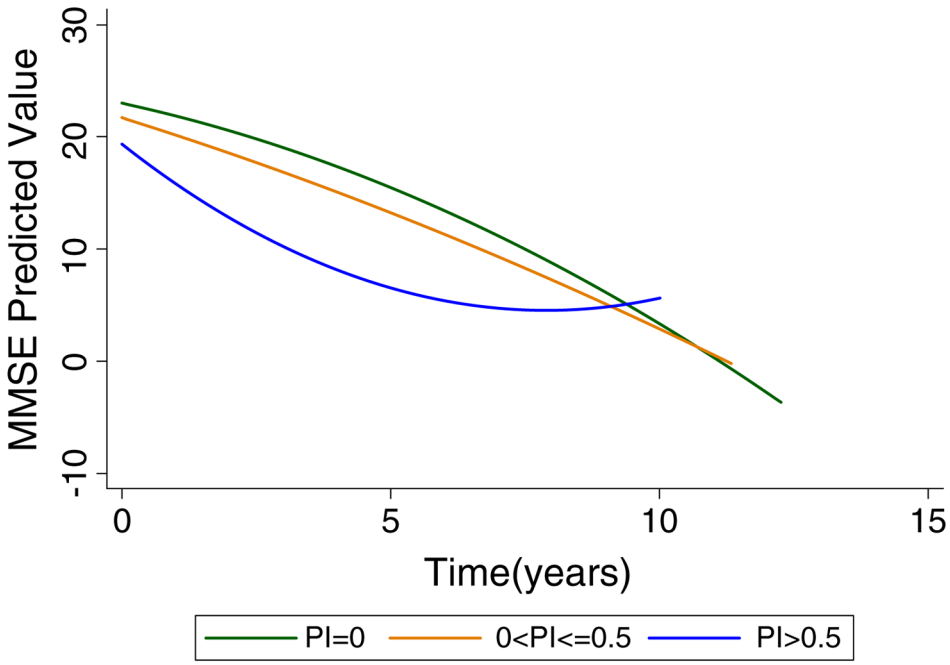

Figure 1.

Mixed effect models of MMSE versus time, stratified by PI. The results of mixed-effect modeling of MMSE versus time stratified by antipsychotic persistency index (PI). These models included two-way interactions between PI and time/time^2 and controlled for baseline age, gender, education, estimated duration of dementia prior to baseline visit, the presence of at least one ApoE4 allele, GMHR baseline use of acetylcholinesterase inhibitors and memantine, and baseline NPI-Q Total. The curves represent bestfit models to observed data and are of different durations due to differing duration of available follow-up data.

Table 1

Baseline clinical and demographic variables

Variable	Baseline only		At least one follow-up		*F*(*p*)*
	N	Mean (SD) or *n*(%)	N	Mean (SD) or *n*(%)	
Demographics					
Baseline DPS age	105	87.8(6.1)	230	85.1(6.2)	13.71(0.000)
Education	105	13.3(3)	230	13.2(3)	0.16(0.688)
Dementia duration, y	105	1.6(1.2)	230	1.7(1.3)	0.24(0.628)
Male	105	29(27.6%)	230	86(37.4%)	0.084**
Any APOe4 allele	104	49(47.1%)	229	102(44.5%)	0.722**
Functional/cognitive measures					
MMSE	93	20.4(5.3)	211	22.6(4.1)	15.22(0.000)
CDR-Sum of boxes	105	6.8(3.9)	229	5.5(3)	11.68(0.001)
NPI total score	100	5.4(11.0)	220	3.6(6.7)	3.02(0.083)
GMHR	101	2.8(0.7)	227	2.8(0.6)	0.23(0.634)
GMHR	101		227		0.656**
Poor+fair		37(36.6%)		73(32.2%)	
Good		52(51.5%)		129(56.8%)	
Excellent		12(11.9%)		25(11%)	
Psychiatric medication use					
Any antidepressant	105	25(23.8%)	230	57(24.8%)	0.892**
SSRI	105	17(16.2%)	230	50(21.7%)	0.303**
Any antipsychotic	105	8(7.6%)	230	10(4.3%)	0.295**
Atypical antipsychotic	105	5(4.8%)	230	6(2.6%)	0.330**
Typical antipsychotic	105	4(3.8%)	230	4(1.7%)	0.264**
Benzodiazepine	105	7(6.7%)	230	17(7.4%)	1.000**
Dementia medication use					
Acetylcholinesterase inhibitors	103	5(4.9%)	222	30(13.5%)	0.020**
Memantine	103	1(1.0%)	222	3(1.4%)	1.000**

Baseline clinical and demographic variables are presented for participants in the DPS. Participants who had only a baseline visit ($N = 105$) are compared with participants who had at least one follow-up visit ($N = 230$).

* ANOVA, df = 1;

** Fisher's exact test.

DPS, dementia progression study; MMSE, mini-mental state exam; CDR-Sum, clinical dementia rating sum of boxes; NPI, neuropsychiatric Inventory; GMHR, general medical health rating; SSRI, selective serotonin reuptake inhibitor; ANOVA, analysis of variance.

Int J Geriatr Psychiatry. Author manuscript; available in PMC 2012 December 01.

Table 2

Persistency index

Medication class	Persistency index [*N*(%)]			
	PI = 0	**0 <PI ≤ 0.5**	**PI >0.5**	**PI >0**
Antidepressants	120(52.2)	41(17.8)	69(30)	110 (47.8)
SSRIs	134(58.3)	37(16.1)	59(25.7)	96 (42.8)
Antipsychotics	163(70.9)	52(22.6)	15(6.5)	67 (29.1)
Atypical antipsychotics	195(84.8)	27(11.7)	8(3.5)	35 (15.2)
Typical antipsychotics	182(79.1)	42(18.3)	6(2.6)	48 (20.9)
Benzodiazepines	172(74.8)	42(18.3)	16(7)	58 (25.3)

PIs are presented for each medication class for the 230 participants who had at least one follow-up visit after baseline in the DPS. The PI was calculated as the ratio of the estimated time participant taking medication to the total duration of follow-up as defined in the Methods. PI was categorized as PI = 0, 0 <PI <≤0.5, and PI >0.5, as well as PI >0 (i.e., any use of medication).

PI, persistency index; SSRIs, selective serotonin reuptake inhibitors; DPS, dementia progression study.

Table 3

Association of medication use with outcomes

Medication class	MMSE					CDR					NPI-Total				
	B	SE	P	95% CI		B	SE	P	95% CI		B	SE	P	95% CI	
Antidepressants															
PI*time	−1.51	0.41	<0.001*	−2.31	−0.71	0.76	0.33	0.020*	0.12	1.41	1.14	0.73	0.117	−0.29	2.56
PI*time^2	0.19	0.05	<0.001*	0.09	0.28	−0.12	0.04	0.002*	−0.20	−0.04	−0.24	0.09	0.010*	−0.42	−0.06
SSRIs															
PI*time	−1.75	0.42	<0.001*	−2.57	−0.93	1.07	0.34	0.001*	0.41	1.73	2.12	0.75	0.005*	0.66	3.59
PI*time^2	0.17	0.05	<0.001*	0.08	0.26	−0.10	0.04	0.014*	−0.18	−0.02	−0.30	0.09	0.001*	−0.49	−0.12
Antipsychotics															
PI*time	−3.54	0.78	<0.001*	−5.07	−2.00	1.09	0.62	0.078	−0.12	2.30	3.71	1.37	0.007*	1.02	6.41
PI*time^2	0.39	0.10	<0.001*	0.20	0.58	−0.20	0.08	0.016*	−0.36	−0.04	−0.57	0.19	0.002*	−0.94	−0.21
Atypical antipsychotics															
PI*time	−5.09	1.06	<0.001*	−7.17	−3.02	1.14	0.82	0.166	−0.47	2.75	3.39	1.80	0.060	−0.14	6.92
PI*time^2	0.45	0.14	0.001*	0.18	0.72	−0.19	0.11	0.101	−0.41	0.04	−0.65	0.25	0.010*	−1.15	−0.16
Typical antipsychotics															
PI*time	−2.87	1.01	0.005*	−4.85	−0.88	1.75	0.82	0.033*	0.14	3.35	4.42	1.88	0.018*	0.74	8.10
PI*time^2	0.45	0.13	0.001*	0.19	0.71	−0.28	0.11	0.012*	−0.50	−0.06	−0.64	0.26	0.013*	−1.15	−0.14
Benzo-diazepines															
PI*time	−2.67	0.73	<0.001*	−4.10	−1.23	1.89	0.59	0.001*	0.74	3.05	1.53	1.36	0.259	−1.13	4.19
PI*time^2	0.30	0.11	0.005*	0.09	0.51	−0.26	0.09	0.004*	−0.43	−0.08	−0.25	0.21	0.222	−0.65	0.15
Co-use of antidepressants and antipsychotics															
PI*time	−2.63	0.87	0.002*	−4.33	−0.93	1.02	0.68	0.136	−0.32	2.35	2.98	1.48	0.045*	0.07	5.88
PI*time^2	0.36	0.10	<0.001*	0.17	0.55	−0.24	0.08	0.004*	−0.40	−0.08	−0.49	0.19	0.012*	−0.86	−0.11

Mixed-effects models were used to model the effects of PI of medication classes on MMSE, CDR-Sum, and NPI total in 230 DPS participants who had at least one follow-up visit after baseline. Medications were classified as: “antidepressants” (i.e., any antidepressant), SSRIs, “antipsychotics” (i.e., any antipsychotic), atypical antipsychotics, typical antipsychotics, benzodiazepines, and “co-use” (i.e., simultaneous use of any antidepressant with any antipsychotic). All models examined the two-way interactions between PI and time/time^2 and controlled for baseline age, gender, education, estimated duration of dementia prior to baseline visit, the presence of at least one ApoE4 allele, GMHR, and baseline use of acetylcholinesterase inhibitors and memantine. MMSE and CDR models additionally controlled for baseline NPI-Q total. p <0.05 was used as the threshold for statistical significance, marked with an asterisk*.

PI, persistency index; MMSE, mini-mental state exam; CDR-Sum, clinical dementia rating sum of boxes; NPI, neuropsychiatric Inventory; SSRIs, selective serotonin reuptake inhibitors; DPS, dementia progression study, NPI-Q,