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Psychotropic medication use and cognition in institutionalized older adults with mild to moderate dementia

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ABSTRACT

Background: Most studies examining psychotropic medication use on cognition in older persons with dementia include measures of global cognitive function. The present study examined the relationship between different types of psychotropic medication and specific cognitive functions in older people with dementia.

Methods: Two hundred and six institutionalized older adults with dementia (180 women, mean age 85 years) were administered neuropsychological tests. Psychotropic medication use was extracted from their medical status and categorized as: sedatives, antidepressants and antipsychotics.

Results: Analysis of covariance revealed that psychotropic consumers, and particularly those who used antipsychotics, performed worse on neuropsychological tests of executive/attentional functioning than non-consumers. There were no differences between consumers of other classes of psychotropic drugs and non-consumers. The number of psychotropic drugs used was inversely related to executive/attentional functioning.

Conclusions: These findings show that in institutionalized older adults with dementia, specific impairment of cognitive function, i.e. executive/attentional impairments, are associated with antipsychotic medication use. Future longitudinal studies are recommended.

Key words: antipsychotic agents, antidepressant agents, hypnotics and sedatives, cognitive performance, cognitive disorders, nursing homes, homes for the aged

Introduction

Psychotropic medications such as sedatives, antipsychotics and antidepressants are commonly prescribed in the nursing home setting. More specifically, studies indicate that between 47% and 59% of the residents are prescribed some type of psychotropic medication (Ruths *et al.*, 2001; Lakey *et al.*, 2006; Snowdon *et al.*, 2006; Tucker and Hosford, 2008). In a study in which almost 70% of the residents were diagnosed with dementia, almost 80% of the total sample was regularly given psychotropic medication (Hosia-Randell and Pitkälä, 2005). In view of this frequent use of psychotropic medication, possible adverse effects are a matter of concern. For instance, in the general population, consumption of psychotropic medication may lead to impairments of memory, attention and executive functioning (Brooks and Hoblyn, 2007). Results of studies examining the relationship between psychotropic medication and cognition in older community-dwelling adults, however, have been mixed. Several studies show worse cognitive performance in psychotropic medications users, e.g. users of benzodiazepines (Wadsworth *et al.*, 2005; Bierman *et al.*, 2007), or improved cognition after cessation of treatment with benzodiazepines (Curran *et al.*, 2003; McAndrews *et al.*, 2003). On the other hand, positive effects of psychotropic use on cognition have been reported as well (Brooks and Hoblyn, 2007).

It has been suggested that presence of an underlying dementia process that does not exhibit apparent cognitive impairment during assessment (i.e. preclinical dementia), often accompanied by depression (Palmer *et al.*, 2007), may play a role in the relationship between psychotropic use and cognition, i.e. memory, in older people (Allard *et al.*, 2003). Older community-dwelling people with dementia who use psychotropic medication show a more rapid global cognitive deterioration, as measured by a dementia scale,

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compared to people with dementia who do not use psychotropic medication (Schäufele *et al.*, 2002). Studies examining the relationship between certain *subtypes* of psychotropic medication (i.e. sedatives, antidepressants and antipsychotics) and cognition in older persons with dementia have found inconsistent results. Some studies show that Alzheimer's disease (AD) patients who were given antipsychotics showed the same rate of cognitive decline as those who were not (Caballero *et al.*, 2006; Livingston *et al.*, 2007). In contrast, other studies with AD patients have revealed positive (De Deyn *et al.*, 2004) and negative effects (Kennedy *et al.*, 2005) on global measures of cognitive functioning after treatment with antipsychotic medication. After adjustment of depressive symptoms, antidepressant use was associated with a reduced cognitive decline (as measured by the Mini-mental State Examination (MMSE; Folstein *et al.*, 1975) in older persons with AD (Mossello *et al.*, 2008). No studies have looked at the relationship between sedatives and cognition in older persons with dementia. Although some studies focus on a specific cognitive function, such as autobiographical memory (Harrison and Therrien, 2007), most studies focus on global cognitive functioning. The present study takes a next step by examining whether certain subtypes of psychotropic medication use are associated with impairment in *specific* cognitive functions, e.g. memory, executive/attentional function, and overall cognition in institutionalized older people with dementia.

Methods

Subjects

A sample of older persons with dementia was recruited from 28 nursing homes and homes for the elderly in the Netherlands. The present study used baseline data from a non-pharmacological intervention study in institutionalized older adults with dementia for which approval was granted by the local Medical Ethical Committee. This intervention study offered a scheduled activity over six weeks and therefore required commitment to the study for a longer period of time. Some 668 older residents (distributed over the 28 homes) were screened for possible inclusion in the intervention study. Inclusion criteria for participation were: (i) >70 years old; (ii) diagnosis of dementia or presence of cognitive impairment reported in the medical chart. Exclusion criteria included: (i) an MMSE (Folstein *et al.*, 1975) score of < 10 or > 24 (the focus was on participants in a mild to moderately advanced stage of dementia since they may still be capable of performing the neuropsychological tests administered in the present study); and (ii) presence of acute psychiatric disorders that may preclude participation in cognitive assessment (e.g. psychosis and delirium, and disturbances of consciousness). A total of 462 residents were excluded from participation in the intervention study: 303 residents did not meet the inclusion criteria; 131 residents refused to participate; and 28 declined because of other reasons (because either the family or carer did not agree, or participants could not perform the neuropsychological test assessment due to reasons of illness, temporal hospitalization, or sudden transfer to another place of residence). Consequently, baseline data were available for 206 residents. For distribution of participants over the 28 nursing homes and homes for the elderly see Table 1.

Table 1. Distribution of participants over the 28 nursing homes and homes for the elderly

NUMBER OF HOMES	PARTICIPANTS (PER HOME)	PSYCHOTROPIC CONSUMERS
1	36	14
1	23	13
1	22	13
1	10	2
1	9	5
4	8	21
3	6	6
4	5	9
2	4	6
8	3	9
2	2	0
28	**206**	**98**

Subtype of dementia, education, and comorbidity

Subtype of dementia was extracted from the medical status by the primary investigator (L.E.) and combined with the data resulting from the neuropsychological assessment. To establish subtype of dementia, DSM-IV criteria were used (American Psychiatric Association, 1994). Level of education was determined on a seven-point scale ranging from 1 (less than elementary school) to 7 (university) (Verhage, 1964). Comorbid conditions were reported from notes in the medical chart and classified into specific categories, including: cardiovascular conditions, skin disorders, tumors, gastrointestinal disease, locomotor disturbances, neuro- and radiculopathy, renal disease, pneumonic disease, and endocrine disorders.

ASSESSMENT OF MOOD

In view of the close relationship between cognitive function and mood (Steffens, 2008), symptoms of depression and anxiety were determined by the Geriatric Depression Scale (GDS; Kok *et al.*, 1993), and the Symptom Checklist (SCL; Arrindell and Ettema, 1986), respectively.

Assessment of specific cognitive functions

To assess various aspects of cognitive functioning, neuropsychological tests were administered by trained research assistants who were blinded to study design. The memory tests comprised "Face and Picture Recognition" from the Rivermead Behavioural Memory Test (RBMT), which is considered a test for measuring everyday memory problems (Wilson *et al.*, 1987), and the "Eight Words Test" (Lindeboom and Jonker, 1989). This word learning test includes three conditions: direct recall, delayed recall, and delayed recognition. This episodic memory test is specifically designed for persons with memory problems (Lindeboom and Jonker, 1989).

The executive/attentional function tests comprised "Digit Span," a subtest of the Wechsler Memory Scale-Revised (WMS-R), frequently administered in the clinical setting (Loewenstein *et al.*, 1995) to measure attention and working memory (Wechsler, 1987), and "Category Fluency," which provides a measure of a participant's ability to retrieve familiar information from semantic memory (Snijders and Verhage, 1983) and is widely used in older persons with cognitive impairment (Beinhoff *et al.*, 2005) .

Classification of psychotropic medication

Use of psychotropic medication was extracted from the medical chart at the same time as the neuropsychological assessment by the primary investigator (L.E.). The medical status provided detailed information on subtypes of drugs, date of prescription, and information of the pharmacist. Psychotropics were classified into three major classes (Brooks and Hoblyn, 2007): (i) anxiolytics/hypnotic/sedatives (including benzodiazepines and non-benzodiazepine sleeping pills); (ii) antidepressants (including tricyclic antidepressants and selective serotonin reuptake inhibitors); and (iii) antipsychotics (including neuroleptics and atypical antipsychotics).

Statistical analysis

Characteristics of the psychotropic medication consumers and non-consumers were compared by means of χ^2 tests, Mann-Whitney U tests, or independent-samples t-tests. For data reduction purposes, the separate variables of the neuropsychological tests were transformed into z-scores and combined to form three cognitive domains, based on a principal components factor analysis. Differences between characteristics of psychotropic consumers and non-consumers were used as covariates. Analyses of covariance (ANCOVA) were conducted on the cognitive domains. Comparisons were made between psychotropic consumers versus non-consumers and between consumers of each psychotropic class separately. In the separate analyses of the specific classes of psychotropic medication, only factors that differed significantly between specific psychotropic consumers and non-consumers were used as covariates. Effect sizes were estimated using partial eta squared (η_p^2), and interpreted as: small ($\eta_p^2 \approx 0.01$), medium ($\eta_p^2 \approx 0.06$), and large ($\eta_p^2 > 0.13$), following Cohen's standard (Cohen, 1992). The relationships between the number of *classes* of psychotropic medications and the cognitive domains were explored by means of Spearman's correlations. Level of significance was set at 0.05.

Results

Participant characteristics

Mean age of all participants was 85.22 years (range 74–99 years). The total group consisted of 180 female and 26 male participants. Mean MMSE score was 17.1 (ranges 10–24). Almost half of the participants were using psychotropic medication (47.6% consumers: n = 98, versus 52.4% non-consumers: n = 108). Details on psychotropic medication use are presented in Table 2. There were no differences between consumers and non-consumers with respect to age, MMSE score, gender, comorbidity and use of cholinesterase-inhibitors (Table 3). Participants revealed diagnoses in their medical status of AD (n = 68), vascular dementia (VaD) (n = 31), a combination of AD and VaD (n = 15), frontotemporal dementia (n = 2), or dementia not otherwise specified (n = 90). The different dementia subtypes were equally distributed between psychotropic consumers and non-consumers (Mann-Whitney U: $z = -0.58$, $p = 0.562$). There was a significant difference in the level of symptoms of depression and anxiety between psychotropic consumers and non-consumers, and psychotropic consumers showed lower levels of education compared to non-consumers (see Table 3).

Cognitive functioning

The separate neuropsychological test variables were combined using factor analysis to form three

Table 2. Number of psychotropic drugs of the entire study sample

	FREQUENCY (%) (N = 206)
Psychotropic medication consumers	98 (47.6)
Anxiolytics/hypnotic/sedatives consumers	61 (29.6)
Antipsychotics consumers	44 (21.4)
Antidepressants consumers	39 (18.9)
Consumers of a single psychotropic drug class	61 (29.6)
Consumers of 2 psychotropic drug classes	28 (13.6)
Consumers of 3 psychotropic drug classes	9 (4.4)

domains: (i) a domain based on tests appealing to executive/attentional functioning (EF/attention domain); (ii) a domain formed by tests appealing to memory (memory domain); and (iii) all the test variables together (overall cognition). The four neuropsychological test variables that formed the EF/attention domain were the digit span forward, digit span backward, category fluency, and eight words test immediate recall (Cronbach's $\alpha = 0.55$). The four neuropsychological variables that formed the Memory domain were RBMT face recognition, RBMT picture recognition, eight words test delayed recall, and the eight words test recognition (Cronbach's $\alpha = 0.67$). All the neuropsychological test variables together formed overall cognition (Cronbach's $\alpha = 0.66$).

Psychotropic medication consumers versus non-consumers

Since level of education and symptoms of depression and anxiety differed significantly between psychotropic medication consumers and non-consumers, all three variables were used as covariates. The ANCOVA revealed that consumers of psychotropic medication showed a significantly worse performance on the EF/attention domain compared to non-consumers ($F(1,197) = 4.79$, $p = 0.030$, $\eta_p^2 = 0.024$). There were no significant differences between the memory domain and overall cognition domain between consumers and non-consumers of psychotropic medication ($F(1,197) = 0.59$, $p = 0.444$, $\eta_p^2 = 0.003$ and $F(1,197) = 0.40$, $p = 0.526$, $\eta_p^2 = 0.002$, respectively). See Table 4 for means and standard deviations of the separate cognitive tests and domains.

Different classes of psychotropic medication

The ANCOVA correcting for age and symptoms of depression, revealed no differences on the three cognitive domains between people taking antidepressants and people who did not take antidepressants

Table 3. Characteristics of the psychotropic medication consumers and non-consumers

	CONSUMERS (N = 98)		NON-CONSUMERS (N = 108)				
	M	SD	M	SD	t	df	p
Age	84.9	5.3	85.5	4.5	−0.84	204	0.40
MMSE score	16.6	4.0	17.5	3.6	−1.61	204	0.11
Education	3.2	1.4	3.8	1.7	−2.83	204	0.005
Symptoms of depression	8.7	5.2	6.0	3.9	4.15	202	< 0.001
Symptoms of anxiety	16.2	5.6	13.9	4.1	3.21	200	0.001
	Frequency (%)				χ^2	df	*p*
Women	87 (89%)		93 (86%)		0.33	1	0.57
Ch-esterase inhibitor use	3 (3%)		5 (5%)		0.34	1	0.56
Cardiovascular disorders	87 (89%)		92 (85%)		0.58	1	0.45
Skin disorders	27 (28%)		21 (19%)		1.89	1	0.17
Tumors	17 (17%)		20 (19%)		0.05	1	0.83
Gastrointestinal disease	37 (38%)		35 (32%)		0.65	1	0.42
Locomotor disturbances	59 (60%)		54 (50%)		2.16	1	0.14
Neuro- and radiculopathy	17 (17%)		22 (20%)		0.31	1	0.58
Renal insufficiency	13 (13%)		16 (15%)		0.10	1	0.75
Pneumonic disease	26 (27%)		22 (20%)		1.09	1	0.30
Endocrine disorders	29 (30%)		26 (24%)		0.80	1	0.37

Ch = choline; MMSE = Mini-mental State Examination.

Table 4. Means and standard deviations of the different neuropsychological test variables and the separate cognitive test variables and the 3 cognitive domains.

TESTS	CONS PT MEDS (N = 98) M (SD)	NON-CONS PT MEDS (N = 108) M (SD)	CONS ANX/HY/SED (N = 61) M (SD)	NON-CONS ANX/ HY/SED (N = 145) M (SD)	CONS ANTIPSY (N = 44) M (SD)	NON-CONS ANTIPSY (N = 162) M (SD)	CONS ANTIDEP (N = 39) M (SD)	NON-CONS ANTIDEP (N = 167) M (SD)
DS forward	4.61 (1.6)	4.92 (1.9)	4.59 (1.7)	4.85 (1.9)	4.59 (1.6)	4.82 (1.9)	4.79 (1.6)	4.77 (1.9)
DS backward	3.46 (1.3)	3.95 (1.6)	3.56 (1.3)	3.79 (1.5)	3.14 (1.4)	3.88 (1.4)	3.62 (1.4)	3.74 (1.5)
Cat fluency	12.15 (5.7)	13.74 (6.5)	12.61 (6.1)	13.14 (6.2)	10.80 (4.7)	13.58 (6.4)	11.79 (4.6)	13.26 (6.5)
Face recog	5.68 (3.2)	5.08 (3.1)	5.67 (3.2)	5.23 (3.2)	5.02 (3.5)	5.45 (3.1)	5.16 (3.1)	5.41 (3.2)
Picture recog	12.29 (6.4)	11.58 (5.7)	12.23 (6.5)	11.78 (5.8)	10.57 (5.9)	12.27 (6.1)	13.00 (5.2)	11.66 (6.2)
8WT imm rec	15.65 (5.4)	17.10 (5.5)	15.92 (5.2)	16.62 (5.6)	13.95 (5.3)	17.08 (5.4)	16.67 (5.4)	16.35 (5.5)
8WT del rec	0.35 (0.9)	0.38 (0.9)	0.38 (0.9)	0.36 (0.9)	0.20 (0.6)	0.41 (1.0)	0.41 (1.1)	0.36 (0.9)
8WT recog	10.91 (2.3)	10.98 (2.2)	10.97 (2.3)	10.94 (2.2)	10.50 (2.2)	11.07 (2.2)	11.26 (1.9)	10.87 (2.3)
Domains§								
EF/attention	−0.13 (0.6)	0.16 (0.6)	−0.09 (0.6)	0.07 (0.7)	−0.33 (0.6)	0.11 (0.6)	−0.05 (0.6)	0.02 (0.7)
Memory	0.04 (0.8)	−0.03 (0.7)	0.04 (0.8)	−0.01 (0.7)	−0.16 (0.7)	0.05 (0.7)	0.08 (0.7)	−0.03 (0.7)
Overall Cog	−0.05 (0.6)	0.06 (0.5)	−0.03 (0.6)	0.02 (0.5)	−0.25 (0.5)	0.07 (0.5)	0.01 (0.6)	−0.00 (0.6)

8WT = Eight words test; antidep = antidepressants; antipsy = antipsychotics; anx/hyp/sed = anxiolytics/hypnotics/sedatives; cat = category; cog = cognition; cons = consumers; del = delayed; DS = digit span; EF = executive function; imm = immediate; M = mean; meds = medications; PT = psychotropic; rec = recall; recog = recognition; SD = standard deviation
§The cognitive domain scores are z-scores.

(EF/attention: $F(1,200) = 0.15$, $p = 0.695$, $\eta_p^2 = 0.001$; memory: $F(1,200) = 0.42$, $p = 0.520$, $\eta_p^2 = 0.002$; overall cognition: $F(1,200) = 0.02$, $p = 0.883$, $\eta_p^2 = 0.000$). The ANCOVA correcting for symptoms of depression and anxiety showed that people taking anxiolytics/hypnotic/sedatives also did not differ from those not taking anxiolytics/hypnotic/sedatives on the three cognitive domains (EF/attention: $F(1,198) = 1.47$, $p = 0.226$, $\eta_p^2 = 0.007$; memory: $F(1,198) = 0.19$, $p = 0.663$, $\eta_p^2 = 0.001$; overall cognition: $F(1,198) = 0.11$, $p = 0.741$, $\eta_p^2 = 0.001$). An ANCOVA correcting for MMSE score, education, symptoms of depression and symptoms of anxiety revealed that compared to people not taking antipsychotics, people who were taking antipsychotics showed worse performance on the EF/attention domain ($F(1,196) = 4.28$, $p = 0.040$, $\eta_p^2 = 0.021$), but not on the memory domain and overall cognition domain ($F(1,196) = 0.09$, $p = 0.767$, $\eta_p^2 = 0.000$, and $F(1,196) = 2.09$, $p = 0.150$, $\eta_p^2 = 0.011$ respectively).

Number of classes of psychotropic medication use

Spearman's correlations between number of *classes* of psychotropic agents and the EF/attention domain were significant and negative (Spearman's $\rho = 0.22$, $p = 0.002$), whereas the correlations between number of classes and either memory or overall cognition were not (Spearman's $\rho = -0.02$, $p = 0.811$, and Spearman's $\rho = -0.13$, $p = 0.065$, respectively).

Discussion

This is the first study to determine the relationship between the use of *different types* of psychotropic use (i.e. antidepressants, anxiolytics/hypnotic/sedatives, and antipsychotics) and cognition in institutionalized older adults with dementia. As in other studies in a nursing home setting, psychotropic medication was used by a large proportion of participants (Ruths *et al.*, 2001; Snowdon *et al.*, 2006; Tucker and Hosford, 2008). Almost half of the current older residents were taking one or more classes of psychotropic medication. Results show that the use of psychotropic medication, particularly antipsychotics, and an increased number of psychotropic agents used was inversely related to executive/attentional functioning. In another study including older people with dementia, antipsychotic medication use was associated with overall cognitive impairment, but that study did not specify particular cognitive domains (Schneider *et al.*, 2006a).

Previous research suggests that older people with worse executive/attentional functioning may be at higher risk for certain adverse events. More specifically, it has been shown that executive function impairments in older people in assisted living facilities require increased levels of care (Burdick *et al.*, 2005). Additionally, executive function impairments in older people with dementia are associated with falls (Sheridan and Hausdorff, 2007). Similarly, a direct relationship between psychotropic medication use and falls was found in older persons living in a nursing home (Cooper *et al.*, 2007). Consequently, the participants of the present study taking antipsychotics are in need of enhanced care, and may be at increased risk for falls. Moreover, antipsychotic use in older persons with dementia is associated with adverse events including increased risk of cerebrovascular events and increased risk of mortality (Valiyeva *et al.*, 2008). Clarifying the other risks of nursing home residents with dementia using antipyschotic medication should be the focus of future research efforts.

The strengths of the present study include specification of different classes of psychotropic medication, the extensive neuropsychological test battery and the nature of the studied population, i.e. institutionalized older adults with dementia who are difficult to include in lengthy neuropsychological assessments (Teng and Manly, 2005). Shortcomings of the present study should be noted as well. The first limitation is that baseline data were used from an intervention study which may have resulted in a reduced generalizibility of the findings. On the other hand, willingness to participate in a non-pharmacological intervention study is not directly related to the present research question. In addition, persons were recruited from several different nursing homes and homes for the elderly that were not part of the same care organization, avoiding the influence of possible treatment tendencies in certain homes. Secondly, the present study did not account for duration of psychotropic treatment. It has been shown in older people that longer treatment duration of a certain subtype of psychotropic medication can have a different effect on cognition; antidepressants can have a positive effect (Allard *et al.*, 2003), but non-benzodiazepines can have a negative effect (Dealberto *et al.*, 1997). The relationship between treatment duration and cognition in older persons with dementia remains unclear. Thirdly, to determine the level of depressive symptoms, the GDS was used which may not have been appropriate in persons with moderately advanced

dementia (Kørner *et al.*, 2006). In future studies it is recommended that an instrument specifically designed for people with dementia be used, e.g. the Cornell Scale for Depression in Dementia (Alexopoulos *et al.*, 1988). Another limitation of the present study is the moderate Cronbach's α of the cognitive domains. Domains were formed to avoid multiple testing and thus potential spurious results. Ideally, Cronbach's α would have been higher; some cognitive tests, however, load on both executive function and memory domains, but were included in the domain that resulted in the highest Cronbach's α. Finally, the cross-sectional design of the present study does not allow inferences about the causation of the findings. More specifically, it is known that a decline in executive function in dementia may lead to symptoms such as impaired judgment, disinhibition, and anxiety (Hannisdottir and Morris, 2007; Tsoi *et al.*, 2008). One may argue that these symptoms may have led to the behavioral disturbances, such as agitation and aggression, for which antipsychotic medication was prescribed (Alexopoulos *et al.*, 2004).

Although effect sizes in the present study are small, there appears to be an association between antipsychotic medication use and impairment in executive/attentional functioning in these older institutionalized adults with dementia. Although several studies have shown that a large proportion of patients with dementia with accompanying psychiatric symptoms are free of symptoms after a cessation of antipsychotic medication (Reekum *et al.*, 2002; Ruths *et al.*, 2008), in view of the possible side effects of antipsychotic treatment (Schneider *et al.*, 2006b; Ballard *et al.*, 2008), and its association with decreased executive function, frequent reconsideration of treatment with antipsychotics is recommended. This recommendation is in line with the current recommendations of international guidelines concerning antipsychotic use in dementia (Alexepoulos *et al.*, 2004; Rabins *et al.*, 2007). Longitudinal studies are needed to further clarify the association between antipsychotic medication use and executive/attentional functioning in institutionalized older people with dementia.

Conflict of interest

None.

Description of authors' roles

L. Eggermont designed the study, coordinated the data collection and wrote the paper; K. de Vries provided expertise on all issues that concerned psychotropic medication; E. Scherder was responsible for critical revision of the manuscript.

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