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Effects of Psychotropic Medication on Cognition, Caregiver Burden, and Neuropsychiatric Symptoms in Alzheimer's Disease over 12 Months: Results from a Prospective Registry of Dementia in Austria (PRODEM)

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Abstract. Behavioral and psychological symptoms of dementia are common in Alzheimer's disease (AD) and associated with a more rapid decline in cognitive function. Psychotropic substances are frequently used in AD, but we lack conclusive evidence of their efficacy in this setting. SSRI and trazodone were reported to have positive effects on cognition. Based on the prospective registry of dementia in Austria (PRODEM), we investigated the effects of psychotropic substances on cognition, behavioral symptoms, and caregiver burden (CB) in patients with AD, followed up prospectively over a 12-month period. We used the Mini-Mental State Examination (MMSE), the Neuropsychiatric Inventory (NPI), and the Zarit caregiver burden interview. The study cohort consisted of 309 patients. Patients taking no psychotropic drugs (NO) or those undergoing consistent monotherapy with a psychotropic drug for 12 months were analyzed further (NO 101 patients, SSRI 22, trazodone 8, atypical neuroleptics or benzodiazepines (ANL/BZD) 18). Additionally, the subgroup of patients who started taking any of the substances during the study period were analyzed further to determine the effects before versus six months after the start of medication. MMSE, NPI, and CB at baseline and during follow-up did not differ between the groups. MMSE and CB declined over 12 months in the overall group (MMSE: 21.2 ± 4 versus 19.7 ± 5, $p = 0.001$ and CB 20.3 ± 12 versus 24.7 ± 14.2, $p = 0.007$), but no statistically significant changes were registered within groups over 12 months. When trazodone was started, only NPI improved significantly after 6 months (33.4 ± 18 versus 18.9 ± 22.7, $p < 0.01$). ANL/BZD or SSRI, when started, did not alter MMSE, NPI, or CB. SSRI had no beneficial effect on cognition. We conclude that trazodone might be helpful in the treatment of behavioral symptoms.

Keywords: Alzheimer's disease, behavioral, caregiver, psychotropic drugs

INTRODUCTION

Behavioral and psychological symptoms are common in patients with Alzheimer's disease (AD), contribute substantially to their morbidity, and may precede cognitive symptoms [1]. Delusions or

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hallucinations, depression, agitation, and aggression have been reported in as many as 70% of patients [2]. A large number of patients fare poorly on cognitive tests, have a more rapid cognitive decline, and pose a greater burden for their caregivers [3]. They also need to be admitted earlier to a nursing home, which signifies a greater expense for the healthcare system [4]. The caregiver burden increases with the patient's cognitive decline [5]. Although the treatment of behavioral symptoms in AD is of high clinical priority, evidence of the effectiveness of psychotropic drugs (antidepressants, antipsychotics, or sedative drugs) in this setting is scarce. In a recent longitudinal observation of 755 patients, selective serotonin reuptake inhibitors (SSRI) were reported to slacken the progression of mild cognitive impairment to AD [6]. Even less is known about the effects of psychotropic drugs on the caregiver's burden [7]. The Depression in Alzheimer's Disease Study-2 (DIADS2) did not show a reduction of caregiver distress among caregivers of patients with AD treated with sertraline for depression [8].

In an observational study comprising 396 patients [9], trazodone (a derivative of phenylpiperazine) had modest effects on behavioral symptoms and caregiver burden, and significant therapeutic effects on the percentage of nightly sleep, but no effects on cognition or functionality [10].

Antipsychotic medication is frequently used to treat behavioral symptoms, but has been associated with higher mortality rates [11, 12] and poorer cognition [13, 14].

Based on these controversial data, we evaluated the effect of psychotropic medication, including antidepressants, antipsychotics, and benzodiazepines (BZD), on cognition, behavioral symptoms, and caregiver burden (CB) in AD over a 12-month follow-up of a naturalistic prospective observational cohort taken from a prospective dementia database (PRODEM).

We hypothesize that patients who take neuroleptic drugs or BZD regularly have low scores on cognitive and behavioral scales, show a more rapid cognitive decline, have more severe behavioral symptoms, and pose a greater burden for their caregivers than patients taking no psychotropic medication or those taking antidepressants (SSRI, trazodone, mirtazapine).

METHODS

The study was approved by the ethics committees of the Medical University of Graz, the Medical University of Innsbruck, the Medical University of Vienna, the Konventhospital Barmherzige Brueder Linz, the Province of Upper Austria, the Province of Lower Austria, and the Province of Carinthia. Written informed consent was obtained from all patients and their caregivers.

Study population

The prospective dementia registry in Austria (PRODEM), started in 2009, is an ongoing longitudinal multicenter cohort study being conducted at 12 memory clinics in Austria. At the time of data analysis, 437 subjects had been included in the investigation. Inclusion criteria were the following: 1) the diagnosis of dementia according to the DSM-IV criteria, 2) not living in a nursing home and not needing 24-h care, 3) the availability of a caregiver willing to provide information on the patient's and his/her own condition.

Exclusion criteria were as follows: patient unable to sign the informed consent form, non-availability of a caregiver who was willing and able to accompany the patient to investigations, the presence of co-morbidities likely to preclude termination of the study (such as end-stage cancer), cognitive decline not due to dementia (such as a developmental mental illness), and severe dementia [Mini-Mental State Examination (MMSE) below 12 at screening].

The study centers were located in six of nine provinces in Austria. The investigators were specialists in neurology and/or psychiatry. Medical history data was collected, and clinical as well as neuropsychological examinations were performed at baseline and every six months over a time period of two years, or until the patient was admitted to a nursing home, withdrew from the study, was lost to follow-up, or died. Baseline evaluation included patient and caregiver demographics, the duration of dementia symptoms, assessment of the patient's living situation and utilization of resources, driving ability, the presence of co-morbidities, records of anti-dementia and concomitant medication, as well as extensive clinical, cognitive, behavioral, and functional assessment, and CB (see below). Clinical, cognitive, behavioral, and functional assessment, CB, and current anti-dementia and concomitant medication were assessed at every follow-up visit.

We used the following scores to assess cognition, behavioral symptoms, and CB: 1) Mini-Mental State Examination (MMSE): The MMSE is a global measure of cognition widely used in AD [16].

A maximum of 30 points can be achieved; 2) Neuropsychiatric Inventory (NPI): The NPI assesses the type and severity of behavioral disorders in dementia. Twelve domains including delusions, agitation/aggression, depression, anxiety, euphoria, apathy, disinhibition, lability, aberrant motor behavior, sleep, appetite, and eating disorders are evaluated; their respective frequency (1–4 points) and severity (1–3 points) are also recorded. The total score for each domain is calculated as the product of frequency and severity; NPI-total is calculated as the sum of frequency*severity of all domains. A maximum of 144 points can be achieved, with higher values indicating more severe behavioral and psychological disturbances; 3) Caregiver burden (CB): CB was assessed using the Zarit Burden Interview. The latter consists of 22 questions and measures the subjective burden experienced by caregivers of patients with AD. Functional and behavioral circumstances are addressed. A maximum of 88 points can be achieved; higher values indicate a more severe burden.

Medication

Current medication was evaluated at baseline and each follow-up investigation by asking the caregiver. Anti-dementia medications were divided into acetylcholinesterase inhibitors and memantine. The present study did not include an analysis of anti-dementia medication.

Psychotropic medication was categorized into antidepressants (subsets: SSRI, tricyclic antidepressants, trazodone, mirtazapine, and noradrenaline reuptake inhibitors), antipsychotics (typical and atypical), and BZD.

Patients

At the time of data analysis, 437 subjects had been included in the PRODEM registry. Patients who were recruited earlier attended three follow-up visits (18 months), whereas those recruited later attended only one or two follow-up visits (at 6 and/or 12 months). The current study cohort consisted of 309 study participants who had been diagnosed with possible or probable AD, and had undergone at least one follow-up visit. One follow-up at 6 months was available for all patients; 218 patients had also attended a follow-up visit at 12 months, and 85 patients had attended another follow-up visit at 18 months.

Of 309 patients, 142 were male. The patients' mean age was 76 ± 9 years and the mean duration of their disease 2.8 ± 2.5 years.

In the first part of the investigation patients were further scrutinized as to whether if they had undergone a follow-up visit at 12 months and had taken no psychotropic medication during a 12-month study period, or whether they had consistently taken one psychotropic substance during the 12-month study period.

One hundred and one patients had taken no psychotropic medication (NO) during the 12-month follow-up period, 22 had taken SSRI, 8 had taken trazodone, and 18 patients had taken either atypical neuroleptics (ANL) or BZD (the latter two were grouped together as the sedative drugs ANL/BZD for further analysis). The flow of patients is shown in Fig. 1.

Since we lacked data about the indication for medication and the duration of intake prior to the patients' entry in the study, we were unable to determine a persistency index [15].

Patients were selected for the second part of the investigation when they 1) started monotherapy with any psychotropic substance during the study period, 2) had attended one visit without any psychotropic medication, and 3) had a follow-up visit after 6 months of monotherapy with any available psychotropic substance. The flow of patients is shown in Fig. 1. During the observation period, 25 patients started to take SSRI, 27 trazodone, and 24 ANL/BZD; these patients were analyzed further.

Anti-dementia drugs used during the study period were the following: rivastigmine in 109 (35%), donepezil in 81 (26%), galantamine in 44 (14%), and memantine in 64 (20%) patients. Thirty-four patients (11%) had taken no anti-dementia medication when they entered the study. Twenty-eight patients (9%) had taken a combination of a cholinesterase inhibitor and memantine. The patients' anti-dementia medication remained unchanged during the observation period.

Table 1 shows the baseline characteristics of patients included versus those excluded from analysis.

Statistical analysis

The Statistical Package of Social Sciences (SPSS) version 20 was used for statistical analysis. Values are expressed as mean ± standard deviation (SD).

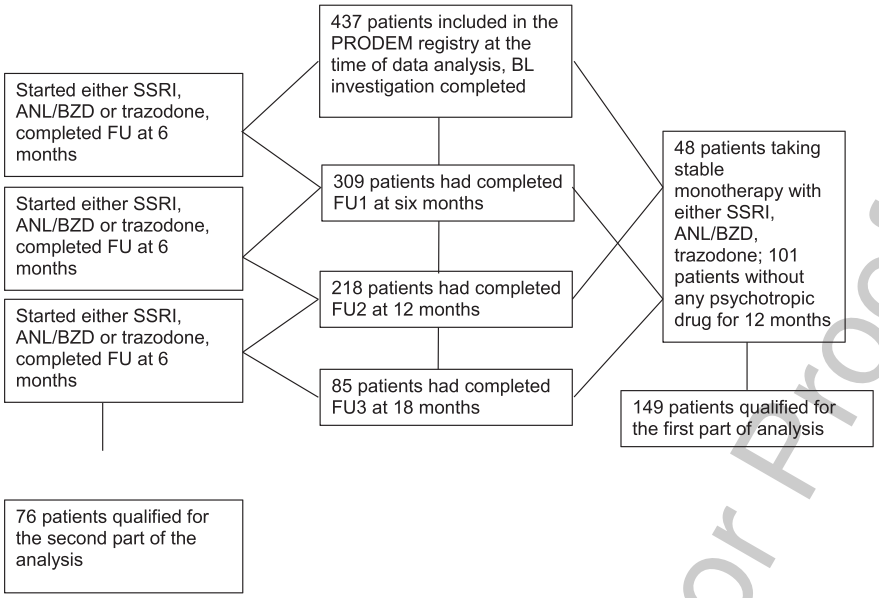

Fig. 1. Flow chart of patients in the study.

Table 1
Patients' baseline characteristics, Mini-Mental State Examination (MMSE), Neuropsychiatric Inventory (NPI), caregiver burden (CB), selective serotonin reuptake inhibitors (SSRI), atypical neuroleptics or benzodiazepines (ANL/BZD), data expressed as mean ± standard deviation

	Age	Sex (% female)	Duration of dementia at inclusion	MMSE	NPI	CB
Patients excluded from further analysis (160)	75 ± 9	56%	2.5 ± 2.1	21 ± 5	15 ± 19	24 ± 15
Patients analyzed further (149)	76 ± 8.8	46%	3 ± 2.2	21 ± 5	13 ± 14.9	22 ± 14.6
No medication	76 ± 8	48%	2.9 ± 2.2	22.2 ± 4	13.1 ± 12.8	18.9 ± 12.1
SSRI	73 ± 10.3	45%	2.6 ± 2	21.5 ± 4.6	11.9 ± 15.2	20.7 ± 12.7
ANL/BZD	77.8 ± 9	37%	2.2 ± 1.3	21.9 ± 3	14.6 ± 21	17.7 ± 14
Trazodone	75.1 ± 8.8	58 %	3 ± 2.1	20.0 ± 5	19.6 ± 32	24.2 ± 20

We used a linear mixed effects model, including each group of medication, time, and interactions between time and each medication group. The following variables were tested: 1) whether there was an overall change over time, 2) whether there were differences between groups over time, and 3) whether there were differences between the rate of change between groups. 95% confidence intervals were calculated. The level of significance was set to $p < 0.05$. Bonferroni correction was done for multiple testing.

RESULTS

Of 149 patients who were analyzed further, 101 had taken no psychotropic medication (NO), 22 had taken SSRI, 8 trazodone, and 18 patients had taken ANL/BZD over the 12-month observation period. Differences in baseline characteristics are shown in Table 1.

No significant difference was noted between groups (NO, SSRI, ANL/BZD, trazodone) at baseline with regards to MMSE, NPI, CB, age, sex distribution, and disease duration (Table 1).

A comparison of baseline data and those registered at 12 months of follow-up revealed that MMSE and CB declined significantly in the entire study population (MMSE: 21.2 ± 4 versus 19.7 ± 5, $p = 0.001$ and CB 20.3 ± 12 versus 24.7 ± 14.2 $p = 0.007$), but none of the individual groups changed significantly over time (Table 2).

In order to determine whether the administration of SSRI, trazodone, or ANL/BZD had beneficial effects on MMSE, NPI, or CB after 6 months, we

Table 2
Mini-Mental State Exam (MMSE), Neuropsychiatric Inventory (NPI), and caregiver burden (CB) at baseline (BL) and after 12 months. data presented as mean ± standard deviation. SSRI, selective serotonin reuptake inhibitors; ANL/BZD, atypical neuroleptics or benzodiazepines

	MMSE		NPI		CB	
	BL	12 months	BL	12 months	BL	12 months
No meds (101)	22.2 ± 4	21.0 ± 4	13.1 ± 12.8	12 ± 14.7	17 ± 12	20 ± 14.6
SSRI (22)	21.5 ± 4.6	20.3 ± 5.3	11.9 ± 15.2	14.5 ± 14	18.9 ± 12.1	22.6 ± 14.6
ANL/BZD (18)	21.9 ± 3	19.2 ± 6.4	14.6 ± 21	12.2 ± 16.6	20.7 ± 12.7	27.8 ± 13.9
Trazodone (8)	20.0 ± 5	19.9 ± 5	19.6 ± 32	12.6 ± 18	17.7 ± 14	22.7 ± 19

extracted a subgroup of patients who started long-term monotherapy with either SSRI, ANL/BZD, or trazodone, and had attended a follow-up visit after 6 months.

Twenty-five patients started to take SSRI, 27 trazodone, and 24 ANL/BZD. MMSE, CB, and NPI did not differ between patients at baseline.

NPI was significantly reduced at six months after the start of trazodone, (33.4 ± 27.7 versus 18.9 ± 22.7, $p = 0.007$), whereas the other parameters remained unchanged (Fig. 2; Table 3).

DISCUSSION

We investigated the effect of the psychotropic drugs SSRIs, trazodone, and ANL/BZDs on cognition, behavioral symptoms, and CB in AD compared to patients taking no psychotropic drugs.

The main findings of the investigation were the following: 1) MMSE and CB declined significantly in the entire study period, but none of the individual medication groups changed significantly over time, 2) NPI was significantly ameliorated at 6 months after the start of trazodone (33.4 ± 27.7 versus 18.9 ± 22.7, $p = 0.007$); the remaining parameters did not change significantly.

The frequency of using any psychotropic drug and ANL was slightly lower in our cohort than that reported earlier in a community-based investigation in Finland. In the latter study, 53% of patients with newly diagnosed AD took any prescribed psychotropic drug and 20% took ANL regularly [17].

The present study did not address indications for antidepressants. Yet, the use of antidepressants in our investigation was similar to that reported in a recent investigation in France, in which 20% of patients with AD used antidepressants regularly [18].

We were unable to confirm any effects of SSRI, trazodone, or ANL/BZD on cognition, as postulated in former investigations [6]. In our cohort, none of the patient groups taking any of those medications on a regular basis showed a significant cognitive decline or amelioration within one year. This might be at least partly due to the small sample size in each group. The overall patient group showed a significant reduction on the MMSE within one year.

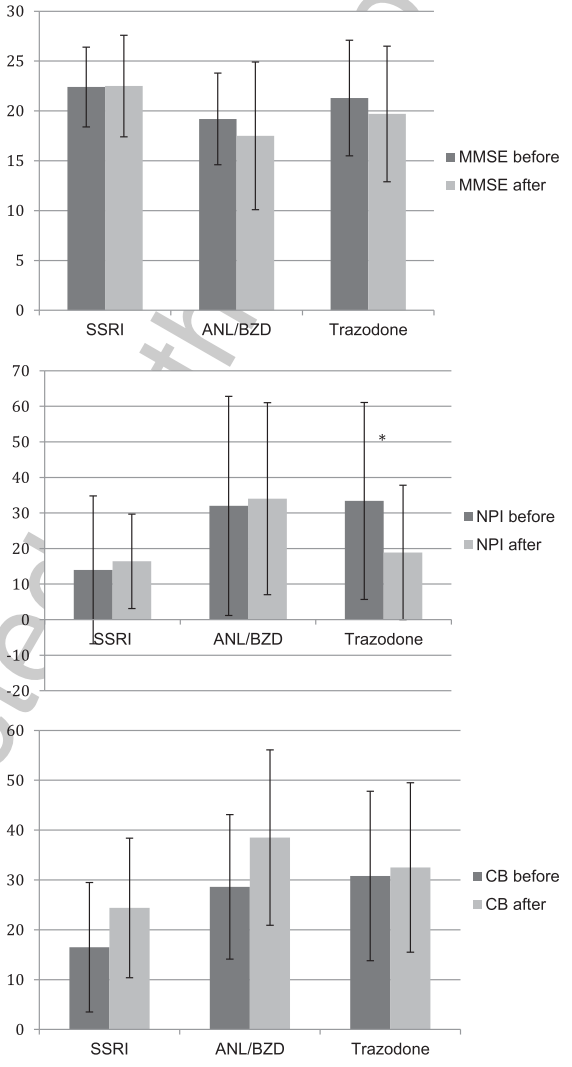

Fig. 2. Change of MMSE, NPI, and CB six months after the start of SSRI, trazodone, or ANL/BZD, $^*p < 0.05$.

Table 3
Mini-Mental State Examination (MMSE), Neuropsychiatric Inventory (NPI), and caregiver burden (CB) before medication and 6 months after the start of either selective serotonin reuptake inhibitors (SSRI), atypical neuroleptics or benzodiazepines (ANL/BZD), or trazodone (number of patients in each group); data expressed as mean ± standard deviation; $^{*}p < 0.01$

	MMSE		NPI		CB	
	Before	After	Before	After	Before	After
SSRI (25)	22.4 ± 4	22.5 ± 5.1	14 ± 20.8	16.4 ± 13.3	16.5 ± 13	24.4 ± 14
ANL/BZD (24)	19.1 ± 4.6	17.5 ± 7.4	32 ± 30.8	34 ± 27	28.6 ± 14.5	38.5 ± 17.6
Trazodone (27)	21.3 ± 5.8	19.7 ± 6.8	33.4 ± 27.7	18.9 ± 22.7*	30.8 ± 17	32.5 ± 17

Behavioral symptoms did not differ significantly at baseline between those taking no medication, and those taking SSRI, ANL/BZD, or trazodone. Behavioral symptoms did not change significantly over 12 months in any group. SSRI might still be beneficial in patients with a history of depression, as the long-term use of SSRI has been reported to delay progression to AD over a 4-year period in patients with a history of depression [19].

When trazodone was newly introduced, we observed a significant improvement of NPI-total within 6 months. This is consistent with the published literature, which confirms the positive effects of trazodone on behavior within 6 months [9]; trazodone is used to an increasing extent in the elderly [20]. Trazodone might be beneficial for patients with behavioral symptoms, although we registered no long-term effects of trazodone on NPI.

The commencement of SSRI or ANL/BZD had no statistically significant effects on NPI within 6 months. MMSE and CB remained unchanged regardless of newly administered medication.

The advantages of trazodone over SSRI in patients with dementia patients might be plausible. Depression in patients with dementia differs clearly from major depression in the brain of younger adults with no neurodegenerative disease; SSRI were developed for the latter. There is evidence of a selective loss of 5HT1A receptors in the hippocampus [21] as well as loss of noradrenergic neurons in the locus coeruleus, and serotoninergic neurons in the raphe nucleus in AD [22, 23]. Depression in mild cognitive impairment was associated with reduced cortical thickness in the entorhinal cortex and accelerated atrophy in the anterior cingulate cortex [24]. Thus, the AD brain might not be able to experience the same effect of SSRIs as that experienced by the non-demented brain, and the non-selective pharmacologic mechanism of trazodone might be advantageous. Former investigations addressing the use of SSRIs for the treatment of depression in AD indicate that the enhancement of moods does not improve cognition [25].

The effect of psychotropic drugs on CB has not been investigated extensively so far. CB increases with cognitive decline [5]. CB worsened over one year in the overall patient group. The small sample size and the heterogenous naturalistic patients in the individual medication groups do not permit a conclusive statement about the effects of these substances in respect of CB.

The limitations of the present investigation are worthy of mention. As it was a naturalistic observational study, some prescription bias could not be excluded. Prescriptions reflect the daily routine at specialized AD outpatient clinics. We had to pool the sedative drugs ANL (olanzapine and risperidone) together with BZD as well as the SSRIs citalopram and escitalopram for statistical analysis (although a previous analysis showed no significant differences within one substance class [26]). We could perform no analysis for mirtazapine. The small sample size limits the statistical power of the data. A large number of patients were taking multiple psychotropic drugs. We selected only those patients who were undergoing monotherapy with either substance. The fact that more than a half of those taking psychotropics had to be excluded limits the applicability of the results. Furthermore, the small sample size restricts the statistical power of the obtained data.

Despite these limitations, the clinical implications of the present investigation are worthy of note. SSRI should be used with caution because its positive effects are limited and controversial. Trazodone might be beneficial when used for the treatment of behavioral symptoms. Notwithstanding these facts, the demented brain poses a challenge for the treating physician because drugs exert different effects on patients with dementia than on younger individuals.

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