Antidementia Drug Treatment in People Screened Positive for Dementia in Primary Care

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Abstract

Background: There is a lack of knowledge about antidementia drug treatment in community dwelling people with dementia in Germany.

Objective: To determine the frequency of treatment with antidementia drugs in patients in primary care, and the socio-demographic and clinical variables associated with antidementia drug treatment.

Methods: Present analyses are based on preliminary data from the DelpHi-trial, an ongoing GP-based, cluster-randomized, controlled intervention trial to implement and evaluate an innovative concept of collaborative dementia care management in Germany. Our sample consists of n = 243 subjects who screened positive for dementia.

Results: 29.6% (n = 72) of participants received antidementia drugs: memantine 44.5% (n = 32); donepezil 30.5% (n = 22); rivastigmine 13.9% (n = 10); galantamine 11.1% (n = 8). A total of 46.4% (n = 45) of the subgroup of participants with a formal dementia diagnosis received antidementia drug treatment. Approximately 37.5% (n = 27) of our sample received treatment with antidementia drugs without having a formal diagnosis. Treatment with antidementia drugs was significantly associated with more severe cognitive impairment and having a formal dementia diagnosis.

Conclusions: One in three people who screened positive for dementia in primary care received antidementia drug treatment, indicating the frequent use of this class of drugs. For those with a formal dementia diagnosis, these drug treatment rates are more than triple, compared to those in nursing homes.

Keywords: DelpHi-MV trial, dementia, donepezil, galantamine, memantine, primary health care, rivastigmine

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INTRODUCTION

The treatment and care of people with dementia (PWD) is a major challenge in aging societies. In accordance with international guidelines [1], the German national guidelines recommend antidementia drug treatment primarily for Alzheimer’s disease (AD) [2, 3]. AD is currently incurable, and primarily the palliative approaches of the pharmacotherapy are discussed in the guidelines. The guidelines recommend acetylcholinesterase inhibitors donepezil, galantamine, and rivastigmine for the treatment of mild to moderate AD, and memantine for the treatment of moderate to severe AD. Oral rivastigmine is recommended for the treatment of dementia in Parkinson’s disease. There is presently no specific recommendation for the treatment
of Lewy body, vascular, and frontotemporal dementia [2, 3]. The individual risk-benefit trade-offs the severity of the disease and the will of patients and their caregivers are to be considered in the treatment decisions [2–4].

Grass-Kapanke et al. showed that 55% of 2,000 community-dwelling subjects with dementia who received ambulatory nursing care received no antidementia drug therapy according to their formal caregivers [5]. Assuming a prevalence of at least 70% AD cases in people with dementia at age 65 and higher, this finding indicates that a large proportion of AD cases does not receive treatment with antidementia drugs. Van den Bussche et al. analyzed the claims data of the ambulatory medical care setting in Germany and found a prescription rate (within one year after the diagnosis) of 19% (acetylcholinesterase inhibitors and memantine) [6]. According to the claims data, only 15% of nursing home residents with formally diagnosed dementia in Germany are treated with antidementia drugs [7]. Studies using primary data reported an even smaller percentage (13%) in Norway [8]. This may indicate a lack of guidelines for the recommended drug treatment of nursing home residents. However, the data vary between countries and data sources. Studies using health insurance claims data reported that 54% of nursing home residents with dementia in France [9] and 40% in the United States [10] received acetylcholinesterase inhibitors or memantine. Primary data on the prevalence of antidementia drug treatment in community dwelling PWD in Germany is lacking. The formal diagnosis is an inclusion criterion for antidementia drug treatment analyses in claims data, and consequently, a considerable proportion of people with dementia are excluded in secondary data analyses because a majority of PWD are not formally diagnosed with dementia [11–14]. Therefore, the main objectives of the present study were to analyze: (1) the frequency and type of antidementia drug treatment in German primary care patients, and (2) the socio-demographic and clinical variables associated with antidementia drug treatment in these subjects.

MATERIALS AND METHODS

Study design

The present analysis is based on data from the DelpHi-MV study (Dementia: life- and person-centered help in Mecklenburg-Western Pomerania). This is an ongoing, general practitioner (GP)-based cluster-randomized controlled intervention trial to implement and evaluate an innovative concept of collaborative dementia care management in Germany that started in January, 2012 [15, 16]. In general practices, patients of 70 years of age or older living at home are screened for dementia. To be eligible for participation in the DelpHi-MV-study, patients need to be screened as positive for dementia (DemTect < 9) and to provide written informed consent.

A caregiver, whose name is provided by the patient, is kindly requested to participate in the study. In the case a patient is unable to give written informed consent, the informed consent form is signed by his or her legal representative (as approved by the Ethical Committee of the Chamber of Physicians of Mecklenburg-Western Pomerania, registry number BB 20/11). All participants participate in a comprehensive standardized baseline assessment delegated to the Dementia Care Manager, specially qualified study nurses [15, 17, 18], at the persons’ homes.

Participants

Of the 4,064 patients (≥ 70 years of age, living at home), screened for dementia in 108 participating GP practices, 629 patients (17%) were eligible for the DelpHi-trial (DemTect < 9), and of these, 406 patients (59%) agreed to participate. The present analyses are based on the data from 243 patients with complete baseline assessments regarding relevant variables on January 1, 2014 (preliminary data). Some 90 participants had not finished the baseline assessment at the time of the analysis, and 58 patients dropped out of the study due to the withdrawal of informed consent (n = 31), death (n = 20), relocation (n = 3), or other reasons (n = 4). There were no significant differences between the patients who were included and those who were dropped regarding the DemTect score, age, and gender (see Supplementary Table 1).

Fifteen patients were excluded because the instruments could not be utilized (patients were either not able to answer the questions due to the severity of dementia or patients refused to answer because of other reasons). Patients included in the analysis showed significantly higher DemTect scores (M = 5.84, SD = 2.02) than patients who were excluded because of missing data (M = 3.73, SD = 2.34; Welch’s t-test: t (15.50) = 3.41, p < 0.01) and used antidementia drugs more often (Fishers exact Test, p < 0.01). No significant differences were observed for the variables age, gender, and formal diagnosis of dementia (see Supplementary Table 2).
Data assessment and analyses

We assessed the variables age, gender, living situation (alone/not alone), cognitive status, medical diagnoses, depression, functional status, and medication. The severity of cognitive impairment was assessed using the Mini-Mental State Examination (MMSE) [19]. The severity of dementia was categorized as: “no cognitive impairment” (score 27–30), “mild” (20–26), “moderate” (10–19), or “severe cognitive impairment” (0–9) [3]. Depression was assessed using the Geriatric Depression Scale and categorized as “no depression” (score 0–5) or “depression” (score 6–15) [20]. Functional status was assessed using the Bayer Activities of Daily Living Scale (B-ADL) [21, 22], which yields a mean score between 1 and 10, where 1 indicates the lowest and 10 indicates the highest possible impairment. In accordance with the International Statistical Classification of Diseases and Related Health Problems (ICD-10, German Modification) [23], the medical diagnoses of dementia were retrieved from the medical records of the treating GP, including the exact date of the initial diagnosis. Dementia diagnoses assigned on the screening day or thereafter were excluded from these analyses. The ICD-10 codes considered were: F00/G30 (dementia due to AD), F01 (vascular dementia), F02 (dementia in other diseases), F03 (unspecified dementia), and G31 (other degenerative diseases of nervous system, not otherwise classified).

A computer-based home medication review [15, 17, 18] encompasses all medications used by the study participants and includes questions about compliance, adverse effects and drug administration. The collection of primary data on medication in the context of the home medication review includes both prescription drugs and over-the-counter drugs. The assignment was then integrated using a master file of the Pharmaceutical Index [24]. The following antidementia drugs were considered: donepezil (N06AD02), rivastigmine (N06AD03), galantamine (N06AD04), and memantine (N06AX01).

The variables describing the sample were summarized using descriptive statistics. We fitted a logistic regression model to determine which variables are associated with the antidementia drug treatment. The regression model includes cognitive status (measured with MMSE) as an explanatory variable and age, gender, living situation, depression, functional status (measured with B-ADL), visit to a specialist (psychiatrists/neurologists) and diagnosis of dementia as covariates to evaluate the association between cognitive status and antidementia drug treatment. To account for the dependency of data from participants that belong to the same cluster (i.e., treating GP), we applied a conditional (fixed effect) logistic regression model, which offers consistent estimates in the case of clustered data. Before running the final regression model, we checked for non-linear relationships using the multivariate fractional polynomial procedure, and no indication of non-linearity was found. A total of 44 observations were excluded from the estimation procedure because of the invariance of the outcome-variables in the respective clusters (i.e., all or none of the patients treated by the same GP take antidementia medication). We found no significant differences between the included and excluded cases regarding the covariates analyzed (see Supplementary Table 3), but the frequency of antidementia drug use differed significantly between these groups. This fact is discussed below.

The final regression analysis was performed with the remaining n = 199 cases belonging to n = 30 clusters (clusters are unbalanced). The standard errors of the regression coefficients were estimated with the Jackknife method, which provides appropriate estimates of standard errors in complex samples. Statistical analyses were performed with STATA® 11 [25].

RESULTS

Socio-demographic and clinical characteristics

The sociodemographic and clinical characteristics of the study population are summarized in Table 1.

Antidementia drug treatment

Of 243 community-dwelling people who screened positive for dementia, a total of n = 72 (29.6%) received antidementia drugs. The most frequently prescribed medications for people receiving antidementia drugs were memantine (n = 32; 44.5%), followed by donepezil (n = 22; 30.5%), rivastigmine (n = 10; 13.9%), and galantamine (n = 10; 13.9%).
13.9%), and galantamine (n = 8; 11.1%) (Fig. 1). No cases of combination therapy with acetylcholinesterase inhibitors and memantine were found. In the group of participants receiving antidementia drug treatment, 62.5% (n = 45) had a formal diagnosis of dementia, leaving 37.5% (n = 27) being treated without a formal diagnosis. In the subgroup of study participants with a formal diagnosis of dementia, 46.4% (n = 31) of the patients with a vascular dementia diagnosis and 47.0% (n = 31) of the patients with an unspecified dementia diagnosis were treated with antidementia drugs (note that 14 patients have more than one dementia diagnosis, retrieved from the medical records of the treating GP, double entries are therefore possible) (Table 1).

Factors associated with the antidementia drug treatment

The results of the multivariate conditional logistic regression analysis (significant model, p = 0.004) are shown in Table 3. The prescription for antidementia drugs was significantly associated with the severity of cognitive impairment (mean MMSE score: 19.2 versus 23.1, OR = 0.84; p = 0.010) and a formal dementia diagnosis (OR = 2.79; p = 0.034). Each additional point in the MMSE score corresponded to an 18% lesser chance of receiving an antidementia drug (OR = 0.84; p = 0.010). Patients who received a formal diagnosis of dementia had approximately a 180% higher chance of receiving

### Table 1

Sociodemographic and clinical characteristics of the study sample

<table>
<thead>
<tr>
<th>Study participants</th>
<th>Total n = 243</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>24 (29.5%)</td>
<td>95 (39%)</td>
</tr>
<tr>
<td>Female</td>
<td>44 (29.7%)</td>
<td>148 (61%)</td>
</tr>
<tr>
<td>Age: mean years</td>
<td>79.0 (SD 5.31)</td>
<td>79.6 (SD 5.44)</td>
</tr>
<tr>
<td>Living situation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>38 (29.2%)</td>
<td>130 (53.5%)</td>
</tr>
<tr>
<td>Not alone</td>
<td>34 (30.1%)</td>
<td>104 (41.6%)</td>
</tr>
<tr>
<td>Cognitive impairment (MMSE): mean score</td>
<td>19.4 (SD 6.20)</td>
<td>23.1 (SD 4.78)</td>
</tr>
<tr>
<td>No cognitive impairment (score, 27–30)</td>
<td>9 (15.5%)</td>
<td>49 (84.5%)</td>
</tr>
<tr>
<td>Mild (score, 20–26)</td>
<td>26 (24.5%)</td>
<td>106 (43.6%)</td>
</tr>
<tr>
<td>Moderate (score, 10–19)</td>
<td>29 (63.3%)</td>
<td>37 (63.6%)</td>
</tr>
<tr>
<td>Severe cognitive impairment (score, 0–9)</td>
<td>8 (61.5%)</td>
<td>5 (38.5%)</td>
</tr>
<tr>
<td>With dementia diagnosis</td>
<td>45 (66.4%)</td>
<td>97 (39.9%)</td>
</tr>
<tr>
<td>Without dementia diagnosis</td>
<td>27 (18.5%)</td>
<td>146 (60.0%)</td>
</tr>
</tbody>
</table>

Standard deviations or percentages are in brackets. MMSE, Mini-Mental State Examination, range 0–30, higher score indicates better cognitive functioning. *at least one diagnosis. *Fisher’s exact test *Welch t-test.

### Table 2

Antidementia drug treatment in study participants with formally diagnosed dementia (n = 97)

<table>
<thead>
<tr>
<th>Antidementia drugs</th>
<th>NMDA-antagonist</th>
<th>Acetylcholinesterase inhibitors</th>
<th>Total (n = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memantine n = 32</td>
<td>Duzepazil n = 22</td>
<td>Rivastigmine n = 10</td>
<td>Galantamine n = 8</td>
</tr>
<tr>
<td>Dementia diagnosis*</td>
<td>16</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>F00-F03: Dementia in Alzheimer’s disease, n = 17</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>F00: Dementia in Alzheimer’s disease, n = 17</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>F02: Dementia in other diseases, n = 1</td>
<td>–</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>F03: Unspecified dementia, n = 66</td>
<td>11</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>G11: Other degenerative diseases of nervous system, not elsewhere classified, n = 4</td>
<td>1</td>
<td>1</td>
<td>–</td>
</tr>
</tbody>
</table>

*at least one diagnosis, double entries possible.
antidementia drug treatment, compared to people with no diagnosis of dementia (OR = 2.79; p = 0.034).

**DISCUSSION**

**Antidementia drug treatment**

Approximately 30% of primary care patients who screened positive for dementia received specific antidementia drug treatment, with the most frequently prescribed antidementia agents being memantine and the acetylcholinesterase inhibitor donepezil. Due to the lack of comparable data (as previously stated, most studies used a formal diagnosis as inclusion criteria), we cannot estimate whether this is a high or low rate. In general, a formal diagnosis is important for adequate treatment and care [14]. However, due to our finding that people without formal diagnosis are treated with antidementia drugs, it is necessary to consider our results on primary care studies on antidementia drug treatment. Our findings support that 43% of people receiving antidementia drug treatment have received specialist treatment (neurologist/psychiatrist), according to their own disclosures. However, our data do not deliver information about the relation between formal diagnosis and drug treatment. The question remains open: were the antidementia drugs prescribed by GPs without a dementia diagnosis? Were the antidementia drugs prescribed by the specialists, but the diagnoses were not registered by the GP in medical records? Not only cases matching with the diagnosis must be considered in the analysis of antidementia drugs, but also the cases without formal diagnosis.

For people with a formal dementia diagnosis in primary care, almost half receive antidementia drug treatment. This finding is comparable to the prevalence of antidementia drug utilization in nursing service-supplied outpatients in Germany (45%) [5]. In comparison to nursing home residents, the rate of antidementia drug treatment was considerably higher (15%) [7]. One explanation could be that there is a high proportion (approximately 60%) of residents with severe dementia in nursing homes [26] where therapy with antidementia drugs has been terminated already. A possible reason for this effect is the multimorbidity of nursing home residents and the associated polypharmacy. The risk of adverse drug interactions or side effects increases with the number of different drugs and may cause non-adherence with the antidementia drug treatment. However, the low rate of antidementia drug treatment likely implies a certain degree of under-treatment of PWD in nursing homes.

The highest frequency of antidementia drug taking was observed in the group of participants with AD diagnosis (65%), which also corresponds to the recommendations of the guidelines. In our analysis this observed frequency is higher than in the comparable analyses with the secondary data. Van den Bussche et al. also found in their analysis of claims data, that the prescription rate for guideline-conform drugs was higher in patients diagnosed with AD (35% within one year after the diagnosis) [6].

In the present analysis, we found that less than half of the patients with the diagnosis of unspecified dementia received antidementia drugs (47%). That finding is interesting, because the use of anti-dementia drugs for unspecified dementia is an off-label treatment, and the difficulty of treatment should be adequately considered. AD is the most common type of dementia and accounts for an estimated 60% to 80% of all cases [27].
We suspect that a majority of the people with dementia who had been diagnosed with unspecified dementia in our analysis could in fact have AD. Although AD is the most recognized form of dementia, the other types have distinct clinical features and are often overlooked [28]. Earlier differential diagnosis provides access to a pathway of evidence-based treatment, care and support across the disease course [12] and should be implemented.

We suppose that in addition to doubts about the effectiveness of antidementia drugs on the part of physicians, the costs of antidementia drugs may be relevant to the prescription of the antidementia drugs [4, 29–31].

Factors associated with antidementia drug treatment

Antidementia drug treatment is significantly associated with more severe cognitive impairment and the presence of a formal diagnosis of dementia. This is in line with the current guidelines. An interesting question, however, is whether different types of diagnosis are associated in multivariate analysis with different prescription rates reflecting the above mentioned descriptive differences. However, in this study, case-numbers for subtypes of dementia were too small to conduct adequate cluster-adjusted inferential statistical analysis.

Our results do not indicate that the visit to a neurologist or psychiatrist is associated with antidementia drug treatment. This finding is only partially consistent with previous studies. Hoffmann et al. found that contact with specialists is strongly associated with acetylcholinesterase inhibitor prescriptions [32] and van den Bussche describes that specialists prescribe antidementia drugs twice often as GPs [6]. We suspect that the insufficient number of cases in our study is the reason why our results are inconsistent with others.

Limitations

The size of the sample was not sufficient to allow for meaningful subgroup analysis regarding patients with the diagnoses F02 (Dementia in other diseases; \(n = 1\)) and G31 (other degenerative diseases of nervous system, not elsewhere classified; \(n = 4\)). In the 44 observations excluded from the logistic regression model, the prevalence of antidementia drug use was lower compared to the observations included in the model (16% versus 33%). These are the patients of those general physicians who generally prescribe the antidementia drugs either for all or for none of their patients with dementia. This could restrict the transferability of the logistic regression results.

Summary

As far as we are aware, our present analysis is the first to analyze primary data of antidementia drug treatment in community dwelling primary care patients in Germany who screened positive for dementia. The effort of primary data collection pays off in terms of the high quality of the data: the rate of antidementia drug treatment in primary care is relevant, and there is considerable number of people treated with antidementia drugs without having a formal diagnosis. In patients with formally diagnosed dementia, antidementia drug treatment was much more frequent compared with PWD in German nursing homes. Complying with treatment guidelines, study participants with a diagnosis of AD showed the highest prevalence of antidementia drug treatment (64.7%). There is more than half (53.6%) formally diagnosed PWD who do not receive any antidementia drug treatment. Antidementia drug treatment should be based on an individual assessment of risks and benefits. GPs should be informed about the benefits and risks of pharmacotherapy for patients with dementia. Likewise, education about options and criteria for antidementia drug treatment should be offered to PWD and their caregivers.

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SUPPLEMENTARY MATERIAL

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