

## Research Article

# The Impact of Antipsychotic Drugs on Long-term Care, Nursing Home Admission, and Death in Dementia Patients

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## Abstract

**Background:** Behavioral and psychological symptoms of dementia are commonly treated with antipsychotic drugs (APDs), which have been associated with adverse health effects. We examine the effect of APDs on long-term care (LTC), nursing home (NH) admission, and death of dementia patients.

**Methods:** We used health claims data of the largest German health insurer from 2004 to 2010 and followed newly-diagnosed dementia patients aged 60 years and older into LTC, NH, and until death. Cox proportional hazards models were estimated to explore whether the risk of these outcomes differed between patients receiving haloperidol, melperone, risperidone, or quetiapine.

**Results:** In a cohort of 6,930 dementia patients who were initially free of LTC dependency, APD users generally faced a twofold increased risk of LTC relative to nonusers. Quetiapine was the exception, showing a comparatively lower risk (HR = 1.64; CI = 1.35–1.98). Among 9,950 dementia patients initially living in private homes, the risk of moving into a NH was generally increased by about 50% among APD users relative to nonusers. Risk of death ( $N = 10,921$ ) was significantly higher for haloperidol-, melperone-, and risperidone- but not for quetiapine users (HR = 0.91; CI = 0.78–1.08). The excess mortality associated with haloperidol and melperone was greater among patients living in private households.

**Conclusions:** In our study, APDs appeared to accelerate adverse health outcomes in German dementia patients. Differentiating between the effect of antipsychotic drug use among dementia patients residing in private households and in NHs, we found that excess mortality for haloperidol and melperone users was higher in private settings.

**Keywords:** Care transitions, Medication, Physical function, Epidemiology, Cohort study

Dementia is one of the most care-intensive diseases of old age. In addition to the cognitive symptoms, there are noncognitive features such as behavioral and psychological symptoms of dementia (BPSD). BPSD comprise apathy, agitation, psychosis, hallucinations and these affect up to 90% of all dementia patients during the course of their disease and is considered to be one of the main predictors of institutionalization (1).

Pharmacological treatment of BPSD is commonly based on antipsychotic drugs (APDs), which are classified either as first-generation antipsychotics (FGAs) or the newer second-generation antipsychotics (SGAs). In the past years, SGAs have increasingly replaced FGAs because of their higher efficacy and fewer extra pyramidal symptoms. However, there are concerns about the safety of both FGAs and SGAs, indicating an elevated risk of death, cerebrovascular

events (2,3), and thromboembolism (4). In addition to these specific events, little is known about the impact of APDs on disability-related outcomes. Thus far, to our knowledge, there have been no studies examining the relationship between APDs and care dependency. Studies exploring activities of daily living have shown a decline of physical functioning among APD users (5,6). Regarding nursing home (NH) admission, Brodaty et al. (7) and Rongve et al. (8) suggested an increased risk of institutionalization for Norwegian (HR = 1.51) and Australian (HR = 4.32) dementia patients taking APDs, while Lopez et al. (9) did not find this association after adjusting for major confounders using U.S. data. APD use and health outcomes may differ by the type of residency but, to our knowledge, there are no studies that have compared APD doses among dementia patients living in private and NHs.

In general, the relation between specific APDs and adverse health outcomes has not yet been evaluated systematically in the German context. Thus, the aim of this study is to examine the effect of frequently prescribed FGAs (haloperidol, melperone) and SGAs (risperidone, quetiapine) in dementia patients on their risk of (i) becoming dependent on long-term care (LTC), (ii) moving into a NH, and (iii) death. In addition, we explore whether APDs have different health outcomes when administered in private households or in NHs.

## Methods

### Data Source

We used routine claims data from the years 2004–2010 collected by the largest German statutory health insurance company, the “Allgemeine Ortskrankenkasse” (AOK). In Germany, about 70 million people are covered by statutory programs, one third of these are members of the AOK. The AOK covers more than 50% of the population at the highest ages (10). We drew an age-stratified random sample of 250,000 persons aged 50 years and above (2% of all AOK-members) in the first quarter of 2004 and followed these individuals through the end of 2010. In addition to many other components, these data also comprise inpatient and outpatient diagnoses by ICD-10, all treatments in the inpatient and outpatient sector relevant for billing, benefits from LTC insurance, type of residency (private household versus NH), and month of death. Information on medical treatments contains drug prescriptions filled in the outpatient sector according to the Anatomical Therapeutic Chemical Classification System (ATC). Data access was legally approved by the Scientific Institute of the AOK (WIdO). This study is based on anonymized administrative claims data that never involved patients directly. Individual patients cannot be identified and the analyses do not affect patients whose anonymized records were used.

### Study Participants

The study population consists of incident dementia patients ages 60 years and above who received their first dementia diagnosis between the first quarter of 2006 and the last quarter of 2010, and who had not been diagnosed with dementia or exposed to APDs in 2004 and 2005. In order to examine the effect of APDs on the risk of any of the three outcomes (LTC, NH, death), three different-sized analysis samples were obtained (see section Outcome Measures and Analyses Samples and Figure 1). The time for assessing the impact of APDs on the outcomes started after the first valid dementia diagnosis.

Dementia was defined according to the ICD-10 codes G30, G31.0, G31.82, G23.1, F00, F01, F02, F03, and F05.1. In order to

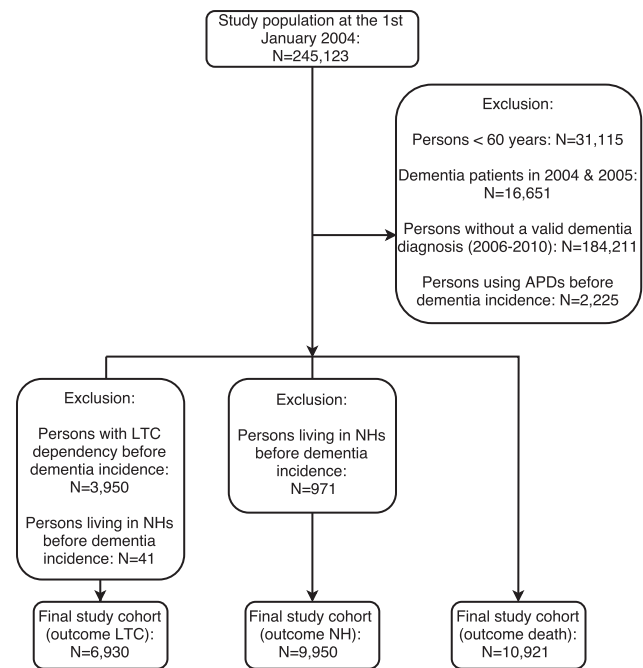


Figure 1. Study flow chart. LTC = Long-term care.

avoid false-positive diagnoses, we considered only those patients with a valid dementia diagnosis based on a two-stage validation procedure. First, we included only those diagnoses internally marked as “verified” in the outpatient sector or as “discharge diagnosis” or “secondary diagnosis” in the inpatient sector. Second, a diagnosis was considered valid if a patient received a confirmative dementia diagnosis in the period 2006–2010.

## Outcome Measures and Analyses Samples

### LTC dependency

LTC dependency was defined as receiving benefits or services from the German statutory LTC insurance. To receive these, individuals must file an application and pass an objective assessment, which is mainly based on impairments in ADLs and does not consider cognitive performance. Thus, LTC dependency mainly reflects physical impairments. Applicants are assigned to one of the three LTC levels if they require care for at least 90 minutes per day, of which at least 46 minutes are reserved for basic activities such as washing, eating, or mobility. LTC comprises day care, home care by nurses or non-professionals, as well as care in a nursing care home. The data indicate whether the patient lives in an institution, but for those patients who live at home there is no information about the care arrangement in terms of nurses or nonprofessionals.

The transition to LTC dependency was defined by the first claim of LTC dependency after an incident dementia diagnosis among patients living in private households. Because benefits or services from German’s statutory LTC insurance were only provided in case of long-term physical limitations, LTC dependency is a permanent state in which a recurrent event is extremely rare. Patients living in NHs at the time of their first dementia diagnosis were excluded and they were censored if they were institutionalized at the time of their first claim. This resulted in an analysis sample of 6,930 dementia patients (10,611 person-years) with 3,842 transitions to LTC dependency (Table 1).

### NH admission

The transition to a NH was defined by the first quarter in which residency changed from a private household to an institution. Once in a NH, dementia patients remain there and did not return to the private setting. All 9,950 incident dementia patients (19,128 person-years) living in a private household at the time of their first dementia diagnosis formed the analysis sample. There were 2,382 transitions into a NH (Table 1).

### Death

The transition to death was defined by the middle of the month of death; all 10,921 incident dementia patients (24,511 person-years), independent of LTC dependency and residency, formed the analysis sample of whom 3,859 died (Table 1).

### Exposure to Antipsychotics

#### Persons exposed to APDs before their first dementia diagnosis were excluded from this study

The time from the incident dementia diagnosis to the first use of APDs was considered unexposed, in order to prevent immortal time bias. A patient was assigned to a specific APD category based on having ever filled a prescription. The assignment starts from the first prescription and continues until the outcome, death, exit from the AOK insurance or the end of the study. The concurrent use of other APDs was defined in a similar way. This strategy resulted in six time-dependent dummy variables (for having ever been prescribed haloperidol, melperone, risperidone, quetiapine, another FGA, another SGA), which take the value of one starting from the first time a respective APD was prescribed and zero otherwise. The category of another FGA includes all APDs (ATC = N05A) except the APDs

mentioned above and other SGA which are amisulpride, zotepine, ziprasidone, aripiprazole, sertindole, olanzapine, and clozapine.

### Covariates

We controlled for sex, age in 5-year age groups (from 60 to 95+), common morbidities in old age (diabetes mellitus, cerebrovascular diseases, hypertension, ischemic heart diseases, atrial fibrillation, hypercholesterolemia, cancer), and use of antedementia drugs (cholinesterase inhibitors or memantine) which were defined as time-dependent dummy variables. We further added a time-dependent dummy variable which takes polypharmacy into account. Patients receiving five or more drugs other than APDs or antedementia drugs during the respective quarter were assigned the value one (11).

### Statistical Method

We used Cox proportional hazards models to examine separately whether (i) LTC dependency in private households, (ii) moving into a NH, or (iii) death were associated with a type of APD use; adjusting for sex, age, major comorbidities, polypharmacy, use of antedementia drugs, and LTC dependency/residency for outcomes (ii) and (iii). Information about the dementia diagnosis and the level of LTC was given by the quarter of the year. We defined the analysis time by the number of months since the incident dementia diagnosis. For people who had experienced a transition to LTC/NH in the same quarter as the dementia diagnosis, the analysis time was set to 0.75 months. For all other cases the transitions took place in the middle of the respective quarter. People were followed until censoring or death, whichever occurred first; deaths were assigned to the middle of the month of death. For subgroup analyses, we implemented interaction terms in our model in order to test whether the mortality of APD users differed

**Table 1.** Selected Characteristics of Analysis Samples (exposures given in person-years)

Variable	Category	LTC dependency		Nursing Home Admission		Death	
		Exposures	Cases	Exposures	Cases	Exposures	Cases
Sex	Men	4,006	1,312	6,628	642	7,911	1,368
	Women	6,605	2,530	12,501	1,740	16,600	2,491
Age	60–64	407	74	568	31	665	24
	65–69	826	131	1,097	68	1,265	94
	70–74	1,744	389	2,491	165	2,888	241
	75–79	2,598	750	4,035	363	4,671	531
	80–84	2,776	1,132	4,953	659	6,202	904
	85–89	1,749	970	4,117	663	5,720	1,124
	90–94	426	311	1,360	302	2,166	607
Haloperidol	95+	86	85	507	131	934	334
	No	10,519	3,700	18,723	2,230	23,720	3,530
Melperone	Yes	93	142	405	152	791	329
	No	10,149	3,267	17,278	1,800	21,182	2,777
Risperidone	Yes	462	575	1,850	582	3,329	1,082
	No	10,239	3,409	17,836	1,976	22,208	3,181
Quetiapine	Yes	373	433	1,292	406	2,303	678
	No	10,502	3,714	18,747	2,263	23,804	3,696
Other FGA	Yes	109	128	381	119	707	163
	No	10,377	3,552	18,244	2,106	22,914	3,385
Other SGA	Yes	235	290	885	276	1,597	474
	No	10,553	3,810	19,001	2,351	24,298	3,817
Total	Yes	58	32	128	31	213	42
		10,611	3,842	19,128	2,382	24,511	3,859

Note: FGA = First-generation antipsychotic; LTC = Long-term care; SGA = Second-generation antipsychotic.

by type of residency. To compare APD dosages between persons in private households and NH residents, we calculated a dose-time index (DTI), defined as the sum of daily defined doses per package during the complete observation period divided by the number of quarters with APD exposure (12). We then compared DTI for specific APDs stratified by age and type of residency using the Kolmogorov–Smirnov test.

We conducted six sensitivity analyses to assess the robustness of our findings. First, we used a 1:1 propensity score matching to conduct an alternative approach of covariate adjustment. Second, to consider death as a competing risk, we performed competing risk models as proposed by Fine and Grey (13) for the outcomes LTC dependency and NH admission. Third, we took the duration of administration of APD use into account by dividing users into short-term (=1 quarter) and long-term users (>1 quarter). Fourth, given that information of dementia incidence and LTC dependency is only available on a quarterly basis, we excluded those patients whose first dementia diagnosis and first claims of LTC fall in the same quarter. Fifth, because APDs were also used in palliative care for cancer patients, we excluded cancer patients in order to rule out this selection bias. Sixth, we omitted patients suffering from Parkinson’s disease, for whom quetiapine is very common, in order to identify a potential indication bias.

**Results**

**LTC Dependency Living in Private Households**

The baseline cohort consisted of 6,930 incident dementia patients (Table 1; Supplementary Table 1 gives a complete overview). The mean age at study entry was 78.8 years (±7.4) and patients were followed for a mean time of 18.4 months (±16.2). Overall, 1,408 (20.3%) patients used at least one APD. Melperone was the most frequently prescribed drug (730 persons; 10.5%), followed by risperidone (556 persons; 8%), haloperidol (177 persons; 2.6%) and quetiapine (169 persons; 2.4%). Of these patients, 372 (5.4%) received at least one other FGA and 52 (0.8%) used at least one other SGA. These prescription frequencies are similar to those of the other outcomes presented below. During the observation period, 3,842 persons (55.4%) became LTC dependent and the mean age for this transition was 81.5 years (±7).

Multivariable analyses showed that dementia patients receiving APDs had about twice the risk of becoming LTC dependent compared to those not receiving the specific drug (Table 2). The only exception was quetiapine, with a significantly lower hazard ratio

(HR = 1.64; CI = 1.35–1.98) of becoming LTC dependent compared to melperone (HR = 2.34; CI = 2.13–2.58). Hazard ratios (HR) of confounding variables for all outcomes are presented in Supplementary Table 8.

**Moving into a NH**

A total of 9,950 incident dementia patients with a mean age of 80.1 years (±7.7) were followed over a mean period of 23.1 months (±16.9). During the observation period, 2,921 patients with dementia (29.4%) received at least one APD and 2,382 persons (23.9%) were admitted to a NH (Table 1). In the multivariable analysis, we did not find much difference in the risk of moving to a NH by single APD type (Table 2). APD users had 1.4–1.7 the risk of moving into a NH compared to nonusers.

**Death**

Of the 10,921 incident dementia patients (median age: 80.4 years; ±7.8 years) who were followed for a median time of 26.9 months (±16.4), a total of 3,677 patients (33.7%) were exposed to at least one APD, and 3,859 (35.3%) died (Table 1).

In the multivariable analyses, we found that haloperidol (HR = 1.56; CI = 1.38–1.75), melperone (HR = 1.43; CI = 1.33–1.54), and risperidone (HR = 1.28; CI = 1.17–1.40) were associated with a significantly higher risk of death compared to quetiapine (HR = 0.91; CI = 0.78–1.08; Table 2).

We found that the excess mortality associated with haloperidol and melperone was significantly higher among dementia patients living in private households (haloperidol: HR = 1.96; CI = 1.67–2.30; melperone: HR = 1.70; CI = 1.53–1.88) than in NHs (haloperidol: HR = 1.24; CI = 1.04–1.48; melperone: HR = 1.19; CI = 1.07–1.33). There were no significant differences for the other APDs. This was true despite the fact that NH residents had an overall increased mortality (Figure 2).

We explored whether differences in APD dosages may explain mortality gaps between persons in private households and in NHs. The mean prescribed dose of haloperidol was lower for persons in private households (DTI = 23.2) than for NH residents (DTI = 27.7), but the Kolmogorov–Smirnov test indicated equal distributions (*p* = .111). Melperone dosages were higher for NH residents (DTI = 11.0) compared to persons in private households (DTI = 9.3) and this was confirmed by the Kolmogorov–Smirnov test (*p* = .001, Supplementary Figure). Thus, differences in dosage cannot explain excess the mortality of APD users in private households.

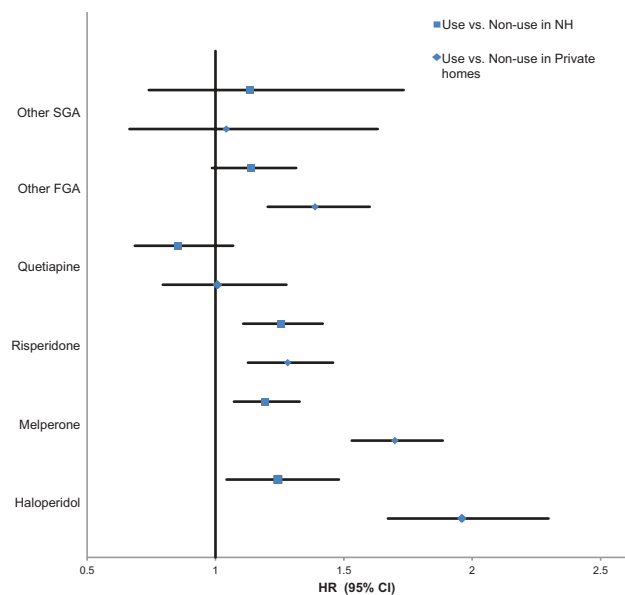
**Table 2.** HR of Becoming LTC Dependent, Moving Into a Nursing Home, and Death by Type of APD (reference group: not receiving the specific drug)

		LTC Dependency <sup>a</sup>			Nursing Home Admission <sup>b</sup>			Death <sup>c</sup>		
		HR	<i>p</i>	95% CI	HR	<i>p</i>	95% CI	HR	<i>p</i>	95% CI
Haloperidol	Yes	2.12	***	1.78 2.52	1.51	***	1.28 1.80	1.56	***	1.38 1.75
Melperone	Yes	2.34	***	2.13 2.58	1.74	***	1.58 1.93	1.43	***	1.33 1.54
Risperidone	Yes	2.08	***	1.87 2.32	1.56	***	1.38 1.75	1.28	***	1.17 1.40
Quetiapine	Yes	1.64	***	1.35 1.98	1.39	***	1.15 1.69	0.91		0.78 1.08
Other FGA	Yes	2.13	***	1.87 2.42	1.49	***	1.31 1.71	1.26	***	1.14 1.39
Other SGA	Yes	0.78		0.54 1.13	1.40		0.97 2.02	1.09		0.80 1.49

Note: APD = Antipsychotic drug; CI = Confidence interval; FGA = First-generation antipsychotic; HR = Hazard ratio; LTC = Long-term care; SGA = Second-generation antipsychotic.

<sup>a</sup>Controlled for sex, age, comorbidities, polypharmacy, antedementia drug use; <sup>b</sup>+ LTC dependency; <sup>c</sup>+ residency.

\**p* < .05; \*\**p* < .01; \*\*\**p* < .001. There are no *p*-values corresponding to \* or \*\*.



**Figure 2.** HR of death and 95% CI for single APDs by residency. CI = Confidence interval; FGA = First-generation antipsychotic; HR = Hazard ratio; NH = Nursing home; SGA = Second-generation antipsychotic.

### Sensitivity Analysis

Cox models based on propensity score matching produced results similar to the primary analysis. However, the effect sizes were somewhat smaller (Supplementary Table 2). Competing risk models revealed no remarkable changes in the risk of LTC dependency and NH admission after accounting for death (Supplementary Table 3). Mortality remained increased for haloperidol and melperone users regardless of their duration of administration, whereas the adverse effect of risperidone appeared only for long-term users. However, the duration of administration did not influence the effect of quetiapine (Supplementary Table 4). The results remained consistent when repeating the primary analysis without patients whose first dementia diagnosis and first claims of LTC fell in the same quarter (Supplementary Table 5). Furthermore, excess mortality for haloperidol and melperone users in NHs was still significantly higher than for those in private homes after excluding cancer patients (Supplementary Table 6). Finally, analyses without persons suffering from Parkinson's disease yielded comparable results (Supplementary Table 7).

### Discussion

Using health claims data from the largest German health insurer, we found that APDs, regardless of whether they are first or second generation, are associated with a higher need for care and an increased risk of death among dementia patients. APD users generally deteriorated more rapidly in physical health and died earlier. The only German studies to have investigated the impact of APDs on health outcomes among dementia patients focused on venous thromboembolism (4) and death (14), whereas the latter study compared single APDs with risperidone. Our study extends these results by using dependency on LTC and NH admission as outcomes which may be considered as measures of different degrees of physical limitations. We further conducted subgroup analyses for persons living in private households or NHs and found less excess mortality for APD users residing in NHs compared to those in private households.

Our results indicating adverse health effects for APD users in general are in line with previous studies. Helvik et al. (5) and Dutcher et al. (6) showed a decline of physical functioning for APD users but did not differentiate among specific APDs. In our study, the relation observed between APDs and LTC dependency may also be explained by indication bias, because the occurrence of BPSD makes physical limitations and LTC dependency more likely. However, we also found differences according to specific APDs, primarily for quetiapine, which was associated with a somewhat lower risk of becoming dependent on long-term care than melperone.

As we have shown, Brodaty et al. and Rongve et al. also found an increased risk of NH admission for APD users (7,8). However, Lopez et al. (9) divided APDs into FGAs and SGAs and did not find any association between using APDs and the risk of moving into a NH. Unlike our approach, they were able to adjust for psychiatric symptoms. Excess mortality for APD users has been well documented in several studies (2,15–18). However, our findings may instead be caused by the occurrence of BPSD and the advanced stage of dementia than the APDs themselves. Additionally, our results suggest that quetiapine is not associated with a significantly increased mortality risk, and this supports the findings of Kales et al. (19), Rossom et al. (20), and Schneider et al. (21) but the mechanisms behind this mortality advantage remain unclear. In our sensitivity analyses, we show that the duration of administration does not explain quetiapine's effect on mortality (Supplementary Table 4). Quetiapine was also not associated with an increased hazard of death after patients with Parkinson's disease were excluded, which is why an indication bias for this relation is not likely (Supplementary Table 7). Further, dose–response analyses of Huybrechts et al. and Gerhardt et al. stated that the mortality advantage of quetiapine cannot be explained by administered doses (22,23). The advantage might be a result of another selection process. Quetiapine has more sedative than antipsychotic mechanisms of action and is frequently used “off-label” for insomnia (24). Thus, patients with early-stage dementia, less severe BPSD and consequently a lower mortality risk might be treated primarily with quetiapine.

Differentiating between the effect of APD use among dementia patients residing in private households and in NHs, we found that the negative effect of haloperidol and melperone on mortality was significantly lower among patients in NHs and comparable to that of risperidone users, which is the only APD approved for BPSD in dementia patients (1). Mortality differences of APD users in favor of NH residents have also been reported by Rochon et al. (25), who showed less pronounced excess mortality rates for Canadian NH residents receiving FGAs and SGAs, while our analysis indicates the only mortality differences by residency are in connection with the FGAs haloperidol and melperone. However, Wang et al. (16) and Schneeweis et al. (18) did not find this relation.

Our results suggest that treatment with haloperidol and melperone in a NH setting is safer than in a private setting. One possible explanation is that the adverse effects of these APDs (eg, heart attack, stroke, thrombosis, falls, pneumonia) result in death less frequently for persons in NHs because these patients are monitored more closely. It may also be a result of a selection bias based on different prescription patterns. Patients in a private setting need to be sicker before they are prescribed with APDs, whereas patients in a NH would receive APDs sooner, after presenting with less severe symptoms. However, this bias is not probable because, in contrast to the outcome death, we found no higher risk of care dependency for patients in private settings compared with NH residents. Finally, reasons for entering a NH may also play a role. Persons in NHs are

generally faced with an increased risk of death and the additional negative impact of APDs may be outweighed. We adjusted for a number of diseases and for LTC but this selection bias cannot be ruled out.

The strength of our study is the assessment of a large cohort of dementia patients from the largest German health insurer for a period of 7 years. The data contain information about both the private and institutionalized population, which is important due to the high prevalence of APDs among NH residents (26). Finally, because the routine documentation of diagnoses is provided by physicians, the potential problems of self-selection, nonresponse, or interviewer bias can be ruled out.

One limitation of our study is that data on medications reflect drug prescriptions that were filled, but we cannot be certain about actual intake. The restriction to incident dementia patients leads to relatively low sample sizes, in particular for haloperidol and quetiapine users, which may bias the respective results. Furthermore, time of dementia incidence (start of observation time), exposure to APDs, LTC dependency, and NH admission were only available on a quarterly basis, which might result in time related biases. Confounding by indication is also possible as dementia patients with BPSD are at a higher risk of physical limitations and death due to these disorders and the advanced stage of dementia. Methods to address indication bias can hardly be conducted using health claims data, because the respective ICD-10 codes were not used in the medical practice and the severity of dementia is also not available.

## Conclusion

There are numerous studies reporting that APDs increase the subsequent risk of serious events among dementia patients. Our study confirms these findings in the German context by showing that incident APD intake predicts (i) LTC dependency, (ii) NH admission, and (iii) death. However, it should be noted that it is not clear whether the increased risk can be reduced to the APDs or the indication of these drugs. Furthermore, excess mortality with the frequently used first-generation APDs haloperidol and melperone was less pronounced for NH residents than for the dementia patients residing in private households. Based on previous studies, the present work and the suggestions from the Beers Criteria Medication List (27) and its German adaption (PRISCUS-Liste) (28), the harmful impact of APDs should be also considered in the light of physical limitations when these drugs were administered to dementia patients.

## Supplementary Material

Supplementary data is available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

## Acknowledgments

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## Conflict of Interest

M.N., K.J., S.G-P., M.E., and B.H. have no conflict of interest to report. G.D. received honoraria for presentations at meetings of Novartis and Eli Lilly.

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