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RESEARCH ARTICLE

Impact of low-value medications on quality of life, hospitalization and costs – A longitudinal analysis of patients living with dementia

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Abstract

Introduction: This study aimed to analyze the impact of low-value medications (Lvm), that is, medications unlikely to benefit patients but to cause harm, on patient-centered outcomes over 24 months.

Methods: This longitudinal analysis was based on baseline, 12 and 24 months follow-up data of 352 patients with dementia. The impact of Lvm on health-related quality of life (HRQoL), hospitalizations, and health care costs were assessed using multiple panel-specific regression models.

Results: Over 24 months, 182 patients (52%) received Lvm at least once and 56 (16%) continuously. Lvm significantly increased the risk of hospitalization by 49% (odds ratio, confidence interval [CI] 95% 1.06–2.09; $p = 0.022$), increased health care costs by €6810 (CI 95% −707€–14,27€; $p = 0.076$), and reduced patients' HRQoL ($b = -1.55$; CI 95% −2.76 to −0.35; $p = 0.011$).

Discussion: More than every second patient received Lvm, negatively impacting patient-reported HRQoL, hospitalizations, and costs. Innovative approaches are needed to encourage prescribers to avoid and replace Lvm in dementia care.

KEYWORDS
Alzheimer's disease, dementia, health care costs, health care resources, health-related quality of life, hospitalization, low-value care

Highlights

- Over 24 months, more than every second patient received low-value medications (Lvm).
- Lvm negatively impact physical, psychological, and financial outcomes.
- Appropriate measures are needed to change prescription behaviors.

RESEARCH IN CONTEXT

1. **Systematic Review**: The authors reviewed the literature using PubMed. Although low-value medications (Lvm) in dementia care, that is, medications unlikely to benefit patients but to cause harm, are associated with negative physical, psychological, and financial outcomes, longitudinal effects on patient-relevant outcomes have rarely been reported.
2. **Interpretation**: This longitudinal analysis revealed a negative impact of Lvm on patient-reported health-related quality of life, hospitalizations, and direct health care costs.
3. **Future Directions**: Appropriate and effective approaches are required to encourage prescribers to avoid Lvm in dementia care wherever possible. Furthermore, adequate alternative treatments are needed as early as possible in the patient journey through the health care system to avoid downstream effects for patients and resource-burdening for health systems.

1 | BACKGROUND

Overtreatment and low-value care, such as potentially inappropriate medications or unnecessary tests and procedures, are unlikely to benefit patients, cause harm, waste scarce health care resources, and increase costs.[1–3] While approaches such as inappropriate drug use, medication interactions or polypharmacy reflect especially the medical perspective on patient safety, low-value care covers a broader perspective that includes ineffective, inefficient or unwanted treatment and care.[4] Low-value care represents approximately US$101.2 billion annually, contributing to 25% of wasteful health care expenditures in the US.[3,5] Despite the ever-expanding evidence underscored by an increased number of guidelines and recommendations against medical overuse through initiatives such as Choosing Wisely or listing of potentially inappropriate medications, the percentage of patients receiving low-value care and spending has not declined significantly in recent years.[6]

Therefore, Korenstein et al.[7] pleaded for comprehensive reporting of the negative effects of medical overuse, including physical, psychological, financial and social effects and consideration of treatment burden. Claims data have been a major source of evidence on trends in the prevalence of low-value tests and procedures.[8] However, claims data cannot provide information about certain relevant patient-centered outcomes. Consequently, the prescription and utilization of low-value medications (Lvm), that is, medications for which the risk of harm exceeds the potential benefit and their downstream effects on patient-reported outcomes, such as health-related quality of life (HRQoL) and hospitalizations, have been underrepresented in recent research.[9–11]

Low-value care is highly prevalent in chronic age-associated diseases, such as dementia. Most patients living with dementia (PwD) have several coexisting diseases (multimorbidities) and receive several medications (polypharmacy).[12–14] Drug-related problems have been found in 93% of PwD associated with increased health care costs.[15–17] According to a recent forecast, the number of PwD will increase from 57 million to 153 million globally in less than 30 years.[18] The costs of dementia were estimated to exceed US$1 trillion worldwide in 2018 and could double by the end of this decade.[19] An approach to reducing Lvm promises to free resources to improve individualized health care for PwD while saving costs.

Previous cross-sectional studies have already revealed that receiving Lvm in dementia was associated with lower HRQoL and an increased risk for hospitalization and greater health care expenditures.[15,16,20,21] However, the longitudinal effects of Lvm on patient-relevant outcomes have been rarely reported. Therefore, the objective of the present analysis was to examine the effects of receiving Lvm on HRQoL, hospitalization and health care expenditures for PwD over 24 months.

2 | METHODS

2.1 | Data and study sample

This longitudinal analysis was based on data from the DelpHi-MV trial (Dementia: life- and person-centered Help in Mecklenburg-Western Pomerania).[22] Initially, 6838 patients were screened by 125 general practitioners (GP) for dementia using the DemTect procedure.[23] A total of 1166 patients (17%) met the eligibility criteria (DemTect < 9, ≥70 years old, living at home) and were subsequently informed about the study. Of these patients, 634 (54%) provided informed consent (approved by the Ethical Committee of the Chamber of Physicians of Mecklenburg-Western Pomerania – registry number: BB 20/11).

Comprehensive data assessments at baseline and after 12 and 24 months were completed by 352 PwD. The detailed participant flow is displayed in Figure S1. Patients who dropped out of the study had a significantly higher functional impairment (odds ratio [OR] 1.10; 95% confidence interval [CI], 1.01–1.19). The drop-out analysis is shown in Table S1. Additional analyses examining the drop-out reason by death revealed no significant differences in the distribution of mortality between those with and without Lvm and no effect of Lvm on drop-out by death (see Tables S2, S3, and Figure S2).The enrollment and data collection at baseline began on January 1, 2012, and ended on December 31, 2014. The detailed design has been described elsewhere.[24]

2.2 | Sociodemographic and clinical characteristics

Sociodemographic data (age, sex, living situation) and the following clinical variables were assessed through a comprehensive,

standardized, computer-assisted interview conducted by dementia-specific qualified nurses at baseline and 12 and 24 months after baseline in the participants' homes; cognitive impairment according to the Mini-Mental State Examination (MMSE)[25]; deficits in daily living activities according to the Bayer Activities of Daily Living Scale (B-ADL)[26]; depression symptoms according to the Geriatric Depression Scale (GDS)[27]; and comorbidities according to the number of ICD-10 (International Statistical Classification of Diseases and Related Health Problems, 10th revision) diagnoses listed in the GP files, complemented by the Charlson Comorbidity Index (CCI).[28,29]

2.3 | Lvm measurement

Medication data were captured within a standardized home medication review to assess all regularly taken drugs, including over-the-counter and prescribed medications, providing a more comprehensive picture of patients' Lvm use beyond documented prescriptions from physicians.[22,30,31] The medications recorded were validated with medication lists provided by the treating GP or, if available, by the administering nursing service. The following three sources were used as references for elaborating Lvm in dementia: (1) the German "S3 guideline: Dementia" published by the German Association for Psychiatry, Psychotherapy and Psychosomatics and the German Society for Neurology,[32] which lists selected medications that are ineffective and should be avoided, (2) the PRISCUS list,[33] including a total of 83 substances of 18 drug classes that are potentially inappropriate for elderly individuals; and (3) recommendations for avoiding harmful treatments of the German counterpart of the international "Choosing Wisely" campaign.[34] Three reviewers selected the Lvm-related recommendations according to the following criteria: (1) relevance; (2) targeted audience; (3) differentiation criteria for inappropriateness; and (4) evaluability in the dataset used for the present analysis. Thirty-nine active substances were identified and assigned to 10 measurable Lvm treatments. The selection process has been described in more detail elsewhere.[15,16]

Lvm variables were categorized as follows: (1) dichotomously (receiving Lvm vs. not receiving Lvm within 24 months); and (2) as a time referencing variable, considering the intensity of Lvm intake as a cumulative effect: (i) receiving Lvm at only one out of the three data assessments ("sporadic"); (ii) over 1 year – from baseline to 12-month follow-up or from 12 to 24 months of follow-up; or (iii) continuously over 2 years – from baseline to 24 months of follow-up. Table 1 demonstrates all Lvm used within this analysis.

2.4 | Patient-relevant outcomes

HRQoL was assessed using the 12-Item Short-Form Health Survey (SF-12), a short form of the SF-36,[35] measuring both physical dimensions (SF-12-PCS), including the perception of general health; physical functioning, bodily pain, and role limitations due to the physical health state; and mental dimensions (SF-12-MSC), comprising social functioning, mental health, vitality, and role limitations due to the emotional state.

Health care resource utilization was assessed using caregivers' and care professionals' proxy ratings to improve data validity and precision, providing detailed information about the frequency (number of visits, days stayed or quantities) of medical service utilization: physician consultations (GP, specialists), medication, aids, therapies (e.g., occupational, physical and speech therapy), and in-hospital care (acute and planned hospital admissions).[22] Additionally, hospitalizations were assessed dichotomously (at least one vs. none). Health care costs were calculated from the payers' perspective using standardized unit costs (inflated to 2022 and calculated in euros [€]).[36] Deltas were calculated (cost difference between baseline and 1 or 2 year(s) after baseline) to assess the change in total health care costs. Table S4 summarizes detailed information about the monetary valuation of the services.

2.5 | Statistical analysis

Data analyses included patients with complete baseline data. Missing follow-up values were imputed using multiple imputations by chained equations separately by randomization treatment allocation (intervention and control group).

Multivariable panel data regression models with specifications corresponding to the scale level of the respective outcome variable were fitted to assess the effects of Lvm on patients' HRQoL (linear regression), hospitalizations (logistic regression), and costs (linear regression). Lvm (independent variable) were operationalized as described above dichotomously (receiving Lvm vs. not receiving Lvm within 24 months) and as a time referencing variable (never, once and over periods of 1 or 2 years). The dependent variables were HRQoL (SF-12-MCS, SF-12-PCS), hospitalization (dichotomous: yes/no), and the delta of direct health care costs and the following cost categories: costs for physician treatments (GP and specialists), hospitalization, medications, medical aids, and therapies (e.g., occupational, physical, and speech therapy). All models were adjusted for sociodemographic (age, sex, living situation) and clinical factors (functional impairment (B-ADL), dementia diagnosis (ICD-10: F00, F01, F02, F03, G30), depression (GDS),coexisting morbidities (yes/no) according to the CCI, multimorbidity (number of ICD-10 diagnoses), and polypharmacy (i.e., ≥ 5 medications, yes/no) as well as the number of potential drug interactions according to the Risk-Check tool CAVE of the ABDA-Database) to consider the context in which Lvm were prescribed and to minimize confounding. Baseline outcome values were also included as a covariate to reduce residual variance and to account for interindividual variance. A lagged Lvm variable was added for models including the cumulative effect, considering whether Lvm had also been present in the previous period. Random effects were used to adjust for individuals regarding the panel-specific structure for HRQoL and hospitalizations and for GP practices concerning the delta of health care costs. Due to the highly skewed distribution of cost data, standard errors and confidence intervals were determined using nonparametric bootstrapping (2000 replications).[37]

TABLE 1 10 Low-value medication treatments: Active substances included, data requirements, and counts.

Lvm by active substance class[a]	Active substance (further condition)	Data requierements[b]	PwD receiving LVM		
			At baseline $n = 126$, n (%)	After 12 months $n = 120$, n (%)	After 24 months $n = 102$, n (%)
Low-value antiphlogistics/ analgesics	Dexketoprofen	ATC (M01AE17)	43 (34.1)	41 (34.2)	32 (31.4)
	Etoricoxib	ATC (M01AH05)			
	Indometacin	ATC (M02AA23, M01AB01)			
	Meloxicam	ATC (M01AC06)			
	Naproxen	ATC (M01AE02)			
	Diclofenac	ATC (M01AB05, M02AA15)			
Low-value antidementia drug treatments	Memantine (does not complies with the guidelines for mild dementia)	ATC (N06DX01) MMSE (≥20)	32 (25.3)	37 (30.8)	6 (5.9)
	Naftidrofuryl	ATC (C04AX21)			
	Piracetam	ATC (N06BX03)			
	Dihydroergotoxine	ATC (N06DX07)			
Low-value sedatives/ hypnotics	Chloral hydrate	ATC (N05CC01)	22 (17.5)	22 (18.3)	18 (17.6)
	Chlordiazepoxide	ATC (N05BA02)			
	Clobazam	ATC (N05BA09)			
	Diazepam	ATC (N05BA01)			
	Zopiclon	ATC (N05CF01)			
	Diphenhydramine	ATC (N05CM20)			
	Doxylamine	ATC (N05CM21)			
	Medazepam	ATC (N05BA03)			
	Nitrazepam	ATC (N05CD02)			
	Zolpidem	ATC (N05CF02)			
Low-value antidepressants	Amitriptyline	ATC (N06AA09)	17 (13.5)	13 (10.8)	10 (9.8)
	Amitriptylinoxide	ATC (N06AA25)			
	Doxepin	ATC (N06AA12)			
	Trimipramine	ATC (N06AA06)			
Low-value antipsychotics	Levomepromazine	ATC (N05AA02)	13 (10.3)	16 (13.3)	19 (18.6)
	Olanzapine	ATC (N05AH03)			
	Haloperidol	ATC (N05AD01)			
	Quetiapin (does not complies with the guidelines for agitation and aggression)	ATC (N05AH04) NPI[c] (≥1)			
Low-value antihypertensives	Clonidine	ATC (S01EA04, C02AC01)	12 (9.5)	9 (7.5)	8 (7.8)
	Doxazosin	ATC (C02CA04)			
	Methyldopa	ATC (C02AB01)			
Low-value spasmolytics	Solifenacin	ATC (G04BD08)	7 (5.6)	5 (4.2)	6 (5.9)
	Tolterodine	ATC (G04BD07)			
Low-value antiarrhythmics	Acetyldigoxin	ATC (C01AA02)	4 (3.2)	4 (3.3)	2 (2.0)
	Flecainide	ATC (C01BC04)			
	Sotalol	ATC (C07AA07)			

(Continues)

TABLE 1 (Continued)

Lvm by active substance class[a]	Active substance (further condition)	Data requierements[b]	PwD receiving LVM		
			At baseline $n = 126$, n (%)	After 12 months $n = 120$, n (%)	After 24 months $n = 102$, n (%)
Low-value muscle relaxants	Baclofen	ATC (M03BX01)	2 (1.6)	2 (1.6)	1 (1.0)
	Tetrazepam	ATC (M03BX07)			
Low-value antiemetics	Dimenhydrinate	ATC (A04AB02)	1 (0.8)	–	–

Abbreviations: ATC, anatomical therapeutic chemical; Lvm, low-value medications; MMSE, Mini-Mental State Examination, range 0–30, higher score indicates better cognitive function; NPI, Neuropsychiatric Inventory, score ≥ 5 indicates clinically relevant symptoms; PwD People with Dementia.
[a]According to DGPPN & DGN (2017) [32], Holt, S. et al. (2010) [33], DGIM (2019) [34].
[b]Beyond demographic data (e.g., age).
[c]Score for agitation and aggression.

Sensitivity analyses were performed using multiple regression models for the most frequent Lvm cluster of drugs, that is, low-value antiphlogistics and analgesics, antidementia drugs, sedatives and hypnotics, antidepressants, and antipsychotics. The cluster of Lvm was implemented as independent variables (received vs. not received within 24 months), and all models were adjusted as described above. All statistical analyses were conducted with STATA/IC software, version 16.[38]

3 | RESULTS

3.1 | Sociodemographic and clinical characteristics at baseline

Table 2 summarizes the participants' baseline characteristics. PwD who received Lvm at baseline were slightly younger, more likely female, more depressed, and more affected by polypharmacy and potential drug interactions compared to PwD who received no Lvm treatments at baseline. There were no significant differences for any other variables.

3.2 | Prevalence of Lvm

Over 24 months, more than every second PwD ($n = 182$, 52%) received Lvm at least once. Sixteen percent of PwD ($n = 56$) received Lvm continuously over 24 months, whereas 48% ($n = 170$) did not receive any Lvm, indicating that another 126 (36%) received Lvm sporadically but not continuously over 24 months. More than 90% of those receiving Lvm at baseline were on nonrecommended antiphlogistics and analgesics ($n = 43$, 34%), sedatives, and hypnotics, such as benzodiazepines ($n = 22$, 18%), low-value antidepressants ($n = 17$, 14%), or nonguideline medications for dementia ($n = 32$, 25%). Lvm prevalence decreased over time from 36% ($n = 126$) at baseline to 34% ($n = 124$) and 29% ($n = 102$) after 12 and 24 months, respectively. Sensitivity analyses revealed no statistically significant differences between the intervention and control groups (Tables S5 and S6). Figure 1 demonstrates the trajectories of Lvm intake over time.

3.3 | Description of outcomes at baseline and after 12 and 24 months

At baseline, PwD receiving Lvm had lower mental (50–52 vs. 55, $p = 0.011$) and physical HRQoL (39–42 vs. 43, $p = 0.077$), were more likely to be hospitalized (up to 45% vs. 28%, $p = 0.029$) and incurred higher costs (up to €12,008 vs. €7052, $p = 0.001$) than those not receiving Lvm. Decreasing physical HRQoL 24 months after baseline was more pronounced in PwD receiving Lvm than in PwD not receiving Lvm (−6.1% vs. −3.5%), with the greatest decrease in PwD taking Lvm continuously over 24 months (−8.3%).

Hospitalizations increased more intensively in patients who took Lvm at least once (from 24% to 42%; +77%) or over 1 year (from 30% to 54%) than in PwD not taking Lvm (from 28% to 35%; +26%). PwD continuously taking Lvm already had a very high hospitalization rate at baseline (46%), which slightly decreased to 38% (−19%) 24 months after baseline; this decrease was also reflected in the health care costs.

PwD receiving Lvm briefly had a greater increase in health care costs over time (Lvm once: +€8919; Lvm over 1 year (+€2573) compared with those not receiving Lvm (+€355). PwD continuously taking Lvm over 24 months already had twice as high costs at baseline compared to those without Lvm (€12008 vs. €7052, $p \leq 0.001$), which slightly decreased over time (−730€). Group differences over time are summarized in Table 3 and Table S7.

3.4 | Impact of Lvm on quality of life, hospitalization and costs

Lvm (receipt vs. nonreceipt) had a significant, negative impact on patients' physical HRQoL ($b = -1.55$; 95% CI, −2.76 to −0.35; $p = 0.011$), subsequently decrease more intensively the longer that the Lvm intake was. Compared to PwD who did not receive Lvm, continuous Lvm intake over 24 months caused a lower physical HRQoL ($b = -3.35$; 95% CI, −6.73 to −0.02; $p = 0.051$) than patients receiving Lvm only once ($b = -1.85$; 95% CI, −3.47 to −0.24; $p = 0.024$). Sensitivity analyses indicated that low-value antiphlogistics/analgesics ($b = -3.41$; 95% CI, −5.15 to −1.67; $p < 0.001$) and sedatives/ hypnotics ($b = -3.11$; 95% CI, −5.42 to −0.80; $p = 0.008$) significantly

TABLE 2 Socio-demographic and clinical sample characteristics at baseline.

	Total sample	PwD receiving Lvm		
		Yes	No	
	n = 352	*n* = 126 (35.8%)	*n* = 226 (64.2%)	*p*-Value*
Age				
Mean (SD)	80.2 (5.3)	79.3 (5.0)	80.7 (5.4)	**0.022**[a]
95% CI	(79.6–80.7)	(78.4–80.2)	(80.0–81.4)	
Sex, *n* (%)				
Female	215 (61.1)	86 (68.3)	129 (57.1)	**0.041**[b]
95% CI	(56.0–66.2)	(60.1–76.4)	(50.6–63.6)	
MMSE				
Mean (SD)	22.4 (5.1)	22.8 (4.2)	22.1 (5.5)	0.241[a]
95% CI	(21.9–22.9)	(22.1–23.6)	(21.4–22.9)	
Living situation, *n* (%)				
Alone	178 (50.6)	69 (54.8)	109 (48.2)	0.267[b]
95% CI	(45.3–55.8)	(46.0–63.5)	(41.7–54.8)	
No. of ICD-10 diagnoses				
Mean (SD)	14.0 (7.8)	14.4 (7.7)	13.8 (7.9)	0.469[a]
95% CI	(13.2–14.8)	(13.1–15.8)	(12.8–14.8)	
No. of drugs taken				
Mean (SD)	7.4 (3.5)	8.6 (3.9)	6.7 (3.1)	<**0.001**[a]
95% CI	(7.0–7.7)	(7.9–9.3)	(6.3–7.1)	
Patients with polypharmacy[c], *n* (%)				
Polypharmacy	290 (83.4)	115 (91.3)	175 (77.4)	<**0.001**[b]
95% CI	(78.4–86.4)	(86.3–96.2)	(72.0–82.9)	
No. of potential drug interactions				
Mean (SD)	0.6 (0.9)	0.8 (1.0)	0.5 (0.8)	**0.007**[a]
95% CI	(0.5–0.7)	(0.6–1.0)	(0.4–0.6)	
Charlson Score				
Mean (SD)	3.4 (2.3)	3.3 (2.2)	3.4 (2.3)	0.675[a]
95% CI	(3.1–3.6)	(2.9–3.7)	(3.1–3.7)	
B-ADL				
Mean (SD)	3.5 (2.5)	3.4 (2.1)	3.6 (2.7)	0.417[a]
95% CI	(3.3–3.8)	(3.0–3.8)	(3.3–4.0)	
GDS				
Mean (SD)	3.1 (2.3)	3.5 (2.7)	2.9 (2.0)	**0.016**[a]
95% CI	(2.8–3.3)	(3.0–3.9)	(2.6–3.1)	

Note: *p*-Values less than 0.05 are highlighted in bold.

Abbreviations: B-ADL Bayer-Activities of Daily Living Scale, range 0–10, lower score indicates better performance; GDS Geriatric Depression Scale, sum score 0–15, score ≥6 indicates depression; ICD, International Statistical Classification of Diseases and Related Health Problems; Lvm, low-value medications; MMSE Mini-Mental State Examination, range 0–30, higher score indicates better cognitive function; PwD, people with dementia; SD standard deviation.

[a]Differences in means: *t*-Test two-tailed.

[b]Differences in proportions: Fisher's exact tests.

[c]Defined as ≥ 5 prescribed medications.

*Referring to PwD who received no Lvm versus at least one Lvm.

TABLE 3 Outcome-related group differences at baseline, 12 months, and 24 months among PwD who never received low-value medications, received low-value medications once in 24 months, received low-value medications for 1 year, or received low-value medications for 2 years.

	Baseline			After 12 mo				After 24 mo			
Mental HRQoL (SF-12-MCS)	**Mean (SD)**	**95% CI**	***p*-Value**	**Mean (SD)**	**95% CI**	**Δ[c] in %**	***p*-Value**	**Mean (SD)**	**95% CI**	**Δ[d] in %**	***p*-Value**
Never, *n* = 170 (48%)	54.5 (7.7)	(53.2–55.6)	**0.011**[b]	54.7 (7.4)	(53.6–55.8)	+0.4	0.140[b]	55.0 (7.7)	(53.8–56.1)	+0.9	0.177[b]
Once in 24 months, *n* = 72 (20%)	51.8 (10.3)	(49.4–54.2)		52.3 (10.3)	(49.9–54.7)	+1.0		53.0 (9.3)	(50.8–55.1)	+2.3	
Over 1 year, *n* = 54 (15%)	50.0 (9.8)	(47.4–52.6)		53.9 (7.3)	(51.9–55.8)	+7.8		52.6 (9.4)	(50.1–55.1)	+5.2	
Over 2 years, *n* = 56 (16%)	52.3 (10.6)	(49.6–55.1)		52.5 (9.0)	(50.1–54.9)	+0.4		53.3 (9.7)	(50.7–55.8)	+1.9	
Physical HRQoL (SF-12-PCS)	**mean (SD)**	**95% CI**	***p*-Value**	**mean (SD)**	**95% CI**	**Δ[c] in %**	***p*-Value**	**mean (SD)**	**95% CI**	**Δ[d] in %**	***p*-Value**
Never, *n* = 170 (48%)	42.8 (10.5)	(41.2–44.4)	0.077[b,*]	42.9 (9.6)	(41.4–44.3)	+0.2	**0.003**[b]	41.3 (9.9)	(39.8–42.8)	−3.5	**0.002**[b]
Once in 24 months, *n* = 72 (20%)	41.7 (10.1)	(39.3–44.0)		41.2 (8.7)	(39.2–43.2)	−1.2		39.2 (10.2)	(36.9–41.6)	−6.0	
Over 1 year, *n* = 54 (15%)	40.9 (9.7)	(38.4–43.5)		38.6 (10.8)	(35.7–41.5)	−5.6		39.3 (9.0)	(36.9–41.7)	−3.9	
Over 2 years, *n* = 56 (16%)	38.7 (9.7)	(36.2–41.3)		37.9 (11.9)	(34.8–41.1)	−2.1		35.5 (10.6)	(32.7–38.3)	−8.3	
Hospitalization	**yes, *n* (%)**	**95% CI**	***p*-Value**	**yes, *n* (%)**	**95% CI**	**Δ[c] in %**	***p*-Value**	**yes, *n* (%)**	**95% CI**	**Δ[d] in %**	***p*-Value**
Never, *n* = 170 (48%)	47 (27.7)	(20.9–34.4)	**0.029**[a]	56 (32.9)	(25.9–40.0)	+19.1	0.174[a]	59 (34.7)	(27.5–41.9)	+25.5	0.093[a,*]
Once in 24 months, *n* = 72 (20%)	17 (23.6)	(13.8–33.5)		20 (27.8)	(17.4–38.2)	+17.6		30 (41.7)	(30.2–53.1)	+76.5	
Over 1 year, *n* = 54 (15%)	16 (29.6)	(17.4–41.9)		25 (46.3)	(33.0–59.6)	+56.3		29 (53.7)	(40.4–67.0)	+81.3	
Over 2 years, *n* = 56 (16%)	26 (46.4)	(33.3–59.5)		20 (35.7)	(23.1–48.3)	−23.1		21 (37.5)	(24.8–50.2)	−19.2	
Healthcare costs	**mean (SD)**	**95% CI**	***p*-Value**	**mean (SD)**	**95% CI**	**Δ[c] in €**	***p*-Value**	**mean (SD)**	**95% CI**	**Δ[d] in €**	***p*-Value**
Never, *n* = 170 (48%)	7052 (7458)	(5927–8177)	**0.001**[b]	7461 (7862)	(6275–8647)	+409	0.328[b]	7407 (6807)	(6380–8433)	+355	**0.008**[b]
Once in 24 months, *n* = 72 (20%)	7483 (7848)	(5664–9302)		9007 (16,538)	(5175–12,841)	+1524		16,402 (36,725)	(7890–24,915)	+8919	
Over 1 year, *n* = 54 (15%)	7916 (6825)	(6089–9742)		11,069 (21,695)	(5263–16,876)	+3153		10,489 (12,545)	(7132–13,847)	+2573	
Over 2 years, *n* = 56 (16%)	12,008 (10,744)	(9185–14,832)		9056 (7167)	(7173–10,940)	−2952		11,278 (13,014)	(7858–14,698)	-730	

Note: *p*-Values less than 0.05 are highlighted in bold.

Abbreviations: CI confidence interval; HRQoL health-related quality of life; Lvm, low-value medications; PwD, people with dementia; SD standard deviation; SF-12 Short Form Health Survey mental/physical dimension, range 0-100, higher score indicates better quality of life.

[a]Differences in proportions: Kruskal-Wallis test.

[b]Differences in means: oneway analysis of variance (ANOVA).

[c]difference between baseline and 1 year after.

[d]difference between baseline and 2 years after.

*$p = < 0.1$.

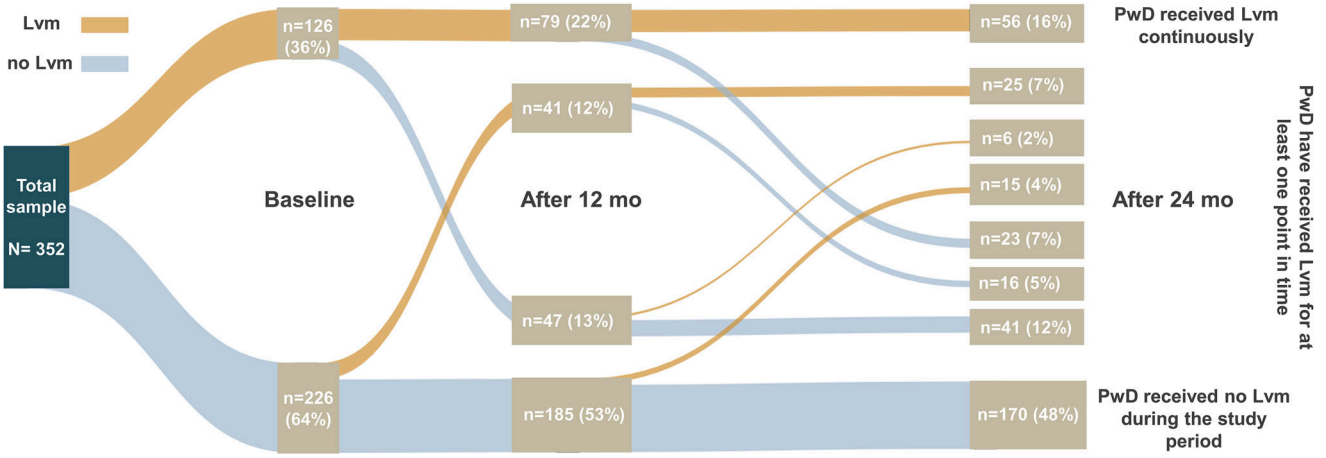

FIGURE 1 Trajectories of Lvm over 24 months. Lvm, low-value medications; PwD people with dementia; mo, months.

reduced patients' physical HRQoL. The impact of Lvm on patients' mental HRQoL was not statistically significant.

The likelihood of hospitalizations significantly increased for patients receiving Lvm (receipt vs. nonreceipt) (OR = 1.49; 95% CI, 1.06–2.09 OR; $p = 0.011$). According to the intensity of Lvm intake and compared to PwD not receiving Lvm, Lvm intake over 1 year had a significantly higher impact on hospitalization (OR = 2.61; 95% CI, 1.22–5.56 OR; $p = 0.013$) than in those receiving Lvm only once over 24 months (OR = 1.61; 95% CI, 1.09–2.36 OR; $p = 0.016$). Taking Lvm continuously over 2 years was not significantly associated with increased adjusted odds of hospitalization. The likelihood of hospitalization was significantly affected by low-value antipsychotics (see sensitivity analyses).

Lvm intake overall and once every 24 months increased medical health care costs (b = €6810; 95% CI, −707–14,327; $p = 0.076$; and b = 8421; 95% CI, €−69–€16,911; $p = 0.052$; respectively) due to significantly higher hospitalization costs. Health care costs increased with a longer duration of Lvm intake (once: €8421 over 1 year: €11,598; continuously over 2 years: €11,871). Sensitivity analyses confirmed that low-value antiphlogistics/analgesics (b = €10,282; 95% CI, 4068–16,497; $p = 0.001$) were the main cause of higher health care costs. Table 4 and Table S8 summarize the results of the multiple regression and sensitivity analyses.

4 | DISCUSSION

This longitudinal study provides valuable evidence about the prevalence of explicitly nonrecommended medications, which are unlikely to benefit patients and could potentially harm them, and their impacts on patient- and health care system-relevant outcomes over 24 months. Fifty-two percent of PwD received Lvm within 2 years, confirming that Lvm are highly prevalent in dementia care. The percentage of PwD receiving Lvm decreased from 36% at baseline to 29% 2 years after baseline, which could be explained by increased attention due to potential adverse drug events. The longitudinal analyses provided for the first time evidence that Lvm decreases physical HRQoL and increases hospitalizations and, hence, costs. HRQoL decline was more pronounced with continuous Lvm intake. In contrast, a sporadic Lvm intake caused a much greater increase in hospitalizations and direct medical care costs than taking Lvm continuously, which could indicate saturation (ceiling effect), implied by a very high hospitalization rate at baseline.

The prevalence of PwD receiving Lvm over time aligns with previous findings presenting a decreasing prevalence over time.[39,40] Given the potential harm of Lvm, this decrease over time could be explained by patients perceived impairments in physical functioning, such as frequent falls. Otherwise, the increased risk of hospitalization could also be perceived by physicians reevaluating prescribed medications after the increased switch between outpatient and inpatient care.

The revealed negative effects of Lvm on physical HRQoL, hospitalizations and health care costs extend previous cross-sectional findings.[15,16] The decrease in patients' physical HRQoL was greater when the Lvm were taken. A retrospective cohort study in PwD demonstrated that each additional drug increased the risk of adverse outcomes, such as mortality or hospitalization.[14] While the number of drugs remained constant for PwD without Lvm, among those with Lvm, it increased on average by one after 24 months. Additionally, Lvm themselves could drive the effect. Antipsychotics and benzodiazepines accounted for 32% of the captured Lvm in this study. Previous studies have underscored especially the increased risk of falls and, thus, the risk of hospitalizations associated with antipsychotics and benzodiazepines among PwD, which could affect self-perceived health.[41,42] The performed sensitivity analyses support these findings, indicating significantly lower physical HRQoL caused by sedatives and hypnotics, including benzodiazepines, and an increased hospitalization risk due to low-value antipsychotics. Our findings suggest a requirement of close patient monitoring by primary care physicians if Lvm are prescribed due to their shortened scope of action as second-line therapies.

The increased hospitalization risk was higher for those who received Lvm for only 1 year (161%) than for PwD taking Lvm continuously over 2 years (60%). PwD who received Lvm continuously demonstrated the

TABLE 4 Impact of low-value medications on quality of life, hospitalizations, and healthcare costs.[a]

	Treatment effect											
	PwD receiving Lvm			Intensity of Lvm intake (cumulative effect)								
	Yes			Once in 24 months			1 Year			1 Year		
Outcome variable	*b*	95% CI	*p*-Value	*b*	95% CI	*p*-Value	*b*	95% CI	*p*-value	*b*	95% CI	*p*-Value
Health-related quality of life												
Mental HRQoL (SF-12-MCS)	−0.38	−1.51–0.75	0.507	−0.33	−1.68–1.01	0.625	−0.61	−3.61–2.39	0.692	−0.07	−3.47–3.33	0.968
Physical HRQoL (SF-12-PCS)	−1.55	−2.76–−0.35	**0.011**	−1.85	−3.47–−0.24	**0.024**	−0.95	−3.71–1.80	0.498	−3.35	−6.73–0.02	0.051*
Hospitalization												
In-hospital treatment	1.49[c]	1.06–2.09[c]	**0.022**	1.61[c]	1.09–2.36[c]	**0.016**	2.61[c]	1.22–5.56[c]	**0.013**	1.60[c]	0.65–3.95[c]	0.309
Healthcare costs from payers' perspective[b]												
Medical care costs[b]	6810	−707–14,327	0.076*	8421	−69–16,911	0.052*	11,598	−11,371–34,566	0.322	11,871	−13,125–36,867	0.352
Physicians[b]	−37	−124–49	0.399	0.3	−87–88	0.995	−53	−401–295	0.765	37	−308–382.1	0.832
In-hospital[b]	6953	−546–14,451	0.069*	7893	−762–16,549	0.074*	11,067	−11,046–33,180	0.327	10,832	−13646–35,310	0.386
Medications[b]	−227	−496–41	0.097*	268	−32–567	0.080*	59	−840–958	0.897	449	−576–1475	0.390
Medical aids[b]	−5	−182–172	0.955	−69	−201–64	0.311	−48	−709–613	0.886	−58	−781–665	0.876
Therapies[b]	101	−37–238	0.152	112	−15–239	0.083*	−28	−292–235	0.832	188	−180–556	0.317

Note: *p*-Values less than 0.05 are highlighted in bold.

Abbreviations: *b*, observed coefficient; CI confidence interval; HRQoL, health-Related Quality of Life; Lvm, low-value medications; PwD, people with pementia; SF-12 Short Form Health Survey mental/physical dimension, range 0-100, higher score indicates better quality of life.

[a]Multiple panel data regression models; standard errors were estimated with a nonparametric bootstrapping (2000 replications) Models were adjusted for socio-demographic and clinical variables: age, sex, dementia diagnosis (ICD-10: F00, F01, F02, F03, G30), functional impairment (B-ADL), depression (GDS), comorbidities (CCI), number of ICD-10 diagnoses, polypharmacy (≥ 5 prescribed medications), number of potential drug interactions, the respective baseline outcome values and a lagged Lvm variable.

[b]Difference between baseline and 2 years after.

[c]Odds ratio (95% CI).

*$p = < 0.1$.

highest hospitalization rate (46%) at baseline with limited potential to increase, indicating saturation (ceiling) effects. While PwD with a continuous Lvm intake showed this saturation, hospitalizations of those with short-term Lvm intake increased (receiving Lvm once: +77%; 12 months Lvm intake: +81%), confirming increased hospitalizations due to Lvm.

The multivariate results also indicated increased medical care costs due to Lvm. This effect seemed primarily driven by PwD, who received Lvm once during the 24 months (€8421), while those continuously receiving Lvm showed no more significant changes (−730€ in 24 months) due to the aforementioned potential saturation (ceiling effect) already at baseline (€12,008). In particular, hospitals (€7893) contributed to the additional costs. According to Badgery-Parker et al.[43] hospitalizations increase the risks of potentially harmful downstream effects, such as using additional treatments and hospital resources, and potentially delay care for patients with greater unmet needs. Thus, our analysis suggests that Lvm result in increased hospitalizations, which are also associated with increased health care costs and decreased HRQoL. However, additional research is needed to gain evidence about the full spectrum of low-value service provision in hospital settings and the consequences for the cost and quality of care over time.

Our data strongly suggest that efforts and interventions are needed to sensitize and motivate prescribers to review and, if necessary, discontinue the prescription of Lvm and to use appropriate alternatives. As long as better alternatives come with additional costs, as indicated by Pohl-Dernick et al.[44] short-term incentives for relevant stakeholders to change low-value prescribing behavior (and reimbursement) are lacking. Therefore, future high-quality studies with large samples, longer follow-up times, and interdisciplinary stakeholders must identify and implement appropriate measures to change prescription behaviors. With increasing numbers of PwD and the growing socioeconomic burden on health systems worldwide, the negative effects of Lvm on patient and health system outcomes emphasize the ethical, economic, and political need for action to shift spending to higher-value resource use.[5,45]

4.1 | Limitations

Data were obtained in a rural area in northeastern Germany, potentially limiting the generalizability of the presented results. PwD with a higher functional impairment were more likely to drop-out due to death which may affect the generalizability of the presented findings for this population. Furthermore, patient-reported primary data were assessed by study nurses at patients' homes, possibly affecting their completeness and accuracy due to recall bias, especially for the assessed hospitalizations and health care costs. Additional claim data from health insurance or the possibility of linking primary and secondary data were unavailable. However, to minimize the recall bias, additional information about medication use was obtained from treating practitioners, care providers, and caregivers in proxy interviews to increase the data validity and gain information about relevant clinical dimensions not usually available from secondary data. Additionally, the SF-12, a practical and adequate instrument for PwD with an MMSE score greater than 16, was used to assess HRQoL.[46] Thirty-six PwD with scores less than 16 at baseline were included, limiting the validity of the quantification of these endpoints. The sources for classifying medications as low-value represent expert consensus and predominantly emphasize clinical rationale, while the patient perspective, that is low-value care as adverse care, could not be included in the analyses. Finally, the PRISCUS List used to classify Lvm is an explicit tool offering practical advantages for large-scale epidemiologic studies due to its directly measuring the relevant data, albeit at the price of clinical contextual factors and individual patient needs.[47,48] Thus, the prevalence of Lvm may have been overestimated since some prescriptions might have been classified as Lvm, although the health service provision was clinically adequate for certain reasons, illustrating a conflict regarding specificity and sensitivity, as described by Schwartz et al.[8]

5 | CONCLUSION

This longitudinal analysis adds crucial evidence regarding Lvm in dementia, demonstrating a negative impact of Lvm on patient-reported HRQoL, hospitalizations, and direct health care costs. While continuous use of Lvm had an increasingly negative impact on patients' HRQoL with saturation effects on hospitalizations and costs already at baseline, receiving Lvm sporadically or for 1 year was relevant regarding further increases in hospitalizations and costs. Adequate alternative treatments are needed as early as possible in the patient journey through the health care system to avoid HRQoL-decreasing downstream effects for patients and resource-burdening for health systems. Further research is needed to develop appropriate and effective interventions to encourage prescribers to avoid Lvm in dementia care wherever possible.

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CONFLICTS OF INTEREST STATEMENT

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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