Medicare claims analysis of agents used to manage dementia-related psychosis: a treatment pattern study

Nazia Rashid[a], James B. Wetmore[b,c], Muna Irfan[d], Yi Peng[c] and Victor Abler[a]

Currently, no agents are approved in the USA to treat dementia-related psychosis. After failure of a nonpharmacologic approach to treatment, antipsychotics or divalproex is often prescribed. We characterized existing treatment patterns in patients with dementia-related psychosis. Medicare claims data from 2008 to 2016 were used to identify patients with dementia-related psychosis. The agents and associated dosages prescribed, time to first use, and patterns of use were evaluated for agents prescribed to treat dementia-related psychosis. In total, 49 509 patients were identified as having dementia-related psychosis. Over three-quarters (76.8%) received an antipsychotic or divalproex. The most prescribed first-line agents were quetiapine (30.5%), risperidone (19.5%), and divalproex (11.2%). More than 80% of patients received a low dose of an agent, and 65.5% switched or discontinued their first-line treatment during a mean follow-up period of 1.8 years. In the absence of US FDA-approved therapies to treat dementia-related psychosis, treatment after behavioral intervention involves frequent use of low-dose antipsychotics or divalproex. The high rate of treatment switching or discontinuation is consistent with current treatment guidelines and suggests a need for an improved, standardized pharmacological approach to treat dementia-related psychosis. *Int Clin Psychopharmacol* 37: 84–91 Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc.

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[a]Acadia Pharmaceuticals Inc., San Diego, California, [b]Division of Nephrology, Hennepin County Medical Center, [c]Chronic Disease Research Group, Hennepin Healthcare Research Institute and [d]Department of Neurology, University of Minnesota and Veterans Affairs Medical Center, Minneapolis, Minnesota, USA

Correspondence to Nazia Rashid, PharmD, MS, Acadia Pharmaceuticals Inc., 12830 El Camino Real, Ste 400, San Diego, CA 92130, USA
Tel: +1 858 558 2871; e-mail: nrashid@acadia-pharm.com

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Introduction

Globally, more than 50 million people are afflicted with dementia, a number that is expected to be more than triple by 2050 (World Health Organization, 2019). The vast majority (80–97%) of patients with dementia experience neuropsychiatric symptoms, such as psychosis (hallucinations and delusions), agitation/aggression, or mood disturbances (e.g. depression and apathy) (Lyketsos *et al.*, 2002; Peters *et al.*, 2006; Steinberg *et al.*, 2008). Neuropsychiatric symptoms in patients with dementia can affect quality of life and hinder patient care, place increased strain on caregivers, and hasten institutionalization (Yaffe *et al.*, 2002; Buhr *et al.*, 2006; Maust *et al.*, 2017; Toot *et al.*, 2017).

Hallucinations and/or delusions are common neuropsychiatric symptoms in patients with dementia (Ballard *et al.*, 2018) and are thus hallmarks of dementia-related psychosis. The presence of hallucinations or delusions is associated with an increased rate of cognitive decline (Chui *et al.*, 1994; Stern *et al.*, 1996). No medication is currently approved by the United States (US) Food and Drug Administration (FDA) for the management of hallucinations and delusions in patients with dementia-related psychosis (Kales *et al.*, 2015; Ballard *et al.*, 2018). Patients that need treatment typically receive agents such as atypical antipsychotics (e.g. quetiapine and risperidone) (Ballard *et al.*, 2018; Ahmed *et al.*, 2019; Bessey and Walaszek, 2019). Although atypical antipsychotics have been used because of their lower risks of extrapyramidal and anticholinergic side effects compared with typical antipsychotics, literature on the use of all antipsychotics in dementia-related psychosis is fraught with contradictory evidence. While there are some studies supporting the use of atypical antipsychotics (De Deyn *et al.*, 2005; Paleacu *et al.*, 2008), others have suggested increased risk of cerebrovascular events associated with some atypical antipsychotic agents (Schneider *et al.*, 2006a; Yunusa *et al.*, 2019), and efficacy in treating psychosis is variable and limited (Smeets *et al.*, 2018). In 2005, Schneider *et al.* published a meta-analysis demonstrating increased mortality in patients treated with atypical antipsychotics compared with the placebo group (3.5% vs. 2.3%; odds ratio, 1.54).

In light of studies suggesting increased risk of cardiovascular events and mortality, the US FDA imposed a boxed warning on several atypical antipsychotic agents (Busko, 2008), which was later extended to all typical

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and atypical antipsychotic medications. Moreover, the American Geriatrics Society (AGS) recommends the use of antipsychotics be avoided in elderly patients unless nonpharmacologic interventions have failed (or are not an option) and the individual threatens harm to self or others (American Geriatrics Society Beers Criteria Update Expert Panel, 2019). The American Psychiatric Association (APA) also recommends limiting the use of antipsychotics and further suggests initiating tapered withdrawal within 4 months, even in patients deriving clinical benefit (Reus *et al.*, 2016). Concern about the potential harm of these agents is widely recognized; however, alternative treatment options for psychosis related to dementia are still limited.

Anticonvulsants (e.g. valproic acid and divalproex) and dextromethorphan/quinidine are also used to treat dementia-related psychosis (Kales *et al.*, 2015; American Geriatrics Society Beers Criteria Update Expert Panel, 2019; Bessey and Walaszek, 2019), but both are associated with an increased risk of falls and drug–drug interactions in elderly patients (American Geriatrics Society Beers Criteria Update Expert Panel, 2019), and efficacy has not been established. As a consequence, the AGS recommends that the use of anticonvulsants be avoided in the presence of two other central nervous system-active drugs in elderly patients (American Geriatrics Society Beers Criteria Update Expert Panel, 2019). Antidepressants that have a generally favorable tolerability profile are also prescribed to patients with dementia-related psychosis. Citalopram, sertraline, and trazodone were observed to have comparable efficacy to both typical and atypical antipsychotics in smaller studies (Pollock *et al.*, 2002; Pollock *et al.*, 2007; Seitz *et al.*, 2011).

To our knowledge, no large-scale analysis has been conducted to identify the agents used to treat dementia-related psychosis. To address this gap and further understand this unmet need, we analyzed Medicare claims data to characterize patterns of drug use and modeled factors associated with treatment for dementia-related psychosis. We hypothesized that antipsychotics and mood stabilizers, such as divalproex, would be initiated and common; furthermore, that switching between medications, rather than escalating doses of index medications, would be the most common treatment approach.

Methods

Study design and data source

A retrospective cohort study was performed using a random sample of 20% of all Medicare beneficiaries age at least 65 that had coverage from Parts A, B, or D. Patients with dementia during the study period, which spanned from 1 January 2008 to 31 December 2016, were identified. Data related to prescription drug use captured in Medicare Part D were extracted from the standard analytic files generated by the Centers for Medicare & Medicaid Services. These methods were also described in a previous report in the same patient population (Wetmore *et al.*, 2021).

The Human Subjects Research Committee of the Hennepin County Medical Center/Hennepin Healthcare System, Inc. provided a waiver of consent since all data were deidentified.

Patient population

We first established the presence of dementia. Patients had to have either: (a) at least two dementia diagnosis codes at least 30 days but 3 years or less apart [see Supplementary Table 1, supplemental digital content 1, *http://links.lww.com/ICP/A98*, for International Classification of Diseases (ICD) codes] or (b) one dementia diagnosis code plus a dementia drug prescription [donepezil hydrochloride (HCL), galantamine hydrobromide, rivastigmine transdermal, rivastigmine tartrate, tacrine HCL (discontinued in the USA), and memantine HCL] in the year before or after the dementia diagnosis claims. The date of the second claims (diagnosis or prescription drug) was used as the dementia index date. For patients who satisfied both inclusion criteria, the earlier qualifying date was used as the dementia index date. Dementia codes could have derived from inpatient or outpatient encounters in any position on the medical claims. Patients were required to have at least 12 months of Medicare coverage with Parts A, B, and D (without health maintenance organization coverage). Comorbidities listed in the Charlson Comorbidity Index (Quan *et al.*, 2011) were defined using qualifying diagnosis codes on either: (a) at least one inpatient, skilled nursing facility, home health, or hospice claims or (b) at least two outpatient, physician encounter, or durable medical equipment claims on different days during the 12-month baseline period prior to the dementia date.

Next, we identified dementia patients who also had evidence of dementia-related psychosis. To increase the likelihood that symptoms of psychosis (i.e. hallucinations and delusions) and the use of any antipsychotic or mood-stabilizing agent were due to dementia-related psychosis, we excluded patients aged less than 40 years and those with chronic psychiatric disease, history of seizures, or other possible causes of psychosis at any time prior to the dementia index date. Because acute stroke can be associated with psychosis, we also excluded patients with a history of stroke 6 months prior to the dementia date. See Supplementary Table 2, supplemental digital content 1, *http://links.lww.com/ICP/A98*, for ICD codes that rendered patients ineligible. Patients with evidence of psychosis, behavioral abnormalities, antipsychotic drug use, or divalproex use at any time prior to the dementia index date were also excluded because these findings would have suggested preexisting psychosis.

Patients with incident dementia-related psychosis were identified on the basis of: (a) at least two codes for psychosis at least 7 days but 3 years or less apart (see Supplementary Table 3, supplemental digital content 1, *http://links.lww.com/ICP/A98*, for ICD codes), (b) at least two antipsychotic or divalproex drug prescriptions at least 180 days apart, or (c) one diagnosis code for psychosis plus a drug prescription for an antipsychotic or divalproex in the year before or after the diagnosis claims. For the three qualifying groups, the date of the second claims (diagnosis or prescription drug) was used as the index date for dementia-related psychosis. The earliest date was used as the index date for dementia-related psychosis, and for patients taking more than one antipsychotic/divalproex, the first agent prescribed was treated as the first therapy. To determine the time from diagnosis to treatment initiation, we excluded patients for whom the dementia-related psychosis index date was defined using a prescription drug versus a diagnosis claims.

Study outcomes

Outcomes were the agents prescribed for dementia-related psychosis, time to first use of an agent to treat dementia-related psychosis, patterns of treatment use, and drug dose. Patients were categorized as treatment continuers, discontinuers, or switchers. Patients who persistently used an index medication for dementia-related psychosis (i.e. filling a 30-day prescription supply within 45 days of the last supply) were categorized as treatment continuers. Patients who did not persistently use the index medication (i.e. no refill by day 46 of the supply gap) and did not switch medications were categorized as treatment discontinuers; patients who switched medications were categorized as treatment switchers. Dosing patterns were characterized using the following: (a) dose of the index prescription, (b) highest prescribed dose, and (c) daily average consumption (DACON) in milligrams [calculated as follows: Σ(dose × days' supply)/(days on treatment)]. Patients were followed from the date of dementia until death, loss of Medicare Part A, B, or D eligibility, or end of the study period (31 December 2016). Doses were categorized as low, medium, or high according to the ranges shown in Table 1, as determined by clinical consensus and guidance from key opinion leaders before the study.

Statistical methods

We used Cox proportional hazards regression modeling—with age, sex, race, and baseline comorbidities as covariates—to evaluate the factors associated with time to first treatment for dementia-related psychosis. With the exception of the analysis of factors associated with time to first treatment for dementia-related psychosis, all outcomes were summarized using descriptive statistics. Data were generated using SAS Version 9.4 (SAS Institute, Cary, North Carolina, USA).

Table 1 Dose category definitions

	Dose category		
Antipsychotic/divalproex	Low	Medium	High
Divalproex	≤500	>500–1000	>1000
Haloperidol	<5	5–10	>10
Aripiprazole	≤10	>10–20	>20
Olanzapine	≤5	>5–10	>10
Risperidone	≤2	>2–4	>4
Quetiapine	≤100	>100–250	>250

All values represent the dose in milligrams.

Results

Patients

From a total of 1 637 656 potential patients identified in the 20% Medicare random sample, 256 408 qualified for inclusion in the analysis (for patient flow, see Supplementary Fig. 1, supplemental digital content 1, *http://links.lww.com/ICP/A98*). Of these 256 408 patients with dementia, 49 509 (19.3%) developed incident dementia-related psychosis on or after the dementia index date. Baseline demographics and clinical characteristics of the total analysis population, including the subgroups of patients who did and did not develop dementia-related psychosis, have been published previously (Wetmore *et al.*, 2021). Briefly, patients with dementia-related psychosis had a mean age of 83 ± 7.9 years, and 68.8% were female. A total of 82.7% of patients were White, and 9.5% of patients were Black (Wetmore *et al.*, 2021). Of the 49 509 patients included, 32 890 (66.4%) were not residing in a long-term care facility at the time they developed dementia-related psychosis. Approximately 60% of patients had at least one comorbid condition at baseline (no comorbid conditions: 36.4%; one comorbid condition: 28.3%; two to three comorbid conditions: 26.7%; and at least three comorbid conditions: 8.6%). Patients with dementia-related psychosis were followed for a mean of 1.8 years.

Antipsychotic or divalproex use

Of the 49 509 patients with incident dementia-related psychosis, 38 004 (76.8%) received either an antipsychotic or divalproex, and 11 505 (23.2%) did not receive these agents for dementia-related psychosis. The most commonly prescribed agents for first-line treatment of dementia-related psychosis were quetiapine [30.5% (n = 15 090) of patients], risperidone [19.5% (n = 9630)], divalproex [11.2% (n = 5539)], haloperidol [6.6% (n = 3279)], olanzapine [6.3% (n = 3097)], and aripiprazole [2.3% (n = 1123)].

At least half of patients treated with an antipsychotic or divalproex were prescribed it on their dementia-related psychosis index date, as indicated by a median time to initiation of 0. Overall, the mean time to drug initiation was 88 days (Table 2). With the exception of haloperidol, time to treatment initiation was generally similar for the most commonly prescribed first-line agents (mean, 75.8–94.6 days after the dementia-related psychosis

index date). Patients who received haloperidol as the index treatment, however, began their treatment later, at a mean of 126.9 days after the dementia-related psychosis index date.

Among patients with incident dementia-related psychosis, 34.5% (13 034/37 758) were categorized as treatment continuers, 41.1% (15 546/37 758) as discontinuers, and 24.3% (9178/37 758) as switchers (Fig. 1 and Supplementary Table 4, supplemental digital content 1, *http://links.lww.com/ICP/A98*). Patients whose first-line treatment was with divalproex had the highest percentage of continuers (39.2%), whereas those treated initially with haloperidol had the lowest (20.3%). Risperidone users had the highest percentage of discontinuers (44.5%). Patients initially treated with haloperidol had the highest percentage of switchers (36.0%), whereas those treated with quetiapine had the lowest (19.2%). Among patients who experienced a switch, quetiapine was the most frequently prescribed second-line agent overall [30.6% (2804/9178)], with percentages of switching from individual first-line agents ranging from 40.3 to 50.2%.

Regarding dose, 80–98% of patients received a relatively low dose of the first-line agent (Table 3). Although increases in dose were observed during the follow-up period, most (65–93%) doses of the index agent remained in the low category, with increases being most common for divalproex, olanzapine, and haloperidol, and least common for aripiprazole and risperidone. For each medication category, the average, median, and 75th percentile DACON values were categorized as low during time on treatment (Table 3).

In the Cox proportional hazards regression model, younger patients (aged 40–70 years compared with >80 years), males, and Whites (compared with non-Whites) were more likely to initiate treatment with an antipsychotic or divalproex (Table 4). Generally, patients with a comorbidity were less likely to initiate treatment compared with patients without that comorbidity.

Table 2 Time to first treatment for dementia-related psychosis

		Time to first treatment for dementia-related psychosis[a], days	
Antipsychotic/divalproex	Patients, *n*	Mean (SD)	Median (IQR)
Any antipsychotic or divalproex	10 978	88.1 (232.2)	0 (0–51)
Divalproex	2236	90.5 (230.1)	0 (0–52)
Haloperidol	1110	126.9 (293.6)	3 (0–98)
Aripiprazole	359	94.6 (222.7)	0 (0–68)
Olanzapine	1282	75.8 (194.2)	1 (0–59)
Risperidone	3527	85.2 (229.5)	0 (0–50)
Quetiapine	5491	89.0 (236.4)	0 (0–49)

IQR, interquartile range.
[a]Data are from patients whose dementia-related psychosis index date was defined using a diagnosis.

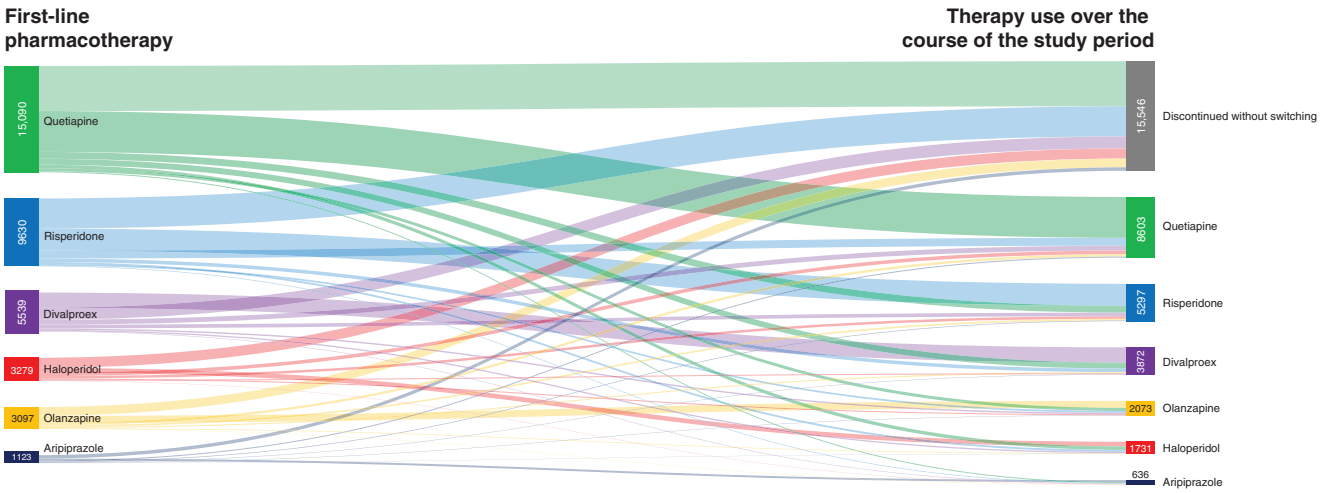
Discussion

In this retrospective analysis of Medicare beneficiaries over 8 years, we found that patients with dementia-related pyschosis treated with a non-FDA–approved agent experienced high rates of switching and discontinuation of agents, and doses utilized were low. Despite the questionable efficacy and safety of antipsychotics and divalproex (Schneider *et al.*, 2005, 2006a,b; Gill *et al.*, 2007; Maher *et al.*, 2011; Maust *et al.*, 2015; Reus *et al.*, 2016; Yunusa *et al.*, 2019), over three-quarters of patients with apparent dementia-related psychosis received pharmacologic treatment with these agents, none of which have FDA approval for the indication of dementia-related psychosis. Among those who received treatment, only about one-third persisted on their initial treatment, whereas about one-quarter switched to a second antipsychotic. Collectively, these results reflect the relatively poor treatment landscape for a condition that is likely to become increasingly common in future decades.

Treatment for dementia-related psychosis is a major challenge for clinicians. All antipsychotics carry a boxed warning regarding the risk of death when used in elderly patients, leaving clinicians with objectionable treatment options for what can be a very disabling condition. While our analysis did not capture patients without coded symptoms or treated with nonpharmacological methods, our findings suggest a division between management guidelines and pharmacologic treatment plans implemented in clinical practice. This may be attributed to limited clear and objective evidence on the risk-benefit analysis of these agents. An association of increased morbidity and mortality risk with antipsychotic use is well established (Schneider *et al.*, 2005; Maust *et al.*, 2017; Watt *et al.*, 2020). However, some reports from observational studies challenge this finding, implicating the presence and severity of psychiatric symptoms rather than use of antipsychotic medication as predictive of adverse outcomes in patients with dementia-related psychosis (Barak *et al.*, 2007; Lopez *et al.*, 2013, Maust *et al.*, 2017). The presence of this treatment dilemma was clearly identified in a survey of geriatrics practitioners, which reported that a lack of treatment alternatives and guidance were common reasons for prescribing antipsychotic medications in elderly patients (Saad *et al.*, 2010).

The most commonly prescribed agents were quetiapine and risperidone, consistent with current guidelines (Reus *et al.*, 2016). However, nearly one in five patients were prescribed divalproex, a medication initially developed and utilized for its antiseizure properties. Further, one in 10 used the typical antipsychotic haloperidol, which is associated with a particularly high incidence of extrapyramidal and Parkinsonian symptoms (Shin and Chung, 2012) and a higher risk of mortality than other antipsychotics (Huybrechts *et al.*, 2012). Of note, pimavanserin, a selective 5-hydroxytryptamine receptor 2A

Fig. 1



Patterns of pharmacotherapy use over the duration of the study period.

Table 3 Dosing patterns in patients with dementia-related psychosis treated with either an antipsychotic or divalproex

	First prescribed dose[b]			Highest prescribed dose[a]			DACON (mg)		
Agent[a]	Low	Medium	High	Low	Medium	High	Mean (SD)	Median	75th percentile
Divalproex ($n = 5530$)	4710 (85.2)	712 (12.9)	108 (2.0)	3598 (65.1)	1524 (27.6)	408 (7.4)	268.9 (663.3)	100.0	255.6
Haloperidol ($n = 3278$)	2640 (80.5)	465 (14.2)	173 (5.3)	2440 (74.4)	597 (18.2)	241 (7.4)	1.0 (3.5)	0.3	0.8
Aripiprazole ($n = 1123$)	1050 (93.5)	53 (4.7)	20 (1.8)	1006 (89.6)	90 (8.0)	27 (2.4)	3.6 (20.8)	0.9	2.5
Olanzapine ($n = 3097$)	2549 (82.3)	387 (12.5)	161 (5.2)	2072 (66.9)	695 (22.4)	330 (10.7)	2.4 (5.6)	0.9	2.5
Risperidone ($n = 9630$)	9414 (97.8)	154 (1.6)	62 (0.6)	8980 (93.2)	490 (5.1)	160 (1.7)	0.5 (3.2)	0.1	0.4
Quetiapine ($n = 15\,057$)	14 227 (94.5)	674 (4.5)	156 (1.0)	12 084 (80.3)	2291 (15.2)	682 (4.5)	42.0 (121.8)	11.5	35.9

Data are number (%) of patients.
DACON, daily average consumption.
[a]Data on dosing were not available for nine patients receiving divalproex, one patient receiving haloperidol, and 33 patients receiving quetiapine. These patients were not included in the denominator for calculating percentages.
[b]See Table 1 for the definitions of each dosing category.

inverse agonist/antagonist, was excluded from this analysis. Pimavanserin was approved to treat hallucinations and delusions associated with Parkinson's disease psychosis in April 2016 (Ballard *et al.*, 2018) and, therefore, was not available during the majority of the study period examined.

Pharmacologic therapy for dementia-related psychosis should ideally be confined to short-term use. The APA guidelines recommend periodic assessment and medication cessation attempts for patients receiving pharmacologic treatment for dementia-related psychosis to mitigate the risk of treatment-related adverse effects. The APA advises that treatment with an antipsychotic be tapered and withdrawn within 1 month in patients who do not achieve adequate response and within 4 months in those exhibiting adequate response (Reus *et al.*, 2016). Thus, while drug discontinuation may indicate therapeutic success, treatment switching may reflect a safety issue or unsatisfactory efficacy. In the case of a moderate response to an antipsychotic, a switch to a second antipsychotic may be pursued in search of a stronger response (Steinberg and Lyketsos, 2012). However, as this was an analysis of claims-based data, no reports of symptom control were available, so the motivations for switching between low-dose antipsychotics are uncertain.

Nearly all medications for dementia-related psychosis were prescribed at relatively modest doses, compared with the wide range of doses available to prescribers for these medications. Unlike common medications such as antihypertensives, oral antidiabetics, and hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins), antipsychotics can be prescribed over a wide range of doses. However, in elderly patients with dementia, the risk of adverse vascular events has been shown to increase with higher antipsychotic doses (Wu *et al.*, 2013). Use of low doses for the index and subsequent medications is partially aligned with APA guidelines, which recommend antipsychotics be initiated at low doses and titrated

Table 4 Factors associated with initiating treatment with an antipsychotic or divalproex for dementia-related psychosis

Covariate	HR (95% CI)	*P* value
Age group		
40–70 years	1.00 (reference)	ND
71–75 years	0.98 (0.91–1.06)	0.6249
76–80 years	0.92 (0.85–0.98)	0.0162
81–85 years	0.84 (0.79–0.90)	<0.0001
86–90 years	0.73 (0.68–0.78)	<0.0001
≥91 years	0.65 (0.60–0.70)	<0.0001
Sex		
Male	1.00 (reference)	ND
Female	0.85 (0.83–0.88)	<0.0001
Race		
White	1.00 (reference)	ND
Black	0.81 (0.77–0.85)	<0.0001
Other	0.89 (0.83–0.94)	0.0001
Comorbidity in the CCI list[a]		
Myocardial infarction	1.00 (0.95–1.06)	0.9505
Congestive heart failure	0.90 (0.87–0.93)	<0.0001
Peripheral vascular disease	0.89 (0.86–0.92)	<0.0001
Cerebrovascular disease	0.90 (0.87–0.93)	<0.0001
Chronic pulmonary disease	0.95 (0.92–0.99)	0.0078
Rheumatologic disease	0.95 (0.88–1.02)	0.1808
Peptic ulcer disease	0.92 (0.82–1.03)	0.1401
Mild liver disease	0.80 (0.71–0.90)	0.0002
Diabetes without chronic complication	0.98 (0.94–1.01)	0.2114
Diabetes with chronic complication	0.90 (0.85–0.95)	0.0001
Hemiplegia or paraplegia	0.77 (0.69–0.86)	<0.0001
Renal disease	0.93 (0.89–0.96)	<0.0001
Any malignancy, including leukemia and lymphoma	0.96 (0.92–1.02)	0.168
Moderate or severe liver disease	0.60 (0.43–0.84)	0.0026
Metastatic solid tumor	0.80 (0.68–0.95)	0.0109

CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio; ND, no data.
[a]Reference was those patients without the respective comorbid condition.

upward to the minimally effective tolerated dose (Reus *et al.*, 2016). However, we found little evidence that patients underwent dose escalation, as even moderate doses were used rarely. Dose escalation may be avoided to limit the risk of safety concerns. Alternatively, switching between low-dose antipsychotics may suggest insufficient improvement or occurrence of intolerable adverse effects by the first agent. Each of these factors reflects the limitations of current agents available.

Our models demonstrated that patients who were older or who had comorbid medical conditions were less likely to be prescribed an antipsychotic or divalproex than younger or healthier patients. This finding may also reflect concerns around the safety and tolerability of currently available drugs or concerns around drug–drug interactions. Such treatment practice highlights the unmet need in this population, as dementia is primarily a disease of the elderly, and the majority of patients aged at least 65 years have comorbidities (Wolff *et al.*, 2002; Fortin *et al.*, 2005; Barnett *et al.*, 2012). Racial differences in treatment were also noted, with Whites being treated more commonly than non-Whites. This is consistent with prior reports of racial disparities in the use of atypical antipsychotics in Whites compared with other races (Daumit *et al.*, 2003; Herzig *et al.*, 2016).

Our study is the largest Medicare claims-based data study to address the topic of pharmacological use in dementia-related psychosis in a large patient population. However, because the data were derived from a Medicare claims database, our results might not be generalizable to nonelderly patients, to patients with other types of insurance, or to patients with dementia-related psychosis outside the USA. By excluding patients with prior history of stroke, patients with vascular dementia may have also been inadvertently excluded. While our approach to identifying patients with dementia-related psychosis was carefully developed, it has not been validated. Patients enrolled in Medicare Advantage (Part C) were not included because data for years 2008–2014 were unavailable, and Medicare Part C was a relatively small portion compared with the number of patients enrolled in fee-for-service Medicare.

Our analysis was likely not comprehensive of all patients who experience dementia-related psychosis, as inclusion required clinician coding of symptoms to define the onset of dementia and psychosis. Further, patients with coded symptoms who may have been successfully treated with nonpharmacological treatment would have been categorized as untreated. It is also possible that some patients categorized as untreated may have received pharmacologic treatment for dementia-related psychosis outside of Medicare, although treatment outside of Medicare in Part D beneficiaries is rare. In addition, it is possible that pharmacologic treatments studied here may have been prescribed for other symptoms (e.g. haloperidol for nausea) or for a preferred route of administration.

Despite these limitations to the interpretation of these results, our study has notable strengths, including a large sample size and use of Medicare, a near-universal entitlement for older individuals in the USA. It provides an in-depth analysis of the current antipsychotic prescription patterns and reveals the unintended deviation from available management guidelines and inconsistencies in treatment plan, reinforcing the need for better options and a standardized approach.

Conclusion

The findings of this analysis suggest that in order to improve patient and caregiver quality of life, the need exists for investigative research in alternative treatment approaches that are both safe and effective. Further studies are needed to steer and develop an evidence-based expert consensus that acknowledges and guides the clinical use of pharmacotherapy for dementia-related psychosis based on the careful selection of agents, dose escalation, and monitoring of adverse effects.

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N.R.: study design, data analysis, interpretation of data, revising the manuscript for critical content. J.B.W. and Y.P.: study design, acquisition of data, data analysis, interpretation of data, revising the manuscript for critical content. M.I.: study design, interpretation of data, revising the manuscript for critical content. V.A.: study design, data analysis, interpretation of data, revising the manuscript for critical content. All authors contributed to the writing and development of this manuscript.

Data availability statement: the data used in this analysis are available for a fee to qualified individuals and institutions from the Centers for Medicare & Medicaid Services and are subject to the terms of a Data Use Agreement.

Conflicts of interest

J.B.W. and Y.P. are employed by the Chronic Disease Research Group, which received research funding from Acadia Pharmaceuticals Inc., and has served on ad hoc advisory boards for the BMS-Pfizer Alliance. V.A. and N.R. are salaried employees of Acadia Pharmaceuticals Inc. M.I. has nothing to disclose.

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