Medicare claims analysis of agents used to manage dementia-related psychosis: a treatment pattern study
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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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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 (Smets 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/valproex, 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: \(\Sigma\) (dose \times 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**

| 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 = 9,630)], divalproex [11.2% (n = 5,539)], haloperidol [6.6% (n = 3,279)], olanzapine [6.3% (n = 3,097)], and aripiprazole [2.3% (n = 1,123)].

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
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% (9,178/37,758) 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% (2,804/9,178)], 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

| Antipsychotic/divalproex       | Patients, n | Mean (SD) | Median (IQR) |
|-------------------------------|-------------|-----------|--------------|
| Any antipsychotic or divalproex| 10,978      | 88.1 (232.2) | 0 (0–51)     |
| Divalproex                    | 2,236       | 90.5 (230.1) | 0 (0–52)     |
| Haloperidol                   | 1,110       | 126.9 (293.6) | 0 (0–98)     |
| Aripiprazole                  | 359         | 94.6 (222.7)  | 0 (0–68)     |
| Olanzapine                    | 1,282       | 75.8 (194.2)  | 1 (0–59)     |
| Risperidone                   | 3,527       | 85.2 (229.5)  | 0 (0–50)     |
| Quetiapine                    | 5,491       | 89.0 (236.4)  | 0 (0–49)     |

IQR, interquartile range.

*Data are from patients whose dementia-related psychosis index date was defined using a diagnosis.

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### Discussion

In this retrospective analysis of Medicare beneficiaries over 8 years, we found that patients with dementia-related psychosis treated with a non-FDA-approved agent experienced higher 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...
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 hydroxymethyl-glutaryl-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 3 Dosing patterns in patients with dementia-related psychosis treated with either an antipsychotic or divalproex

| Agenta | First prescribed doseb | Highest prescribed dosea | DACION (mg) |
|--------|------------------------|--------------------------|------------|
|        | 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 = 9330) | 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. DACION, daily average consumption. *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. See Table 1 for the definitions of each dosing category.
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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### 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 (0.86–0.98)| 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*   |                 |           |
| 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 (0.98–1.02)| 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 injury| 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)| 0.0025    |
| Metastatic solid tumor         | 0.80 (0.68–0.95)| 0.0109    |

CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio; ND, no data.

*Reference was those patients without the respective comorbid condition.
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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.

References
Ahmed M, Malik M, Teselink J, Lancot KL, Herrmann N (2019). Current agents in development for treating behavioral and psychological symptoms associated with dementia. Drugs Aging 36:589–605.

American Geriatrics Society Beers Criteria Update Expert Panel (2019). American Geriatrics Society 2019 updated AGS Beers Criteria(R) for potentially inappropriate medication use in older adults. J Am Geriatr Soc 67:674–694.

Ballard C, Banister C, Khan Z, Cummings J, Demos G, Coate B.; ADP et al. (2019). Current agents in psychotic drug treatment for dementia: number needed to harm. Int J Geriatr Psychiatry 23:393–400.

Chui HC, Lyness SA, Sobel E, Schneider LS (1994). Extrapyramidal signs and psychiatric symptoms predict faster cognitive decline in Alzheimer’s disease. Ann Neurol 1:51–56.

Daumit GL, Crum RM, Guallar E, Powe NR, Primm AB, Steinwachs DM, Ford DE (2003). Outpatient prescriptions for atypical antipsychotics for African Americans, Hispanics, and whites in the United States. Arch Gen Psychiatry 60:121–128.

De Deyn PP, Katz IR, Brodaty H, Lyons B, Greenspan A, Burns A (2005). Management of agitation, aggression, and psychosis associated with dementia: a pooled analysis including three randomized, placebo-controlled double-blind trials in nursing home residents treated with risperidone. Clin Neurol Neurosurg 107:497–508.

Fortin M, Bravo G, Hudon C, Vanasse A, Lapointe L (2005). Prevalence of multimorbidity among adults seen in family practice. Ann Fam Med 3:225–228.

Gilliss DT, Kaicki SE, Normand SL, Anderson GM, Sykora K, Lam K, et al. (2007). Antipsychotic drug use and mortality in older adults with dementia. Ann Intern Med 146:775–786.

Herzig SJ, Rothberg MB, Guess JR, Stevens JP, Marshall J, Gwurtz JH, Marcantonio ER (2016). Antipsychotic use in hospitalized adults: rates, indications, and predictors. J Am Geriatr Soc 64:299–305.

Hugbrechts KE, Gerhard T, Crystal S, Olfsen M, Avm J, Levin R, Lucas JA, et al. (2012). Differential risk of death in older residents in nursing homes prescribed specific atypical antipsychotic drugs: population based cohort study. BMJ 344:e977.

Kales HC, Gittin LN, Lyketsos CG (2018). Assessment and management of behavioral and psychological symptoms of dementia. BMJ 350:h369.

Lopez OL, Becker JT, Chang YF, Sweet RA, Aizenstein H, Sibitz B, et al. (2013). The long-term effects of conventional and atypical antipsychotics in patients with probable Alzheimer’s disease. Am J Psychiatry 170:1051–1058.

Lyketsos CG, Lopez O, Jones B, Fitzpatrick AL., Breitner J, Dekosky S (2002). Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. JAMA 288:1475–1483.

Maher AR, Maglione M, Bagley S, Suttrop M, Hu JH, Ewing B, et al. (2011). Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults: a systematic review and meta-analysis. JAMA 306:1359–1369.

Maust DT, Kales HC, McCammon RJ, Blow FC, Leggett A, Langa KM (2017). Distress associated with dementia-related psychosis and agitation in relation to healthcare utilization and costs. Am J Geriatr Psychiatry 25:1074–1082.

Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, et al. (2011). Updating the American Psychiatric Association Practice Guideline on the use of antipsychotic drug treatment for dementia: a pooled analysis including three randomized, placebo-controlled double-blind trials in nursing home residents treated with risperidone. Clin Neurol Neurosurg 107:497–508.

Peters KR, Rockwood K, Black SE, Bouchard R, Gauthier S, Hogan D, et al. (2006). Characterizing neuropsychiatric symptoms in subjects referred to dementia clinics. Neurology 66:523–528.

Pollock BG, Mulsant BH, Rosen J, Mazumdar S, Blakeley RE, Houck PR, Huber KA (2007). A double-blind comparison of clozapine and risperidone for the treatment of behavioral and psychotic symptoms associated with dementia. Am J Geriatr Psychiatry 15:942–952.

Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, et al. (2011). Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol 173:676–682.

Reus VI, Fochtmann LJ, Eyler AE, Hilty DM, Horvitz-Lennon M, Jibson MD, et al. (2016). The American Psychiatric Association Practice Guideline on the use of antipsychotics to treat agitation or psychosis in patients with dementia. Am J Psychiatry 173:543–546.

Schneider LS, Dagerman K, Insel PS (2006a). Efficacy and adverse effects of antipsychotics in clinical practice: a survey. Consult Pharm 25:739–744.

Schneider LS, Dagerman KS, Insel PS (2005). Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized, placebo-controlled trials. Am J Geriatr Psychiatry 14:191–210.

Schneider LS, Dagerman KS, Insel P (2005). Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA 294:1934–1943.
Schneider LS, Tariot PN, Dagerman KS, Davis SM, Hsiao JK, Ismail MS, et al.; Catie-Ad Study Group (2006b). Effectiveness of atypical antipsychotic drugs in patients with Alzheimer’s disease. N Engl J Med 355:1526–1538.

Seitz DP, Adunuri N, Gill SS, Gruneir A, Herrmann N, Rochon P (2011). Antidepressants for agitation and psychosis in dementia. Cochrane Database Syst Rev CD008191.

Shin HW, Chung SJ (2012). Drug-induced parkinsonism. J Clin Neurof 8:15–21.

Smeets CHW, Zuidema SU, Hulshof TA, Smalbrugge M, Gerritsen DL, Koopmans R, Luijendijk HJ (2018). Efficacy of antipsychotics in dementia depended on the definition of patients and outcomes: a meta-epidemiological study. J Clin Epidemiol 101:17–27.

Steinberg M, Lyketsos CG (2012). Atypical antipsychotic use in patients with dementia: managing safety concerns. Am J Psychiatry 169:900–906.

Steinberg M, Shao H, Zandi P, Lyketsos CG, Welsh-Bohmer KA, Norton MC, et al. (2008). Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: the Cache County Study. Int J Geriatr Psychiatry 23:170–177.

Stern Y, Liu X, Albert M, Brandt J, Jacobs DM, Del Castillo-Castaneda C, et al. (1996). Modeling the influence of extrapyramidal signs on the progression of Alzheimer disease. Arch Neurol 53:1121–1126.

Toot S, Swinson T, Devine M, Challis D, Orrell M (2017). Causes of nursing home placement for older people with dementia: a systematic review and meta-analysis. Int Psychogeriatr 29:195–208.

Watt JA, Goodarzi Z, Veroniki AA, Nincic V, Khan PA, Ghassemi M, et al. (2020). Safety of pharmacologic interventions for neuropsychiatric symptoms in dementia: a systematic review and network meta-analysis. BMC Geriatr 20:212.

Wetmore JB, Peng Y, Yan H, Li S, Irfan M, Shim A, et al. (2021). Association of dementia-related psychosis with long-term care use and death. Neurology 96:e1620–e1631.

Wolff JL, Starfield B, Anderson G (2002). Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. Arch Intern Med 162:2269–2276.

World Health Organization (2019). Dementia. [Online]. https://www.who.int/news-room/fact-sheets/detail/dementia. [Accessed 12 May 2020]

Wu CS, Wang SC, Gau SS, Tsai HJ, Cheng YC (2013). Association of stroke with the receptor-binding profiles of antipsychotics—a case-crossover study. Biol Psychiatry 73:414–421.

Yaffe K, Fox P, Newcomer R, Sands L, Lindquist K, Dane K, Covinsky KE (2002). Patient and caregiver characteristics and nursing home placement in patients with dementia. JAMA 287:2090–2097.

Yunusa I, Alsumali A, Garba AE, Regestein QR, Eguale T (2019). Assessment of reported comparative effectiveness and safety of atypical antipsychotics in the treatment of behavioral and psychological symptoms of dementia: a network meta-analysis. JAMA Netw Open 2:e190828.