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Use of Direct-Acting Antiviral Agents and Survival among Medicare Beneficiaries with Dementia and Chronic Hepatitis C

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Abstract

Background: Many patients with Alzheimer's disease and related dementia (ADRD) have chronic hepatitis C due to the high prevalence of both conditions among elderly populations. Direct-acting antivirals (DAAs) are effective in treating hepatitis C virus (HCV). However, the complexity of ADRD care may affect DAA use and outcomes among patients with HCV and ADRD. Little information exists on uptake of DAAs, factors associated with DAA use, and health benefits of DAAs among patients with HCV and ADRD.

Objective: To examine use and survival benefits of DAAs in Medicare patients with HCV and ADRD.

Methods: The study included Medicare patients with HCV between 2014 and 2017. We estimated Cox proportional hazards regressions to examine the association between having ADRD and DAA use, and the relation between DAA use and survival among patients with HCV and ADRD.

Results: The adjusted hazard of initiating a DAA was 50% lower in patients with ADRD than those without ADRD (adjusted HR = 0.50, 95% CI: 0.46–0.54). The hazard of DAA use among ADRD patients with behavioral disturbances was 68% lower than non-ADRD patients (adjusted

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HR = 0.32, 95% CI: 0.28–0.37). DAA treatment was associated with a significant reduction in mortality among ADRD patients (adjusted HR = 0.52, 95% CI: 0.44–0.61).

Conclusion: The rate of DAA treatment in patients with HCV and ADRD was low – particularly among those with behavioral disturbance. The survival benefits of DAA treatment for patients with ADRD were substantial.

Keywords

Alzheimer's Disease; dementia; hepatitis C; direct-acting antivirals; comorbidity

Alzheimer's disease and related dementia (ADRD) is an increasingly important public health concern. Alzheimer's is the sixth leading cause of death in the United States [1]. Dementia is a general term for conditions that impair memory, thought processes, and functioning, primarily among older adults [2]. Alzheimer's disease is the most common cause of dementia in older adults. Other common dementias include Lewy Body dementia, frontotemporal dementia (FTD) (leading cause of dementia in those under age 60) and vascular dementia [2]. ADRD currently affects over 5.8 million Americans, most of whom are 65 years or older [1]. The number of ADRD patients is estimated to reach 7.1 million in 2025 and 13.8 million in 2050 [1,3]. Patients with ADRD usually have multiple comorbid conditions, which may exacerbate the progression of dementia and increase the risk of death [1,4]. Health care costs associated with ADRD are also high: average Medicare payments for beneficiaries with ADRD are over three times the payments for those without ADRD, and Medicaid costs are over 23 times higher [1].

Growing evidence indicates that individuals with ADRD experience lower levels of recommended services than those without ADRD [3,5,6]. For example, Medicare patients with dementia were less likely to receive eye care compared to those without dementia, and individuals with dementia or cognitive impairment were at higher risk of medication non-adherence than those without [3,5,6]. ADRD also reduced the likelihood of receiving treatment for other medical conditions: people with ADRD had lower rates of cataract surgery, diabetes care, invasive diagnostic tests or curative therapies for colon cancer, and intravenous thrombolysis for stroke [4], [7–12].

A variety of factors may contribute to the findings that patients with ADRD are less likely to receive treatment and monitoring for comorbid conditions than those with similar conditions but without ADRD. The presence of ADRD complicates clinical care due to increased risk of complications, discomforts, and adverse drug events [4,7]. In addition, dementia patients have limited ability to self-manage chronic conditions and show great dependency, which challenges primary and secondary care [4,7]. All of these factors – including increased risk and care burden – must be considered in determining the appropriate level of care for comorbid conditions among ADRD patients.

An estimated 2.4 million people in the United States are living with hepatitis C virus infection (HCV) [13]. HCV is most prevalent among baby boomers – an aging population that is at high risk of developing ADRD. Many of those HCV patients were unknowingly infected through blood transfusions before 1980, when comprehensive screening of the

blood supply was introduced [14,15]. Untreated HCV can lead to serious health outcomes, such as cirrhosis, hepatocellular cancer, liver damage, and increased mortality [16]. HCV also has extrahepatic manifestations, which bring on or aggravates other conditions, such as rheumatoid arthritis, cardiovascular diseases, or diabetes [17–19]. Recently introduced HCV treatments – direct-acting antivirals (DAAs) – have over 90% cure rates. DAAs reduce the HCV disease progression and extrahepatic manifestations of HCV [19–22]. Recent studies reported that DAA therapy was associated with a 49%–68% reduction in mortality risk among HCV patients [23,24]. In addition, DAAs are easy to administer (one pill per day) and have a short treatment period (8–12 weeks).

These features of DAAs have raised hope that HCV infection can be eradicated, and calls have been made for all HCV patients to take DAAs as a national goal [25,26]. The World Health Organization has also proposed to eliminate viral hepatitis as a public health threat and recommended treating all adults with chronic HCV infection with DAAs [27].

Despite these potential benefits of DAAs and national efforts to improve DAA uptake, adults with HCV and ADRD present unique challenges with regard to the optimal course of treatment. First, ADRD is prevalent among older adults, who often have multiple comorbidities and are on multiple medications [28]. Taking multiple medications might be a burden for ADRD patients, particularly when their condition progresses and swallowing pills becomes difficult or if they have significant agitation. Also, with their cognitive impairment, ADRD patients may find it increasingly challenging to adhere to their prescribed medication(s). Hence, physicians may consider the number of medications and the complexity of the patient's entire pharmaceutical regimen in the decision to prescribe a DAA.

Second, DAAs might not be an optimal choice of therapy when people have ADRD with behavioral disturbances, not only because medication administration is difficult but also behavioral and psychological symptoms may become clinically dominant, shifting attention away from treating HCV.

Third, physicians may be reluctant to prescribe DAAs for patients with HCV and ADRD because of adverse drug reactions. Reported side effects of DAAs are fatigue and gastrointestinal symptoms, while they are not frequent [29]. ADRD medication, such as cholinesterase inhibitors, also causes gastrointestinal symptoms; therefore, physicians might not recommend DAAs to those currently taking any type of cholinesterase inhibitors [30].

Furthermore, when life expectancy is short (i.e. patients who are in the late stage of Alzheimer's), the complication of initiating a drug treatment may outweigh the benefits of DAAs.

Finally, the high cost of ADRD care increases financial burden for ADRD patients, which might also lead to lower use of DAA treatments for patients with both ADRD and HCV.

Given the complexity of treating ADRD but the significant health benefits of DAAs, understanding whether an ADRD diagnosis is associated with lower use of DAA therapy is an important unanswered question. To address this gap, we examined whether use of DAA

treatment differed between HCV patients with and without ADRD using national Medicare administrative claims data. Medicare is a federal health insurance program in the United States that provides health insurance to the elderly and to some younger people with disabilities. Most ADRD patients are enrolled in the Medicare because they are usually 65 years or older [1]. Our study also evaluated whether ADRD-related factors, such as behavioral disturbances, years since ADRD diagnosis, use of ADRD medications, and pharmacy burden affected uptake of DAA treatments in the ADRD population. We then assessed whether the use of DAAs increased survival among HCV patients with ADRD. To our knowledge, this is the first study to examine the health benefits of treatment for a comorbid condition in adults with ADRD.

METHODS

Data

We used Medicare claims from 2013 through 2017 for inpatient, skilled nursing facility, outpatient, and physician services to identify HCV patients. The 2013 data were used only to ensure that patients did not have any HCV-related claims in 2013. Medicare Master Beneficiary Summary Files (MBSF) were used to obtain patient demographics and health risks (indicators of chronic conditions, including ADRD). DAA treatment was identified from 2014–2017 Medicare Part D data. The American Community Survey (ACS) supplied information on ZIP-level education and income, and the Area Health Resources Files (AHRF) provided information on the rurality of patient residence based on ZIP. Institutional Review Board approval from the first author's institution was obtained prior to the study.

HCV care was defined by the standard algorithm used by the Centers for Medicare and Medicaid Services [31]: at least 1 inpatient or skill nursing facility claim, or at least 2 hospital outpatient or carrier (physician) claims of HCV in a given year. HCV claims were identified based of International Classification of Diseases, Ninth Revision (ICD-9) codes of 070.44, 070.54, 070.70, 070.71 or ICD-10 codes B18.2, B19.20, B19.21, Patients in Medicare Advantage were not eligible to be in the sample because we did not have claims for them.

Sample selection

We selected beneficiaries in the traditional fee-for-service (FFS) Medicare program who newly sought HCV care between January 1, 2014 and December 31, 2017 after a one-year washout period. This criterion identified patients who were at a relatively similar stage of seeking HCV care. We defined an index date for each beneficiary as the date of the first HCV claim after the one-year washout period.

Patients were required to be continuously enrolled in both Part A (coverage for hospital and post-acute care services) and Part B (coverage for outpatient medical care), and to have Part D outpatient prescription drug coverage through the entire study period to identify DAA use.

We excluded individuals who died within 12 months after the index date because DAA treatment is not recommended for patients with life expectancy less than one year [31]. We also excluded those who initiated a DAA before the index date. They were likely to be

diagnosed with HCV before the one-year washout period (i.e., before they were selected for our analysis). Finally, we excluded beneficiaries with missing information on ACS or AHRF variables (ZIP-level education/income or rurality of residence). Figure 1 presents a diagram of the study sample selection.

Identifying patients with ADRD

We identified individuals with ADRD based on a chronic condition flag included in MBSF (Supplementary Table 1). This flag was constructed by CMS based on a standard algorithm [32]: having at least one inpatient or skilled nursing facility, hospital outpatient, or carrier (physician) claim with ADRD diagnosis during the past 3 years prior to the index date (Supplementary Table 2). Information on the date when the beneficiary first met the criteria for the ADRD indicator was also obtained from MBSF. We then used this variable to calculate how long the patient had been diagnosed with ADRD.

Identifying DAA use

DAA use was defined as having at least one prescription for one of the following DAAs between January 1, 2014 and December 31, 2017: elbasvir/grazoprevir, glecaprevir/pibrentasvir, ledipasvir/sofosbuvir, ombitasvir/paritaprevir/ritonavir plus dasabuvir, sofosbuvir, sofosbuvir/velpatasvir, or sofosbuvir/velpatasvir/voxilaprevir. We considered patients who did not initiate DAAs during the study period as DAA non-users.

Covariates

We controlled for patients' demographic and neighborhood characteristics, including sex, race/ethnicity (White, African-American, Hispanic, and other race), age (<55, 55–60, 60–65, 65–70, 70–75, >75), and ZIP-level income and education. We included a variable indicating whether a beneficiary received a Part D low-income subsidy to capture an individual's income level. We also included indicators of conditions (HIV/AIDS, cancer, cardiac diseases, diabetes, eye diseases, kidney disorders, drug and alcohol related disorder, and bone diseases), and a variable indicating whether patients had cirrhosis (the most advanced form of fibrosis due to HCV progression) identified by applying the Chronic Condition Data Warehouse algorithm to claims data (Supplementary Table 2). To represent the pharmacy burden, we created a variable indicating whether patients were taking drugs in 10 or more therapeutic classes. Additionally, we included a rural/urban indicator and U.S. Census Bureau region indicators: Northeast (omitted), Midwest, South, and West.

To partially control for ADRD progression, we created a variable for ADRD patients representing years since the ADRD diagnosis (less than one year versus more than one year). We also used variables indicating whether patients were on any ADRD medications (donepezil, galantamine, memantine, memantine plus donepezil, or rivastigmine), and whether the patient had ADRD with behavioral disturbances (Supplementary Table 2).

Analysis of DAA use by the presence of ADRD

The outcome measure for this analysis was time to DAA initiation from the index date. The initiation date of DAA therapy was constructed as the date of the first DAA prescription fill.

All patients were followed up from the index date until they initiated a DAA, died or reached the end of the study period (December 31, 2017).

We first compared the cumulative rates of DAA use between patients with and without ADRD using a Nelson-Aalen curve. We then estimated Cox proportional hazards regression to examine the association between having ADRD and use of DAAs. We used Cox proportional hazards regression for several reasons, including different follow-up periods across beneficiaries, the presence of loss to follow-up, and the nature of the outcome (i.e., DAA use is an one-time event). We estimated hazard ratios of DAA initiation after adjusting for all covariates described above, as well as interaction effects between ADRD and factors that may affect DAA use: years since ADRD diagnosis, whether patients were on any ADRD medication, whether ADRD patients had behavioral disturbance, the presence of cirrhosis, and whether patients were on medications in 10 or more therapeutic classes.

Analysis of Mortality by DAA use among ADRD patients

A Kaplan-Meier curve was drawn to compare the unadjusted survival rates between DAA users and DAA non-users among patients with ADRD. The log rank test was used to test whether the survival curves differed between the two groups. We used Cox proportional hazards regression to estimate adjusted hazard ratios of death between the two groups after controlling for all the covariates described above. We further ensured that patient characteristics of DAA users and non-users were balanced, based on inverse propensity score weighting. We constructed time from DAA initiation to death as a time-varying exposure measure to reflect differences in time from index date to DAA use across patients [33]. This allows us to address “immortal bias,” which arises because treated individuals need to survive at least until exposure and thus favors survival for the treatment group [34,35].

The Cox model relies on the proportional hazards (PH) assumption, implying that the effect of a predictor of interest does not change over time. We evaluated the PH assumption by comparing estimated $-\ln(-\ln)$ survival curves over different groups of factors investigated in both analysis: DAA use and mortality. We observed a constant distance between the estimated log-log survival curves, suggesting that the predictor is proportional and PH assumption was satisfied (Supplementary Figure 1 and Supplementary Figure 2).

We considered $p < 0.05$ as statistically significant in all analyses. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and Stata version 15 (Stata- Corp LP, College Station, TX).

RESULTS

Study sample

A total of 217,560 Medicare beneficiaries with HCV met our study inclusion criteria, 17,196 (8%) with ADRD and 200,364 (92%) without ADRD (Figure 1). Table 1 presents characteristics of the study sample. Approximately 40% were female. The relatively low share of females reflects the higher prevalence of HCV among males than in females [36]. About 67% were white, 24% were African-American, and 43% were aged 65 and older. The

most common comorbidities were cardiac diseases (74%), drug and alcohol related disorders (52%), bone diseases (37%), and diabetes (32%). Patients with ADRD were more likely to be female, African-American, and older, receive a Part D low-income subsidy, live in urban settings, and have other conditions such as cirrhosis, HIV/AIDS, cancer, cardiac diseases, diabetes, kidney diseases, bone diseases, and drug and alcohol related disorders than patients without ADRD.

DAA use by the presence of ADRD

The Nelson-Aalen curve in Figure 2 indicates lower cumulative rates of DAA use among patients with ADRD compared with those without ADRD. During the first year of follow-up after the index date, 9% of ADRD patients initiated a DAA, whereas 23% of individuals without ADRD used a DAA. By the end of the follow-up period, the cumulative DAA use rate was 24% among those with ADRD and approximately 55% among those without ADRD.

Table 2 presents DAA use rates by select factors within the ADRD group (the comparison of DAA use by all factors in the group is reported in Supplement Table 2). DAA users were less likely to have behavioral disturbances than DAA non-users, 12% and 18%, respectively. We observed no difference in the rate of DAA initiation by ADRD duration, use of ADRD medications, and pharmacy burden (≥ 10 drug therapeutic classes) within the ADRD group. Compared to DAA non-users, DAA users were more likely to have cirrhosis.

The results from the Cox regression are shown in Table 3. The adjusted hazard ratio of initiating a DAA was 50% lower in patients with ADRD compared with those without ADRD (adjusted HR = 0.50, 95% CI: 0.46–0.54). The interaction term between ADRD and behavioral disturbances indicators showed that having behavioral disturbances significantly lowered DAA use among ADRD patients: the hazard of DAA use was 35% lower in ADRD patients with behavioral disturbances than in ADRD patients without behavioral disturbances. This interaction effect indicates that the hazard of DAA use in those with behavioral disturbances was 68% lower than non-ADRD patients.

Taking drugs in 10 or more drug therapeutic classes was positively associated with DAA use among ADRD patients. The association was significant but small: the hazard of DAA use in ADRD patients taking 10 or more drugs was 11% higher than ADRD patients with fewer medications (adjusted HR = 1.11, 95% CI: 1.01–1.21). ADRD patients with cirrhosis experienced a significant but small increase in the hazard of DAA initiation compared to ADRD patients without cirrhosis (adjusted HR = 1.11, 95% CI: 1.00–1.23).

The interactions between ADRD and other ADRD-related factors show that those factors did not significantly change the risk of DAA use among ADRD patients. The hazard of DAA initiation was the same between patients living with ADRD more than one year and those with ADRD less than one-year (adjusted HR = 1.00, 95% CI: 0.92–1.09). The adjusted HR of DAA initiation between patients who were taking any ADRD medications and those who were not was 0.99 (95% CI: 0.90–1.09).

We observed significant associations between other patient characteristics and DAA initiation. The hazard of DAA use increased with every 5-year increase in age, except for beneficiaries age 75 and older. Females and patients living in urban areas had lower hazards of initiating a DAA. The hazard of DAA initiation was 37% higher in African-Americans compared to whites, consistent with a prior study [33]. The presence of most comorbidities, such as HIV/AIDS, cancer, diabetes, and cardiac diseases, were associated with lower hazards of DAA initiation, whereas patients with cirrhosis and eye diseases had higher hazards of DAA use.

Survival by DAA use among ADRD patients

Figure 3 depicts the Kaplan-Meier survival curves for DAA users and DAA non-users among ADRD patients. DAA treatment was associated with improved survival among ADRD patients ($p < 0.001$). The 1-year mortality rate was 2.0% among DAA users and 8.4% among DAA non-users.

DAA treatment was significantly associated with a reduction in mortality among beneficiaries with ADRD after adjusting for patient characteristics (Table 4). The adjusted hazard ratio of dying between DAA users and DAA non-users with ADRD was 0.52 (95% CI: 0.48–0.52). Patient characteristics other than DAA treatment were also associated with mortality levels. The hazard of dying was slightly lower among patients with more than one year since ADRD diagnosis than those diagnosed with ADRD within one year (adjusted HR = 0.96; 95% CI: 0.93–0.99). The hazard of dying was also lower among ADRD patients who were on medications treating Alzheimer's symptoms, compared to those who were not (adjusted HR = 0.89; 95% CI: 0.86–0.92). In contrast, ADRD with behavioral disturbances was associated with increased hazard of mortality (adjusted HR = 1.31; 95% CI: 1.26–1.35). The hazard of death was also higher among patients taking 10 or more prescription medications (adjusted HR = 1.15; 95% CI: 1.11–1.18).

Several patient factors were significantly associated with the hazard of death among beneficiaries with ADRD. One of these was patient age: the adjusted hazard ratio of dying between patients age 75 and older and those younger than age 55 was 2.45 (95% CI: 2.27–2.64). Additionally, being male and white, residing in the Midwest or South, living in neighborhoods with higher income, and having other conditions were associated with increased mortality. The hazard of dying was not affected by receiving a Part D low-income subsidy – a variable capturing individual-level income.

DISCUSSION

The hazard of initiating a DAA was 50% lower in patients with ADRD compared with those without ADRD after adjusting for patient demographics, neighborhood factors, and comorbidities. This result is consistent with previous studies, which showed that ADRD reduced the likelihood of receiving treatment for comorbid conditions [7–12]. A possible explanation for lower access to DAA treatment is that ADRD patients have complicated clinical situations, such as cognitive declines, recurrent falls, or reduced mobility [37]. Lower use of DAAs may reflect physicians' decisions not to treat, based on patients' medical needs and/or caregivers' preferences.

Treatment decisions related to ADRD are subject to multiple factors such as the severity of ADRD, the presence of comorbidities, pharmacy burdens, and the complexity of ADRD care. We observed a 68% decrease in the hazard of DAA use among individuals who had ADRD with behavioral disturbances compared to those without ADRD. ADRD patients with behavioral disturbances frequently experience neuropsychological symptoms, such as agitation, which present considerable challenges for medication administration. These patients often require multiple medications, including antipsychotics and antidepressants to treat behavioral disturbances, and have complex prescribed regimens. Hence, physicians or caregivers may choose not to pursue DAA treatment for those patients.

Besides behavioral disturbances, other clinical factors were expected to influence physicians' treatment decisions for patients with ADRD. However, our results suggest that the hazards of initiating a DAA across years since ADRD diagnosis and use of any ADRD medications were not significantly different from the hazard of DAA use among ADRD patients in general. The presence of cirrhosis and use of more than 10 medications resulted in slightly elevated hazards of DAA use, but the effects were small (11% increase in the adjusted hazard ratio).

Another notable finding from our study was that DAA treatment was associated with a 48% lower hazard of mortality among ADRD patients. This survival benefit is very similar to what is reported for general HCV populations [23]. It is an encouraging finding because physicians and caregivers may be reluctant to provide additional services, given the high disease burden and increased clinical risk of ADRD patients. It suggests that better care coordination among primary care physicians, neurologists, and hepatologists is needed to enable evaluation for diagnosis and to ensure that ADRD patients receive the appropriate level of care for comorbid conditions.

The number of Americans with ADRD is expected to continue to grow, increasing the burden of ADRD on the community and the health care system. Determining the appropriate level of care for patients with dementia is complex. Developing guidelines for dementia care requires that the unique needs and desires of ADRD patients be considered. The Alzheimer's Association highlights a need for efforts to enhance evidence-based quality of care for people with ADRD in order to reduce complications from other chronic conditions, improve health outcomes, and reduce associated health care costs of ADRD patients [38]. Our analysis provides evidence that can be used for those efforts when ADRD patients present with HCV.

Limitations

Our results should be interpreted in the light of several limitations. First, we did not have detailed clinical information, such as stages of ADRD. This is an inherent limitation of Medicare claims data. However, we were able to partially control for that limitation using indicators of newly diagnosed ADRD patients (within one year) and use of any Alzheimer's medications. Also, we did not observe clinical severity of other comorbid conditions. However, we included variables indicating chronic condition indicators and whether patients were taking drugs in more than 10 therapeutic classes. Second, we did not have information on the presence or extent of informal caregivers (e.g. spouses or family members), which

can affect the receipt of treatments for other conditions. We also lacked information regarding the physician's decision-making process. For example, it is possible that physicians avoid DAAs because of concern for side effects, drug interactions, or poor prognosis of the patient. Third, unobservable factors may lead to selection bias in the analysis of survival from DAA treatment, even with inverse propensity score weighting. In addition, we used all-cause mortality as our outcome since information on condition-specific deaths was not available in claims data; therefore, some deaths in our analysis may not be HCV-related. Fourth, our sample might not represent the general ADRD population because we included patients with both HCV and ADRD. Approximately two-thirds of the ADRD population are female [39], the share of females in our analysis was relatively low because HCV is more prevalent in males than in females [36]. Finally, our study was limited to traditional fee-for-service Medicare beneficiaries; thus, our findings may not apply to the entire population of older adults with ADRD.

Conclusions and implications

HCV patients with ADRD were less likely to receive DAA treatment compared with HCV patients without ADRD. The survival benefit of DAAs for patients with ADRD were substantial. These findings can help inform treatment decision-making and guideline development for the treatment of people with both dementia and HCV.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- [1]. (2020) 2020 Alzheimer's disease facts and figures. *Alzheimer's & Dementia* 16, 391–460.
- [2]. Centers for Disease Control and Prevention, Alzheimer's Disease, Last updated October 9, 2018, Accessed on October 9, 2018.
- [3]. Pershing S, Goldstein MK, Henderson VW, Bundorf MK, Lu Y, Rahman M, Stein JD (2020) Receipt of Eye Care Services among Medicare Beneficiaries with and without Dementia. *Ophthalmology*.
- [4]. Bunn F, Burn A-M, Goodman C, Rait G, Norton S, Robinson L, Schoeman J, Brayne C (2014) Comorbidity and dementia: a scoping review of the literature. *BMC Med* 12, 1–15.
- [5]. Barat I, Andreasen F, Damsgaard EMS (2001) Drug therapy in the elderly: what doctors believe and patients actually do. *Br J Clin Pharmacol* 51, 615–622. [PubMed: 11422022]
- [6]. Salas M, In't Veld BA, van der Linden PD, Hofman A, Breteler M, Stricker BH (2001) Impaired cognitive function and compliance with antihypertensive drugs in elderly: the Rotterdam Study. *Clin. Pharmacol. Ther* 70, 561–566. [PubMed: 11753273]
- [7]. Thorpe CT, Thorpe JM, Kind AJH, Bartels CM, Everett CM, Smith MA (2012) Receipt of monitoring of diabetes mellitus in older adults with comorbid dementia. *J Am Geriatr Soc* 60, 644–651. [PubMed: 22428535]
- [8]. Pershing S, Henderson VW, Bundorf MK, Lu Y, Rahman M, Andrews CA, Goldstein M, Stein JD (2019) Differences in Cataract Surgery Rates Based on Dementia Status. *J. Alzheimers Dis* 69, 423–432. [PubMed: 30958371]

- [9]. Gupta SK, Lamont EB (2004) Patterns of presentation, diagnosis, and treatment in older patients with colon cancer and comorbid dementia. *J Am Geriatr Soc* 52, 1681–1687. [PubMed: 15450045]
- [10]. Saposnik G, Cote R, Rochon PA, Mamdani M, Liu Y, Raptis S, Kapral MK, Black SE, Registry of the Canadian Stroke Network, Stroke Outcome Research Canada (SORCan) Working Group (2011) Care and outcomes in patients with ischemic stroke with and without preexisting dementia. *Neurology* 77, 1664–1673. [PubMed: 22042795]
- [11]. Vitry AI, Roughead EE, Preiss AK, Ryan P, Ramsay EN, Gilbert AL, Caughey GE, Shakib S, Esterman A, Zhang Y, McDermott RA (2010) Influence of comorbidities on therapeutic progression of diabetes treatment in Australian veterans: a cohort study. *PLoS ONE* 5, e14024. [PubMed: 21103337]
- [12]. Zhang Y, Vitry A, Roughead E, Ryan P, Gilbert A (2010) Co-morbidity and the utilization of health care for Australian veterans with diabetes. *Diabet. Med* 27, 65–71. [PubMed: 20121891]
- [13]. Hofmeister MG, Rosenthal EM, Barker LK, Rosenberg ES, Barranco MA, Hall EW, Edlin BR, Mermin J, Ward JW, Ryerson AB (2019) Estimating Prevalence of Hepatitis C Virus Infection in the United States, 2013–2016. *Hepatology* 69, 1020–1031. [PubMed: 30398671]
- [14]. Commentary | U.S. 2014 Surveillance Data for Viral Hepatitis | Statistics & Surveillance | Division of Viral Hepatitis | CDC, Last updated February 5, 2019, <http://www.cdc.gov/hepatitis/statistics/2014surveillance/commentary.htm>, Accessed on February 5, 2019.
- [15]. Moorman AC, Gordon SC, Rupp LB, Spradling PR, Teshale EH, Lu M, Nerenz DR, Nakasato CC, Boscarino JA, Henkle EM, Oja-Tebbe NJ, Xing J, Ward JW, Holmberg SD, Chronic Hepatitis Cohort Study Investigators (2013) Baseline characteristics and mortality among people in care for chronic viral hepatitis: the chronic hepatitis cohort study. *Clin. Infect. Dis* 56, 40–50. [PubMed: 22990852]
- [16]. Hepatitis C Questions and Answers for Health Professionals | CDC, Last updated May 27, 2020, <https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm>, Accessed on May 27, 2020.
- [17]. Gill K, Ghazianian H, Manch R, Gish R (2016) Hepatitis C virus as a systemic disease: reaching beyond the liver. *Hepatol Int* 10, 415–423. [PubMed: 26660706]
- [18]. Cacoub P, Comarmond C, Domont F, Savey L, Desbois AC, Saadoun D (2016) Extrahepatic manifestations of chronic hepatitis C virus infection. *Ther Adv Infect Dis* 3, 3–14. [PubMed: 26862398]
- [19]. Negro F, Forton D, Craxi A, Sulkowski MS, Feld JJ, Manns MP (2015) Extrahepatic Morbidity and Mortality of Chronic Hepatitis C. *Gastroenterology* 149, 1345–1360. [PubMed: 26319013]
- [20]. Singal AG, Rich NE, Mehta N, Branch AD, Pillai A, Hoteit M, Volk M, Odewole M, Scaglione S, Guy J, Said A, Feld JJ, John BV, Frenette C, Mantry P, Rangnekar AS, Oloruntoba O, Leise M, Jou JH, Bhamidimarri KR, Kulik L, Ioannou GN, Huang A, Tran T, Samant H, Dhanasekaran R, Duarte-Rojo A, Salgia R, Eswaran S, Jalal P, Flores A, Satapathy SK, Kagan S, Gopal P, Wong R, Parikh ND, Murphy CC (2019) Direct-Acting Antiviral Therapy for Hepatitis C Virus Infection Is Associated With Increased Survival in Patients With a History of Hepatocellular Carcinoma. *Gastroenterology* 157, 1253–1263.e2. [PubMed: 31374215]
- [21]. Polo ML, Laufer N (2017) Extrahepatic manifestations of HCV: the role of direct acting antivirals. *Expert Review of Anti-infective Therapy* 15, 737–746. [PubMed: 28696154]
- [22]. Kamp WM, Sellers CM, Stein S, Lim JK, Kim HS (2019) Impact of Direct Acting Antivirals on Survival in Patients with Chronic Hepatitis C and Hepatocellular Carcinoma. *Scientific Reports* 9, 17081. [PubMed: 31745132]
- [23]. Kalidindi Y, Jung J, Feldman R, Riley T (2020) Association of Direct-Acting Antiviral Treatment With Mortality Among Medicare Beneficiaries With Hepatitis C. *JAMA Netw Open* 3, e2011055–e2011055. [PubMed: 32692371]
- [24]. Backus LI, Belperio PS, Shahoumian TA, Mole LA (2018) Direct-acting antiviral sustained virologic response: Impact on mortality in patients without advanced liver disease. *Hepatology* 68, 827–838. [PubMed: 29377196]
- [25]. Sussman NL, Remien CH, Kanwal F (2014) The End of Hepatitis C. *Clinical Gastroenterology and Hepatology* 12, 533–536. [PubMed: 24480676]

- [26]. National Academies of Sciences E (2017) A National Strategy for the Elimination of Hepatitis B and C: Phase Two Report.
- [27]. Hepatitis C| World Health Organization, 7 27, 2020, <https://www.who.int/news-room/fact-sheets/detail/hepatitis-c>, Accessed on July 27, 2020.
- [28]. Hudani ZK, Rojas-Fernandez CH (2016) A scoping review on medication adherence in older patients with cognitive impairment or dementia. *Res Social Adm Pharm* 12, 815–829. [PubMed: 26797263]
- [29]. Gonzales Zamora JA (2018) Adverse Effects of Direct Acting Antivirals in HIV/HCV Coinfected Patients: A 4-Year Experience in Miami, Florida. *Diseases* 6,.
- [30]. Hughes A, Musher J, Thomas S, Beusterien K, Strunk B, Arcona S (2004) Gastrointestinal Adverse Events in a General Population Sample of Nursing Home Residents Taking Cholinesterase Inhibitors. *The Consultant Pharmacist* 19, 713–720. [PubMed: 16553494]
- [31]. Core Concepts - Making a Decision on When to Initiate HCV Therapy - Evaluation and Preparation for Hepatitis C Treatment - Hepatitis C Online. <https://www.hepatitisc.uw.edu/go/evaluation-treatment/treatment-initiation-decision/core-concept/all>. Accessed on June 01, 2020.
- [32]. Condition Categories - Chronic Conditions Data Warehouse. <https://www2.ccwdata.org/web/guest/condition-categories>. Accessed on June 01, 2020.
- [33]. Jung J, Du P, Feldman R, Kong L, Riley T (2019) Racial/Ethnic and Socioeconomic Disparities in Use of Direct-Acting Antivirals Among Medicare Beneficiaries with Chronic Hepatitis C, 2014–2016. *J Manag Care Spec Pharm* 25, 1236–1242. [PubMed: 31663464]
- [34]. Cho IS, Chae YR, Kim JH, Yoo HR, Jang SY, Kim GR, Nam CM (2017) Statistical methods for elimination of guarantee-time bias in cohort studies: a simulation study. *BMC Med Res Methodol* 17, 126. [PubMed: 28830373]
- [35]. Gleiss A, Oberbauer R, Heinze G (2018) An unjustified benefit: immortal time bias in the analysis of time-dependent events. *Transpl. Int* 31, 125–130. [PubMed: 29024071]
- [36]. Baden R, Rockstroh JK, Buti M (2014) Natural History and Management of Hepatitis C: Does Sex Play a Role? *J Infect Dis* 209, S81–S85. [PubMed: 24966194]
- [37]. Hernández MH, Mestres C, Modamio P, Junyent J, Costa-Tutusaus L, Lastra CF, Mariño EL (2019) Adverse Drug Events in Patients with Dementia and Neuropsychiatric/Behavioral, and Psychological Symptoms, a One-Year Prospective Study. *Int J Environ Res Public Health* 16,.
- [38]. Alzheimer's Disease and Dementia, Quality of Care. <https://www.alz.org/professionals/public-health/core-areas/quality-of-care>. Accessed on June 01, 2020.
- [39]. Alzheimer's Disease and Dementia, Women and Alzheimer's. <https://alz.org/alzheimers-dementia/what-is-alzheimers/women-and-alzheimer-s>. Accessed on August 24, 2020.

Figure 1.

Study sample selection

Abbreviations: ADRD, Alzheimer's disease and related dementia; DAA, Direct-acting antiviral agent; FFS, fee-for-service

Figure 2.

Nelson-Aalen Cumulative Hazard of DAA use

Abbreviations: DAA, Direct-acting antiviral agent; ADRD, Alzheimer's disease and related dementia; HCV, hepatitis C Virus.

Note: *Index date is the first HCV claim date after a one-year washout period.

Figure 3.

Kaplan Meier Survival Plot Among ADRD Beneficiaries

Abbreviations: DAA, Direct-acting antiviral agent; ADRD, Alzheimer's disease and related dementia

Note: *Index date is the first HCV claim date after a one-year washout period

Table 1.

Characteristics of Medicare Beneficiaries with Hepatitis C, 2014–2017

	Overall (N=217,650)	ADRD (N=17,196)	Non-ADRD (N=200,364)	<i>p</i>
	N (%)	N (%)	N (%)	
With ADRD	17,196 (7.9%)			
Age				0.000
Age 55–60	35,399 (16.3)	1,908 (11.1)	33,491 (16.7)	
Age 60–65	32,596 (15.0)	2,525 (14.7)	30,071 (15.0)	
Age 65–70	63,088 (29.0)	4,489 (26.1)	58,599 (29.2)	
Age 70–75	16,002 (7.36)	2,289 (13.31)	13,713 (6.84)	
Age >75	14,921 (6.86)	3,921 (22.8)	11,000 (5.49)	
Gender				0.000
Female	88,061 (40.5)	7,217 (42.0)	80,844 (40.3)	
Race/ ethnicity				0.000
African American	51,986 (23.9)	5,035 (29.3)	46,951 (23.4)	
Hispanic	7,270 (3.3)	642 (3.7)	6,628 (3.3)	
Other	11,542 (5.3)	981 (5.7)	10,561 (5.3)	
Geographic location				0.000
Rural	37,984 (17.5)	2,287 (13.3)	35,697 (17.8)	
Region				0.000
Midwest	40,175 (18.5)	3,143 (18.3)	37,032 (18.5)	
South	83,305 (38.3)	6,839 (39.8)	76,466 (38.2)	
West	49,530 (22.8)	3,564 (20.7)	45,966 (22.9)	
Neighborhood characteristics				
Per capita income (tertile)				0.000
Medium	68,605 (31.5)	5,039 (29.3)	63,566 (31.7)	
High	69,226 (31.8)	5,669 (33.0)	63,557 (31.7)	
Education above average ^I	101,152 (46.5)	8,402 (48.9)	92,750 (46.3)	0.000
Part D low-income subsidy	165,353 (76.0)	13,929 (81.0)	151,424 (75.6)	0.000
Use of 10 or more medications	92,292 (42.42)	10,610 (61.7)	81,682 (40.77)	0.000
Clinical Comorbidities				
Cirrhosis	30,788 (14.2)	2,738 (15.9)	28,050 (14.0)	0.000
HIV/AIDS	9,826 (4.5)	846 (4.9)	8,980 (4.5)	0.008
Cancer	27,681 (12.7)	3,639 (21.2)	24,042 (12.0)	0.000
Diabetes	69,903 (32.1)	8,412 (48.9)	61,491 (30.7)	0.000
Cardiac disease	160,812 (73.9)	15,709 (91.4)	145,103 (72.4)	0.000
Eye disease	31,195 (14.3)	3,783 (22.0)	27,412 (13.7)	0.000
Bone disease	79,645 (36.6)	8,727 (50.8)	70,918 (35.4)	0.000
Kidney disease	62,977 (28.9)	9,139 (53.1)	53,838 (26.9)	0.000
Drug and alcohol related disorder	113,593 (52.2)	9,617 (55.9)	103,976 (51.9)	0.000

Abbreviations: ADRD, Alzheimer's disease and related dementia; AIDS, Acquired immunodeficiency syndrome

^ICompared to average percentage of the U.S. population had attained at least a Bachelor's degree

Table 2.

Direct-Acting Antiviral (DAA) Use Rates by Clinical Factors among Medicare Beneficiaries with ADRD and Hepatitis C

	ADRD (N=17,196)		<i>p</i>
	DAA users (N=2,277)	DAA non-users (N=14,919)	
	N (%)	N (%)	
ADRD with behavioral disturbances			0.000
Yes	277 (12.17%)	2,715 (18.20%)	
No	2000 (87.83%)	12,204 (81.80%)	
Diagnosed with ADRD			0.893
Within 1 year	1,086 (47.69)	7,093 (47.54)	
More than 1 year	1,191 (52.31)	7,826 (52.46)	
ADRD medication			
Do not use any ADRD medications	1,672 (73.43)	11,024 (73.89)	0.640
Use any ADRD medications	605 (26.57)	3,895 (26.11)	
Number of drug therapeutic classes			0.246
Use less than 10 drug therapeutic classes	847 (37.20)	5,739 (38.47)	
Use more than 10 drug therapeutic classes	1,430 (62.80)	9,180 (61.53)	
Cirrhosis			0.000
Yes	482 (21.17)	2,256 (15.12)	
No	1,795 (78.83)	12,663 (84.88)	

Abbreviations: ADRD, Alzheimer's disease and related dementia; DAA, Direct-acting antiviral drug

¹ Compared to average percentage of the U.S. population had attained at least a Bachelor's degree

Table 3.

Adjusted Hazard Ratios of Direct-Acting Antiviral (DAA) Initiation (N=217,560)

	Hazard Ratio	95% CI	p
ADRD	0.50	(0.46–0.54)	0.000
Interaction			
ADRD × ADRD with behavioral disturbances	0.65	(0.57–0.74)	0.000
ADRD × Diagnosed with ADRD more than 1 year	1.00	(0.92–1.09)	0.947
ADRD × Use of any ADRD medications	0.99	(0.90–1.09)	0.801
ADRD × Use of 10 or more medications	1.11	(1.01–1.21)	0.022
ADRD × Cirrhosis	1.11	(1.00–1.23)	0.044
Age (ref. Age <55)			
Age 55–60	1.30	(1.26–1.33)	0.000
Age 60–65	1.32	(1.28–1.35)	0.000
Age 65–70	1.33	(1.30–1.37)	0.000
Age 70–75	1.07	(1.03–1.11)	0.001
Age >75	0.72	(0.68–0.75)	0.000
Gender (ref. Male)			
Female	0.91	(0.90–0.93)	0.000
Race/ ethnicity (ref. White)			
African American	1.37	(1.34–1.40)	0.000
Hispanic	0.93	(0.89–0.97)	0.002
Other	0.88	(0.84–0.91)	0.000
Geographic location (ref. Urban)			
Rural	1.05	(1.03–1.07)	0.000
Region (ref. Northeast)			
Midwest	1.02	(0.99–1.03)	0.127
South	1.01	(0.99–1.03)	0.282
West	0.92	(0.90–0.95)	0.000
Neighborhood characteristics			
Per capita income (tertile) (ref. Low)			
Medium	1.05	(1.03–1.07)	0.000
High	1.08	(1.05–1.11)	0.000
Education (ref. Education below average)			
Education above average ^I	1.01	(0.98–1.03)	0.546
Part D low-income subsidy	0.99	(0.97–1.01)	0.170
Use of 10 or more medications	1.17	(1.14–1.19)	0.000
Clinical comorbidities			
Cirrhosis	1.52	(1.48–1.55)	0.000
HIV/AIDS	0.87	(0.83–0.90)	0.000
Cancer	0.83	(0.81–0.85)	0.000
Diabetes	0.90	(0.88–0.91)	0.000
Cardiac disease	0.75	(0.74–0.76)	0.000

	Hazard Ratio	95% CI	<i>p</i>
Eye disease	1.08	(1.05–1.10)	0.000
Bone disease	0.91	(0.89–0.92)	0.000
Kidney disease	0.65	(0.63–0.66)	0.000
Drug and alcohol related disorder	0.63	(0.63–0.65)	0.000

Abbreviations: ADRD, Alzheimer's disease and related dementia; AIDS, Acquired immunodeficiency syndrome

¹ Compared to average percentage of the U.S. population had attained at least a Bachelor's degree

Table 4.

Adjusted Hazard Ratios of Mortality Comparing Direct-Acting Antiviral Agent (DAA) Users and DAA Non-Users among Medicare Beneficiaries with ADRD and Hepatitis C (N=17,196)

	Hazard Ratio	95% CI	p
DAA initiation as time-varying exposure	0.52	(0.44–0.61)	0.000
ADRD with behavioral disturbances	1.31	(1.26–1.35)	0.000
Diagnosed with ADRD more than 1 year (<i>ref. Diagnosed with ADRD within 1 year</i>)	0.96	(0.93–0.99)	0.008
Use of any ADRD medication	0.89	(0.86–0.92)	0.000
Age (<i>ref. Age <55</i>)			
Age 55–60	1.12	(1.02–1.23)	0.037
Age 60–65	1.32	(1.21–1.44)	0.000
Age 65–70	1.67	(1.54–1.80)	0.000
Age 70–75	2.09	(1.94–2.25)	0.000
Age >75	2.45	(2.27–2.64)	0.000
Gender (<i>ref. Male</i>)			
Female	0.90	(0.87–0.93)	0.000
Race/ ethnicity (<i>ref. White</i>)			
African American	0.95	(0.92–0.99)	0.013
Hispanic	1.05	(0.99–1.13)	0.114
Other	0.95	(0.90–1.01)	0.104
Geographic location (<i>ref. Urban</i>)			
Rural	1.05	(1.00–1.10)	0.064
Region (<i>ref. Northeast</i>)			
Midwest	1.25	(1.19–1.31)	0.000
South	1.29	(1.24–1.35)	0.000
West	1.07	(1.02–1.12)	0.006
Neighborhood characteristics			
Per capital income (tertile) (<i>ref. Low</i>)			
Medium	1.05	(1.01–1.09)	0.021
High	1.24	(1.18–1.31)	0.000
Education (<i>ref. Education below average</i>)			
Education above average ¹	0.96	(0.92–1.01)	0.090
Part D low-income subsidy	0.98	(0.95–1.02)	0.398
Use of 10 or more medications	1.15	(1.11–1.18)	0.000
Clinical comorbidities			
Cirrhosis	1.59	(1.52–1.66)	0.000
HIV/AIDS	0.97	(0.89–1.06)	0.520
Cancer	1.04	(1.00–1.08)	0.035
Diabetes	1.16	(1.12–1.19)	0.000
Cardiac disease	1.22	(1.09–1.36)	0.000
Eye disease	0.93	(0.90–0.96)	0.000
Bone disease	0.99	(0.96–1.02)	0.373

	Hazard Ratio	95% CI	<i>p</i>
Kidney disease	1.56	(1.50–1.61)	0.000
Drug and alcohol related disorder	0.92	(0.89–0.95)	0.000

Abbreviations: ADRD, Alzheimer's disease and related dementia; DAA, Direct-acting antiviral drug; AIDS, Acquired immunodeficiency syndrome

¹ Compared to average percentage of the U.S. population had attained at least a Bachelor's degree