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Original Contribution

Comparative Effectiveness of Direct-Acting Antivirals for Posttraumatic Stress Disorder in Veterans Affairs Patients With Hepatitis C Virus Infection

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We recently conducted an exploratory study that indicated that several direct-acting antivirals (DAAs), highly effective medications for hepatitis C virus (HCV) infection, were also associated with improvement in posttraumatic stress disorder (PTSD) among a national cohort of US Department of Veterans Affairs (VA) patients treated between October 1, 1999, and September 30, 2019. Limiting the same cohort to patients with PTSD and HCV, we compared the associations of individual DAAs with PTSD symptom improvement using propensity score weighting. After identifying patients who had available baseline and endpoint PTSD symptom data as measured with the PTSD Checklist (PCL), we compared changes over the 8–12 weeks of DAA treatment. The DAAs most prescribed in conjunction with PCL measurement were glecaprevir/pibrentasvir (GLE/PIB; $n = 54$), sofosbuvir/velpatasvir (SOF/VEL; $n = 54$), and ledipasvir/sofosbuvir (LDV/SOF; $n = 145$). GLE/PIB was superior to LDV/SOF, with a mean difference in improvement of 7.3 points on the PCL (95% confidence interval (CI): 1.1, 13.6). The mean differences in improvement on the PCL were smaller between GLE/PIB and SOF/VEL (3.0, 95% CI: −6.3, 12.2) and between SOF/VEL and LDV/SOF (4.4, 95% CI: −2.4, 11.2). While almost all patients were cured of HCV (92.5%) regardless of the agent received, PTSD outcomes were superior for those receiving GLE/PIB compared with those receiving LDV/SOF, indicating that GLE/PIB may merit further investigation as a potential PTSD treatment.

comparative effectiveness research; medical records systems, computerized; patient outcome assessment; psychopharmacology; stress disorders, posttraumatic; veterans

Abbreviations: CDW, VA Corporate Data Warehouse; DAA, direct-acting antiviral; FDA, Food and Drug Administration; GLE/PIB, glecaprevir/pibrentasvir; HCV, hepatitis C virus; LDV/SOF, ledipasvir/sofosbuvir; PCL, PTSD Checklist; PTSD, posttraumatic stress disorder; SOF/VEL, sofosbuvir/velpatasvir; VA, US Department of Veterans Affairs.

Posttraumatic stress disorder (PTSD) is one of the most common mental disorders in the United States, with a lifetime prevalence of 6.4% (1). Yet there are only 2 US Food and Drug Administration (FDA)–approved medications for PTSD, and they have limited effectiveness in reducing symptoms and improving functioning (2). Thus, there is interest in developing novel agents that target mechanisms involved in PTSD pathophysiology (3, 4). At the same time, some existing medications may have the potential to ameliorate PTSD symptoms (5, 6). Several of these medications have been recently tested in randomized clinical trials as their mechanism of action aligns with known PTSD-related pathophysiologic deficits (7–9). However, the pathophysiology of PTSD is incompletely understood (6), and there are over a thousand FDA-approved medications affecting an expansive range of known and unknown biological targets (10, 11). Thus, a therapeutic discovery approach that matches known PTSD pathophysiology to medications' known mechanisms of action may overlook potentially effective treatments. Real-world studies of the association between medication receipt and PTSD symptom change may suggest additional treatments (12), and these intersections of disease and treatment may suggest unrecognized pathophysiology and therapeutic targets.

We recently conducted an exploratory study using US Department of Veterans Affairs (VA) medical records and uncovered an unexpected association between receipt of several direct-acting antiviral (DAA) medications used in the treatment of hepatitis C virus (HCV) and improvement in PTSD symptoms (13). In that study, we used a tree-based scanning statistic to identify potential associations between all FDA-approved medications or mechanistic classes of medications prescribed in the VA and improvement in PTSD symptoms. Among 25 potential associations, 3 agents, including glecaprevir, pibrentasvir, and velpatasvir, were all associated with over double the expected number of patients experiencing a clinically meaningful improvement in PTSD symptoms (observed to expected ratio > 2.0). Glecaprevir is a NS3/4A protease inhibitor while pibrentasvir and velpatasvir are NS5A protein inhibitors. As a point of comparison, the selective serotonin reuptake inhibitor sertraline, which is FDA-approved for PTSD, was associated with only a slightly higher than expected improvement (observed to expected ratio = 1.2). DAA treatment is exceptionally effective for HCV, with the VA reporting cure rates of greater than 90% (14). While it is possible that patients' PTSD symptoms improved when they were cured of HCV, we found a differential pattern of PTSD response among patients receiving DAA regimens that have similar efficacy for HCV. Glecaprevir and pibrentasvir (GLE/PIB) are always prescribed together under the brand name Mavyret (AbbVie, North Chicago, Illinois). Velpatasvir is commonly prescribed in combination with the NS5B polymerase inhibitor sofosbuvir (SOF/VEL) under the brand name Epclusa (Gilead, Foster City, California). Sofosbuvir is also commonly prescribed with the NS5A protein inhibitor ledipasvir (LDV/SOF) under the brand name Harvoni (Gilead, Foster City, California). Neither sofosbuvir nor ledipasvir were associated with a significantly higher than expected improvement in PTSD symptoms. Although the effects of DAA combinations on the hepatocyte have been studied extensively (15), little is known about their psychotropic effects. We postulated that several potential mechanisms related to cellular signaling could be involved in ameliorating PTSD symptoms, and that differences between the agents could be explained by exogenous factors such as blood-brain barrier permeability (13). If this exploratory finding is confirmed in subsequent analyses using more rigorous methods, the discovery that several DAAs have an off-target effect on PTSD symptoms could inform both the deployment of a new class of PTSD medications and an improved understanding of PTSD pathophysiology.

While the strongest evidence for the efficacy of DAAs in treating PTSD would be prospective randomized clinical trials in patients who have PTSD without HCV, additional analysis of existing medical records data can also provide useful information, in a resource- and time-efficient manner (16). We have completed several VA registry–based observational studies comparing established medications for PTSD, providing a template to evaluate novel agents using real-world data (17–19). A similar registry-based study focusing on the association of individual DAAs with PTSD symptom improvement could rule out some sources of bias, narrow the list of candidate agents, and provide a preliminary estimate of effectiveness. In addition to the possibility that improvements in PTSD symptoms could be related more directly to curing HCV, there are other sources of bias that could have affected our exploratory study results (13). First, patients were nonrandomly assigned to DAA treatment. For example, the DAA combinations that were FDA approved first (e.g., LDV/SOF in 2014) were given to many chronically ill patients (14), while DAA combinations that were approved later (e.g., SOF/VEL in 2016 and GLE/PIB in 2017) may have been given more often to patients with new disease because chronically ill patients were already cured. This could lead to differences in age, gender, PTSD chronicity, and other factors between patients who receive each DAA combination. Second, it is possible that patients received other treatments that affected their PTSD symptoms. Although our previous study included a sensitivity analysis that removed patients who received evidence-based PTSD treatments recommended by the VA, including several trauma-focused psychotherapies and antidepressants (13), it remains possible that patients received additional treatments for co-occurring mental health disorders that led to improvement in PTSD symptoms.

As a next step in evaluating the association of individual DAAs with PTSD symptom improvement, we performed a VA registry–based study comparing the 3 most commonly prescribed DAA combinations (13), including LDV/SOF, SOF/VEL, and GLE/PIB. To control for possible confounding, we used a weighting approach that accounted for patients' propensity to receive each DAA combination based on a set of known covariates related to hepatitis disease status, other medical and mental illness, and concurrent mental health treatments. We hypothesized that patients receiving SOF/VEL and GLE/PIB would have superior PTSD symptomatic outcomes compared with those receiving LDV/SOF.

METHOD

Data sources

We used a subset of the parent cohort constructed for the exploratory study to conduct the present study. To construct the parent cohort, we used the VA Corporate Data Warehouse (CDW) to identify all VA users with a clinical diagnosis of PTSD (*International Classification of Diseases* (ICD) codes: 309.81, F43.1x) from October 1, 1999, to September 30, 2019. We obtained information on services use, clinical diagnoses, prescription fills, laboratory tests, and patient-reported outcome measures (PROMs) from the CDW for these patients. In the present study, we limited the cohort to patients who also had a diagnosis of HCV (ICD codes: 070.41, 070.44, 070.51, 070.54, 070.7, 070.70, 070.71, B17.1x, B18.2, B19.2x). This study was approved by the Veterans Institutional Review Board of Northern New England.

Direct-acting antiviral cohort selection

We identified patients who completed a course of LDV/SOF, SOF/VEL, and GLE/PIB (Web Figure 1, available at https://doi.org/10.1093/aje/kwac104). We required at least

56 days of continuous treatment. We restricted the cohort to those who received baseline PTSD symptom measurement within 90 days prior to DAA initiation and follow-up PTSD symptom measurement after a minimum of 28 days of continuous DAA receipt. We chose 28 days as it was the minimum exposure for a drug to be included in our exploratory study and we had no prior information about the etiologically relevant outcome window. We allowed up to an additional 90 days to capture the follow-up PTSD symptom measure. Although not required for cohort inclusion, we further conducted a sensitivity analysis to examine associations among only patients who were cured of HCV to determine whether HCV cure accounts for observed associations. We defined cure as an undetectable HCV viral load up to a year after the completion of DAA therapy, provided there was no additional course of DAA.

PTSD symptoms

To maximize sample size within our clinical subgroups, we integrated 2 different versions of a patient-reported outcome measure for PTSD, captured from up to 2 data sources within the CDW, to obtain our baseline and follow-up symptom measurements. This included scores obtained from structured data produced by psychometric assessment software in the VA medical record and scores documented by clinicians in their treatment notes. We used a previously published natural language processing (NLP) algorithm with 98% precision in identifying the correct score and version of the PTSD Checklist (PCL) to abstract scores from clinical notes (20, 21). Scores abstracted from structured data and from NLP of clinical notes were integrated into a single data set, which has been described in detail elsewhere (22).

Briefly, the 2 patient-reported outcome measures were the PCL versions aligned to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), versions IV and 5 (23, 24), which we will hereinafter call the PCL-IV and the PCL-5 (25, 26). Validation work shows a correlation of 0.87 between PCL versions in a large sample of veterans (27). We used a validated crosswalk (intraclass correlation coefficient = 0.96) to convert all values to PCL-5 scoring (28). To preserve sample size, we did not require a minimum severity score. However, we created a covariate for baseline severity score of $\geq$31 out of 80, as scores of 31–33 are optimally efficient for diagnosing PTSD (27). In addition to calculating continuous change from baseline to follow-up, we assessed a categorical outcome of clinically meaningful improvement, which was a decrease of 15 points or more from baseline to follow-up (29). When patients had multiple PCL measurements in the baseline or follow-up period, we calculated mean values.

Potential confounders

We measured 7 groups of potential confounders (Table 1). Potential confounders spanned categories of HCV disease status, PTSD treatment history, PCL checklist availability, concurrent treatment, patient characteristics, health services use, and comorbid diagnoses.

Analysis

The first step in our analysis was to balance confounders across our DAA medication exposure groups. Consistent with modern epidemiologic principles of confounder identification (30), we considered as confounders covariates with a standardized mean difference of greater than or equal to 0.2 for the univariate association with clinically meaningful improvement and for the bivariate relationship between exposure to one DAA versus each of the other DAAs. After identification of confounders, we calculated propensity scores representing the probability that a particular trial would be of each DAA combination (31). We estimated propensity scores with multinomial logistic regression using generalized booster effects (32), in which the dependent variable is an indicator for each of the 3 medications and variables meeting our definition of confounders (i.e., variables associated with the exposure and the outcome with a standardized mean difference of 0.2) are the independent variables (31, 32). We estimated weights based on the population average treatment effect model.

The second step in our analysis was to compare continuous and categorical PCL outcomes among the 3 DAA combinations with weighted regression analyses, using DAA combination received as the independent variable. These weighted medication groups were defined by the inverse of the propensity scores and adjusted for covariates that remained unbalanced at the standardized mean difference level of 0.2 after propensity score weighting. For our continuous outcome of change in total PCL score, we used weighted linear regression analysis, whereby the coefficient of the variable tests the hypothesis that each of the 3 DAA combinations, coded as a multilevel categorical variable, has the same mean change from baseline to follow-up. For our categorical outcome of clinically meaningful improvement, we used weighted logistic regression analysis, whereby the coefficient of the variable tests the hypothesis that each of the 3 DAA combinations results in the same percentage of patients achieving clinically meaningful improvement. To examine the possibility that any association we observe is due to HCV cure, we repeated all analyses, excluding patients without evidence of HCV cure. If HCV cure explains the association of DAA receipt with PTSD symptom improvement, we would expect a stronger association between medication and PCL improvement in the group containing only patients who were cured. We performed data management in SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina), and statistical modeling in R, version 4.0.2 (R Core Team, Vienna, Austria).

RESULTS

A total of 253 patients met our inclusion criteria, including 54 who received GLE/PIB, 145 who received LDV/SOF, and 54 who received SOF/VEL (Web Table 1). There were several differences between patients across groups (Table 2). Particularly, those who received LDV/SOF had a longer duration of HCV illness, higher levels of fibrosis, greater concurrent use of sedative hypnotics and prazosin, less concurrent use of medications for alcohol use disorder, older

Table 1. Explanation of Covariates, National Cohort of US Department of Veterans Affairs Patients With Posttraumatic Stress Disorder and Hepatitis C Virus, United States, October 1999 to September 2019

General Variable Category	Detailed Description
Hepatitis C disease status	
Chronicity	Days from HCV diagnosis to direct acting antiviral medication start[a]
Fibrosis	FIB-4[b] score rated as mild, moderate, or advanced
PTSD treatment history	
Chronicity	Days from PTSD diagnosis to direct acting antiviral medication start[a]
Evidence-based antidepressants	Receipt of at least 12 weeks of continuous treatment with medications recommended by VA clinical practice guidelines for PTSD[c]
Evidence-based psychotherapy	Receipt of at least 8 sessions prolonged exposure or cognitive processing therapy over the course of 1 year[d]
PTSD Checklist availability	
Timing	Days between baseline and follow-up PCL scores relative to medication start and stop dates
Severity	Baseline score and whether the baseline score met diagnostic threshold[e,f]
Concurrent treatments	
Evidence-based antidepressants	Number of weeks of treatment with mediations recommended medications recommended by VA clinical practice guidelines for PTSD[c]
Evidence-based psychotherapy	Number of sessions of prolonged exposure or cognitive processing therapy[d]
Other medications	Categorical receipt of other antidepressants, anticonvulsants, sedative hypnotics, opioids, atypical antipsychotics, and prazosin, as well as medications for alcohol use disorder and opioid agonist treatments
Patient characteristics at baseline	
Age	Continuous
Sex	Categorical male or female
Race	Categorical Black non-Hispanic, Hispanic, White non-Hispanic, Other
Military exposures	Combat, sexual trauma, service-connected disability
VA Health Service use characteristics in the year preceding baseline	
Outpatient visits	Such as visits to specialized PTSD clinics or to primary care clinics
Acute psychiatric care use	Emergency department and urgent care visits for psychiatric indications, psychiatric hospitalizations
Residential treatment	Stays in residential PTSD or substance abuse programs
Diagnoses in the 2 years preceding baseline	
Psychiatric comorbidities	Number of non-PTSD diagnoses and 3 most common diagnoses[g]
Medical comorbidities	Number of non-HCV diagnoses and 3 most common diagnoses[g]

Abbreviations: CPT, cognitive processing therapy; HCV, hepatitis C virus; PCL, PTSD Checklist; PE, prolonged exposure; PTSD, posttraumatic stress disorder; VA, US Department of Veterans Affairs.

[a] Variable was assessed with a look-back period to October 1, 1999.

[b] FIB-4 grades level of hepatic fibrosis based on age, platelet counts, and aminotransferase levels (45, 46).

[c] Including fluoxetine, paroxetine, sertraline, and venlafaxine (33).

[d] Measured using a natural language processing algorithm that classifies psychotherapy note text (47).

[e] PCL-IV scores were converted to PCL-5 scoring using a validated crosswalk (28).

[f] Score cutoff of 31 based on optimal diagnostic efficiency (27).

[g] Using a previously published index of mental and physical comorbidities adapted for VA medical record data (48).

Table 2. Patient and Clinical Characteristics According to Drug Combination Received, National Cohort of US Department of Veterans Affairs Patients With Posttraumatic Stress Disorder and Hepatitis C Virus, United States, October 1999 to September 2019

Characteristic	GLE/PIB (*n* = 54)			LDV/SOF (*n* = 145)			SOF/VEL (*n* = 54)		
	Mean (SD)	%	No.	Mean (SD)	%	No.	Mean (SD)	%	No.
Hepatitis disease status									
Thousands of days since HCV diagnosis	1.8 (1.9)			2.3 (2.1)			1.4 (1.9)		
Fibrosis (FIB-4 score)									
Mild (<1.45)		59.3	32		51.7	75		68.5	37
Moderate (1.45–3.25)		33.3	18		42.1	61		24.1	13
Advanced (>3.25)		7.4	4		6.2	9		7.4	4
HCV cure following DAA treatment[a]		92.6	50		94.5	137		87.0	47
PTSD treatment history									
Thousands of days since PTSD diagnosis	1.7 (1.7)			2.0 (2.0)			1.7 (1.8)		
Number of prior EBA trials	0.5 (0.8)			0.4 (0.8)			0.4 (0.7)		
Number of prior EBP trials	0.2 (0.4)			0.2 (0.4)			0.2 (0.4)		
PCL timing, version, and severity									
Days from DAA start to baseline PCL	26.9 (24.8)			38.7 (26.3)			32.1 (27.7)		
Days from baseline to follow-up PCL	110.4 (41.7)			118.7 (37.7)			113.4 (42.2)		
Days from DAA end to follow-up PCL	16.1 (32.6)			6.7 (28.8)			1.2 (32.0)		
Baseline PCL	48.4 (16.3)			49.1 (15.9)			50.9 (16.1)		
Baseline PCL score ≥31		83.3	45		84.1	122		90.7	49
Concurrent treatment									
Sessions of EBP for PTSD	4.3 (6.1)			3.2 (5.1)			3.5 (5.4)		
Weeks of EBA for PTSD	4.8 (6.7)			4.9 (7.1)			3.3 (5.5)		
Any non-EBA antidepressant		51.9	28		71.7	104		68.5	37
Any anticonvulsant		13.0	7		14.5	21		16.7	9
Any sedative/hypnotics		SL[b]			20.7	30		SL[b]	
Any opioid		27.8	15		34.5	50		16.7	9
Any atypical antipsychotic		20.4	11		26.2	38		27.8	15
Any prazosin		27.8	15		44.8	65		29.6	16
Any FDA-approved AUD medication		18.5	10		6.9	10		14.8	8
Any opioid agonist therapy		25.9	14		14.5	21		16.7	9
Patient characteristics at baseline									
Age, years	48.1 (13.8)			50.9 (14.0)			43.8 (13.2)		
Women		*SL*[b]			9.0	13		11.1	6
Married		24.1	13		29.0	42		18.5	10
Rural		22.2	12		28.3	41		20.4	11
White non-Hispanic		72.2	39		62.1	90		74.1	40
Black non-Hispanic		22.2	12		30.3	44		16.7	9
Hispanic		SL[b]			6.9	10		5.6	3
Other racial or ethnic group		SL[b]			SL[b]			SL[b]	
Combat exposure		38.9	21		46.2	67		42.6	23
Sexual trauma while in military		22.2	12		23.4	34		25.9	14
VA disability level ≥70%		35.2	19		43.4	63		50.0	27

Table continues

Table 2. Continued

Characteristic	GLE/PIB (*n* = 54)			LDV/SOF (*n* = 145)			SOF/VEL (*n* = 54)		
	Mean (SD)	%	No.	Mean (SD)	%	No.	Mean (SD)	%	No.
Service use characteristics in the 1 year preceding baseline									
PTSD outpatient clinical team visits	3.9 (7.0)			6.8 (12.1)			7.3 (14.5)		
Outpatient mental health visits	58.5 (46.2)			51.2 (41.3)			64.7 (49.9)		
Outpatient substance abuse visits	22.6 (22.6)			17.8 (23.8)			23.0 (26.0)		
Outpatient primary care visits	5.4 (4.7)			9.4 (7.3)			6.8 (6.1)		
Outpatient specialty medical visits	3.0 (3.8)			3.4 (2.6)			3.8 (3.4)		
ED visits for psychiatric indication	1.3 (1.7)			0.6 (1.3)			1.6 (2.4)		
Days of acute inpatient mental health	9.2 (18.5)			3.6 (12.7)			9.4 (18.8)		
Days of residential PTSD treatment	4.6 (19.5)			3.1 (17.6)			6.8 (30.6)		
Days residential substance treatment	35.6 (59.5)			7.4 (25.7)			17.2 (40.2)		
Comorbidities in the 2 years preceding baseline									
Number of non-PTSD MH comorbidities	3.8 (2.0)			3.2 (1.6)			3.5 (1.7)		
Substance use disorders		SH[b]			78.6	114		92.6	50
Depressive disorders		79.6	43		75.2	109		75.9	41
Anxiety disorders		53.7	29		40.0	58		44.4	24
Number of non-PTSD PH comorbidities	2.3 (1.7)			2.3 (1.6)			2.1 (1.9)		
Non-HCV liver disease		92.6	50		74.5	108		88.9	48
Uncomplicated hypertension		40.7	22		42.8	62		33.3	18
Obesity		7.4	4		15.9	23		16.7	9

Abbreviations: DAA, direct-acting antiviral; EBA, evidence-based antidepressant; EBP, evidence-based psychotherapy; ED, emergency department; GLE/PIB, glecaprevir/pibrentasvir; HCV, hepatitis C virus; LDV/SOF, ledipasvir/sofosbuvir; MH, mental health; PCL, PTSD Checklist; PH, physical health; PTSD, posttraumatic stress disorder; SD, standard deviation; SH, suppressed high; SL, suppressed low; SOF/VEL, sofosbuvir/velpatasvir; VA, US Department of Veterans Affairs.

[a] This variable was considered a potential moderator rather than a potential confounder.

[b] SH: cell is suppressed due to all but fewer than 3 patients; SL: cell is suppressed due to fewer than 3 patients.

age, more primary care visits, fewer emergency department visits for mental health indications, fewer days of acute inpatient mental health and residential substance abuse treatment, lower rates of substance use disorder diagnoses, and lower rates of non-HCV liver disease diagnoses compared with patients in the other groups. Patients in the GLE/PIB group were less likely to be women. Additionally, there were several differences in the timing of PCL scores relative to DAA trials, with the shortest time from baseline PCL to DAA start in the GLE/PIB group and the shortest time from follow-up PCL to DAA end in the SOF/VEL group. Mean baseline PCL scores were very similar and in the severe range at approximately 50 across groups, although patients in the SOF/VEL group were more likely to have a baseline score of $\geq$31.

Among our potential confounders, 14 were associated with both the outcome and the exposure and thus considered to be confounders (Web Table 2). Two of the confounders, sedative-hypnotic use and substance use disorder diagnoses, were insufficiently represented in 1 or more exposure groups and we did not include them in our propensity score model; this required creating weights based on 1 or 2 patients, which prevented our models from converging. Once those variables were removed, our inverse propensity of treatment weighting model successfully reached the minimum for the loss function over 4,000 gradient-boosting machine iterations. Web Figure 2 shows there is no clear outlier in the propensity score distributions, indicating that our weights are robust. Of the remaining 12 covariates, 5 remained imbalanced at the standardized mean difference of 0.2 level after inverse propensity of treatment weighting (Table 3). The 5 unbalanced covariates, including concurrent prescription of opioids, concurrent prescription of prazosin, the number of primary care visits in the year preceding baseline, the number of emergency department visits for psychiatric indications in the year preceding baseline, and non-HCV liver disease diagnoses, were maintained as covariates in all weighted outcomes models (Web Table 3).

Table 3. Postweighting Balance of Confounders According to Drug Combination Received, National Cohort of US Department of Veterans Affairs Patients With Posttraumatic Stress Disorder and Hepatitis C Virus, United States, October 1999 to September 2019

Variable	GLE/PIB (*n* = 54)			LDV/SOF (*n* = 145)			SOF/VEL (*n* = 54)		
	Mean (SD)	%	No.	Mean (SD)	%	No.	Mean (SD)	%	No.
Mild fibrosis		54.9	32		55.3	75		59.9	37
Moderate fibrosis		32.8	18		38.0	61		32.2	13
Number of prior EBA trials	0.4 (0.8)			0.4 (0.8)			0.4 (0.7)		
Days from baseline to follow-up PCL	114.2 (38.2)			117.2 (37.2)			114.5 (39.2)		
Baseline PCL score ≥31		84.3	45		85.1	122		90.5	49
Any opioid[a]		28.1	15		31.3	50		22.2	9
Any prazosin[a]		30.0	15		40.2	65		25.3	16
Any FDA-approved AUD medication		12.4	10		7.0	10		11.6	8
PTSD outpatient clinical team visits	4.4 (7.0)			6.2 (11.4)			5.8 (12.3)		
Outpatient primary care visits[a]	6.1 (4.6)			8.4 (7.1)			7.8 (7.0)		
ED visits for psychiatric indication[a]	1.0 (1.6)			0.9 (1.5)			1.3 (2.1)		
Non-HCV liver disease[a]		86.2	50		79.3	108		89.7	48

Abbreviations: AUD, alcohol use disorder; EBA, evidence-based antidepressant; ED, emergency department; GLE/PIB, glecaprevir/pibrentasvir; HCV, hepatitis C virus; LDV/SOF, ledipasvir/sofosbuvir; PCL, PTSD Checklist; PTSD, posttraumatic stress disorder; SD, standard deviation; SOF/VEL, sofosbuvir/velpatasvir.

[a] Variable was not balanced (standardized mean difference of <0.2) after weighting and was retained as a covariate in outcomes models.

When including all patients (Table 4), the largest adjusted mean improvement in PCL score was 14.9 points (SD = 33.2) for the GLE/PIB group, and the smallest adjusted mean improvement in PCL score was 7.5 points (SD = 66.8) for the LDV/SOF group. This translated to a mean difference of 7.34 points between the GLE/PIB and LDV/SOF groups (95% confidence interval: 1.05, 13.63). Similarly, the adjusted proportion of patients improving by 15 points or more on the PCL was highest for the GLE/PIB group at 43.6% and lowest for the LDV/SOF group at 26.3%. Accordingly, the odds of clinically meaningful improvement were greater for recipients of GLE/PIB than of LDV/SOF; however, the confidence interval indicates that this association was imprecisely measured (odds ratio = 2.17, 95% confidence interval: 0.93, 5.06). The differences between agents were smaller and imprecisely measured in all other comparisons that included patients regardless of HCV outcome. Finally, when excluding patients without evidence of HCV cure (Table 5), the association of GLE/PIB relative to LDV/SOF with PTSD symptom improvement was somewhat weaker in magnitude. This argues against the idea that HCV cure is required to observe an association with PTSD symptom improvement.

DISCUSSION

Although almost all patients in our study were cured of HCV, those receiving GLE/PIB experienced greater PTSD symptom improvement than those receiving LDV/SOF. Consistent with the results of our exploratory study, patients in both the GLE/PIB group and the SOF/VEL group had outcomes superior to those of patients in the LDV/SOF group in unadjusted analyses. However, after controlling for measured confounding, only GLE/PIB appears to be more strongly associated with PTSD symptom improvement than LDV/SOF. This suggests that among DAAs commonly used in the VA, GLE/PIB is a more promising candidate than SOF/VEL for continued research as a potential PTSD treatment. In the present study, patients receiving GLE/PIB improved by a mean of approximately 15 points on the PCL. Other recent analyses using the same VA PCL data set indicate that this level of improvement is larger than typically observed in routine practice for evidence-based treatments recommended by the clinical practice guideline for PTSD from the VA and Department of Defense (33). First, in a study of almost 7,000 patients receiving adequately dosed antidepressants, PTSD symptoms improved by only 5–6 points over 12 weeks (19). Second, in over 100,000 patients receiving ≥8 sessions of prolonged exposure or cognitive processing therapy over ≤14 weeks, patients improved by a mean of 8–10 points (22). However, these comparisons are indirect and could be the result of population differences between patients with PTSD who do and do not have HCV.

When considering known mechanisms of action for the 3 DAA combinations that we studied, all contain NS5A protein inhibitors (ledipasvir, pibrentasvir, and velpatasvir). Two of the DAAs contain a NS5B polymerase inhibitor (sofosbuvir). Our most promising agent, GLE/PIB, is unique in that it contains a NS3/4A protease inhibitor (glecaprevir). HCV NS3 protein has been found to cross the blood-brain barrier, activating microglia, resulting in the release of

Table 4. Baseline PTSD Checklist and Outcomes (All Patients) According to Drug Combination Received, National Cohort of US Department of Veterans Affairs Patients With Posttraumatic Stress Disorder and Hepatitis C Virus, United States, October 1999 to September 2019

Analysis	GLE/PIB (*n* = 54)			LDV/SOF (*n* = 145)			SOF/VEL (*n* = 54)			GLE/PIB Versus LDV/SOF			GLE/PIB Versus SOF/VEL			SOF/VEL Versus LDV/SOF		
	Mean (SD)	%	No.	Mean (SD)	%	No.	Mean (SD)	%	No.	MD	OR	95% CI	MD	OR	95% CI	MD	OR	95% CI
Baseline PCL																		
Unweighted	48.4 (16.3)			49.1 (15.9)			50.9 (16.1)			0.67		−4.39, 5.73	2.47		−3.63, 8.57	−1.80		−6.81, 3.21
IPTW	44.1 (20.8)			47.2 (49.1)			48.0 (32.2)			3.10		−2.64, 8.84	3.89		−2.67, 10.46	−0.80		−9.52, 7.92
Change in PCL																		
Unweighted	−12.9 (14.3)			−3.1 (14.1)			−9.2 (14.7)			9.79		5.33, 14.25	3.78		−1.68, 9.25	6.01		1.47, 10.54
IPTW	−14.9 (33.2)			−7.5 (66.8)			−10.5 (41.9)			7.34		1.05, 13.63	4.39		−2.43, 11.21	2.95		−6.33, 12.23
Clinically meaningful improvement																		
Unweighted		40.7	22		17.9	26		35.2	19		2.27	1.42, 3.65		1.16	0.71, 1.88		1.97	1.18, 3.28
IPTW		43.6	22		26.3	26		30.3	19		2.17	0.93, 5.06		1.41	0.58, 3.42		1.54	0.45, 5.24

Abbreviations: CI, confidence interval; GLE/PIB, glecaprevir/pibrentasvir; IPTW, inverse propensity of treatment weighting; LDV/SOF, ledipasvir/sofosbuvir; MD, mean difference; OR, odds ratio; PCL, PTSD Checklist; PTSD, posttraumatic stress disorder; SD, standard deviation; SOF/VEL, sofosbuvir/velpatasvir.

Table 5. Baseline PTSD Checklist and Outcomes (Excluding Patients Without Evidence of Hepatitis C Virus Cure) According to Drug Combination Received, National Cohort of US Department of Veterans Affairs Patients With Posttraumatic Stress Disorder and Hepatitis C Virus, United States, October 1999 to September 2019

Analysis	GLE/PIB (*n* = 50)			LDV/SOF (*n* = 137)			SOF/VEL (*n* = 47)			GLE/PIB Versus LDV/SOF			GLE/PIB Versus SOF/VEL			SOF/VEL Versus LDV/SOF		
	Mean (SD)	%	No.	Mean (SD)	%	No.	Mean (SD)	%	No.	MD	OR	95% CI	MD	OR	95% CI	MD	OR	95% CI
Baseline PCL																		
Unweighted	48.3 (16.3)			48.7 (16.0)			51.5 (14.5)			0.40		−4.86, 5.66	3.20		−2.95, 9.35	−2.80		−7.74, 2.14
IPTW	43.8 (23.1)			47.2 (53.3)			48.1 (34.5)			3.44		−2.67, 9.55	4.29		−2.54, 11.12	−0.85		−10.02, 8.31
Change in PCL																		
Unweighted	−12.6 (13.6)			−2.4 (13.7)			−8.8 (13.4)			10.21		5.80, 14.62	3.87		−1.50, 9.24	6.34		1.87, 10.81
IPTW	−11.9 (26.5)			−5.7 (56.3)			−7.6 (35.8)			6.17		0.34, 12.01	4.26		−2.17, 10.69	1.92		−6.77, 10.60
Clinically meaningful improvement																		
Unweighted		40.0	20		16.8	23		31.9	15		2.38	1.44, 3.94		1.25	0.73, 2.15		1.90	1.08, 3.32
IPTW		30.1	20		19.0	23		21.6	15		1.83	0.77, 4.36		1.57	0.62, 3.98		1.17	0.33, 4.18

Abbreviations: CI, confidence interval; GLE/PIB, glecaprevir/pibrentasvir; IPTW, inverse propensity of treatment weighting; LDV/SOF, ledipasvir/sofosbuvir; MD, mean difference; OR, odds ratio; PCL, PTSD Checklist; PTSD, posttraumatic stress disorder; SD, standard deviation; SOF/VEL, sofosbuvir/velpatasvir.

proinflammatory cytokines, which has been linked to neurological impairment (34, 35). By inhibiting the HCV NS3/4A protease, glecaprevir prevents HCV viral replication (15). Given that the FDA clinical review of glecaprevir notes poor blood-brain barrier permeability (36), the medication could potentially block HCV from passing the blood-brain barrier altogether to activate microglia. While it is unclear how this mechanism would target PTSD symptoms (6), many of the proinflammatory cytokines that are released in the presence of HCV infection are consistent with those identified as biomarkers for PTSD, which lends to systemic inflammation in PTSD pathophysiology (37–39). While this would explain GLE/PIB's association with PTSD symptom improvement following HCV clearance, it would not necessarily explain why PTSD might improve in the absence of HCV infection. However, given current knowledge on NS3 and NS5 inhibitors (40, 41), it is plausible that GLE/PIB is acting on a cellular as opposed to a viral level with off-target PTSD effects via the inflammatory process.

There are several limitations to this study. First, this study is based on the same data that were used by our previous work to initially document PTSD symptom improvement among people taking these medications (13). A strength of the present study is that we expand on that previous exploratory work by conducting more rigorous causal analyses. Ideally, we would have further explored this result in a new independent data set (42). The US Department of Defense Behavioral Health Data Portal represents a potential avenue for replication if there are enough patients receiving repeat PCL assessment while receiving DAA treatment (43). Second, we used a less strict criterion for confounder selection than is frequently used (standardized mean difference ≤ 0.2 as opposed to standardized mean difference ≤ 0.1) due to our small sample size (44). Thus, there is potential for residual confounding. Future research using more targeted sampling, including randomized clinical trials, will address these concerns. Finally, the sample for this study is VA patients with PTSD and HCV, and it is unclear how the findings from this study generalize to other populations.

In conclusion, this study provides a more valid estimate of the association of DAAs with PTSD symptom improvement than our exploratory study by accounting for potential sources of confounding, and indicates that GLE/PIB may have a stronger association with PTSD symptom improvement than LDV/SOF among VA patients with HCV and PTSD. This finding merits further study with continued enhancements in the causal methods applied. Research priorities include replication in an independent data set, collaboration with neuroscientists who can help delineate potential mechanism of action, and prospective controlled research evaluating changes both in related biomarkers and standardized clinical assessments.

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The VA Corporate Data Warehouse (CDW) contains electronic medical record data compiled from individual VA facilities and is described at http://www.hsrd.research.va.gov/for_researchers/vinci/cdw.cfm. Data are stored on geographically dispersed server farms. To access the CDW, researchers generally need to have an employment relationship with the US Department of Veterans Affairs. After local institutional review board approval, requests for data are submitted to VA National Data Systems using the Data Access Request Tracker. Data sets are then built and analyzed in secure virtual project workspaces within the VA Informatics and Computing Infrastructure environment. Researchers with VA network access can obtain descriptions of CDW data at http://vaww.virec.research.va.gov/.

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