JAMA Neurology | Original Investigation

Association of Antiviral Therapy With Risk of Parkinson Disease in Patients With Chronic Hepatitis C Virus Infection

Wey-Yil Lin, MD; Ming-Shyan Lin, MD; Yi-Hsin Weng, MD, PhD; Tu-Hsueh Yeh, MD, PhD; Yu-Sheng Lin, MD; Po-Yu Fong, MD; Yih-Ru Wu, MD; Chin-Song Lu, MD; Rou-Shayn Chen, MD; Ying-Zu Huang, MD, PhD

IMPORTANCE Epidemiologic evidence suggests that hepatitis C virus (HCV) could be a risk factor for Parkinson disease (PD), but treatment for HCV infection has never been considered in these studies; hence, the association between antiviral therapy and PD incidence has remained unclear. Understanding this association may help in developing strategies to reduce PD occurrence.

OBJECTIVE To identify the risk of PD development in patients with HCV infection receiving antiviral treatment and in patients not receiving this treatment.

DESIGN, SETTING, AND PARTICIPANTS This cohort study obtained claims data from the Taiwan National Health Insurance Research Database. Adult patients with a new HCV diagnosis with or without hepatitis per *International Classification of Diseases, Ninth Revision, Clinical Modification* codes and anti-PD medications from January 1, 2003, to December 31, 2013, were selected for inclusion. After excluding participants not eligible for analysis, the remaining patients (n = 188 152) were categorized into treated and untreated groups according to whether they received antiviral therapy. Propensity score matching was performed to balance the covariates across groups for comparison of main outcomes. This study was conducted from July 1, 2017, to December 31, 2017.

MAIN OUTCOMES AND MEASURES Development of PD was the main outcome. A Cox proportional hazards regression model was used to compare the risk of PD, and the hazard ratio (HR) was calculated at 1 year, 3 years, and 5 years after the index date and at the end of the cohort.

RESULTS A total of 188 152 patients were included in the analysis. An equal number (n = 39 936) and comparable characteristics of participants were retained in the treated group (with 17 970 female [45.0%] and a mean [SD] age of 52.8 [11.4] years) and untreated group (with 17 725 female [44.4%] and a mean [SD] age of 52.5 [12.9] years) after matching. The incidence density of PD was 1.00 (95% CI, 0.85-1.15) in the treated group and 1.39 (95% CI, 1.21-1.57) per 1000 person-years in the untreated group. The advantage of antiviral therapy reached statistical significance at the 5-year follow-up (HR, 0.75; 95% CI, 0.59-0.96), and this advantage continued to increase until the end of follow-up (HR, 0.71; 95% CI, 0.58-0.87).

CONCLUSIONS AND RELEVANCE Evidence suggested that the PD incidence was lower in patients with chronic HCV infection who received interferon-based antiviral therapy; this finding may support the hypothesis that HCV could be a risk factor for PD.

Editorial

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Authors: Ying-Zu Huang, MD, PhD (yzhuang@cgmh.org.tw), and Rou-Shayn Chen, MD (cerebrum@cgmh.org.tw), Department of Neurology, Chang Gung Memorial Hospital, Linkou Medical Center, No. 5, Fuxing St, Guishan District, Taoyuan, Taiwan 333.

JAMA Neurol. doi:10.1001/jamaneurol.2019.1368
Published online June 5, 2019.

Hepatitis C virus (HCV) infection has been associated worldwide with hepatocellular carcinoma, liver failure, and cirrhosis.[1] Chronic HCV infection not only affects the liver but also is a risk factor in extrahepatic diseases, such as diabetes, chronic kidney disease, atherosclerosis, coronary artery disease, and stroke.[2-5] Several epidemiologic studies found an association between HCV infection and Parkinson disease (PD),[6-9] and HCV infection has been suggested as a risk factor for PD. However, inconsistent results showing no association between HCV infection and PD have also been reported.[10]

Interferon-based antiviral therapy may reduce the cardiovascular events and stroke in patients with HCV infection,[11-13] in addition to its positive outcome on the hepatic disease. A few patients with HCV infection, nevertheless, were found to develop parkinsonian symptoms after receiving interferon therapy, and the possibility of drug-induced parkinsonism in patients with HCV infection was raised.[14] In the epidemiologic studies of HCV infection and PD,[6-10] the intervention with antiviral treatment was never considered, and the detection of PD incidence after administration of antiviral therapy was not possible. For these reasons, the association of HCV infection and antiviral therapy with the development of PD has been debated.[15-18]

In this cohort study, we investigated patients with chronic HCV infection who were treated with antiviral therapy and those with the same condition who went untreated, and we compared the incidence of PD between these groups. The findings would clarify whether antiviral therapy has an association with the development of PD.

Key Points

Question Is interferon-based antiviral therapy associated with Parkinson disease incidence in patients with chronic hepatitis C virus infection?

Findings In this cohort study of 188 152 patients with hepatitis C virus infection, the group treated with antiviral therapy had lower incidence density and risk of developing PD compared with the untreated group.

Meaning Results of treatment with interferon-based antiviral therapy appeared to support the hypothesis that hepatitis C virus may be a probable risk factor for Parkinson disease.

Methods

We conducted this research from July 1, 2017, to December 31, 2017, using the Taiwan National Health Insurance Research Database (NHIRD), which includes claims data for all health care services covered by the Taiwan National Health Insurance (TNHI), a single-payer health insurance initiated in 1995 that provides insurance to up to 99% of the entire population of Taiwan (approximately 23.5 million people by the end of 2013).[19] In the NHIRD, all diseases before 2015 were coded according to the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*). For this population-based cohort study, we selected all patients with a new HCV diagnosis with or without hepatitis (*ICD-9-CM* codes 070.41, 070.44, 070.51, 070.54, 070.70, 070.71, and V02.62) from January 1, 2003 (the starting date that TNHI paid out for the interferon-based therapy), to December 31, 2013. The study protocol was approved by the institutional review board of Chang Gung Medical Foundation. Because patient information in the NHIRD was deidentified and anonymized before being released to the researchers, the informed consent requirement was waived by the Chang Gung Medical Foundation Institutional Review Board.

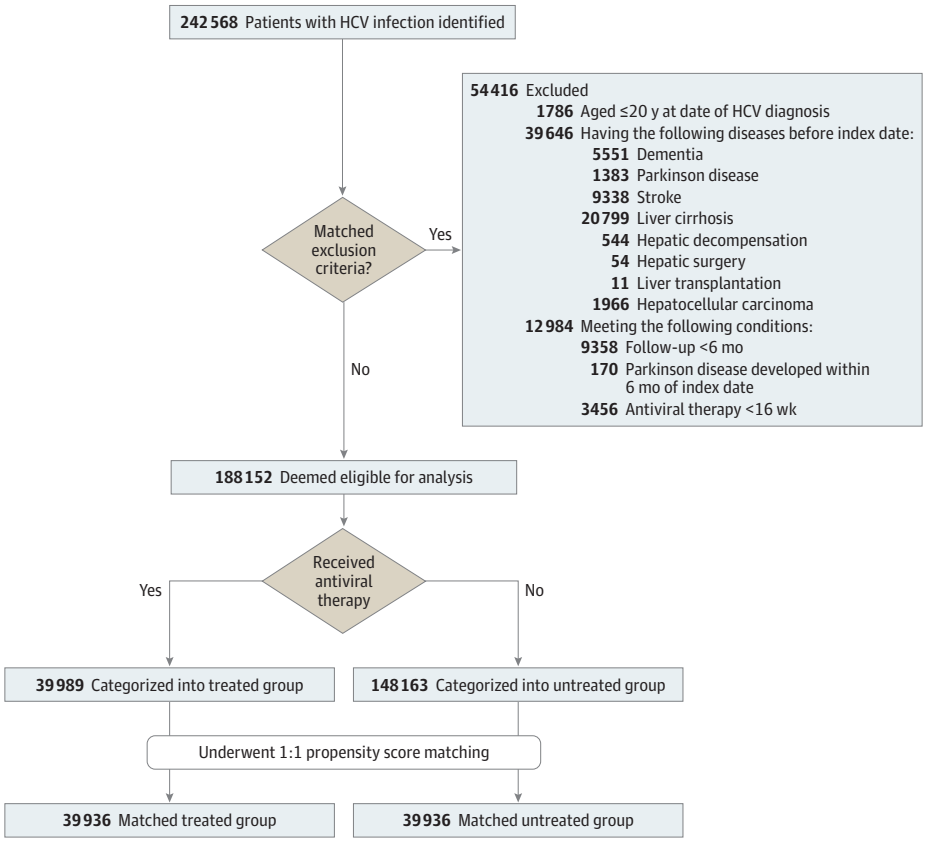
We excluded patients who were identified on the index date as (1) being aged 20 years or younger; (2) having a PD, dementia, or stroke diagnosis; or (3) having had major hepatic diseases (**Figure 1**). We defined the index date as the time the HCV infection or carrier status was first confirmed in patients who were untreated with antiviral therapy. For patients treated with antiviral therapy, the index date was defined as the time the interferon-based antiviral therapy was initiated.

The regimen of interferon-based antiviral therapy was a combination of pegylated interferon α-2b and ribavirin. To ensure the adequate effectiveness of antiviral therapy, we excluded patients who fulfilled any of the following conditions: (1) lost to follow-up within 6 months after the index date, (2) received antiviral therapy for less than 16 weeks, and (3) developed PD within 6 months after the index date. The duration of antiviral therapy ranged from 16 to 48 weeks. In clinical practice, the duration of therapy mainly depended on the serum virologic response and the adverse effects of treatment. Less than 16 weeks of an interferon-based therapy has been suggested as inadequate and premature termination of therapy.[20,21] Such termination usually follows adverse effects, lack of early virologic response, and failure of viral clearance.

The HCV protease inhibitor was not available in the TNHI during the study period (2003-2013). As a result, a total of 242 568 patients with HCV infection were identified in the NHIRD, and 188 152 patients were eligible for the analysis (Figure 1). These participants were subsequently divided into 2 cohorts: antiviral therapy (treated) and non-antiviral therapy (untreated).

The demographics included sex and age. The age of patients at the index date was stratified into 3 levels: 21 to 50, 51 to 75, and older than 75 years. We controlled the age factor in the study because the incidence of PD increased with age. We selected as the covariates the confounding comorbidities and medications that could be associated with chronic HCV infection (including renal disease,[22] diabetes,[23] hypertension,[23] and coronary artery disease[4]) or with the occurrence of PD (either protective or risky, including head injury,[24] diabetes,[25] nonliver cancers,[26] hepatitis B virus infection,[6] statins,[27] anxiety,[28] nonsteroidal anti-inflammatory drugs,[24] dihydropyridine calcium channel blockers [dCCBs],[24] depression, and antidepressants[29]) (**Table 1**). We identified all of the diagnoses of comorbidities by the *ICD-9-CM* codes in the NHIRD, and they were confirmed by at least 2 consecutive clinic visits or any hospitalization in the previous year before the index date.

Figure 1. Flowchart of the Study Cohorts



HCV indicates hepatitis C virus.

We obtained the details of medications from the pharmacy database in the NHIRD. Prescribing of medication was recorded from the index date to the PD occurrence date (or the end of follow-up). Use of medications was dichotomized into either medication possession ratio of 50% or higher or medication possession ratio lower than 50%. We divided the statins into lipophilic and hydrophilic groups by their pharmacokinetic properties because the tissue selectivity of statins might exert a different association on the incidence of PD.[30] The hydrophilic statins included rosuvastatin calcium and pravastatin sodium, whereas the others were classified as lipophilic statins.

The outcome of the study was the development of PD, which we defined by these criteria: (1) any hospital discharge or outpatient visit with the diagnosis of PD (*ICD-9-CM* code 332.0) and (2) receipt of medications for PD. Data on medications (including levodopa, carbidopa, bromocriptine mesylate, pergolide mesylate, amantadine hydrochloride, selegiline hydrochloride, rasagiline mesylate, cabergoline, ropinirole hydrochloride, pramipexole dihydrochloride monohydrate, and rotigotine) were acquired from the pharmacy database of the NHIRD.

The method used here was validated in a previous NHIRD study, and the accuracy of PD diagnosis in the NHIRD was 94.8%.[30] Participants with a diagnosis of stroke and dementia before the index date were excluded to minimize the possibility of enrolling those with secondary and atypical parkinsonism.

Unlike randomized clinical trials, observational studies designed to compare treatment effect are prone to selection bias owing to the nonrandom assignment. Propensity score analysis, in which matching is considered most effective and transparent, is widely used in nonrandomized clinical trials to reduce confounding.[31] Hence, we performed propensity score matching with the covariates described earlier (Table 1) to balance the characteristics of patients between groups to achieve comparability between the treated and untreated cohorts. The matching was processed using a greedy-nearest-neighbor algorithm with a caliper width of 0.2 times of the SD of logit of the propensity score. The quality of matching was checked using the absolute standardized mean difference between the groups after matching, and a value less than 0.1 was considered a well-balanced distribution between the study groups.[32] Each treated patient was matched with a corresponding untreated patient to minimize the treatment selection bias.[33] After matching, each group comprised 39 936 patients.

The event number was defined as the ascertained number with PD. The event rate, expressed as a number per thousand, was the proportion of event number in all observed participants of the cohort. Because the length of the observed period across participants was different, we used the incidence density as an estimate of incidence rate in the study. The

Table 1. Characteristics of Patients Before and After Propensity Score Matching

Variable	Before Matching, No. (%)			After Matching, No. (%)		
	Treated Group (n = 39 989)	Untreated Group (n = 148 163)	ASMD	Treated Group (n = 39 936)	Untreated Group (n = 39 936)	ASMD
Sex						
Male	22 018 (55.1)	70 906 (47.9)	0.145	21 966 (55.0)	22 211 (55.6)	0.012
Female	17 971 (44.9)	77 257 (52.1)	0.145	17 970 (45.0)	17 725 (44.4)	0.012
Age, mean (SD), y	52.8 (11.4)	54.4 (14.7)	0.119	52.8 (11.4)	52.5 (12.9)	0.030
Age group, y						
21-50	14 622 (36.6)	56 166 (37.9)	0.028	14 621 (36.6)	15 206 (38.1)	0.030
51-75	24 874 (62.2)	80 410 (54.3)	0.161	24 822 (62.2)	24 313 (60.9)	0.026
>75	493 (1.2)	11 587 (7.8)	0.321	493 (1.2)	417 (1.0)	0.018
Comorbidities						
CKD or dialysis	1576 (3.9)	9995 (6.7)	0.125	1576 (3.9)	1472 (3.7)	0.014
Diabetes	5485 (13.7)	17 811 (12.0)	0.051	5451 (13.6)	5128 (12.8)	0.024
Hypertension	11 071 (27.7)	40 167 (27.1)	0.013	11 035 (27.6)	10 428 (26.1)	0.034
Coronary artery disease	2466 (6.2)	11 777 (7.9)	0.070	2465 (6.2)	2275 (5.7)	0.020
Hepatitis B virus infection	3486 (8.7)	9093 (6.1)	0.099	3458 (8.7)	3441 (8.6)	0.002
Nonliver cancers	1177 (2.9)	5262 (3.6)	0.034	1177 (2.9)	1114 (2.8)	0.009
Anxiety	5060 (12.7)	16 567 (11.2)	0.045	5030 (12.6)	4832 (12.1)	0.015
Depression	555 (1.4)	1849 (1.2)	0.012	552 (1.4)	551 (1.4)	0.000
Head injury	2360 (5.9)	9108 (6.1)	0.010	2360 (5.9)	2265 (5.7)	0.010
Medication (MPR ≥50%)						
Hydrophilic statin	780 (2.0)	2817 (1.9)	0.004	780 (2.0)	766 (1.9)	0.003
Lipophilic statin	812 (2.0)	3755 (2.5)	0.034	812 (2.0)	778 (1.9)	0.006
NSAID	1580 (4.0)	7746 (5.2)	0.061	1579 (4.0)	1482 (3.7)	0.013
dCCB	5377 (13.4)	21 780 (14.7)	0.036	5361 (13.4)	5153 (12.9)	0.015
Antidepressant	1986 (5.0)	5859 (4.0)	0.049	1969 (4.9)	1877 (4.7)	0.011

Abbreviations: ASMD, absolute standardized mean difference; CKD, chronic kidney disease; dCCB, dihydropyridine calcium channel blocker; MPR, medication possession ratio; NSAID, nonsteroidal anti-inflammatory drug.

incidence density of PD was calculated by the event number divided by sum of the observed duration of each participant and then expressed as a number per 1000 person-years after the index date. We compared the risk of PD incidence between the treated and untreated groups using a Cox proportional hazards regression model, and then we obtained the hazard ratio (HR; treated vs untreated) and 95% CI. The incidence density of each cohort and the HR was calculated at 1 year, 3 years, and 5 years after the index date as well as at the end of the cohort. Patients with missing information (<0.1%) were excluded from the analysis. A 2-sided $P < .05$ was considered statistically significant. All of the statistical analyses were performed with SAS, version 9.4 (SAS Institute Inc).

Results

A total of 188 152 patients were included in this analysis. An equal number (n = 39 936) and comparable characteristics of participants were retained in the treated group (with 17 970 female [45.0%] and a mean [SD] age of 52.8 [11.4] years) and untreated group (with 17 725 female [44.4%] and a mean [SD] age of 52.5 [12.9] years) after matching.

Before propensity score matching, patients who received antiviral therapy were more likely to be male and younger compared with those who were not treated (absolute standardized mean difference, >0.1). The prevalence of chronic kidney disease was lower in the treated group. After propensity score matching, the values of absolute standardized mean difference were less than 0.1, indicating a well-balanced distribution of covariates between groups.

The incidence density of PD was 1.00 (95% CI, 0.85-1.15) in the treated group and 1.39 (95% CI, 1.21-1.57) per 1000 person-years in the untreated group. The risk of PD between the treated and untreated groups was statistically significantly different at year 5 of follow-up (HR, 0.75; 95% CI, 0.59-0.96) and the end of the cohort (HR, 0.71; 95% CI, 0.58-0.87), although the risk was not different at year 1 and year 3 (**Table 2**). The event number and incidence density increased gradually over the years in both groups. The event rate in the treated group increased statistically significantly slower (3.03 per thousand to 4.06 per thousand) than in the untreated group (3.93 per thousand to 5.51 per thousand) (**Figure 2**).

Furthermore, we conducted a subgroup analysis using the variables selected for propensity score matching (**Figure 3**). The subgroup analysis demonstrated more apparent advantages of antiviral therapy in patients who concurrently used dCCBs (HRs of non-dCCBs and CCBs, 0.81 vs 0.44; P for interaction = .02). On the contrary, patients without cancer compared with those with nonliver cancers did not get the advan-

Table 2. Incidence Density and Hazard Ratio of Parkinson Disease Between the Groups

Outcome	Treated Group (n = 39 936)	Untreated Group (n = 39 936)	*P* Value for Comparisons Between HRs
1-y Follow-up			
Event, No. (per thousand)	15 (0.38)	20 (0.50)	
ID (95% CI)	0.38 (0.19-0.57)	0.51 (0.29-0.73)	
HR (95% CI)	0.75 (0.38-1.46)	1 [Reference]	.39
3-y Follow-up			
Event, No. (per thousand)	82 (2.05)	97 (2.43)	
ID (95% CI)	0.83 (0.65-1.01)	0.99 (0.79-1.19)	
HR (95% CI)	0.83 (0.62-1.12)	1 [Reference]	.22
5-y Follow-up			
Event, No. (per thousand)	121 (3.03)	157 (3.93)	
ID (95% CI)	0.92 (0.76-1.08)	1.21 (1.02-1.40)	
HR (95% CI)	0.75 (0.59-0.96)	1 [Reference]	.02
End of follow-up			
Event, No. (per thousand)	162 (4.06)	220 (5.51)	
ID (95% CI)	1.00 (0.85-1.15)	1.39 (1.21-1.57)	
HR (95% CI)	0.71 (0.58-0.87)	1 [Reference]	.001

Abbreviations: HR, hazard ratio; ID, incidence density.

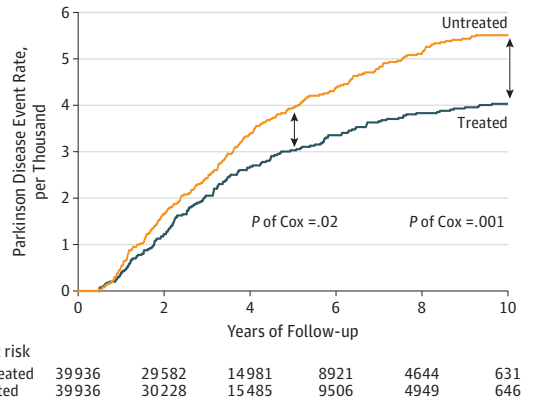
tage of antiviral therapy (HRs of nonliver cancers and liver cancers, 0.67 vs 2.23; *P* for interaction = .02).

Discussion

To our knowledge, this is the first cohort study to investigate the association between antiviral therapy and risk of PD in patients with chronic HCV infection. The results demonstrated a reduced incidence of PD in patients who received interferon-based antiviral treatment. The reduction appeared obvious at 5 years after antiviral therapy and became more statistically significant at the end of follow-up. The lower rate of PD occurrence in the treated patients may suggest that HCV infection is a risk factor for PD development, and antiviral therapy lowers the risk. It cannot be fully excluded that interferon-based antiviral therapy had a direct protective quality against the development of PD. However, the short exposure of antiviral agent, 16 to 48 weeks in most treated participants, makes protecting against PD development in 5 years less likely.

Neuroinflammation has been suggested as a characteristic finding in the PD pathologic condition, and some studies suggest that an innate immune reaction may result in neuronal loss in PD.[34] The HCV infection and PD also share elevated inflammatory biomarkers, such as interleukin 6 (IL-6), tumor necrosis factor, IL-1β, and IL-2, in peripheral blood.[35,36] However, we do not fully comprehend the causality between the PD, peripheral inflammation, and neuroinflammation. In magnetic resonance imaging studies, chronic HCV infection was associated with cerebral inflammatory response, cognitive impairment, and neuropsychiatric symptoms, even when the liver disease was mild and the hepatic encephalopathy was absent.[37,38] In another iodine 123–labeled β-carboxymethyoxy-3-β-(4-iodophenyl) tropane single-photon emission computed tomography study, serotonin and dopamine transmission were disrupted in patients with HCV infection, including those whose virus had been cleared.[39] The underlying mechanism of the protective potential of interferon-based antiviral therapy could be complicated and may involve the modulation of anti-inflammatory cytokines.[40]

Figure 2. Event Rate of Parkinson Disease (PD) in Each Study Cohort

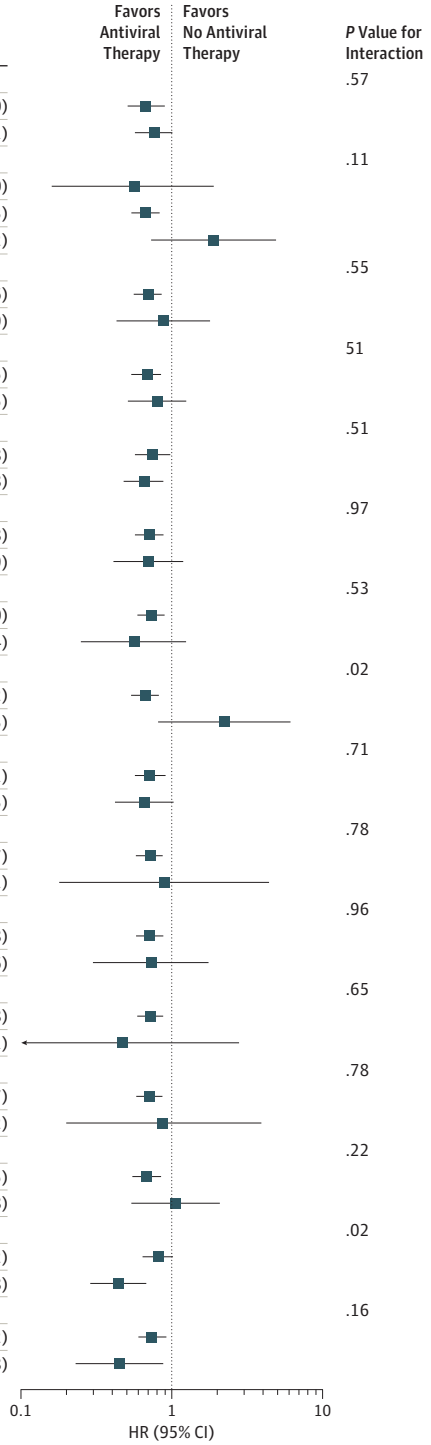


The difference in the development of Parkinson disease in the treated and untreated cohorts enlarged gradually with time and reached statistical significance since year 5 (hazard ratio [HR], 0.75; 95% CI, 0.59-0.96) to the end of the cohort (HR, 0.71; 95% CI, 0.58-0.87).

In contrast, the reduced incidence of PD by antiviral therapy could be associated with the reduction or clearance of HCV in patients. Hepatitis C virus, but not hepatitis B virus, particles were found to induce loss of tyrosine hydroxylase(+) neurons in midbrain neuron-glia cocultures, suggesting a neurotoxic effect of HCV on the dopamine cells.[7] Microvascular endothelial cells of the human brain express receptors as the entries for HCV, and the viral replication in the endothelial cells may subsequently disrupt the

Figure 3. Subgroup Analysis of the Hazard Ratio (HR) of Parkinson Disease Between Treated and Untreated Cohorts

Source	Events, % Treated	Events, % Untreated	Treated vs Untreated HR (95% CI)	P Value for Interaction
Sex				.57
Male	81 (0.37)	113 (0.51)	0.67 (0.51-0.90)	
Female	81 (0.45)	107 (0.60)	0.76 (0.57-1.01)	
Age group, y				.11
21-50	4 (0.03)	7 (0.05)	0.56 (0.16-1.90)	
51-75	144 (0.58)	207 (0.85)	0.67 (0.54-0.83)	
>75	14 (2.84)	6 (1.44)	1.89 (0.73-4.92)	
CKD or dialysis				.55
No	147 (0.38)	205 (0.53)	0.70 (0.56-0.86)	
Yes	15 (0.95)	15 (1.02)	0.87 (0.43-1.79)	
Diabetes				51
No	124 (0.36)	180 (0.52)	0.68 (0.54-0.85)	
Yes	38 (0.70)	40 (0.78)	0.80 (0.51-1.25)	
Hypertension				.51
No	90 (0.31)	119 (0.40)	0.75 (0.57-0.98)	
Yes	72 (0.65)	101 (0.97)	0.65 (0.48-0.88)	
Coronary artery diseases				.97
No	138 (0.37)	189 (0.50)	0.71 (0.57-0.88)	
Yes	24 (0.97)	31 (1.36)	0.70 (0.41-1.19)	
Hepatitis B virus infection				.53
No	152 (0.42)	205 (0.56)	0.73 (0.59-0.90)	
Yes	10 (0.29)	15 (0.44)	0.56 (0.25-1.24)	
Non-liver cancers				.02
No	147 (0.38)	215 (0.55)	0.67 (0.54-0.82)	
Yes	15 (1.27)	5 (0.45)	2.23 (0.81-6.13)	
Anxiety				.71
No	129 (0.37)	175 (0.50)	0.72 (0.57-0.91)	
Yes	33 (0.66)	45 (0.93)	0.65 (0.42-1.03)	
Depression				.78
No	159 (0.40)	217 (0.55)	0.71 (0.58-0.87)	
Yes	3 (0.54)	3 (0.54)	0.89 (0.18-4.41)	
Head injury				.96
No	153 (0.41)	209 (0.55)	0.71 (0.58-0.88)	
Yes	9 (0.38)	11 (0.49)	0.73 (0.30-1.76)	
Hydrophilic statin				.65
No	160 (0.41)	217 (0.55)	0.72 (0.59-0.88)	
Yes	2 (0.26)	3 (0.39)	0.47 (0.08-2.81)	
Lipophilic statin				.78
No	158 (0.40)	217 (0.55)	0.71 (0.58-0.87)	
Yes	4 (0.49)	3 (0.39)	0.88 (0.20-3.92)	
NSAIDs				.22
No	144 (0.38)	204 (0.53)	0.68 (0.55-0.85)	
Yes	18 (1.14)	16 (1.08)	1.06 (0.54-2.08)	
dCCBs				.02
No	132 (0.38)	159 (0.46)	0.81 (0.64-1.02)	
Yes	30 (0.56)	61 (1.18)	0.44 (0.29-0.68)	
Antidepressants				.16
No	149 (0.39)	195 (0.51)	0.74 (0.60-0.92)	
Yes	13 (0.66)	25 (1.33)	0.45 (0.23-0.88)	



The protective potential against Parkinson disease occurrence was obvious in the patients who concurrently used dihydropyridine calcium channel blockers (dCCBs) (HR of non-dCCBs was 0.81 and dCCBs was 0.44; *P* for interaction = .02). Substantially different from patients without nonliver cancers, the patients with nonliver cancers did not gain the advantage of antiviral therapy (HR of nonliver cancers was 0.67 and liver cancers was 2.23; *P* for interaction = .02). CKD indicates chronic kidney disease; NSAIDs, nonsteroidal anti-inflammatory drugs.

blood-brain barrier.[41] Concurrent HCV-related systemic inflammation, exposure of neurotoxin, and a disrupted blood-brain barrier could exert a greater detrimental power on the neuron.[36,42] In addition, a few postmortem studies provide the evidence that viral replication happens in a human's brain. The genotype of HCV in the brain, blood cells, and liver is diverse, and the virus with a brain-specific mutation may survive in the brain.[43-45] These researches support the epidemiologic finding of the association between HCV infection and PD occurrence. Moreover, it has been confirmed that interferon is capable of passing the blood-brain and blood-spinal cord barriers.[46] The antiviral

therapy may, therefore, reduce the opportunity of central nervous system damage caused by HCV.

The incidence of PD is statistically significantly lower in patients with HCV infection who are treated with antiviral therapy, but a proportion of patients in this group still develop PD every year. The origins of PD are complex and largely unclear. An HCV infection could be only 1 source. Hence, the advantage of antiviral therapy is restricted. However, some participants in this study could be enrolled at the premotor stage of PD, when diagnosis as PD was not possible.[47-49] Participants at the premotor stage had pathologically developed PD and inevitably presented PD motor symptoms (clinically diagnosed as PD) somewhere during the follow-up period. Protection from antiviral therapy may be possible only when patients with HCV infection received antiviral therapy before the premotor stage. Although interferon can enter the brain,[46] ribavirin, included in the regimen of antiviral therapy, is a water-soluble molecule that can hardly penetrate the blood-brain barrier.[50] Once the HCV enters the neuron or glia cell, the advantage of antiviral therapy may be dampened. Some studies reported cases of HCV infection who developed parkinsonian symptoms during or after interferon-based antiviral therapy and suspected that interferon-based antiviral therapy could be the origin of PD.[14,51] However, the conclusion of this study refutes the conclusions of observational studies. The discrepancy could be explained by patients who received antiviral therapy at the premotor stage of PD but eventually developed PD.

In the subgroup analysis, the advantage of antiviral therapy was not observed in patients with nonliver cancers; any advantage was probably associated with the short lifespan of patients. The mean follow-up duration in patients with nonliver cancers was 3.36 (2.3) years and in patients without nonliver cancers was 4.05 (2.6) years. The mortality of patients with nonliver cancers was statistically significantly higher than that of patients without nonliver cancers (15.1% vs 5.6%; $P < .001$). Accordingly, the advantage of antiviral therapy did not emerge from the cohort in this subgroup. On the contrary, the protective potential of antiviral therapy against PD was most statistically significant in the subgroup of patients treated with dCCBs. This finding corresponds to study results, which concluded that dCCBs may be associated with reduced risk of PD.[52-54] In patients with HCV infection who used dCCBs, antiviral therapy may provide an added advantage of reducing PD development.

Although the interaction in the age subgroup (21-50, 51-75, or >75 years) was not statistically significant (HR, 0.56 vs 0.67 vs 1.89; P for interaction = .11), the trend of association in the participants older than 75 years was different from that in the other groups. However, only a small number of patients received antiviral therapy in this age range. Hence, the results may be less conclusive. Moreover, considering age as a strong risk factor for PD, patients older than 75 years may be too advanced in age to find antiviral therapy advantageous.

Limitations

This study has some limitations. First, the hepatic function profile, serum virologic response, viral genotype, and HCV RNA-level data were unavailable in the NHIRD. However, the TNHI has strict regulations. All of the laboratory data of patients with HCV infection, including serum alanine aminotransferase level, HCV RNA, HCV antibody, and liver biopsy, have to be reviewed by experts before approval of the antiviral therapy. This requirement strengthens the authenticity of the data in our work. However, lack of the viral profiles made it impossible to associate PD incidence with severity of HCV infection. Second, the NHIRD lacked patients' lifestyle information (eg, smoking status, consumption of coffee and alcohol), which may have affected the incidence of PD.[24]

Third, ascertaining the diagnosis of PD according to the *ICD-9-CM* code and anti-PD medications in the NHIRD may not be the ideal method, although the method used here was validated and shown to have a diagnostic accuracy of 94.8%.[30] Differentiating PD from other similar parkinsonian syndromes is sometimes challenging in clinical practice. Long-term medical records and pathological diagnoses for PD are helpful in the accurate diagnosis of the disorder but were unavailable in the NHIRD. However, diagnostic bias was not relevant to the decision making of antiviral therapy and may have equally distributed to the treated and untreated groups and thus may not have confounded the estimate of treatment association.

Fourth, PD is a slow, progressive neurodegenerative disorder. A maximum 11-year follow-up period limited by the availability of antiviral therapy was not a long enough period in which to observe the full course of infection, inflammation, or treatment. A cohort study with a longer follow-up period may give a better answer in the future. In addition, prospective studies would be required for assessing the association between PD, viral genotype, RNA level, and severity of hepatic disease in patients with HCV infection and, if possible, the association between interferon, antiviral regimen, and PD development in participants without HCV infection.

Conclusions

This study found that PD incidence appeared to be lower in patients who were receiving interferon-based antiviral therapy for chronic HCV infection. The results seem to support the theory that HCV infection is a risk factor for developing PD. Antiviral therapy has shown potential in lowering this risk.

ARTICLE INFORMATION

Accepted for Publication: March 18, 2019.

Published Online: June 5, 2019. doi:10.1001/jamaneurol.2019.1368

Author Affiliations: Department of Neurology, Landseed International Hospital, Taoyuan, Taiwan (W.-Y. Lin, Lu); Department of Neurology, Chang Gung Memorial Hospital, Linkou Medical Center, Taoyuan, Taiwan (W.-Y. Lin, Weng, Fong, Wu, Lu, Chen, Huang); Neuroscience Research Center, Chang Gung Memorial Hospital, Linkou Medical Center, Taoyuan, Taiwan (W.-Y. Lin, Weng, Fong, Lu, Chen, Huang); Department of Cardiology, Chang Gung Memorial Hospital, Chiayi, Taiwan (M.-S. Lin, Y.-S. Lin); School of Medicine, Chang Gung University, Taoyuan, Taiwan (Weng, Fong, Wu, Lu,

Chen, Huang); Healthy Aging Research Center, Chang Gung University, Taoyuan, Taiwan (Weng, Lu, Huang); Department of Neurology, Taipei Medical University Hospital, Taipei, Taiwan (Yeh); School of Medicine, Taipei Medical University, Taipei, Taiwan (Yeh); Institute of Cognitive Neuroscience, National Central University, Taoyuan, Taiwan (Huang).

Author Contributions: Drs W.-Y. Lin and M.-S. Lin contributed equally to the work. Drs Chen and Huang had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: M.-S. Lin, Weng, Fong, Wu, Lu, Huang.
Acquisition, analysis, or interpretation of data: W.-Y. Lin, M.-S. Lin, Yeh, Y.-S. Lin, Chen.
Drafting of the manuscript: W.-Y. Lin, Yeh.
Critical revision of the manuscript for important intellectual content: M.-S. Lin, Weng, Y.-S. Lin, Fong, Wu, Lu, Chen, Huang.
Statistical analysis: W.-Y. Lin, M.-S. Lin, Y.-S. Lin.
Obtained funding: W.-Y. Lin.
Administrative, technical, or material support: W.-Y. Lin, M.-S. Lin, Yeh, Lu.
Supervision: Weng, Wu, Lu, Chen, Huang.

Conflict of Interest Disclosures: None reported.

Funding/Support: This study was funded by grant BMRPD45 from Chang Gung Medical Research Fund of Chang Gung Memorial Hospital, Linkou and by grant CMRPGME0011 from Chang Gung Memorial Hospital, Chiayi.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Meeting Presentation: This paper was presented as a poster at the 5th World Parkinson Congress; June 6, 2019; Kyoto, Japan.

Additional Contributions: We thank Alfred Hsing-Fen Lin, MS, and Zoe Ya-Jhu Syu, MPH, Raising Statistics Consultant Inc, for their statistical assistance. These individuals received compensation and declared no competing interest between the findings of this study and their company.

REFERENCES

1. Messina JP, Humphreys I, Flaxman A, et al. Global distribution and prevalence of hepatitis C virus genotypes. *Hepatology*. 2015;61(1):77-87. doi:10.1002/hep.27259

2. Negro F, Forton D, Craxì A, Sulkowski MS, Feld JJ, Manns MP. Extrahepatic morbidity and mortality of chronic hepatitis C. *Gastroenterology*. 2015;149(6):1345-1360. doi:10.1053/j.gastro.2015.08.035

3. Gill K, Ghazinian H, Manch R, Gish R. Hepatitis C virus as a systemic disease: reaching beyond the liver. *Hepatol Int*. 2016;10(3):415-423. doi:10.1007/s12072-015-9684-3

4. Olubamwo OO, Aregbesola AO, Miettola J, Kauhanen J, Tuomainen TP. Hepatitis C and risk of coronary atherosclerosis: a systematic review. *Public Health*. 2016;138:12-25. doi:10.1016/j.puhe.2016.04.005

5. Lin MS, Guo SE, Chen MY, et al. The impact of hepatitis C infection on ischemic heart disease via ischemic electrocardiogram. *Am J Med Sci*. 2014;347(6):478-484. doi:10.1097/MAJ.0b013e3182a5587d

6. Pakpoor J, Noyce A, Goldacre R, et al. Viral hepatitis and Parkinson disease: a national record-linkage study. *Neurology*. 2017;88(17):1630-1633. doi:10.1212/WNL.0000000000003848

7. Wu WY, Kang KH, Chen SL, et al. Hepatitis C virus infection: a risk factor for Parkinson's disease. *J Viral Hepat*. 2015;22(10):784-791. doi:10.1111/jvh.12392

8. Tsai HH, Liou HH, Muo CH, Lee CZ, Yen RF, Kao CH. Hepatitis C virus infection as a risk factor for Parkinson disease: a nationwide cohort study. *Neurology*. 2016;86(9):840-846. doi:10.1212/WNL.0000000000002307

9. Kim JM, Jang ES, Ok K, et al. Association between hepatitis C virus infection and Parkinson's disease. *Mov Disord*. 2016;31(10):1584-1585. doi:10.1002/mds.26755

10. Golabi P, Otgonsuren M, Sayiner M, Arsalla A, Gogoll T, Younossi ZM. The prevalence of Parkinson disease among patients with hepatitis C infection. *Ann Hepatol*. 2017;16(3):342-348. doi:10.5604/01.3001.0009.8588

11. Nahon P, Bourcier V, Layese R, et al; ANRS CO12 CirVir Group. Eradication of hepatitis C virus infection in patients with cirrhosis reduces risk of liver and non-liver complications. *Gastroenterology*. 2017;152(1):142-156.e2. doi:10.1053/j.gastro.2016.09.009

12. Hsu YC, Ho HJ, Huang YT, et al. Association between antiviral treatment and extrahepatic outcomes in patients with hepatitis C virus infection. *Gut*. 2015;64(3):495-503. doi:10.1136/gutjnl-2014-308163

13. Lin MS, Chung CM, Lin WY, et al. Antiviral therapy reduces risk of haemorrhagic stroke in patients with HCV infection: a nationwide cohort study. *Antivir Ther*. 2018;23(1):43-52. doi:10.3851/IMP3172

14. Wangensteen KJ, Krawitt EL, Hamill RW, Boyd JT. Parkinsonism in patients with chronic hepatitis C treated with interferons: case reports and review of the literature. *Clin Neuropharmacol*. 2016;39(1):1-5. doi:10.1097/WNF.0000000000000120

15. Wangensteen KJ, Krawitt EL, Hamill RW, Boyd JT. Hepatitis C virus infection: a risk factor for Parkinson's disease. *J Viral Hepat*. 2016;23(7):535. doi:10.1111/jvh.12517

16. Boyd JT, Wangensteen KJ, Krawitt EL, Hamill RW, Kao CH, Tsai HH. Hepatitis C virus infection as a risk factor for Parkinson disease: a nationwide cohort study. *Neurology*. 2016;87(3):342. doi:10.1212/01.wnl.0000489939.73359.c3

17. Abushouk AI, El-Husseny MWA, Magdy M, et al. Evidence for association between hepatitis C virus and Parkinson's disease. *Neurol Sci*. 2017;38(11):1913-1920. doi:10.1007/s10072-017-3077-4

18. Wijarnpreecha K, Chesdachai S, Jaruvongvanich V, Ungprasert P. Hepatitis C virus infection and risk of Parkinson's disease: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol*. 2018;30(1):9-13. doi:10.1097/MEG.0000000000000991

19. National Health Insurance Administration, Ministry of Health and Welfare. 2014-2015 National Health Insurance annual report. http://www.nhi.gov.tw/Resource/webdata/28140_1_National%20Health%20Insurance%20in%20Taiwan%202014-2015%20(bilingual).pdf. Accessed April 29, 2015.

20. Yu ML, Chuang WL. Treatment of chronic hepatitis C in Asia: when East meets West. *J Gastroenterol Hepatol*. 2009;24(3):336-345. doi:10.1111/j.1440-1746.2009.05789.x

21. Omata M, Kanda T, Yu ML, et al. APASL consensus statements and management algorithms for hepatitis C virus infection. *Hepatol Int*. 2012;6(2):409-435. doi:10.1007/s12072-012-9342-y

22. Perico N, Cattaneo D, Bikbov B, Remuzzi G. Hepatitis C infection and chronic renal diseases. *Clin J Am Soc Nephrol*. 2009;4(1):207-220. doi:10.2215/CJN.03710708

23. Younossi ZM, Stepanova M, Nader F, Younossi Z, Elsheikh E. Associations of chronic hepatitis C with metabolic and cardiac outcomes. *Aliment Pharmacol Ther*. 2013;37(6):647-652. doi:10.1111/apt.12234

24. Ascherio A, Schwarzschild MA. The epidemiology of Parkinson's disease: risk factors and prevention. *Lancet Neurol*. 2016;15(12):1257-1272. doi:10.1016/S1474-4422(16)30230-7

25. De Pablo-Fernandez E, Goldacre R, Pakpoor J, Noyce AJ, Warner TT. Association between diabetes and subsequent Parkinson disease: a record-linkage cohort study. *Neurology*. 2018;91(2):e139-e142. doi:10.1212/WNL.0000000000005771

26. Lin PY, Chang SN, Hsiao TH, Huang BT, Lin CH, Yang PC. Association between Parkinson disease and risk of cancer in Taiwan. *JAMA Oncol*. 2015;1(5):633-640. doi:10.1001/jamaoncol.2015.1752

27. Lin KD, Yang CY, Lee MY, Ho SC, Liu CK, Shin SJ. Statin therapy prevents the onset of Parkinson disease in patients with diabetes. *Ann Neurol*. 2016;80(4):532-540. doi:10.1002/ana.24751

28. Lin CH, Lin JW, Liu YC, Chang CH, Wu RM. Risk of Parkinson's disease following anxiety disorders: a nationwide population-based cohort study. *Eur J Neurol*. 2015;22(9):1280-1287. doi:10.1111/ene.12740

29. Postuma RB, Aarsland D, Barone P, et al. Identifying prodromal Parkinson's disease: pre-motor disorders in Parkinson's disease. *Mov Disord*. 2012;27(5):617-626. doi:10.1002/mds.24996

30. Lee YC, Lin CH, Wu RM, et al. Discontinuation of statin therapy associates with Parkinson disease: a population-based study. *Neurology*. 2013;81(5):410-416. doi:10.1212/WNL.0b013e31829d873c

31. Kim DH, Pieper CF, Ahmed A, Colón-Emeric CS. Use and interpretation of propensity scores in aging research: a guide for clinical researchers. *J Am Geriatr Soc*. 2016;64(10):2065-2073. doi:10.1111/jgs.14253

32. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res*. 2011;46(3):399-424. doi:10.1080/00273171.2011.568786

33. Austin PC. Statistical criteria for selecting the optimal number of untreated subjects matched to each treated subject when using many-to-one matching on the propensity score. *Am J Epidemiol*. 2010;172(9):1092-1097. doi:10.1093/aje/kwq224

34. De Virgilio A, Greco A, Fabbrini G, et al. Parkinson's disease: autoimmunity and neuroinflammation. *Autoimmun Rev*. 2016;15(10):1005-1011. doi:10.1016/j.autrev.2016.07.022

35. Qin XY, Zhang SP, Cao C, Loh YP, Cheng Y. Aberrations in peripheral inflammatory cytokine levels in Parkinson disease: a systematic review and

meta-analysis. *JAMA Neurol*. 2016;73(11):1316-1324. doi:10.1001/jamaneurol.2016.2742

36. Zampino R, Marrone A, Restivo L, et al. Chronic HCV infection and inflammation: clinical impact on hepatic and extra-hepatic manifestations. *World J Hepatol*. 2013;5(10):528-540. doi:10.4254/wjh.v5.i10.528

37. Bokemeyer M, Ding XQ, Goldbecker A, et al. Evidence for neuroinflammation and neuroprotection in HCV infection-associated encephalopathy. *Gut*. 2011;60(3):370-377. doi:10.1136/gut.2010.217976

38. Forton DM, Hamilton G, Allsop JM, et al. Cerebral immune activation in chronic hepatitis C infection: a magnetic resonance spectroscopy study. *J Hepatol*. 2008;49(3):316-322. doi:10.1016/j.jhep.2008.03.022

39. Weissenborn K, Ennen JC, Bokemeyer M, et al. Monoaminergic neurotransmission is altered in hepatitis C virus infected patients with chronic fatigue and cognitive impairment. *Gut*. 2006;55(11):1624-1630. doi:10.1136/gut.2005.080267

40. Marín-Serrano E, Rodríguez-Ramos C, Díaz F, Martín-Herrera L, Girón-González JA. Modulation of the anti-inflammatory interleukin 10 and of proapoptotic IL-18 in patients with chronic hepatitis C treated with interferon alpha and ribavirin. *J Viral Hepat*. 2006;13(4):230-234. doi:10.1111/j.1365-2893.2005.00679.x

41. Fletcher NF, Wilson GK, Murray J, et al. Hepatitis C virus infects the endothelial cells of the blood-brain barrier. *Gastroenterology*. 2012;142(3):634-643.e6. doi:10.1053/j.gastro.2011.11.028

42. Fletcher NF, McKeating JA. Hepatitis C virus and the brain. *J Viral Hepat*. 2012;19(5):301-306. doi:10.1111/j.1365-2893.2012.01591.x

43. Fishman SL, Murray JM, Eng FJ, Walewski JL, Morgello S, Branch AD. Molecular and bioinformatic evidence of hepatitis C virus evolution in brain. *J Infect Dis*. 2008;197(4):597-607. doi:10.1086/526519

44. Radkowski M, Wilkinson J, Nowicki M, et al. Search for hepatitis C virus negative-strand RNA sequences and analysis of viral sequences in the central nervous system: evidence of replication. *J Virol*. 2002;76(2):600-608. doi:10.1128/JVI.76.2.600-608.2002

45. Vargas HE, Laskus T, Radkowski M, et al. Detection of hepatitis C virus sequences in brain tissue obtained in recurrent hepatitis C after liver transplantation. *Liver Transpl*. 2002;8(11):1014-1019. doi:10.1053/jlts.2002.36393

46. Pan W, Banks WA, Kastin AJ. Permeability of the blood-brain and blood-spinal cord barriers to interferons. *J Neuroimmunol*. 1997;76(1-2):105-111. doi:10.1016/S0165-5728(97)00034-9

47. Goldman JG, Postuma R. Premotor and nonmotor features of Parkinson's disease. *Curr Opin Neurol*. 2014;27(4):434-441. doi:10.1097/WCO.0000000000000112

48. Mollenhauer B, Zhang J. Biochemical premotor biomarkers for Parkinson's disease. *Mov Disord*. 2012;27(5):644-650. doi:10.1002/mds.24956

49. Reichmann H. Premotor diagnosis of Parkinson's disease. *Neurosci Bull*. 2017;33(5):526-534. doi:10.1007/s12264-017-0159-5

50. Colombo G, Lorenzini L, Zironi E, et al. Brain distribution of ribavirin after intranasal administration. *Antiviral Res*. 2011;92(3):408-414. doi:10.1016/j.antiviral.2011.09.012

51. Kajihara M, Montagnese S, Khanna P, et al. Parkinsonism in patients with chronic hepatitis C treated with interferon-alpha2b: a report of two cases. *Eur J Gastroenterol Hepatol*. 2010;22(5):628-631. doi:10.1097/MEG.0b013e32833383e3

52. Ritz B, Rhodes SL, Qian L, Schernhammer E, Olsen JH, Friis S. L-type calcium channel blockers and Parkinson disease in Denmark. *Ann Neurol*. 2010;67(5):600-606.

53. Pasternak B, Svanström H, Nielsen NM, Fugger L, Melbye M, Hviid A. Use of calcium channel blockers and Parkinson's disease. *Am J Epidemiol*. 2012;175(7):627-635. doi:10.1093/aje/kwr362

54. Lee YC, Lin CH, Wu RM, Lin JW, Chang CH, Lai MS. Antihypertensive agents and risk of Parkinson's disease: a nationwide cohort study. *PLoS One*. 2014;9(6):e98961. doi:10.1371/journal.pone.0098961