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Medication Use and Medical Comorbidity in Patients with Chronic Hepatitis C from a U.S. Commercial Claims Database: High Utilization of Drugs with Interaction Potential

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Abstract

Background—With the advent of the direct-acting antiviral agents (DAAs), significant drug-drug interaction (DDI) potential now exists for patients treated for chronic hepatitis C virus (HCV) infection. However, little is known about how often patients with HCV use medications that may interact with newer HCV treatments, especially those with CYP3A DDI potential.

Methods—Using a large United States commercial insurance database, medication use and comorbidity burden was examined among adult patients with a chronic HCV diagnosis from 2006-2010. Medications were examined by total number of prescription claims, proportion of patients exposed, and DDI potential with prototypical CYP3A DAAs, boceprevir and telaprevir, for which data were available.

Results—Patient comorbidity burden was high and increased over the study period. Medication use was investigated in 53,461 patients with chronic HCV. Twenty-one (53%) of the top 40 most utilized medications were classified as having interaction potential, with 62% of patients received at least one of the top 22 interacting medications by exposure. Of these, 59% and 41% were listed in a common DDI resource but not in medication prescribing information, 77% and 77% had not been investigated in DDI studies, 32% and 27% did not have clear recommendations for DDI management, and only 14% and 23% carried a recommendation to avoid coadministration for boceprevir and telaprevir, respectively.

Conclusion—Practitioners may expect a medication with CYP3A DDI potential in two-thirds of patients with HCV and almost one-half of the most frequently used medications. However, DDI potential may not be reflected in prescribing information.

Keywords

boceprevir; drug interactions; hepatitis C; telaprevir; protease inhibitors; comorbidities

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Introduction

Chronic hepatitis C virus infection (HCV) affects an estimated 3.2 million people in the United States (U.S.), while in the European Union HCV affects approximately 8.1 million people and contributes to one-third of deaths in patients with cirrhosis or liver cancer [1-3]. The introduction of direct-acting antivirals (DAAs), beginning with telaprevir (TVR) and boceprevir (BOC) in 2011, has revolutionized the treatment of genotype 1 chronic HCV by improving rates of sustained virologic response dramatically in conjunction with peginterferon and ribavirin (triple therapy) [4]. Currently, there are three classes of DAAs that target different steps in the viral replication cycle: NS3/4A protease inhibitors, NS5B polymerase inhibitors, and NS5A inhibitors. Despite advantages in improving virologic response, many of these new DAAs also carry high drug-drug interaction (DDI) potential due to their metabolism by cytochrome P450 3A (CYP3A) or transport by P-glycoprotein (P-gp) [5].

A number of DDI studies for DAAs have been conducted in both healthy volunteers and diseased populations [6-9] with a focus on medications that have the potential for significant drug interaction or which may be highly utilized in certain patient populations [6, 10, 11]. Recent review articles have provided some guidance for the clinical management of DDIs with the use of NS3/4A protease inhibitors TVR and BOC based on a composite of available literature and theoretical considerations of their clinical pharmacology [5, 12-15]. However, there is a paucity of information on their actual DDI risk in the outpatient setting. Recently, DDI risk with initiation of NS3/4A protease inhibitor therapy was determined to be substantial for about one-half of a small cohort of German HCV patients at a tertiary referral center [16]. Knowledge of the medication use patterns in a larger heterogeneous population would add vital insight to our understanding of the potential for interactions with current and emerging agents [5, 13].

The primary objective of this study was to characterize medication utilization in a representative chronic HCV population. Specific aims included: (1) to assess the most highly utilized medications from 2006-2010 by prescription claims and by exposure, and (2) to evaluate the telaprevir and boceprevir DDI potential of highly utilized medications in patients with HCV. In order to provide a context for interpretation of the medication use data, comorbidities and other demographic and clinical characteristics of the patients with chronic HCV also were explored. The DDI risk for boceprevir and telaprevir, prototypical CYP3A-metabolized DAAs, will be similar to the DDI risk for other DAAs which are substrates or inhibitors of CYP3A such as simeprevir, faldaprevir, or daclatasvir and especially for DAAs that will be co-administered with ritonavir to inhibit their CYP3A-dependent metabolism (ABT-450 and danoprevir). These agents will soon be used extensively in patients with HCV throughout the world.

Materials and Methods

Study Population and Data

A retrospective observational study design was employed using the Truven Health Analytics Marketscan® Commercial Claims and Encounters Research Database for the years 2006 to

2010. The database includes de-identified medical inpatient and outpatient claims, outpatient pharmaceutical claims, and enrollment data files and provides demographic information, medical diagnoses, health care procedures, and pharmacy claims for approximately 20 million enrollees from over 100 nationwide U.S. insurers.

Five different 1-year cross-sectional cohorts were constructed for each year from 2006 to 2010 to examine demographic characteristics, medication use, and comorbid health conditions in chronic HCV patients. Within each 1-year cross-section, patients were selected for inclusion if they 1) had at least 1 inpatient or 2 outpatient International Classification of Diseases, 9th edition (ICD-9) codes for chronic HCV (070.54 or 070.44) occurring on separate days, 2) were ≥18 years of age, 3) and had continuous enrollment for the entire 1-year period. This cohort was used to investigate demographic and clinical characteristics. A subcohort of these patients with prescription insurance benefits filling at least one prescription per year was further selected to examine concomitant medication use. This subcohort was identified to ensure adequate capture of prescription claims information. Given the prevalent cross-sectional nature of this study, patients could contribute to multiple cross-sections if meeting eligibility criteria for multiple years.

Demographic and Clinical Characteristics

To characterize patients with HCV eligible to receive telaprevir or boceprevir, information was captured for each 1-year calendar period including demographic (age and gender), type of insurance coverage, and region of residence (e.g., Northeast, North Central, South or West). In addition, comorbidities that were reported previously as highly prevalent in chronic HCV patients or otherwise believed to be clinically relevant were identified for each 1-year cross-sectional cohort in either the inpatient or outpatient files using compiled ICD-9 code definitions from the medical literature (Appendix A) [17, 18]. Compensated cirrhosis was defined directly by ICD-9 code definition; advanced liver disease was a composite definition representing decompensated disease and included codes for ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, portal hypertension, esophageal varices, hepatorenal syndrome, or hepatocellular carcinoma. The Charlson Comorbidity Index (CCI), a general measure of comorbidity and predicted mortality, was calculated for each 1-year cross-sectional cohort [19, 20].

Medication Use

Medication use was characterized among the subcohort of chronic HCV patients with prescription insurance benefits. Prescription drug use was identified through national drug codes (NDCs) in the outpatient pharmaceutical files merged with the REDBOOK supplement, which identifies specific medications and therapeutic categories. As standard of care during the study period was dual therapy with interferon and ribavirin, a ‘treated’ patient was defined as having ≥ 1 prescription claim for ribavirin plus ≥1 prescription claim for peginterferon alfa-2a/2b or interferon alfacon-1 during each 1-year eligible calendar period. The average number of distinct medications per individual (drug name without regard to strength or form) also was calculated within the 1-year calendar period for eligible enrollees.

Drug-Drug Interaction Potential

To identify highly utilized medications in the chronic HCV cohort, the 200 most commonly used medications were identified and ranked according to the total number of prescription claims. These medications were then assessed for the potential to interact with telaprevir or boceprevir using the University of Liverpool Hepatitis DDI website (as of September 2013), a recommended international resource from the American Association for the Study of Liver Diseases (AASLD) HCV treatment guidelines [21]. This resource was used as prior data, because it has been suggested to be a more comprehensive resource than the prescribing information [22, 23]. Drug interactions with telaprevir and boceprevir are designated on this site as: “should not be coadministered”, “potential interaction”, or “no clinically significant interaction expected” [21].

To identify the annual proportion of HCV patients exposed to medications with known telaprevir and boceprevir DDI potential, medications were selected from the Liverpool resource's printable charts (as of April 2013) if classified as either “should not be coadministered” or “potential interaction” [21]. For each of these medications, the proportion of patients with ≥1 outpatient prescription claim during each 1-year period of eligibility was determined. Medications were then ranked by average annual proportion of patients exposed within each 1-year cross-sectional cohort. Medications were queried by individual drug ingredients such that one query could span multiple products, identifying usage by total exposure rather than through individually marketed products. For example, codeine was not ranked on the top 40 medications by claims when comparing individual drug products, but its total population exposure was 8.9% across multiple drug products.

Medications with drug interaction potential in the Liverpool resources' complete recommendations were selected for subanalysis if they were listed in the top 40 most utilized medications by prescription claims or had high patient exposure. The prescribing information was compared with the Liverpool resource charts for the selected medications. Drug interaction details in the Liverpool resource were used to further analyze the proportion of these drugs with DDI potential formally investigated in studies, the proportion with clear and actionable recommendations for DDI management, and the proportion not recommended for coadministration. A recommendation for DDI management was considered clear and actionable if there was a statement advising an action such as avoiding, adjusting dose, monitoring, or therapeutic drug monitoring.

Statistical Analysis

For each 1-year cross-sectional cohort, descriptive statistics were performed to assess each demographic and clinical characteristic, including the proportion of patients ‘treated’ with PEG-interferon and ribavirin and comorbid conditions. An average from 2006-2010 across each characteristic was weighted by the total number of patients in each year. In addition, the annual proportions of patients utilizing medications present in the top 200 drug list and those defined by our team as clinically relevant in the chronic HCV population were also described.

All analyses were performed using SAS 9.2 (SAS institute, Cary, NC). This study was approved by the University of North Carolina at Chapel Hill Institutional Review Board.

Results

Of 197,381 individuals aged ≥18 with any HCV diagnosis in the study period, 71,584 patients (106,283 1-year cross-sections) received a diagnosis of chronic HCV in at least one inpatient or two outpatient visits and maintained continuous enrollment for at least one 1-year period. Demographic and clinical comorbidity characteristics are reported in Table 1. There were fewer eligible individuals in 2006 and 2007 relative to the successive years. Average overall age of the study sample was 51.2 ± 7.5 years with an increasing trend over the 5-year period from age 49.7 in 2006 to age 52.4 in 2010; 62.2% were male. The majority of the study patients resided in the Southern region of the U.S. (48.6%) and had a preferred provider organization insurance plan (65.7%). Comorbid conditions prevalent in ≥5% of patients (in order of decreasing prevalence) were hypertension, lipid metabolism disorders, compensated cirrhosis, advanced liver disease, type 2 diabetes, depression, non-alcoholic fatty liver disease (NAFLD), and chronic obstructive pulmonary disease (COPD)/asthma. Prevalence increased over the study period for the majority of conditions queried, with the highest increases observed for obesity, hepatocellular carcinoma, and alcohol abuse/dependence. Average rates of liver transplant and human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) in the cohort were 3.9% and 2.8%, respectively.

A subcohort of 53,461 individuals (79,185 cross-sections) had prescription insurance benefits and was followed to examine medication use patterns. HCV treatment rates and comorbidity measures for this subcohort are reported in Table 2. On average, 31.2% of patients were classified as ‘treated’, having received both interferon and ribavirin. The mean Charlson Comorbidity Index score was 2.2 and increased over the study period; the average for the treated group was lower than the untreated group (1.9 vs 2.4, respectively). The average number of unique medications filled per patient for the treated group was higher than the untreated group (11.5 vs 8.9, respectively).

The top 10 therapeutic medication categories used in this chronic HCV cohort included (1) analgesics/antipyretics and opiate agonists, (2) antidepressants, (3) antivirals, (4) gastrointestinal drugs, (5) benzodiazepines, (6) beta-blockers, (7) ACE-inhibitors, (8) anxiolytic/sedative hypnotics, (9) calcium channel blockers, and (10) interferons. The top 40 medications used by HCV patients from 2006-2010 are displayed in Table 3, with the top 200 listed in Appendix B. The most common medication with DDI potential used by HCV patients was acetaminophen/hydrocodone, which was filled 367,166 times among the 53,461 patients with HCV who had prescription insurance benefits between 2006 and 2010. Examination of the top 40 medications for DDI potential with boceprevir or telaprevir in the Liverpool resource showed that 17 were classified as “no clinically significant interaction expected” (42.5%), 21 contained at least one component that was classified as “potential interaction” (52.5%, 5 of which indicated an unlikely pharmacokinetic interaction and/or a drug-disease interaction only), zero medications were classified as “should not be coadministered” (0%), and 2 medications (5.0%) were not listed in the resource.

Of 225 drugs listed in the Liverpool resource, 143 were categorized as “potential interaction” or “should not be coadministered” with boceprevir or telaprevir. Of these, 109 were selected for analysis if they had FDA approval during the study period and were not classified as a drug-disease interaction. The medication with the highest exposure was zolpidem, which was used by 14.1% of the subcohort. Medications demonstrating increasing utilization over the study period included pravastatin, tenofovir, buprenorphine, simvastatin, amlodipine, tacrolimus, and prednisone; decreasing utilization was observed for escitalopram and venlafaxine. Simvastatin, which is contraindicated with telaprevir and boceprevir, showed a notable increase in utilization between 2006 and 2010.

Of the most utilized medications by prescription claims or exposure, a subset of 22 highly utilized medications was examined further. The Liverpool resource recommendations are summarized in Table 4. For telaprevir, 13 (59.1%) were listed in the prescribing information, 16 (72.7%) carried a clear recommendation for DDI management, 5 (22.7%) carried a recommendation to avoid coadministration, and 5 (22.7%) were investigated formally in a DDI study. For boceprevir, 9 (40.9%) were listed in the prescribing information, 15 (68.2%) carried a clear recommendation for DDI management, 3 (13.6%) carried a recommendation to avoid coadministration, and 5 (22.7%) were investigated formally in a DDI study. These 22 medications with drug interaction potential are listed by exposure in Table 5. On average, 62.1% of chronic HCV patients were exposed to any of these 22 medications.

A complete listing of percentages using specific queried medications can be found in Appendix C, including rates of utilization for the medications with DDI potential.

Discussion

Medication utilization has been historically inferred from clinical knowledge or extracted from limited clinical trial data. To our knowledge, this is the first published systematic investigation of modern day clinical medication utilization in a large, real-world database of patients with chronic HCV. Previous studies have been smaller or examined potential interactions within a strictly controlled setting. A 2011 analysis examined the use of certain co-medications with boceprevir triple therapy in three major late phase studies; however, patients with certain comorbidities were excluded, limiting the study's generalizability. [10, 24-26]. Recently, Maasoumy et al. investigated DDI risk during initiation of HCV protease inhibitor therapy in 115 consecutively treated patients seen at a German tertiary referral center. They reported that 38% of 116 outpatient medications used in their cohort had DDI potential or unknown DDI risk and that 49% of patients were exposed to at least one drug with DDI potential during treatment [16]. The four most frequently encountered medication classes in the German cohort included beta-blockers, proton pump inhibitors (PPIs), thyroid hormones, and dihydropyridine calcium channel blockers (CCBs) (e.g., amlodipine), and only 4% of encountered drugs were strictly contraindicated [16]. In contrast, in our large U.S. cohort of chronic HCV subjects (not restricted by treatment), the four most frequently used drug categories included analgesics/antipyretics and opiate agonists, antidepressants, antivirals, and gastrointestinal drugs including PPIs. In our study, 57.5% of the top 40 outpatient medications had DDI potential or unknown DDI risk, and 62% of patients were

exposed to at least one of the twenty-two most highly utilized medications with DDI potential. Medications with DDI potential used by greater than 9% of patients included zolpidem, alprazolam, amlodipine, and prednisone. Based on both studies, the DDI risk appears to be substantial among chronic HCV patients.

Our study also demonstrates increasingly high comorbidity burden in patients with chronic HCV, based on rates of specific comorbidities as well as Charlson Comorbidity Index. A small cross-sectional retrospective study investigating comorbidities associated with HCV from 1998 to 2007 found that HIV/AIDS, renal disease, diabetes, and obesity were more prevalent in patients with HCV compared with the U.S. population [27]. Higher comorbidity rates may reflect the selective age distribution of the HCV population, but there is also some recent evidence that comorbidity rates may be higher in the HCV population even after adjusting for age [17]. In our study, the potential increasing comorbidity rates may be related to the increasing average age of the underlying HCV population and have implications for increasing polypharmacy and complexity of DDI assessment.

As a result, it is important that practitioners be familiar with current DDI management recommendations. However, as observed with approximately one-third of the drugs identified in this study, many potential DDIs have not been studied formally and thus clear and actionable DDI recommendations often are absent. For those DDIs that do provide actionable recommendations, DDI management depends upon the nature of the interaction. The most well characterized DDIs with telaprevir and boceprevir are those involving the inhibition or induction of oxidative metabolism by CYP3A. For simvastatin (the most highly utilized statin in this population, Appendix B), reasonable intervention options exist and include employing a “statin holiday” by removing medication for the duration of treatment, or stabilizing a patient on an alternative statin with lower interaction potential prior to therapy [28]. For other drugs such as salmeterol, fluticasone, or other inhaled corticosteroids, alternatives such as formoterol or beclomethasone may be employed [5]. Comparatively, use of systemic corticosteroids may be unavoidable in some settings such as maintenance immunosuppression in the transplant setting, and providers must weigh the risk of reduced efficacy of telaprevir and boceprevir due to the possible induction of CYP3A [5, 29, 30]. Management of depression-like symptoms during treatment with peginterferon-based therapies has been shown to affect treatment outcomes and often involves the use of antidepressants such as selective serotonin reuptake inhibitors (SSRIs). [31] SSRIs are generally metabolized by multiple CYP450 enzymes with CYP3A providing only partial contribution, and therefore, the risk of a clinically significant CYP3A-mediated DDI with DAAs is low [5, 14]. In addition, a recent review of data from major clinical trials by Sockalingam et al investigating the neuropsychiatric adverse effects of DAAs as well as DDIs between DAAs and psychiatric medications concluded that DAAs have minimal neuropsychiatric risk [32]. Opioids and other analgesics also are metabolized by multiple pathways including CYP3A, but they are often self-titrated by patients for pain control, complicating the risk of DDIs [33, 34]. In addition, they often are used in combination with acetaminophen, which may represent the greatest risk to patients because providers may not recognize the daily acetaminophen dose from all sources [35].

Less characterized DDIs with boceprevir and telaprevir are those involving hepatic transport proteins [36]. Boceprevir appears to be an inhibitor of organic anion transporting polypeptide 1B (OATP1B) while telaprevir is an inhibitor of OATP1B1 and OATP1B3, organic cation transporter 1 (OCT1), and multidrug and toxin extrusion 1 (MATE1); these transporters are involved in the active uptake of drugs in the liver [36, 37]. Inhibition of these transporters may result in higher systemic exposures but reduced hepatic exposure and efficacy of drugs targeting the liver (e.g., statins, metformin, valsartan) [38-40]. Boceprevir also appears to be a substrate of breast cancer resistance protein (BCRP), a hepatic transporter involved in the active biliary elimination of drugs from the liver [37]. Drugs that are substrates/inhibitors of BCRP (e.g., eltrombopag, cyclosporine) may potentially inhibit the biliary elimination of boceprevir resulting in higher hepatic exposure [41, 42]. Alternatively, boceprevir could increase the hepatotoxic potential of other co-administered BCRP substrates (e.g., methotrexate, rosuvastatin, lapatinib) [43-45]. Additional examination of the potential interactions involving elimination pathways mediated by hepatic transport proteins is needed.

While many drug interactions are predicted from a theoretical understanding of the drug's clinical pharmacology, most are never investigated in DDI studies. Accordingly, at the time of this study, many drugs with theoretical DDI potential through CYP3A had not been formally investigated. While it is impractical and cost-prohibitive to study every possible drug interaction in a formal DDI study, it is also imprudent to risk treatment failure or toxicity without a sound understanding of the DDI potential in a real-world setting. Theoretical prediction is limited by our scientific understanding, which is particularly evident with transporter interactions where the science is in its infancy. In order to mitigate risk, computer simulation with tools such as SimCyp should be considered prior to drug approval to complement formal in vivo studies and establish a better framework for reliable DDI prediction [46, 47]. However, much of the DDI knowledge will still be derived from post-marketing studies and expert opinion, as demonstrated by the majority of interacting medications in this study that were listed in the Liverpool resource but not in the prescribing information. Here, methods such as DDI registries and pharmacovigilance algorithms may complement *in vivo studies* for detection of DDIs quickly and efficiently [21, 48]. As DDI information is discovered, the prescribing information will remain a reliable source of information about formal DDI studies that were performed by the pharmaceutical company, but resources that are comprehensive, regularly updated, and maintained by clinical experts, such as the Liverpool database, may provide a more optimal model for access to actionable DDI information [21]. The sensitivity and specificity of disease-specific resources such as the Liverpool database also should be compared with other widely-used, validated interaction checking software such as ePocrates [49].

This study has several limitations. ICD-9 definitions, though applied from validated studies, may differ from other definitions such as the *Clinical Classification Software* from the U.S. Agency for Healthcare Research and Quality; this may partially account for slight differences in comorbidity rates observed in other reports [17, 27]. Medication use was explored in the chronic HCV cohort and not limited to treated patients, so conclusions should be drawn in this context. In addition, only outpatient medication claims were

evaluated, so utilization rates may not appropriately estimate medications with use limited to hospital settings. Over-the-counter medications could not be evaluated in this database. This study also was restricted to insured HCV subjects in the U.S. and may not be fully representative of the typical U.S. HCV population [50] or populations in other parts of the world where treatment patterns and comorbidities may differ. However, this study is significant because it examined a wide range of potential prescription medications available both in the U.S. and worldwide for their interaction potential with boceprevir and telepravir, and this information was integrated with the actual exposure to these medications in a real-world setting.

While the focus of this study was to inform DDI assessment for currently available agents, these findings also may have strong implications for other candidates in development. Two new DAAs, simeprevir and sofosbuvir, have been recently approved and others are in Phase 3 evaluation for HCV treatment [51, 52]. An all-oral regimen utilizing a protease inhibitor boosted with ritonavir (ABT-450/r), combined with an NS5A inhibitor and a non-nucleoside polymerase, will likely be licensed by the end of 2014. Moreover, faldaprevir and daclatasvir, which are currently undergoing approval in both the U.S. and Europe, have been shown to be CYP3A substrates and require dose-reductions when used in combination with a ritonavir-boosted anti-retroviral [3, 53-55]. Thus, the information learned here from examining the first two prototypical CYP3A DAAs will remain highly relevant and applicable [56]. As knowledge increases regarding the mechanism(s) and role(s) of metabolism and transport for various drugs, particularly in the setting of liver disease, the information provided here will become highly relevant.

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Appendix A. ICD-9 Code Definitions for Selected Comorbidities

Disease State	ICD-9 Codes
Advanced liver disease (includes any of the following: ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, portal hypertension, esophageal varices, hepatorenal syndrome, hepatocellular carcinoma)	070.44, 070.71, 456.0, 456.1, 456.2x, 572.2, 572.3, 572.4, 572.8, 789.59, 567.23, 155.x
Alcohol abuse or dependence	303.xx, 305.0x, 291.xx
Alcoholic liver disease (includes alcoholic fatty liver, acute alcoholic hepatitis, alcoholic cirrhosis of liver, alcoholic liver damage unspecified)	571.0-, 571.1-, 571.2-, 571.3-
Bipolar disorders	296.0x, 296.1x, 296.4x-296.7x, 296.80, 296.89

Disease State	ICD-9 Codes
Compensated cirrhosis (alcoholic, nonalcoholic, biliary)	571.2-, 571.5-, 571.6-
COPD/asthma	491.xx-493.xx, 496.x
Depression	296.2x, 296.3x, 311, 309.1, 300.4
Diabetes	250.xx
Drug abuse or dependence (non-tobacco)	292.xx, 304.xx, 305.2x-305.9x
Hepatocellular carcinoma (malignant neoplasm of liver and intrahepatic bile ducts)	155.x
HIV/AIDS, asymptomatic HIV infection, HIV-2	042.xx, V08, 079.53
Hypertension	401.xx, 402.xx, 403.xx, 404.xx, 405.xx
Lipid metabolism disorders	272.xx
Liver transplant	V42.7, 50.5x; 996.82, CPT codes 47135, 47136
Non-alcoholic fatty liver disease	571.8
Overweight and obesity	278.0x
Rheumatologic disease	710.xx, 714.xx, 725.xx
Viral hepatitis B with or without hepatic coma, or carrier	070.2x, 070.3x, V02.61

Abbreviations: ICD-9, International classification of disease, 9th edition; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; CPT: Current Procedural Terminology

Appendix B. Drug Interaction Potential of Top 200 Drugs in Chronic HCV Cohort by Prescriptions Filled

Medication	Boceprevir	Telaprevir
1. Acetaminophen/Hydrocodone Bitartrate[A]		
2. Ribavirin		
3. Zolpidem Tartrate		

Medication	Boceprevir	Telaprevir
4. Levothyroxine Sodium		
5. Alprazolam		
6. Lisinopril		
7. Peginterferon Alfa-2a		
8. Oxycodone HCl		
9. Furosemide		

Medication	Boceprevir	Telaprevir
10. Amlodipine Besylate		
11. Omeprazole		
12.Acetaminophen/Oxycodone HCl[A]		
13. Esomeprazole Magnesium		
14. Metformin HCl		
15. Escitalopram Oxalate		

Medication	Boceprevir	Telaprevir
16. Spironolactone		
17. Hydrochlorothiazide		
18. Bupropion HCl		
19. Tramadol HCl		
20. Pantoprazole Sodium		
21. Metoprolol Succinate		

Medication	Boceprevir	Telaprevir
22. Lorazepam		
23. Azithromycin		
24. Atenolol		
25. Peginterferon Alfa-2b		
26. Sertraline HCl		
27. Clonazepam		

Medication	Boceprevir	Telaprevir
28. Citalopram Hydrobromide		
29. Gabapentin		
30. Trazodone HCl		
31. Prednisone		
32. Tacrolimus		
33. Amoxicillin		
34. Cyclobenzaprine HCl	NL	NL

Medication	Boceprevir	Telaprevir
35. Diazepam		
36. Potassium Chloride		
37. Sulfamethoxazole/Trimethoprim		
38. Venlafaxine HCl		
39. Metoprolol Tartrate		
40. Carisoprodol	NL	NL
41. Fluoxetine HCl		

Medication	Boceprevir	Telaprevir
42. Propranolol HCl		
43. Morphine Sulfate		
44. Lactulose		
45. Insulin Glargine, Recombinant	NL	NL
46. Lansoprazole		
47. Acetaminophen/Propoxyphene Napsylate[A]		
48. Hydrochlorothiazide/Lisinopril		

Medication	Boceprevir	Telaprevir
49. Ciprofloxacin HCl		
50. Sildenafil Citrate[B]		
51. Albuterol Sulfate[A]		
52. Fluticasone Propionate		
53. Ibuprofen		
54. Estradiol	NL	NL
55. Simvastatin		

Medication	Boceprevir	Telaprevir
56. Promethazine HCl		
57. Paroxetine HCl		
58. Temazepam		
59. Amlodipine Besylate/Benazepril HCl		
60. Nadolol	NL	NL
61. Levofloxacin		
62. Duloxetine HCl		

Medication	Boceprevir	Telaprevir
63. Cephalexin[A]		
64. Hydrochlorothiazide/Triamterene		
65. Epoetin Alfa		
66. Amoxicillin/Clavulanate Potassium		
67. Glipizide	NL	NL
68. Fexofenadine HCl		
69. Tamsulosin HCl		

Medication	Boceprevir	Telaprevir
70. Methadone HCl		
71. Fentanyl		
72. Atorvastatin Calcium		
73. Pregabalin		
74. Valsartan		
75. Quetiapine Fumarate		
76. Fluticasone Propionate/Salmeterol Xinafoate		

Medication	Boceprevir	Telaprevir
77. Clopidogrel Hydrogen Sulfate		
78. Triamcinolone Acetonide	NL	NL
79. Amitriptyline HCl		
80. Hydrocodone Bitartrate/Ibuprofen		
81. Valacyclovir HCl	NL	NL
82. Hydrochlorothiazide/Valsartan		
83. Warfarin Sodium		
84. Eszopiclone	NL	NL
85. Methylprednisolone		
86. Ursodiol[A]		

Medication	Boceprevir	Telaprevir
87. Diltiazem HCl		
88. Mycophenolate Mofetil		
89. Conjugated Estrogens	NL	NL
90. Acetaminophen/Codeine Phosphate[A]		
91. Hydromorphone HCl		
92. Hydroxyzine HCl		
93. Carvedilol		
94. Tadalafil[B]		

Medication	Boceprevir	Telaprevir
95. Montelukast Sodium		
96. Nifedipine		
97. Acyclovir	NL	NL
98. Naproxen		
99. Doxycycline Hyclate		
100. Meloxicam	NL	NL
101. Alendronate Sodium[A 101]		

Medication	Boceprevir	Telaprevir
102. Mometasone Furoate		
103. Clonidine HCl	NL	NL
104. Folic Acid		
105. Ezetimibe		
106. Ramipril		
107. Celecoxib		
108. Fluconazole		

Medication	Boceprevir	Telaprevir
109. Buprenorphine HCl/Naloxone HCl	/ NL	/ NL
110. Glimepiride		
111. Lamotrigine		
112. Pioglitazone HCl		
113. Allopurinol		
114. Losartan Potassium		

Medication	Boceprevir	Telaprevir
115. Metronidazole		
116. Rabeprazole Sodium	NL	NL
117. Rifaximin		
118. Verapamil HCl		
119. Amphetamine Salt Combination		
120. Clindamycin HCl		

Medication	Boceprevir	Telaprevir
121. Filgrastim		
122. Ergocalciferol	NL	NL
123. Glyburide	NL	NL
124. Fenofibrate		
125. Mirtazapine		
126. Enalapril Maleate		
127. Hydrochlorothiazide/Olmesartan Medoxomil		
128. Clobetasol Propionate	NL	NL
129. Olmesartan Medoxomil		
130. Insulin Aspart, Recombinant	NL	NL
131. Benazepril HCl	NL	NL

Medication	Boceprevir	Telaprevir
132. Ranitidine HCl		
133. Albuterol[A]		
134. Insulin Lispro, Recombinant	NL	NL
135. Emtricitabine/Tenofovir Disoproxil Fumarate		
136. Vardenafil HCl		
137. Topiramate		
138. Metoclopramide HCl		
139. Tizanidine HCl	NL	NL

Medication	Boceprevir	Telaprevir
140. Rosuvastatin Calcium		
141. Sumatriptan Succinate	NL	NL
142. Varenicline		
143. Hydrochlorothiazide/Losartan Potassium		
144. Interferon Alfacon-1	NL	NL
145. Pravastatin Sodium		
146. Codeine Phosphate/Guaifenesin		
147. Diclofenac Sodium		
148. Chlorpheniramine Polistirex/Hydrocodone Polistirex		

Medication	Boceprevir	Telaprevir
149. Moxifloxacin HCl		
150. Modafinil	NL	NL
151. Penicillin V Potassium		
152. Tiotropium Bromide	NL	NL
153. Testosterone	NL	NL
154. Codeine Phosphate/Promethazine HCl		
155. Ritonavir		
156. Methocarbamol	NL	NL
157. Sitagliptin Phosphate		
158. Ondansetron HCl		

Medication	Boceprevir	Telaprevir
159. Nystatin	NL	NL
160. Hydroxychloroquine Sulfate		
161. Acetaminophen/Butalbital/Caffeine[A]	◊ / NL / NL	◊ / NL / NL
162. Benzonatate	NL	NL
163. Methylphenidate HCl		
164. Albuterol Sulfate/Ipratropium Bromide[A]		
165. Buspirone HCl	NL	NL
166. Ezetimibe/Simvastatin		
167. Doxazosin Mesylate		
168. Conjugated Estrogens/ Medroxyprogesterone Acetate	NL / NL	NL / NL
169. Quinapril HCl		
170. Cetirizine HCl	NL	NL

Medication	Boceprevir	Telaprevir
171. Irbesartan		
172. Ropinirole HCl	NL	NL
173. Insulin Human Isophane (NPH)	NL	NL
174. Lithium Carbonate		
175. Metaxalone	NL	NL
176. Clarithromycin		
177. Risedronate Sodium	NL	NL
178. Aripiprazole		
179. Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate		
180. Ibandronate Sodium		
181. Lidocaine		

Medication	Boceprevir	Telaprevir
182. Betamethasone Dipropionate/ Clotrimazole	NL / NL	NL / NL
183. Omega-3-Acid Ethyl Esters[A]		
184. Cyclosporine[A]		
185. Atazanavir Sulfate		
186. Glyburide/Metformin HCl		
187. Cyclosporine, Modified[A]		
188. Mupirocin	NL	NL
189. Colchicine		
190. Niacin	NL	NL
191. Hydrochlorothiazide/Irbesartan		
192. Famotidine	NL	NL

Medication	Boceprevir	Telaprevir
193. Atropine Sulfate/Diphenoxylate HCl	NL / NL	NL / NL
194. Fluocinonide	NL	NL
195. Terazosin HCl	NL	NL
196. Etanercept		
197. Nortriptyline HCl		
198. Azathioprine		
199. Chlorhexidine Gluconate	NL	NL
200. PEG Electrolyte Lavage Solution	NL	NL

Abbreviations: HCV, Hepatitis C Virus; NL, Not listed;

[A] Names differ between MarketScan database and hep-druginteractions.org as follows, respectively: acetaminophen listed as paracetamol, propoxyphene listed as dextropropoxyphene, albuterol listed as salbutamol, cephalexin listed as cefalexin, ursodiol listed as ursodeoxycholic acid, alendronate listed as alendronic acid, Omega-3-Acid Ethyl Esters listed as fish oils, cyclosporine listed as ciclosporin

[B] Drugs list different recommendation for different indication/usage

*Hep-druginteractions.org last accessed 9/11/2013

◊ /♦ No clinically significant interaction expected

□/ ■ Potential interaction – may require close monitoring, alteration of drug dosage or timing of administration

○ / • These drugs should not be coadministered

Empty symbols indicate the interaction has not been assessed and has been predicted based on the metabolic profiles of the drugs.

Appendix C. Comprehensive List of Queried Drugs with Population Exposures from 2006-2010, by Medication Class

	2006	2007	2008	2009	2010	Weighted Average
	(53,461 beneficiaries, 79,185 cross-sections)					
Enrollees with Pharmacy Benefit, n	11,424	11,517	19,379	18,882	17,983	79,185
Medication, %						
HEPATITIS C RELATED						
Treatment						
ribavirin	27.6	24.3	21.1	20.1	16.9	21.3
peginterferon alfa-2a	16.2	14.2	13.3	14.0	12.5	13.8
peginterferon alfa-2b	10.5	9.3	6.9	5.2	4.0	6.7
interferon alfacon-1	2.2	1.8	1.2	1.1	0.9	1.3
Side Effect Management						
epoetin alfa	5.6	4.5	3.5	3.0	2.5	3.6
filgrastim	2.8	2.6	2.2	2.1	1.7	2.2
darbepoetin alfa	0.4	0.3	0.2	0.2	0.2	0.2
Transplant						
tacrolimus	2.5	2.7	2.9	3.3	3.5	3.0
mycophenolate	1.6	1.7	1.9	2.2	2.3	2.0
cyclosporine	1.2	1.1	1.1	1.2	1.4	1.2
sirolimus	0.5	0.4	0.4	0.5	0.5	0.5
azathioprine	0.6	0.5	0.5	0.6	0.5	0.5
NERVOUS SYSTEM						
Antidepressants						
escitalopram	7.9	7.4	6.2	6.0	5.1	6.4
bupropion	6.8	6.0	5.2	5.7	5.4	5.7
citalopram	4.2	4.7	4.8	6.1	6.4	5.4
trazodone	5.2	5.0	4.8	5.5	6.0	5.3
sertraline	5.3	5.2	4.9	5.1	4.9	5.1
fluoxetine	3.7	3.5	3.4	3.7	3.4	3.5
venlafaxine	4.5	4.3	3.4	3.1	2.4	3.4
paroxetine	3.7	3.3	2.9	2.8	2.4	3.0
duloxetine	2.6	3.0	2.8	2.8	2.5	2.7
amitriptyline	2.7	2.7	2.3	2.5	2.3	2.5
mirtazapine	1.4	1.5	1.3	1.4	1.5	1.4
nortriptyline	0.8	0.8	0.8	1.0	1.0	0.9

	2006	2007	2008	2009	2010	Weighted Average
doxepin	0.7	0.7	0.6	0.8	0.7	0.7
desipramine	0.1	0.1	0.1	0.1	0.1	0.1
Antipsychotics / Neuroleptics						
quetiapine	1.9	2.2	2.1	2.2	2.2	2.1
prochlorperazine	1.8	1.9	1.9	1.7	1.8	1.8
aripiprazole	0.6	0.5	0.7	1.1	1.1	0.8
lithium carbonate	0.6	0.6	0.5	0.6	0.7	0.6
risperidone	0.6	0.6	0.6	0.6	0.7	0.6
olanzapine	0.9	0.6	0.5	0.6	0.5	0.6
clozapine	0.0	0.0	0.0	0.0	0.0	0.0
pimozide	0.0	0.0	0.0	0.0	0.0	0.0
Anxiolytics / Sedatives / Hypnotics						
zolpidem	15.0	14.4	13.6	14.1	14.0	14.1
alprazolam	9.7	10.6	9.2	10.0	9.9	9.8
lorazepam	5.5	5.4	5.4	5.9	6.1	5.7
diazepam	4.9	5.0	5.0	5.4	5.1	5.1
temazepam	3.2	3.6	2.9	3.2	3.1	3.2
eszopiclone	3.8	3.5	2.4	1.9	1.9	2.5
buspirone	1.0	1.0	0.9	1.0	1.0	1.0
triazolam	0.4	0.5	0.4	0.5	0.4	0.5
midazolam (iv)	0.0	0.0	0.0	0.0	0.0	0.0
midazolam (po)	0.0	0.0	0.0	0.0	0.0	0.0
Opioid Dependence						
methadone	1.4	1.2	1.2	1.3	1.4	1.3
buprenorphine	0.6	0.7	1.0	1.3	1.5	1.1
Pain						
hydrocodone	33.7	35.0	32.0	35.5	34.9	34.2
oxycodone	14.6	14.9	15.1	16.5	17.7	15.9
tramadol	7.8	8.7	8.2	9.7	10.0	9.0
codeine	8.0	7.9	9.0	9.6	9.1	8.9
gabapentin	4.3	4.8	4.9	5.7	6.6	5.4
morphine sulfate	1.8	2.2	2.1	2.6	2.6	2.3
hydromorphone	1.5	1.8	2.1	2.6	2.5	2.2
fentanyl	1.8	1.8	1.8	1.7	1.6	1.7
meperidine	1.5	1.1	1.0	0.7	0.7	0.9
oxymorphone	0.0	0.3	0.4	0.4	0.4	0.3
Muscle Relaxants						

	2006	2007	2008	2009	2010	Weighted Average
cyclobenzaprine	7.8	7.6	7.5	8.6	8.5	8.1
carisoprodol	3.2	3.5	3.0	3.2	3.0	3.2
methocarbamol	1.5	1.8	1.6	1.7	2.1	1.8
metaxalone	2.1	2.2	1.7	1.3	1.1	1.6
tizanidine	1.3	1.4	1.2	1.2	1.3	1.3
Migraine						
sumatriptan	1.3	1.2	1.2	1.2	1.5	1.3
ergotamine	0.2	0.1	0.0	0.1	0.0	0.1
dihydroergotamine	0.1	0.0	0.0	0.0	0.0	0.0
methylergonovine	0.0	0.0	0.0	0.0	0.0	0.0
Anticonvulsants						
clonazepam	3.9	4.1	3.9	4.3	4.4	4.1
lamotrigine	1.0	1.0	1.1	1.2	1.4	1.2
topiramate	1.2	1.2	1.0	1.1	1.2	1.1
levetiracetam	0.3	0.4	0.5	0.7	0.7	0.5
phenytoin	0.4	0.4	0.4	0.4	0.4	0.4
carbamazepine	0.3	0.4	0.3	0.3	0.3	0.3
phenobarbital	0.1	0.1	0.1	0.2	0.2	0.1
Miscellaneous						
pregabalin	2.0	2.8	2.8	2.6	2.1	2.5
varenicline	0.8	4.1	2.9	2.5	1.9	2.4
modafinil	1.2	1.2	1.1	1.0	0.8	1.0
amphetamine salt	0.9	0.8	0.8	0.9	1.0	0.9
methylphenidate	0.8	0.8	0.6	0.7	0.9	0.7
ropinirole	0.7	0.8	0.5	0.7	0.8	0.7
METABOLIC						
Hypertension / Cardiovascular						
hydrochlorothiazide	14.4	15.6	15.0	16.0	16.3	15.5
lisinopril	8.6	10.9	11.4	13.1	14.5	12.0
furosemide	8.1	9.1	8.9	9.8	10.8	9.5
spironolactone	6.5	6.4	6.3	7.2	8.1	7.0
valsartan	3.4	3.4	3.8	3.7	4.0	3.7
benazepril	3.1	3.3	2.9	3.0	2.7	3.0
lidocaine (IV)	2.2	2.3	2.5	2.6	2.4	2.4
triamterene	2.8	2.6	2.3	2.4	2.2	2.4
clonidine	2.1	2.3	2.0	2.1	2.3	2.1
olmesartan	1.7	2.2	2.1	2.4	2.1	2.1
losartan	1.9	2.0	1.7	2.1	2.7	2.1

	2006	2007	2008	2009	2010	Weighted Average
clopidogrel	1.7	2.0	1.9	2.1	1.9	1.9
ramipril	1.7	1.4	1.2	1.1	1.0	1.2
enalapril	1.2	1.0	1.2	1.1	1.0	1.1
irbesartan	1.3	1.0	1.3	1.1	0.8	1.1
digoxin (oral)	0.5	0.6	0.6	0.5	0.5	0.5
amiodarone	0.1	0.2	0.2	0.2	0.3	0.2
flecainide	0.1	0.0	0.1	0.1	0.1	0.1
propafenone	0.0	0.1	0.1	0.1	0.1	0.1
sildenafil (Revatio)	0.1	0.1	0.1	0.1	0.2	0.1
bosentan	0.0	0.0	0.0	0.0	0.0	0.0
quinidine	0.0	0.0	0.0	0.0	0.0	0.0
tadalafil (Adcirca)	0.0	0.0	0.0	0.0	0.0	0.0
Beta Blockers						
metoprolol	7.1	8.0	7.7	8.0	8.1	7.8
atenolol	4.4	4.6	4.4	4.5	4.0	4.4
propranolol	3.1	3.5	3.3	3.7	3.8	3.5
nadolol	2.3	2.3	2.6	3.0	3.4	2.8
carvedilol	1.0	1.5	1.8	2.2	2.3	1.8
bisoprolol	0.5	0.5	0.4	0.4	0.4	0.5
nebivolol	N/A	N/A	0.2	0.6	0.8	0.5
Calcium Channel Blockers						
amlodipine	7.5	7.7	8.8	10.3	10.9	9.3
diltiazem	1.8	1.5	1.3	1.4	1.6	1.5
nifedipine	1.2	1.3	1.4	1.4	1.4	1.4
verapamil	1.5	1.3	1.1	1.1	1.0	1.2
felodipine	0.5	0.5	0.4	0.3	0.3	0.4
nisoldipine	0.2	0.3	0.2	0.1	0.1	0.2
nicardipine	0.0	0.0	0.0	0.0	0.0	0.0
Hyperlipidemia						
nicardipine	0.0	0.0	0.0	0.0	0.0	0.0
Hyperlipidemia						
any statin queried	5.9	7.3	7.4	9.3	9.1	8.0
simvastatin	2.0	3.1	3.6	4.7	4.7	3.8
atorvastatin	2.4	2.2	2.1	2.2	1.7	2.1
rosuvastatin	0.8	0.9	0.9	1.2	1.2	1.0
pravastatin	0.4	0.7	0.8	1.3	1.4	1.0
lovastatin	0.7	0.8	0.5	0.5	0.4	0.5
fluvastatin	0.1	0.0	0.1	0.1	0.1	0.1
ezetimibe	2.7	3.0	2.2	1.6	1.2	2.0

	2006	2007	2008	2009	2010	Weighted Average
fenofibrate	1.4	1.2	1.2	1.3	1.2	1.3
gemfibrozil	0.5	0.6	0.6	0.5	0.6	0.5
Niacin	0.5	0.6	0.8	0.7	0.8	0.7
colesevelam	0.6	0.6	0.6	0.7	0.8	0.7
Diabetes						
insulin (any type)	7.3	7.1	7.2	7.7	7.8	7.4
metformin	5.6	6.2	6.6	7.2	7.5	6.7
glipizide	2.2	2.2	2.1	2.2	2.0	2.1
glyburide	1.7	1.8	1.7	1.7	1.4	1.6
pioglitazone	1.1	1.8	1.6	1.6	1.4	1.5
glimepiride	1.4	1.3	1.4	1.4	1.4	1.4
sitagliptin	0.0	0.8	1.2	1.5	1.6	1.1
rosiglitazone	1.1	1.0	0.4	0.3	0.3	0.5
INFECTIOUS DISEASE						
Antibacterials						
amoxicillin	20.8	20.2	19.4	20.0	21.0	20.2
azithromycin	14.1	15.4	16.0	16.8	17.4	16.2
ciprofloxacin (systemic)	9.2	10.3	10.4	11.3	12.2	10.8
levofloxacin	11.2	11.2	9.9	8.9	7.9	9.6
trimethoprim/sulfamethoxazole	8.0	8.8	8.7	9.8	10.3	9.2
cephalexin	10.1	9.9	8.4	8.8	9.2	9.1
doxycycline	4.5	4.9	5.1	5.4	5.6	5.2
clindamycin (systemic)	5.0	5.1	4.9	5.4	5.3	5.2
moxifloxacin	3.5	3.8	3.6	3.2	2.9	3.4
penicillin v potassium	3.8	3.4	3.1	3.0	2.8	3.2
clarithromycin	3.8	3.3	3.2	2.8	2.8	3.1
rifaximin	1.1	1.5	1.6	2.0	3.0	1.9
erythromycin (systemic)	1.5	1.4	1.3	1.2	1.2	1.3
neomycin sulfate (systemic)	1.0	1.0	0.8	0.7	0.7	0.8
tetracycline	0.7	0.7	0.6	0.5	0.6	0.6
gentamicin	0.5	0.5	0.5	0.7	0.6	0.6
ofloxacin	0.5	0.7	0.5	0.4	0.4	0.5
rifampin	0.3	0.4	0.3	0.3	0.4	0.3
Antifungals						
metronidazole	4.8	5.2	5.1	5.2	5.5	5.2
fluconazole	3.8	4.0	3.7	4.0	4.2	3.9
nystatin	2.6	2.8	2.5	2.7	3.0	2.7
ketoconazole	1.5	1.7	1.5	1.7	1.6	1.6
terbinafine	0.4	0.4	0.4	0.4	0.3	0.4

	2006	2007	2008	2009	2010	Weighted Average
itraconazole	0.0	0.1	0.1	0.1	0.1	0.1
voriconazole	0.0	0.0	0.0	0.1	0.1	0.1
posaconazole	0.0	0.0	0.0	0.0	0.0	0.0
Antivirals						
valacyclovir	3.0	3.1	3.2	3.2	3.3	3.2
acyclovir	2.9	2.8	2.8	3.0	3.0	2.9
HIV						
tenofovir	0.7	1.0	1.5	1.9	2.2	1.6
emtricitabine	0.5	0.9	1.3	1.6	1.8	1.3
ritonavir	0.5	0.8	1.0	1.2	1.1	1.0
lamivudine	1.0	0.8	0.9	1.0	0.9	0.9
efavirenz	0.6	0.5	0.8	0.9	1.0	0.8
atazanavir	0.2	0.4	0.4	0.6	0.6	0.5
abacavir	0.3	0.4	0.4	0.5	0.5	0.4
zidovudine	0.5	0.3	0.4	0.4	0.3	0.4
lopinavir/ritonavir	0.2	0.4	0.4	0.4	0.3	0.4
raltegravir	N/A	0.0	0.1	0.3	0.4	0.2
darunavir	0.0	0.1	0.1	0.2	0.2	0.1
fosamprenavir	0.1	0.1	0.2	0.2	0.1	0.1
nevirapine	0.1	0.1	0.1	0.1	0.2	0.1
nelfinavir	0.1	0.1	0.1	0.1	0.1	0.1
didanosine	0.1	0.1	0.1	0.1	0.1	0.1
stavudine	0.1	0.1	0.1	0.1	0.1	0.1
etravirine	0.0	0.0	0.1	0.1	0.1	0.1
saquinavir	0.1	0.1	0.1	0.0	0.0	0.1
maraviroc	0.0	0.0	0.0	0.0	0.0	0.0
indinavir	0.0	0.0	0.0	0.0	0.0	0.0
delavirdine	0.0	0.0	0.0	0.0	0.0	0.0
tipranavir	0.0	0.0	0.0	0.0	0.0	0.0
MEN & WOMEN'S HEALTH						
Hormone therapy						
estradiol (excluding EE)	3.6	3.4	2.9	3.2	3.4	2.9
conjugated estrogens	3.1	2.8	2.3	2.3	2.0	2.4
testosterone	1.3	1.5	1.6	1.7	2.0	1.7
ethinyl estradiol (EE)	1.8	1.7	1.5	1.5	1.3	1.5
medroxyprogresterone	1.0	1.0	1.1	1.0	1.1	1.0
norethindrone	0.8	1.0	0.8	0.9	0.9	0.9
progesterone	0.5	0.6	0.6	0.7	0.7	0.6
drospirenone	0.3	0.3	0.3	0.3	0.2	0.3

	2006	2007	2008	2009	2010	Weighted Average
Erectile dysfunction						
sildenafil (Viagra)	4.1	3.3	4.1	4.3	3.7	3.9
tadalafil (Cialis)	1.7	1.8	2.4	2.5	2.4	2.2
vardenafil	1.3	1.4	1.4	1.6	1.4	1.5
Benign prostatic hyperplasia						
tamsulosin	1.8	2.3	2.5	3.0	3.0	2.6
doxazosin	0.6	0.6	0.7	0.7	0.7	0.7
terazosin	0.5	0.6	0.5	0.7	0.8	0.6
alfuzosin	0.2	0.3	0.4	0.3	0.3	0.3
GASTROINTESTINAL						
Reflux						
omeprazole	5.2	7.2	8.3	10.8	12.4	9.2
esomeprazole	8.4	8.4	7.1	7.1	6.1	7.2
pantoprazole	6.1	5.3	5.4	6.2	5.3	5.6
lansoprazole	5.8	5.0	4.1	3.7	3.8	4.3
ranitidine	1.7	1.7	1.5	1.7	1.7	1.7
rabeprazole	2.1	1.6	1.6	1.4	0.9	1.5
famotidine	1.0	1.2	0.9	1.3	1.2	1.1
cimetidine	0.2	0.2	0.2	0.1	0.2	0.2
Other						
promethazine	10.6	10.8	9.8	10.3	9.7	10.1
lactulose	4.6	5.1	5.0	5.7	6.3	5.4
ondansetron	1.5	1.9	2.6	3.6	4.5	3.0
metoclopramide	3.0	3.4	3.0	2.9	2.0	2.8
ursodiol	2.0	1.8	1.8	2.1	2.2	2.0
mesalamine	0.6	0.6	0.5	0.6	0.6	0.6
domperidone	0.0	0.0	0.0	0.0	0.0	0.0
cisapride	0.0	0.0	0.0	0.0	0.0	0.0
OTHER						
Asthma / Pulmonary disease						
albuterol	8.8	8.8	8.7	9.9	10.2	9.4
fluticasone (in any product)	8.0	8.1	7.9	9.3	10.2	8.8
fluticasone (not in combination)	5.2	5.4	5.5	6.7	7.8	6.2
mometasone	3.8	3.7	3.5	3.2	3.2	3.4
salmeterol	3.5	3.3	3.0	3.2	3.0	3.2
fluticasone proprionate/salmeterol	3.4	3.2	2.9	3.2	2.9	3.1
montelukast	2.1	2.1	1.9	1.9	1.8	1.9

	2006	2007	2008	2009	2010	Weighted Average
ipratropium	1.9	1.9	1.8	2.0	1.8	1.9
tiotropium	1.1	1.3	1.2	1.3	1.4	1.3
budesonide	1.1	1.1	1.1	1.2	1.4	1.2
Arthritis / Osteoporosis						
meloxicam	1.7	2.2	2.8	3.2	3.8	2.9
celecoxib	2.5	2.4	2.1	2.1	1.7	2.1
alendronate	1.9	1.7	1.8	1.8	1.7	1.8
hydroxychloroquine sulfate	0.8	0.8	0.8	0.9	1.0	0.9
risedronate	1.0	0.8	0.8	0.7	0.5	0.8
etanercept	0.4	0.4	0.4	0.5	0.5	0.4
Gout						
allopurinol	1.3	1.2	1.3	1.6	1.6	1.5
colchicine	0.9	0.9	0.8	1.0	1.1	1.0
Steroids						
prednisone	8.5	8.7	8.8	9.7	10.0	9.2
methylprednisolone	6.3	6.0	6.3	7.0	7.1	6.6
dexamethasone (systemic)	2.1	2.1	2.0	2.2	2.3	2.2
prednisolone	0.1	0.1	0.1	0.1	0.1	0.1
Other						
levothyroxine	8.5	8.2	8.0	9.2	9.3	8.7
potassium chloride	5.4	5.2	5.3	5.6	5.5	5.4
benzonatate	2.5	2.4	2.7	3.0	2.9	2.7
diclofenac	2.0	1.9	2.5	3.0	3.5	2.7
warfarin	1.6	1.8	1.7	1.8	2.1	1.8
atropine	1.9	1.8	1.6	1.8	1.6	1.7
tamoxifen	0.1	0.2	0.1	0.1	0.1	0.1
ergonovine	0.0	0.0	0.0	0.0	0.0	0.0

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Table 1

Demographic and clinical characteristics of a U.S. chronic HCV population in a commercial insurance database, 2006-2010

	2006	2007	2008	2009	2010	Weighted Average
Enrollees, n	(71,584 individuals, 106,283 cross-sections)					
	16,216	16,235	25,380	24,683	23,769	N=106,283
Sociodemographics, %						
Age in years, mean	49.7	50.4	51.2	51.8	52.4	51.2
(±SD)	(7.3)	(7.3)	(7.5)	(7.5)	(7.6)	(7.5)
Gender, male	61.5	61.4	62.1	62.6	62.8	62.2
Health plan type						
Comprehensive	4.9	2.0	2.7	2.3	2.8	2.9
HMO	14.7	15.1	23.1	18.5	16.7	18.1
POS	10.6	11.0	9.3	8.4	8.0	9.3
PPO	67.3	69.4	62.1	67.7	64.0	65.7
Region						
Northeast	8.8	7.5	18.6	12.5	16.2	13.5
North Central	19.8	18.7	15.5	16.3	15.6	16.8
South	51.5	52.5	48.1	50.6	42.6	48.6
West	19.5	20.9	17.6	20.5	24.8	20.7
Comorbidities, %						
Metabolic						
Hypertension	32.0	34.8	37.5	43.2	44.7	39.2
Lipid metabolism disorders	19.2	20.8	22.4	26.7	27.5	23.8
Type II diabetes	16.4	17.3	18.7	20.0	20.3	18.8
Clinically-defined obesity	2.1	2.8	3.2	5.9	6.5	4.3
Psychiatric						
Depression	12.2	13.0	12.6	16.2	16.7	14.4
Drug abuse/dependence	3.3	3.1	3.7	5.3	5.6	4.3

	2006	2007	2008	2009	2010	Weighted Average
Alcohol abuse/dependence	2.9	3.1	3.8	5.3	5.8	4.3
Bipolar disorders	2.2	2.4	2.5	2.9	2.9	2.6
Hepatic						
Compensated cirrhosis	18.0	19.9	20.2	23.6	26.5	22.0
Advanced liver disease	9.9	10.7	11.1	13.8	15.5	12.5
NAFLD	5.0	5.7	6.5	8.1	8.8	7.0
Alcoholic liver disease	3.9	4.0	4.2	5.0	5.9	4.7
Liver transplant	3.2	3.4	3.7	4.3	4.7	3.9
Viral hepatitis B	3.6	3.5	4.0	3.5	3.6	3.7
Hepatocellular carcinoma	1.8	2.3	3.1	3.3	4.0	3.0
Other						
COPD or asthma	8.0	8.8	9.4	11.1	11.6	10.0
Rheumatoid arthritis	3.1	3.0	3.1	3.4	3.4	3.2
HIV/AIDS	1.9	2.2	3.0	3.2	3.2	2.8

Abbreviations: SD, standard deviation; chronic HCV, chronic Hepatitis C virus infection; HMO, Health Maintenance Organization; POS, Point of Service; PPO, Preferred Provider Organization; NAFLD: non-alcoholic fatty liver disease; COPD, chronic obstructive pulmonary disease; HIV/AIDS: human immunodeficiency virus/acquired immunodeficiency syndrome

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Table 2

Comorbidity and medication use characteristics of a U.S. chronic HCV population in a commercial insurance database, 2006-2010

	2006	2007	2008	2009	2010	Weighted Average
Enrollees with pharmacy benefit, n	(53,461 individuals, 79,185 cross-sections)					
	11,424	11,517	19,379	18,882	17,983	(sum) 79,185
HCV Treated						
Ribavirin + interferon, %	24.8	21.9	19.1	18.4	15.7	19.4
Comorbidity Measures[†]						
CCI: Treated, mean	1.7	1.7	1.9	2.0	2.1	1.9
CCI: Untreated, mean	2.1	2.2	2.3	2.5	2.6	2.4
Number of distinct medications per capita: Treated, mean	11.5	11.3	11.3	11.5	11.5	11.4
Number of distrinct medications per capita: Untreated, mean	8.7	9.0	8.5	9.2	9.3	9.0

Abbreviations: HCV, Hepatitis C virus; CCI, Charlson Comorbidity Index

[†]Treated: received ribavirin + PEG-interferon or interferon alfacon in a given year; Untreated: did not receive ribavirin + peg-interferon or interferon alfacon in a given year

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Table 3

Drug interaction potential of the most utilized medications in U.S. patients with HCV by total number of prescriptions filled

Medication	Number of claims	Boceprevir*				Telaprevir*			
		None	Interaction	CI	NL	None	Interaction	CI	NL
1. Acetaminophen/hydrocodone bitartrate	367,166		X§				X§		
2. Ribavirin	176,842	X				X			
3. Zolpidem tartrate	169,811		X				X		
4. Levothyroxine sodium	155,926		X				X		
5. Alprazolam	146,362		X				X		
6. Lisinopril†	123,616		X				X		
7. Peginterferon alfa-2a	120,191	X				X			
8. Oxycodone	118,753		X				X		
9. Furosemide	100,413	X				X			
10. Amlodipine besylate	93,776		X				X		
11. Omeprazole	87,895	X				X			
12. Acetaminophen/oxycodone	81,332		X§				X§		
13. Esomeprazole magnesium	80,526	X§				X			
14. Metformin HCl†	78,229		X				X		
15. Escitalopram oxalate	74,171		X				X		
16. Spironolactone	72,277	X				X			
17. Hydrochlorothiazide	71,311	X				X			
18. Bupropion HCl	66,680	X				X			
19. Tramadol HCl	65,803		X				X		
20. Pantoprazole sodium	62,622	X				X			
21. Metoprolol succinate†	61,663		X				X		
22. Lorazepam	59,950	X				X			
23. Azithromycin	59,784	X				X			
24. Atenolol	59,054	X				X			
25. Peginterferon alfa-2b	58,846	X				X			
26. Sertraline	58,004		X				X		

Medication	Number of claims	Boceprevir*				Telaprevir*			
		None	Interaction	CI	NL	None	Interaction	CI	NL
27. Clonazepam	57,336		X				X		
28. Citalopram hydrobromide†	55,375		X				X		
29. Gabapentin	53,583	X				X			
30. Trazodone	53,564		X				X		
31. Prednisone	53,292		X				X		
32. Tacrolimus	50,389		X				X		
33. Amoxicillin	49,285	X				X			
34. Cyclobenzaprine	48,168				X				X
35. Diazepam	48,097		X				X		
36. Potassium chloride	47,627	X				X			
37. Sulfamethoxazole/trimethoprim	46,555	X§				X§			
38. Venlafaxine	46,376		X				X		
39. Metoprolol tartrate†	45,848		X				X		
40. Carisoprodol	45,149				X				X

Abbreviations: HCV, Hepatitis C Virus; CI, Contraindicated; NL, Not listed

*Interaction potential based on Liverpool Drug Interaction charts[21] with None: “No clinically significant interaction expected”; Interaction: “Potential interaction – may require close monitoring, alteration of drug dosage or timing of administration; Contraindicated: “These drugs should not be coadministered”

†Chart indicates drug-disease interaction only with hepatic insufficiency/cirrhosis and/or pharmacokinetic interaction unlikely

§Interaction has not been assessed and has been predicted based on metabolic profiles of the drugs

Table 4

Liverpool resource recommendations for top medications reported to have interaction potential with boceprevir and telaprevir[21]

Medication	Classification*						Studied	Clear recommendation	Listed in prescribing information
	Boceprevir			Telaprevir					
	N	I	C	N	I	C	BOC/TVR	BOC/TVR	BOC/TVR
zolpidem		X			X		No / Yes	No / Yes	No / Yes
alprazolam		X			X		Yes / Yes	Yes / Yes	Yes / Yes
amlodipine		X			X		No / Yes	Yes / Yes	Yes / Yes
prednisone		X			X[C]		Yes / No	Yes[PI] / Yes	No / Yes
tramadol		X			X		No / No	No / No	No / No
codeine		X			X		No / No	Yes / Yes	No / No
fluticasone		X[C]			X[C]		No / No	Yes / Yes	Yes / Yes
methylprednisolone		X			X[C]		No / No	Yes / Yes	No / Yes
escitalopram		X			X		Yes / Yes	Yes / Yes	No / Yes
trazodone		X			X		No / No	Yes / Yes	Yes / Yes
clindamycin (systemic)		X			X		No / No	No / No	No / No
diazepam		X			X		No / No	No / No	No / No
sertraline		X			X		No / No	No / No	No / No
lansoprazole		X			X		No / No	No / No	No / No
clonazepam		X			X		No / No	No / No	No / No
sildenafil (Viagra only)		X			X		No / No	Yes / Yes	Yes / Yes
fluconazole		X			X		No / No	No / No	No / No
simvastatin			X			X	No / No	Yes / Yes	Yes / Yes
venlafaxine		X			X		No / No	No / No	No / No
salmeterol		X[C]			X[C]		No / No	Yes / Yes	Yes / Yes
clarithromycin		X			X		Yes / No	Yes / Yes	Yes / Yes
tacrolimus		X			X		Yes / Yes	Yes / Yes	Yes / Yes

Abbreviations: N, None; I, Potential interaction; C, Contraindicated; BOC, Boceprevir; TVR, Telaprevir; PI, prescribing information

*Interaction potential based on Liverpool Drug Interaction charts with None: “No clinically significant interaction expected”; Potential interaction: “Potential interaction – may require close monitoring, alteration of drug dosage or timing of administration; Contraindicated: “These drugs should not be coadministered”

Bold indicates drug also listed in Table 3

[C] Although drug is classified as potential interaction, recommendation is to avoid coadministration

Table 5

Exposure to drugs reported to have DDI potential with telaprevir or boceprevir in a U.S. Commercial Claims Database, 2006-2010

	2006	2007	2008	2009	2010	Weighted Average
Beneficiaries with pharmacy benefit, n*	(53,461 beneficiaries, 79,185 cross-sections)					
	11,424	11,517	19,379	18,882	17,983	79,185
Medication	**Proportion exposed, %**					
zolpidem	15.0	14.4	13.6	14.1	14.0	14.1
alprazolam	9.7	10.6	9.2	10.0	9.9	9.8
amlodipine	7.5	7.7	8.8	10.3	10.9	9.3
prednisone	8.5	8.7	8.8	9.7	10.0	9.2
tramadol	7.8	8.7	8.2	9.7	10.0	9.0
codeine	8.0	7.9	9.0	9.6	9.1	8.9
fluticasone	8.0	8.1	7.9	9.3	10.2	8.8
methylprednisolone	6.3	6.0	6.3	7.0	7.1	6.6
escitalopram	7.9	7.4	6.2	6.0	5.1	6.4
trazodone	5.2	5.0	4.8	5.5	6.0	5.3
clindamycin (systemic)	5.0	5.1	4.9	5.4	5.3	5.2
diazepam	4.9	5.0	5.0	5.4	5.1	5.1
sertraline	5.3	5.2	4.9	5.1	4.9	5.1
lansoprazole	5.8	5.0	4.1	3.7	3.8	4.3
clonazepam	3.9	4.1	3.9	4.3	4.4	4.1
sildenafil (Viagra only)	4.1	3.3	4.1	4.3	3.7	3.9
fluconazole	3.8	4.0	3.7	4.0	4.2	3.9
simvastatin	2.0	3.1	3.6	4.7	4.7	3.8
venlafaxine	4.5	4.3	3.4	3.1	2.4	3.4
salmeterol	3.5	3.3	3.0	3.2	3.0	3.2
clarithromycin	3.8	3.3	3.2	2.8	2.8	3.1
tacrolimus	2.5	2.7	2.9	3.3	3.5	3.0
Any medication above	60.9	61.1	59.5	63.9	64.3	62.1

Abbreviations: DDI, Drug-drug interaction

* defined using a subcohort of chronic HCV patients with prescription drug benefits and filling at least one prescription per year