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RESEARCH ARTICLE

Pharmacist-led pre-treatment assessment, management and outcomes in a Hepatitis C treatment patient cohort

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Abstract

Background Medication reconciliation and drug–drug interaction management represent important patient safety processes completed by pharmacists as part of Hepatitis C patient care. *Objectives* To describe the pharmacist-led interventions of medication reconciliation and drug–drug interaction assessment, grading and management in a real-world Hepatitis C treatment cohort and to assesses the impact on patient outcomes. *Setting* Two Hepatitis C hospital outpatient clinics at St. James's Hospital, Dublin. *Method* Patients treated with Hepatitis C direct acting anti-viral agents between December 2014 and February 2017 were included in this retrospective cohort study. The study employed a standardised medication reconciliation proforma and drug–drug interaction reference list. *Main outcome measures* Analyse medication variances identified during pharmacist-led medication reconciliation. Assess the prevalence, type and severity of drug–drug interactions between direct acting anti-virals and co-medications. Assess the rate of prescriber acceptance of the pharmacist-developed drug–drug interaction management strategies. *Results* Among the 300 patients in this study, medication reconciliation identified 1543 co-medications, with 71% of patients prescribed co-medications which were subject to a potential drug–drug interaction. Drug–drug interaction assessments assigned a rating of severe to 68 interaction episodes. At least one co-medication was stopped during treatment in 25% of patients to facilitate drug–drug interaction management. Pharmacist proposed management recommendations were accepted by prescribers in 96.9% of cases. The sustained virological response rate among the cohort was 92.7%. *Conclusions* In this Hepatitis C pre-treatment pharmacist assessment analysis, a significant number of medication reconciliation variances and clinically significant drug–drug interactions were identified which present unique and important patient safety risks. Pharmacist-led management strategies aided the achievement of optimum treatment response while promoting patient safety and antiviral stewardship.

Impact on practice

- Pharmacist-led medication reconciliation in this Hepatitis C outpatient cohort identified many medication discrepancies in medication lists documented in patient medical notes.
- Hepatitis C pre-treatment pharmacist drug-drug interaction review identified that a significant proportion of patients were at risk of clinically significant drug-drug interactions between co-medications and direct acting antiviral therapy.
- Drug-drug interactions between co-medications and direct acting antivirals, classified as potentially severe, affected 14% of the study population (68 drug-drug interactions).
- The acceptance rate of pharmacist-led drug-drug interactions management plans was high overall, at 96.9%.

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- Pharmacist-led medication reconciliation and drug-drug interaction assessment are key roles in the stewardship of direct acting antivirals to ensure optimum patient outcomes and to reduce the risk of drug-related problems.

Introduction

Hepatitis C (HCV) virus infection places a significant burden upon healthcare services worldwide [1]. Sustained virological response (SVR) is associated with lower all-cause mortality [2]. SVR is defined as the absence of detectable Hepatitis C virus ribonucleic acid (RNA) 12 weeks after the end of HCV treatment and attainment of SVR is the primary goal of treatment [3]. Direct-acting anti-virals (DAAs) now provide multiple regimen choices for prescribers, all with high rates of SVR and good tolerability profiles [4–6]. One area of risk which has been reported is the potential for drug–drug interactions (DDIs) between HCV DAAs and patient co-medications [7–12]. Unidentified or mismanaged DAA DDIs have the potential to lead to patient harm, HCV treatment failure, and development of DAA resistance, which may limit future retreatment options [13, 14].

Medication reconciliation and DDI assessment and management are core components of the HCV pre-treatment pharmacist assessment. The pharmacist-led medication reconciliation process aims to identify all prescription medicines, over the counter (OTC) products, herbal supplements, multivitamins and any other medications prescribed or in use by each patient. It is widely accepted that medication reconciliation is integral to reducing medication errors [15, 16]. The majority of research assessing the impact of the medication reconciliation has focused on its benefits in the hospital inpatient setting [17–20]. A small number of studies in ambulatory care have also identified a high prevalence of medication discrepancies which pose risks for patient safety and healthcare outcomes [16, 21–23]. No studies assessing the impact of medication reconciliation in a Hepatitis C outpatient clinic setting have been published to date.

Once an accurate list of patient co-medications has been obtained via medication reconciliation, the process of DDI review can be undertaken. A review of co-prescribed medicines among patients with chronic HCV in Europe in 2016 determined that 20% of patients would have a least one contra-indicated DDI with a DAA, if they were to progress to treatment [8]. The risk of DDIs associated with herbal supplements and multivitamins was highlighted by Langness et al., with 36% of patients identified as at risk of a DDI between prescribed DAAs and herbal supplements or vitamins [24]. Studies have also identified the potential for interaction with anti-retroviral therapy in the HIV co-infection patient population [25–27].

It is clear that a significant number of patients are at risk for DDIs when treated with HCV DAAs. There are published datasets from real-world cohorts in the United States and Germany reporting the pharmacist-led intervention of DDI assessment [10, 11, 24]. Only one of these studies discusses the management and outcomes of DDIs identified [10]. Ottman et al. identified within their study that 80.3% of patients had at least 1 DDI, with an average of 1.85 DDIs per patient. Among DDIs identified, 76% were categorized as either potentially clinically significant or a critical interaction [10]. The most common DDI management strategy utilised within this study was increased patient monitoring (59%) [10].

However, this study population consisted mainly of African American males and almost exclusively of patients with genotype 1 infection which limits its extrapolation to other healthcare populations. In addition, these studies do not report the process of medication reconciliation. There is a paucity of data on pharmacist-led medication reconciliation and DDI occurrence and management strategies within real world Hepatitis C treatment cohorts.

Aim of the study

The primary aims of this study are to:

- Analyse medication variances identified during pharmacist-led medication reconciliation in a cohort of patients with Hepatitis C infection being treated with DAA therapy.
- Assess the prevalence, type, and severity of DDIs between DAAs and identified patient co-medications.
- Assess the rate of acceptance, among prescribers, of the pharmacist-developed DDI management strategies.

The secondary aims of this study are to:

- Evaluate the association between baseline patient characteristics and the risk of DAA DDI occurrence.
- Evaluate the association between potential DDIs identified as part of pre-treatment pharmacist assessment and attainment of SVR.

Ethics approval

Ethics approval was obtained from the Tallaght University Hospital/St. James's Hospital Joint Research Ethics Committee (Reference REC 2016-05;12).

Method

Study design

A retrospective study of patients with chronic HCV infection treated with DAAs at two outpatient clinics at St. James Hospital.

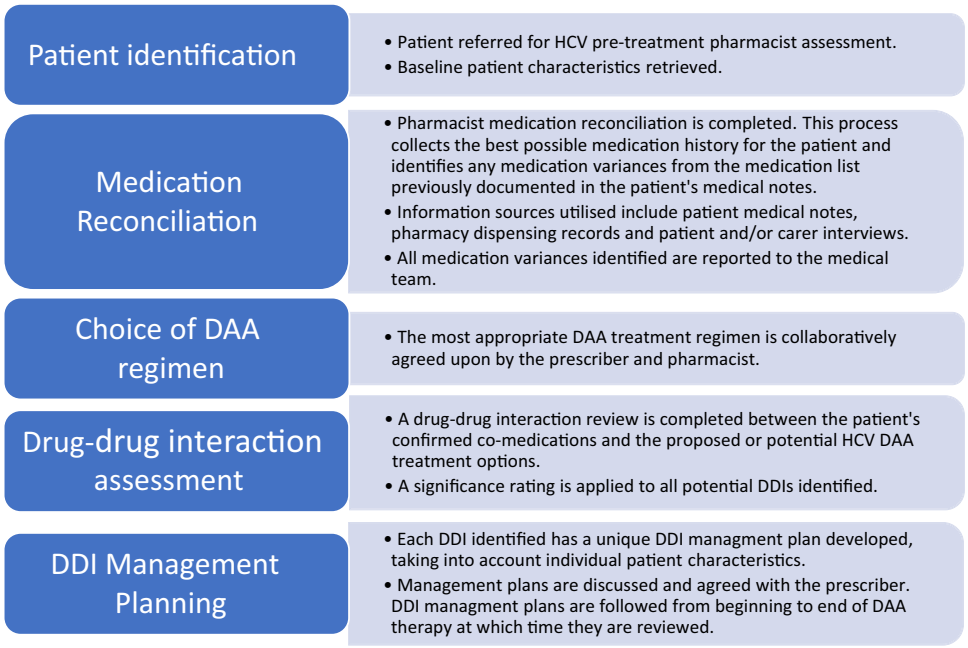


Fig. 1 Study methodology flowchart

Study population

Patients treated with DAA therapies between December 2014 and February 2017 were included in this study if they had a pre-treatment pharmacist assessment completed by an on-site clinical pharmacist which was part of standard practice during the study period (Fig. 1). Patients were excluded from this study if they were enrolled in a clinical trial or did not start DAA therapy.

Data collection

The pre-treatment pharmacist assessment proforma captured patient information pertaining to baseline patient demographics, laboratory markers, co-morbidities, liver disease status and proposed HCV treatment. This information was obtained through patient interview and review of patient medical records. Pharmacist-led medication reconciliation was then completed. Variables collected included patient age, gender, presence of cirrhosis, co-morbidities and co-medications, HCV acquisition risk and HCV genotype.

Pre-treatment pharmacist assessment: medication reconciliation

The medication list obtained through the medication reconciliation process was compared with the medication list documented in the patient medical notes. Any reconciliation variances identified were classified into five categories; medication omission, medication commission, dose variation, frequency variation and medication formulation variation. Variances identified were communicated to the medical team verbally and in writing. Patient co-medications were classified using the World Health Organisation anatomical chemical classification system [28].

Pre-treatment assessment: DDI assessment and management

The most appropriate DAA treatment regimen was collaboratively agreed upon by the prescriber and pharmacist. The pre-treatment pharmacist assessment then progressed to DDI review with the proposed DAA regimen, which employed a standardised DDI reference list including the specialised University of Liverpool online resource [29]. DDI outcome assessments resulted in three descriptive categories based on the potential for a DDI to occur: nil interaction found, potential interaction identified or potential for DDI unknown (Fig. 2). When a potential interaction was identified a clinical significance rating was applied (Nil DDI; Mild DDI; Moderate DDI; Severe DDI). DDI significance ratings applied were based on classification systems in use by established DDI reference sources [29–31]. When the potential for interaction between DAA therapy and a co-medication was unknown, a review of co-medication indication was completed.

Where a potential interaction was identified, six DDI management recommendations were incorporated into the pre-treatment pharmacist assessment DDI review to guide patient care (Fig. 2). The type of DDI management recommendation chosen for each DDI identified in this study was based on the clinical significance rating applied to the DDI,

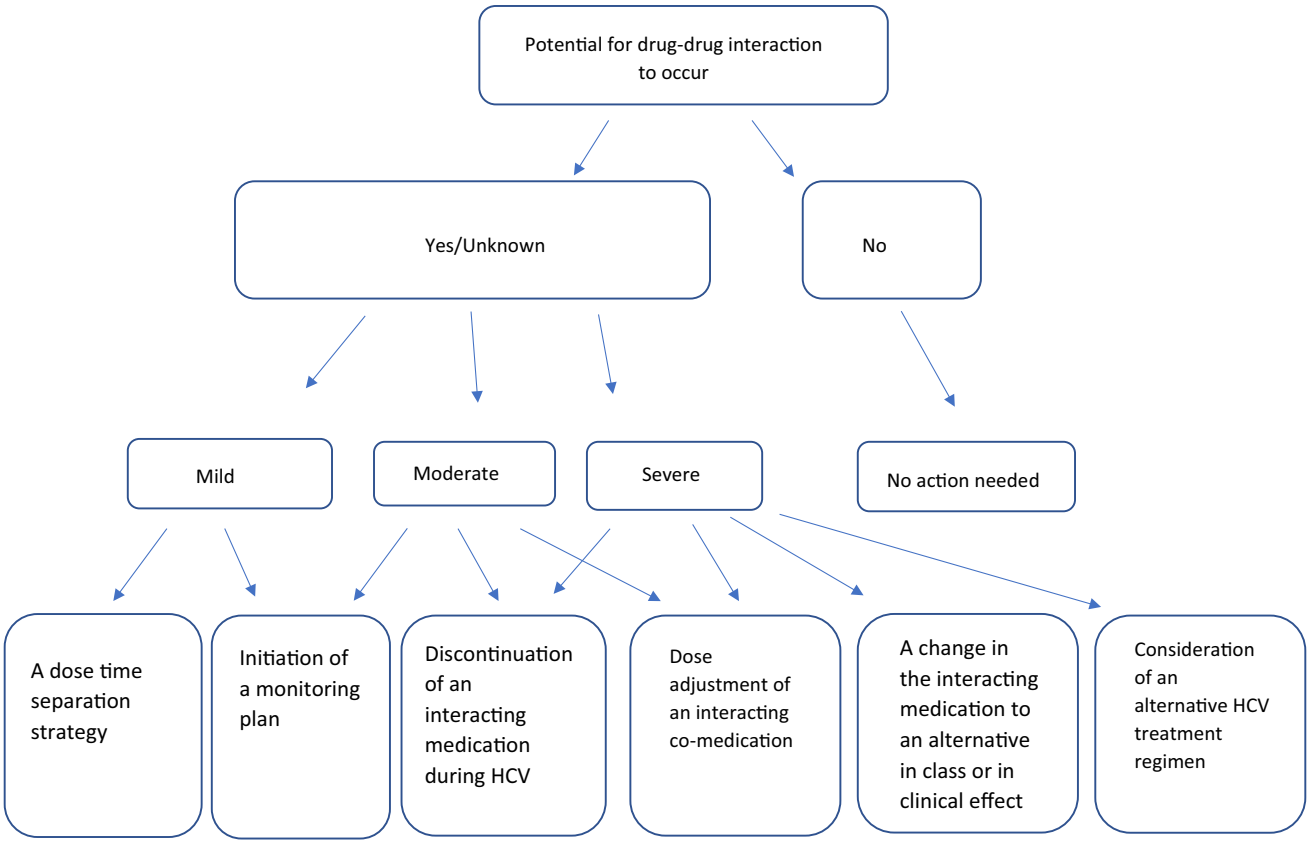


Fig. 2 DDI assessment, classification and management recommendations

the indication for the co-medication and the alternative treatment options that were available for that specific co-morbidity for that specific patient. Management recommendations were communicated to the medical team verbally and in writing. DDI management strategies were adhered to from commencement to completion of DAA treatment, at which point they were reviewed.

Outcomes measured

Outcomes measured as part of this study included the rate and type of medication variances identified as part of medication reconciliation process, the rate and severity of DDIs identified and how they were managed in practice. The acceptance rate of pharmacist DDI management strategies and SVR rate post treatment were also measured.

Statistical analysis

Descriptive statistics were used to describe study cohort demographics. Statistical analyses of the study findings were performed using IBM SPSS (version 24.0) with significance levels set at $p \leq 0.05$. Odds ratios were calculated to assess the level of association between the baseline characteristics of study patients and the risk of DAA DDI occurrence. The impact of DDI occurrence on SVR rates was also assessed.

Results

A total of 300 patients were included in this study of whom 71%, (N = 213) were male (Table 1). The average age of the study population was 50 ± 10.6 years. Common co-morbidities included gastro-intestinal conditions and depression (Table 1). Among the study population, 88% were taking at least one medication at baseline.

Pre-treatment pharmacist assessment *Step 1: Medication reconciliation*

The medication reconciliation process identified 1543 co-medications. The three most commonly used information sources for completion of medication reconciliation were patient interview (94%, N = 282), electronic patient records (74%, N = 222) and the patient medical notes (68%, N = 204). Medication reconciliation identified

Table 1 Baseline characteristics

	N = 300
Age at time of PTPA review (mean ± SD) (range), years	50 years ± 10.6 (25–81)
Male, n (%)	214 (71.3)
Presence of cirrhosis, n (%)	188 (62.7)
Route of acquisition, n (%)	
PWID	180 (60)
Sexual transmission	14 (4.67)
Infected blood products	71 (23.7)
Vertical transmission	1 (0.33)
Unknown risk	20 (6.67)
Origin from country of high prevalence	11 (3.67)
No. of co-morbidities (mean ± SD (range))	3.5 ± 2.21 (0–11)
Types of co-morbidities, n (%)	
Gastro-intestinal conditions	112 (37.33)
Depression/anxiety	84 (28)
HIV Co-infection	70 (23.3)
Respiratory conditions	65 (21.67)
Cardiovascular disease	61 (20.3)
Chronic pain	45 (15)
Dermatological conditions	29 (9.7)
Diabetes mellitus	22 (7.33)
Epilepsy	13 (4.3)
Malignancy	12 (4)
Total number of co-medications identified	1543
No. of concomitant medication per patient (mean ± SD (range))	5 ± 4.6 (0–27)
Patients taking at least one co-medication	264 (88)
Patients taking > 3 co-medications	203 (67.6)
HCV genotype, n (%)	G1[a]: 207 (69) G2: 3 (1) G3: 74 (24.7) G4: 12 (4) Mixed genotype: 4 (1.3)

PWID people who inject drugs

[a]No differentiation was made between G1a and G1b in this study as DAA treatment choice was not influenced by the genotype 1 subtype

episodes of medication variances affecting 74% (N = 222) of the study population with medication omission occurring most frequently (87%, N = 588 episodes). Other variances identified included omission of medication dosage information (7%, N = 41), medication dose variance (5%, N = 30) and omission of medication dosage frequency (1%, N = 7)

Co-medications most frequently identified during the pre-treatment pharmacist assessment process included proton pump inhibitors (PPIs)/H2 receptor antagonists (27.6%, N = 83) and methadone (28.7%, N = 86) (Fig. 3, Table S1). A high usage of multivitamin (16%, N = 48) and mineral supplements (10%, N = 30) was identified, accounting for 9.5% of total co-medications. Usage of complementary and alternative medicines was identified in 12% (N = 36) of the patient population.

Pre-treatment pharmacist assessment *Step 2a: Initial choice of HCV treatment and reconciliation & evaluation of potential DDI episodes*

Available licensed DAAs during the study time period were sofosbuvir, ledipasvir, daclatasvir, paritaprevir/ritonavir/ombitasvir and dasabuvir. The most commonly prescribed DAA regimens were sofosbuvir/ledipasvir (SOF/LDV) (53.3%, N = 160), sofosbuvir/daclatasvir (SOF/DCV) (24%, N = 72) and paritaprevir/ritonavir/ombitasvir and dasabuvir (P/rOD) (22.3%, N = 67). It should be noted that for the first five months of the study period, DAA access was limited to SOF/LDV. For the remainder of the study period there was no restriction of DAA regimen choice by the prescriber.

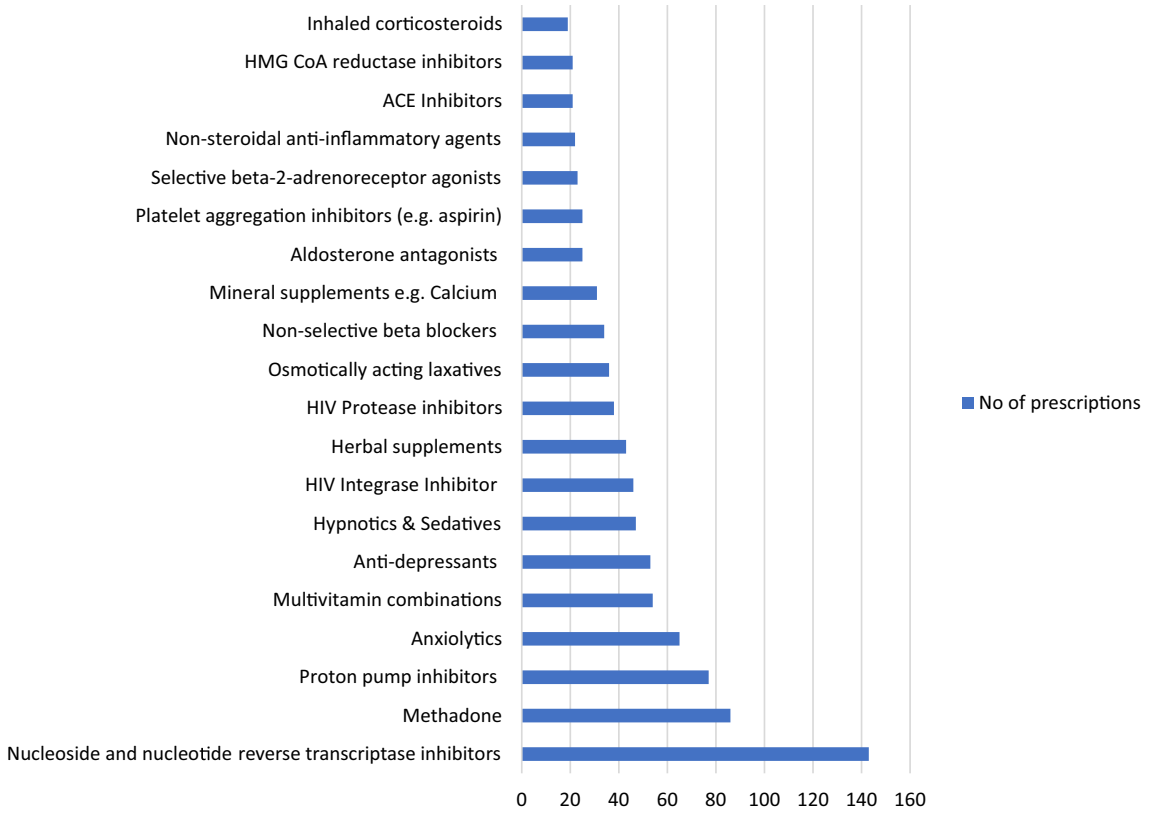


Fig. 3 Top 20 co-medications identified through the medication reconciliation process

Pre-treatment pharmacist assessment *Step 2b: Drug–drug interaction assessment*

From a total of 1543 concomitant medicines identified, 477 potential DDIs were identified, involving 160 different co-medications and affecting 71% (N = 187) of patients taking medicines. This corresponds to an average of 1.59 DDIs per patient. Prescription and OTC medications accounted for 85.1% (N = 406 episodes) and 4.8% (N = 23 episodes) of potential DDI episodes respectively. The medications most commonly associated with any severity level of potential DDI with DAAs were PPIs (22%, N = 65 episodes) (Table 2). Among the OTC medications linked with potential for DDI occurrence were four episodes involving PPIs purchased as OTC products. Complementary and alternative medicine products and vitamin products accounted for 5.7% (N = 27) and 4.4% (N = 21) of potential DDI episodes respectively. The most significant patient factor associated with DDI occurrence was the number of co-medications taken by the patient (> 3 co-medications OR 10.92 [CI 95% 6.2, 19.22; $p < 0.05$]) (Fig. 4).

Classification of DDI severity

A rating of mild was assigned to 192 (40.2%) potential DDIs identified. A rating of moderate was applied to 217 (45.5%) DDI episodes. A rating of severe was applied to 68 DDI episodes involving 14.3% of the study population. Of these, 27 DDI episodes affecting 7.5% of patients were identified as having the potential to reduce DAA efficacy. Examples of co-medications involved in these severe DDI episodes included oxcarbazepine, lansoprazole, etravirine, phenytoin, nevirapine and phenobarbital (Table 3).

A total of 41 severe DDI episodes, which had the potential to negatively impact the efficacy and safety of co-medications, were identified among 6.8% of patients. Examples of co-medications involved in these severe DDI episodes include inhaled fluticasone and salmeterol, lercanidipine, quetiapine, tadalafil and atorvastatin (Table 3). One in three patients with a history of cardiovascular disease and one in eight HIV co-infected patients were found to be at risk of a severe DDI.

Table 2 Commonly prescribed co-medication classes found to be at risk of DDI with DAAs and the proportion of the study population affected

ATC drug class	Number of patients affected by this DDI episode type N (% study cohort)
Proton pump inhibitors	65 (21.7)
Nucleoside and nucleotide reverse transcriptase inhibitor (NRTI)	28 (9.3)
Herbal supplements	27 (9)
Multivitamins and minerals	21 (7)
HMG CoA reductase inhibitors	21 (7)
Protease inhibitors	14 (4.7)
Dihydropyridine derivatives e.g. amlodipine	13 (4.33)
Osmotic laxatives	12 (4)
Antacids	11 (3.7)
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	10 (3.3)
Hypnotics and sedatives	10 (3.3)

DDI management strategies

The most commonly utilised management strategy was initiation of a monitoring plan (36.2%, N = 173 episodes). Temporary medication discontinuation was required in 25% (N = 90 DDI episodes) of the study population. The majority of these cases of medication discontinuation involved herbal supplements and multivitamins (54.3%, N = 49) for which limited or no interaction data was available. Medications requiring dose adjustments included PPIs, statins and anti-hypertensives. The most common patient groups requiring co-medication changes prior to initiation of HCV DAA therapy (15.1%, N = 72 episodes) were patients with HIV (52.8%, N = 38 episodes) or epilepsy (15.3%, N = 11 episodes). Dosage adjustments of co-medications and dose time separation strategies were recommended in 60 (12.6%) episodes and 72 (15.1%) episodes respectively. A change in planned HCV DAA regimen was required for eight patients due to severe unavoidable DDIs with anti-epileptic medications and antiretroviral therapy [32]. No published study to date has described the complex nature of DAA DDIs in the epilepsy patient group [32].

Acceptance of pharmacist-led DDI management plans

A total of 477 DDI management recommendations were given to prescribers (Table 4). The rate of acceptance of pharmacist-led DDI management plans was high overall, at 96.9% (N = 462). Actionable management interventions were accepted in 100% of cases in this study. In cases of potentially severe DDIs, 100% of pharmacist-developed management plans were accepted (Table 4).

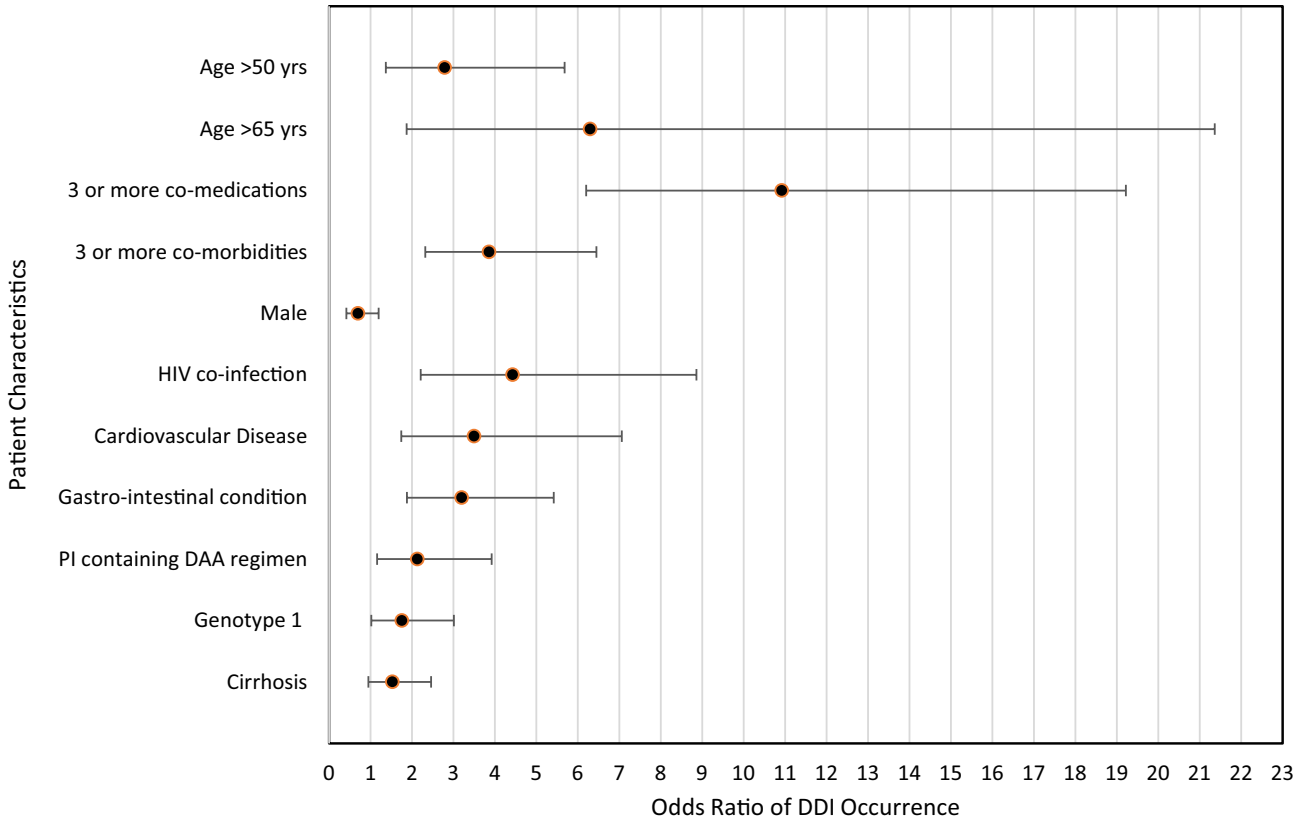
Patient outcomes

SVR12 was achieved by 92.7% of the study population. Treatment was self-discontinued by eight patients, none of whom achieved SVR. Five patients were lost to follow up. HCV relapse occurred in nine patients. For these cases, the pre-treatment pharmacist assessment process was repeated by a different clinical pharmacist. No new or previously unidentified DDI issues were identified which may have contributed to DAA treatment failure. Retrospective resistance analysis of baseline viral load samples identified that three patients whom experienced HCV relapse had NS5A resistance associated mutations present at baseline, which may have impacted treatment efficacy. No patient within the study group discontinued treatment due to a suspected adverse drug event driven by a DDI between DAAs and co-medications. Statistical analysis found that identification of a potential DDI as part of the pre-treatment pharmacist assessment was not associated with a reduction in SVR attainment (OR 1.38 [CI 95% 0.36, 5.28; p 0.73]).

Discussion

The first step of the pre-treatment pharmacist assessment process, medication reconciliation, identified medication variances affecting 74% of the study population, thus highlighting the importance of completing this key process to ensure an accurate list of co-medications is obtained prior to DDI review. Approximately 90% of patients starting DAA therapy were found to be taking at least one co-medication at baseline and 71% of the total study population were at risk of a potential DDI with their proposed DAA treatment regimen as compared with 80.3% in a recent US study [10].

The average number of DDIs per patient was 1.59. This is less than the DDI rate described by Ottman et al. (1.85 DDIs



Factors	Odds Ratio	95% Confidence Interval
Age >50 years	2.79	(1.37, 5.68)
Age >65 years	6.3	(1.87, 21.36)
3 or more co-medications	10.92	(6.2, 19.22)
3 or more co-morbidities	3.86	(2.32, 6.45)
Male	0.7	(0.416, 1.19)
HIV co-infection	4.43	(2.21, 8.86)
Cardiovascular Disease	3.5	(1.74, 7.06)
Gastro-intestinal condition	3.2	(1.88, 5.42)
PI based DAA regimen	2.13	(1.16, 3.92)
Genotype 1	1.76	(1.02, 3.01)
Cirrhosis	1.53	(0.95, 2.46)

Fig. 4 Odds of an association between patient characteristics and DDI occurrence

per patient). The difference in DDI rate between these two real world cohorts may, in part, be due to the older age of the Veterans Affairs (VA) cohort [10]. However, when compared with studies by Vermehren et al., our findings report a higher DDI rate per patient even with a lower average patient age [11]. Another factor which may have led to an increased DDI rate in the VA study is the disproportionally high rate of genotype 1 patients in the cohort (94.3%) which in turn may have impacted on the choice of DAA regimen and the potential for DDIs. This study's cohort is more consistent with the genotype mix among the wider HCV patient population. However, our study results still highlight a significant DDI rate among the patient population as a whole.

A high rate of PPI prescribing in this cohort and their potential for DDI with DAA therapies mirrors findings internationally and highlights again the pattern of overprescribing [8, 10, 33]. This high level of PPI prescribing greatly increases the DDI potential of ledipasvir and velpatasvir containing regimens. As both of these DAAs are still widely prescribed, this particular DDI issue will continue to hinder treatment efficacy into the future if not appropriately assessed and managed [34].

Table 3 Most common medications involved in DDIs with DAAs and monitoring plans/recommendations used

Concomitant medication	No. of interaction episodes	Examples of monitoring plans
Antiretroviral therapy	47	Monitor renal function when TDF co-prescribed with SOF/LDV
PPIs	16	Ensure patient is taking PPI simultaneously with SOF/LDV
Anxiolytics	14	Monitor diazepam dosing schedule when co-prescribed with P/rOD
Antipsychotics	11	Monitor patients for increased morning sedation when mirtazapine and P/rOD co-prescribed
Calcium channel blockers	10	Monitor BP & HR when amlodipine co-prescribed with SOF/LDV or P/rOD
Hypnotics & sedatives	10	Ensure lowest suitable dose of zopiclone is prescribed with P/rOD
Levothyroxine	7	Monitor TFTs monthly when co-prescribed with P/rOD
Beta blockers	6	Monitor BP when bisoprolol co-prescribed with SOF/LDV
Rifaximin	4	Monitor for potential increased rifaximin exposure when co-prescribed with SOF/LDV in patients with cirrhosis
Warfarin	4	Monitor INR with all DAA regimens

TDF Tenofovir disoproxil fumarate, *BP* blood pressure, *HR* heart rate, *TFTs* thyroid function tests, *INR* international normalised ratio

Table 4 Acceptance of pharmacist DDI management recommendations stratified by potential DDI severity

Potential DDI severity rating	N = 477 Acceptance of proposed DDI management recommendation
Mild, n (%)	179 (93.2)
Moderate, n (%)	215 (99.1)
Severe, n (%)	68 (100)

It is important to remember that the DAA may not always be impacted in potential DDIs. DAA DDIs also have the potential to negatively impact management of co-morbidities which may impact patient safety. Patients with cardiovascular disease are an example of one such group identified in this study. All DAA regimens were found to have the potential to interact with statins and dihydropyridine derivatives. In another example from this study, co-prescription of oxybutynin with P/rOD has the potential to increase oxybutynin adverse effects due to the inhibition of the cytochrome P450 3A4 (CYP 3A4) isoenzyme by ritonavir. Oxybutynin dose reduction was required in the case of two patients in this study.

This study cohort included seventy patients with HIV infection. Previous studies in this area describe the inclusion of minimal numbers of co-infected patients [10–12]. An important consideration in the treatment of HIV patients with DAAs, is assessment for potential DDIs with antiretroviral therapy [7, 35]. A previous study identified that 75% of co-infected patients would require antiretroviral therapy interchange prior to HCV DAA treatment due to DDIs [36, 37]. The findings from this cohort confirm this, with antiretroviral therapy alterations required in 49% of patients prior to DAA treatment. Clinical pharmacists play a critical role in this process to ensure that the effectiveness of HIV therapy is not compromised [37]. This study represents the largest real-world DDI analysis of anti-retrovirals and DAAs to date.

A US study has highlighted the growing prevalence of use of herbal supplements, complementary and alternative medicines and multivitamins among HCV patients [12]. The study also identified significant usage of these products. Given that 8% of all severe DDI risks identified in this study were linked to these products, it is imperative that their use is identified as part of the pre-treatment pharmacist assessment and assessed, to negate any potential impact on DAA treatment efficacy. This is a key benefit of pharmacist-led medication reconciliation, which helps to identify all patient medications.

Across all potential DDIs identified in this study, the majority (59.5%) were found to be clinically significant, and were rated moderate (45.5%) or severe (14.3%) respectively. This represents a higher overall incidence of potentially severe DDIs, as compared with previous studies [7, 8, 24]. Co-medications most frequently associated with severe DDIs included statins, inhaled glucocorticoids and antiretroviral therapy. One example was that of inhaled fluticasone and the DAA regimen, P/rOD. The ritonavir component of this regimen has the potential to cause a significant increase in fluticasone exposure due to inhibition of CYP3A4 isoenzymes which may cause Cushing's syndrome [38–40].

Effective management of DAA DDIs identified is something that is not widely described in real-world cohorts to date. Ottman et al. report DDI management among the VA cohort, with 59% of DDIs identified managed through implementation of an increased monitoring plan [10]. Actionable management interventions were much more prevalent in this study (66.5% vs. 41%).

This study reports a five-fold increase in the number of medications discontinued during DAA therapy as compared

with the VA cohort. This may in part be driven by the inclusion of complementary and alternative medicines, herbal supplements and multivitamins in the DDI review process. However, as highlighted by their potential to be involved in clinically relevant, severe DDIs, this inclusion is warranted. Another factor which may explain the higher rate of medication cessation relates to the significant number of inappropriate PPI prescriptions identified during the medication reconciliation process. Completion of medication reconciliation alongside DDI review permitted identification of these prescriptions which were then reviewed by the clinician to clarify clinical need. This study has also identified that in some cases co-medications will determine the choice of DAA regimen, something which has not been previously described in published research in this area i.e. refractory epilepsy. For example, co-administration of oxcarbazepine is contra-indicated with all available DAA regimens due to induction of drug transporter P-gp and CYP3A4 which may lead to a loss of efficacy of the DAA regimen. Therefore, for HCV treatment to proceed, the patient's epilepsy treatment regimen was changed [32]. A change in planned HCV DAA regimen was required for eight patients due to severe unavoidable DDIs with anti-epileptic medications and antiretroviral therapy [32].

A unique feature of this study is that all DDIs reported in this study's findings were identified, investigated, rated for severity and had management plans created, by an onsite clinical pharmacist. The majority of management plans (96.9%) proposed by the clinical pharmacist were accepted by the prescribing team with 100% of plans proposed for potentially severe DDIs accepted. This is a higher rate of acceptance than that reported by Ottman et al. [10] and it highlights the success of this HCV pre-treatment pharmacist assessment. In addition, this is the first publication to our knowledge which describes this specialist clinical pharmacist role of medication reconciliation among a cohort of HCV treatment patients [7, 10–12, 41]. It represents a key part of the HCV pre-treatment pharmacist assessment as accurate DDI review cannot happen without first obtaining an accurate list of all medications in use by a patient.

With multiple DAA regimens now licensed, medication reconciliation and DDI assessment are key, in ensuring that all patients achieve their potential SVR outcomes [38]. The findings of this study aim to build on the real-world DDI evidence available in the setting of DAA therapy. Pharmacists are an integral component of the HCV team, leading on DAA treatment options, DDIs, patient education, medication supply and adverse effects management [10, 11, 24]. Following the licensing of co-formulated sofosbuvir/velpatasvir/voxilaprevir in 2017, there are now no new DAA regimens on the horizon. Therefore, the role of the pharmacist as outlined in this study will be key to ensuring HCV antiviral stewardship in the coming years. This description and assessment of the pre-treatment pharmacist assessment process in the HCV treatment setting may also serve as a model for other HCV treatment services or healthcare specialities of the value gained in terms of patient safety outcomes.

Limitations of this study

This study does not include the more newly licensed DAAs including grazoprevir, elbasvir, glecaprevir, pibrentasvir, voxilaprevir or velpatasvir. However, the practices described in this study are applicable to all treatments utilised in HCV care. The regimen P/rOD is no longer recommended for first-line use in the United States however it is still included in the European guidelines for treatment of genotype 1b infection [5, 42]. This study contains a high proportion of patients with HIV, however it is representative of the patient case mix at the study site. There was no control arm in this study.

Conclusion

In this analysis, a high rate of clinically significant DDIs were consistently observed between DAAs and co-medications upon completion of pharmacist-led medication reconciliation and DDI assessment. DDI management strategies described, accepted and implemented, aided optimisation of HCV treatment outcomes. The availability of real-world data from large heterogenous patient cohorts aids the provision of clear recommendations to healthcare professionals with regard to safe and effective management of a broad spectrum of potential DDIs. This study also highlights for the first time, the importance of medication reconciliation as part of the HCV pre-treatment patient assessment.

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