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Clinical impact of drug interaction in the use of antipsychotics by HCV patients treated with pangenotypic direct-acting antivirals

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INTRODUCTION

- Infection with **hepatitis C virus** (HCV) is an important public health priority, as it is a leading cause of liver diseases, liver cirrhosis and hepatocellular carcinoma[1,2]
- Previous studies showed that patients infected with HCV have a high prevalence of psychiatric disorders, and that **central nervous system drugs** were the most commonly prescribed drugs in HCV patients.[3]
- Antipsychotic medication may interact with pangenotypic direct acting antivirals (pDAA).[4]
- This sub-analysis focused on patients taking antipsychotics was performed on an HCV Spanish cohort previously described.[5]

AIM

- The objective is to describe the use, drug-drug interactions (DDIs) and clinical impact of antipsychotic use in real-world HCV patients treated with pDAA.

METHODS

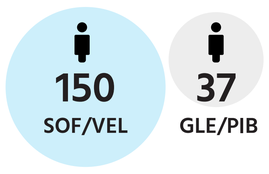
- This is a retrospective and observational study based on the electronic medical records from the BIG-PAC® database, which collects data from 1.8 million individuals in Spain.[6,7]
- The study population includes HCV patients ≥18 years old; treated between 2017 to 2020 with at least one of the following pDAAs:
  - Sofosbuvir/Velpatasvir [SOF/VEL]
  - Glecaprevir/Pibrentasvir [GLE/PIB]
- Potential DDIs between concomitant medication and the pDAAs, SOF/VEL and GLE/PIB, were evaluated using the University of Liverpool Hepatitis Interactions database.[8]
- The strength of DDIs and the clinical actions linked to the management of DDIs with antipsychotics (dose reduction; change of antipsychotic or pDAAs; electrocardiogram-ECG and discontinuation antipsychotic or pDAAs) were analyzed.
- Adverse events (AEs) potentially connected to DDIs were identified by the ICD-9-CM, codes 990–995 and E930–E949 during pDAA treatment period. The comedications associated to the AEs and their classification were recorded.

STRENGTH OF INTERACTION CONTRAINDICATED | SIGNIFICANT INTERACTION | WEAK INTERACTION | NO INTERACTION

RESULTS

Patients' characteristics

- The study included **187 HCV patients** with prescribed antipsychotics:
  - **150 treated with SOF/VEL**
  - **37 treated with GLE/PIB**



- The group of patients treated with SOF/VEL were numerically older than the group treated with GLE/PIB. The proportion of males and F3/F4 liver fibrosis were similar in both groups. (Table 1).

Table 1. Demographics in the study population

Study groups Number of patients, %	SOF / VEL 150 (100)	GLE / PIB 37 (100)	P value
Age, median (P25-P75)	53 (46 - 56)	48 (36 - 61)	0.219[&]
Gender male, N (%)	88 (59)	22 (60)	0.932
F3/4, N (%)*	66 (44)	17 (46)	0.387

*& P-value calculated with arithmetic mean. *Fibrosis (F3 – F4) > 3.25 points (FIB-4 score).*

Concomitant medication and DDI risk

- Considering all comedication prescribed, GLE/PIB was associated with a higher risk of single and multiple DDIs (≥ 2 comedications with DDIs with pDAAs) compared to SOF/VEL (Table 2).

Table 2. Concomitant medication and treatment in the study population

Patients prescribed antipsychotics # patients, N (%)	SOF / VEL 150 (100)	GLE / PIB 37 (100)	P value
# comedication, mean (SD)*	5.0 (1.2)	5.9 (1.2)	0.328
Patients with DDI, N (%)	65 (43.3)	27 (73)	**<0.001**
≥ 2 DDI comedications, N (%)	23 (15.3)	9 (24.3)	**0.002**

**Average active ingredients prescribed per patient.*

Quetiapine use and clinical actions to manage DDI risk

- Quetiapine was the most prescribed antipsychotic in both groups (n = 42 for SOF/VEL, n = 7 for GLE/PIB).
- In patients prescribed with quetiapine, a higher percentage of clinical actions were reported for GLE/PIB (100%; 7/7 patients) vs SOF/VEL (5%; 2/42 patients) treated group; p <0.001 (Figure 1; Table 3).

Figure 1. Clinical actions reported in patients prescribed quetiapine

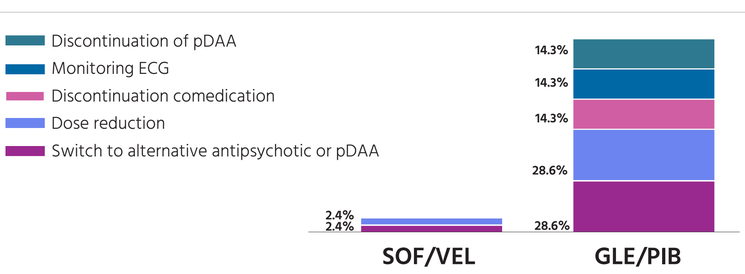


Table 3. Clinical actions in patients prescribed quetiapine by DDA

pDAA	SOF / VEL	GLE / PIB	P-value
Total patients prescribed quetiapine, N (%)	42 (100)	7 (100)	
Total clinical actions performed in patients taking quetiapine, N (%)	2 (4.8)	7 (100)	<0.001

N= number of patients prescribed quetiapine by pDAA. %: percentage calculated based on the number of patients with quetiapine requiring any medical action, divided by the total number patients prescribed quetiapine.

- Reported clinical actions in patients were higher for GLE/PIB compared to SOF/VEL and consisted of: ECG monitoring (1 vs 0), dose reduction (2 vs 1), change of pDAA/antipsychotic (2 vs 1), comedication discontinuation (1 vs 0), and pDAA discontinuation (1 vs 0) respectively (Figure 1; Table 3).
- The clinical actions reported with quetiapine and GLE/PIB occurred with both doses of < and > 300 mg/day in 100% of cases. In the case of SOF/VEL group, no clinical actions were performed with quetiapine at < 300 mg/day and 20% clinical actions with > 300 mg/day (Figure 2; Table 4).

Figure 2. Proportion of total clinical actions performed in patients with quetiapine (< and > 300mg/day) during pDAA treatment

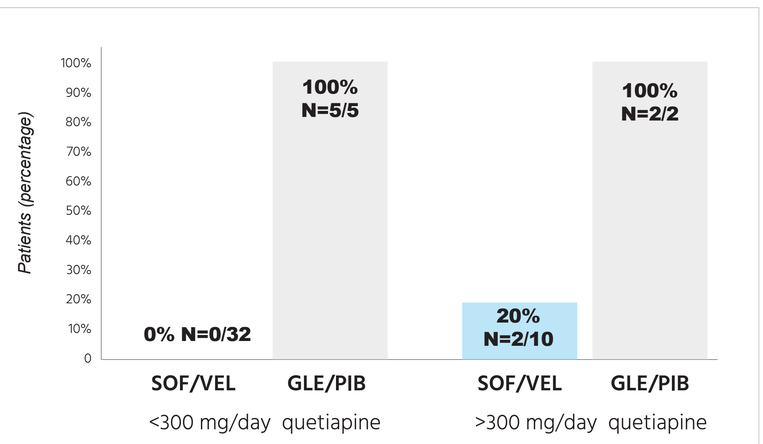


Table 4. Clasification of clinical actions reported in patients prescribed quetiapine (< and > 300mg/day)

	<300 mg quetiapine		>300 mg quetiapine	
	SOF/VEL	GLE/PIB	SOF/VEL	GLE/PIB
# patients, N (%)	**32 (100)**	**5 (100)**	**10 (100)**	**2 (100)**
Discontinuation of pDAA	0	1**	0	0
Monitoring ECG (electrocardiogram)	0	1	0	0
Discontinuation (co-medication)	0	1	0	0
Dose reduction	0	1	1	1
Switch to alternative antipsychotic or pDAA	0	1	1	1
Total clinical actions	**0 (0)**	**5 (100)**	**2 (20)**	**2 (100)**

***This patient (with reported AE with quetiapine) discontinued the corresponding pDAA treatment.*

Potential DDIs and adverse effects (AE)

- Considering only antipsychotic medication, there was a higher number of antipsychotic active ingredients with potential DDIs with GLE/PIB vs SOF/VEL (6 vs 2), linked to a higher percentage of patients at risk of DDIs with GLE/PIB compared to SOF/VEL (51% vs 23% respectively, p<0.001) (Table 5).

Table 5. Strenght of DDIs between pDDAs and antipsychotics

pDAA group # total patients prescribed antipsychotics; N (%) prescription	SOF/VEL 150 (100%)	GLE/PIB 37 (100%)
Aripiprazole	11	3
Clotiapine	9	1
Clozapine	3	0
Quetiapine	42	7
Paliperidone	28	5
Risperidone	6	3
N (%) patients at risk of DDIs betwen antipsichotic and corresponding pDAA	**34 (23%)**	**19 (51%)**

Only patients prescribed antipsychotics with predicted potential DDIs with any of pDAA were included in this table. DDIs: potential drug-drug interactions between antipsychotic & correspon-ding pDAA. Green color means no interaction expected. N: patients prescribed antipsychotics. Percentage (%) calculated versus total number of patients with prescribed antipsychotics or in specific antipsychotic treatment group, by pDAA group.

- The percentage of adverse events (AE) was higher for the GLE/PIB treated group 5,4% (2/37) vs SOF/VEL 0% (0/150).
- The two AE reported in the GLE/PIB group were associated to quetiapine and paliperidone. Those AEs were reported only in patients presenting potential DDIs between antipsychotics and GLE/PIB:
  - In the case of quetiapine, 1 patient out of 7 patients treated with quetiapine presented AE (14% AE); and with Paliperidone 1 patient out of 5 treated with this comedication presented AE (20%). (Table 6).
  - The AE reported with quetiapine (extrapyramidal symptoms) in the GLE/PIB group occurred with doses <300 mg/day. (Table 6).

Table 6. Communicated AE linked to antipsychotics with risk of DDIs

pDAA group number of AE (nAE) / number of patient prescribed the antipsicotic (N): (n AE/N; % AE)	SOF/VEL n AE/N; %	GLE/PIB n AE/N; %
Quetiapine	0 AE/42; **0%**	1 AE/7; **14%**
Paliperidone	0 AE/28; **0%**	1 AE/5; **20%**
Total nAE / total number of patients prescribed antipsychotics with DDIs, by pDAA	0 AE/34; **0%**	2 AE/19; **11%**

DDIs: potential drug-drug interactions between antipsychotic & correspon-ding pDAA. Only patients taking antipsychotics and having DDIs with any of pDAA were included in the table. nAE: number of patients with Adverse Events. N: number of patients prescribed antipsychotic comedication. Percentage of pacients with DDIs and EA was calculated dividing total number of AE in the antipsichotic group by by the total number of patients with DDIs (taken from table 5), by pDAA group.

CONCLUSIONS

- Quetiapine was the most frequently used antipsychotic in HCV patients and shows no potential interaction with SOF/VEL.
- The greater use of SOF/VEL in HCV patients treated with antipsychotic medication may be due to its favorable DDI profile, which implies a lower number of adverse effects and a lower number of required clinical actions.

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