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CLINICAL IMPACT OF PHARMACIST-LED INTERVENTIONS FOR MANAGING CHRONIC HEPATITIS C: A PROSPECTIVE OPEN-LABEL COHORT STUDY IN A SPECIALIZED HEPATITIS CLINIC

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ABSTRACT

In a prospective open-label study aimed at evaluating the impact of pharmacist interventions on hepatitis C patients undergoing interferon α 2a and ribavirin therapy, patients aged 20 to 60 were divided into seven cohorts, with one serving as a control group. A pharmaceutical care plan, structured under the SOAP (Subjective, Objective, Assessment, and Plan) format, was developed and implemented for all cohorts. Monthly interviews and questionnaires were utilized to assess compliance and adverse drug reactions (ADRs). The results demonstrated significant improvements in pharmaceutical care indicators with pharmacist integration into the healthcare system. Patients who received pharmacist intervention exhibited enhanced compliance and a reduced occurrence of ADRs compared to the control group. These findings underscore the valuable role of pharmacists within the healthcare team, particularly in optimizing patient care during hepatitis C treatment. The incorporation of pharmacists into the treatment process not only led to better adherence to therapy but also contributed to minimizing adverse reactions, thus emphasizing the importance of structured pharmaceutical care plans in improving outcomes for hepatitis C patients undergoing interferon α 2a and ribavirin therapy.

Keywords: Prospective study, Pharmacists counseling, Hepatitis C, Hepatitis clinic.

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INTRODUCTION

Hepatitis, literally an “inflammation of the liver,” has several causes: microbial infections, toxins exposure and autoimmunity. Viral infections can cause hepatitis, with the most common types being hepatitis A, hepatitis B, and hepatitis C. Hepatitis C, in particular, is the most prevalent bloodborne viral infection globally. It occurs when the blood of an infected person enters the body of someone who is uninfected.

Unlike hepatitis A and B, there is currently no vaccine available for hepatitis C. Approximately 80% of individuals who contract hepatitis C show no signs or symptoms during the initial stages of the infection. In 75%-85% of those infected, the virus persists in the body and the person develops chronic infection. Over several decades,

approximately 50%-60% of individuals with chronic infections develop mild to moderate chronic liver disease, which can lead to fibrosis. Around 10%-20% progress to severe liver disease, potentially resulting in cirrhosis and, in some instances, liver cancer. Of those affected, about 1%-5% may die from liver cancer [1, 2].

The condition can either resolve on its own or advance to liver scarring. Hepatitis can be classified as acute (with recovery within six months), fulminant (characterized by acute critical illness and a high mortality rate), or chronic (persistent disease lasting more than six months). Manifestations of hepatic disease include jaundice, cirrhosis, hepatocellular carcinoma, and hepatic [3].

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PATIENTS AND METHODS

Inclusion Criteria

Patients eligible for this study included those aged 18 to 65 years, of both sexes, with chronic Hepatitis C confirmed by HCV RNA via PCR. Participants must have compensated liver disease and be receiving a combination therapy of Interferon α 2a and Ribavirin.

Exclusion Criteria

Patients were excluded from the study if they were co-infected with hepatitis B, had any cardiac issues, diabetes, hypertension, thyroid disorders, or other significant underlying complications such as hepatic or renal failure. Additionally, individuals who died during the study period ($n = 1$) or had a leukocyte count of less than $3000/\text{mm}^3$ and a platelet count of less than $80,000/\text{mm}^3$ were also excluded.

Patient Cohorts

This study covered 150 patients in total. Following their sequential enrollment in accordance with the predefined inclusion criteria, these patients were given a participant identification number (PIN) and split into seven cohorts, each with fifteen patients, at random.

Dose and Dosage Regimen

Dosage of Ribavirin was calculated for each patient on the basis of body weight

400 mg in morning + 600 mg in evening (for body weight < 75 kg).

600 mg in morning + 600 mg in evening (for body weight > 75 kg).

Dosage of Interferon α 2a was 3 MIU / 3 times a week (For age $> 3y < 65$).

All patients were treated with Interferon α 2a (3 MIU) administered three times a week along with Ribavirin (200 mg capsule) orally as a function of body weight; for patients less than 75 kg, a dose of 1000 mg/day (2 capsules of Ribavirin 200 mg in morning and 3 in evening), and for more than 75 kg, a dose of 1200 mg/day (3 capsule in morning and 3 in evening). The doses of Ribavirin and Interferon were adjusted if anemia or neutropenia developed after the start of therapy. The treatment duration was set for 24 weeks; however, all patients initially received only one month's supply of medication from the hospital pharmacy. They were required to return to the hospital after one month to collect additional medications and for follow-up.

In addition to the standard information about the disease and treatment provided by physicians, the project pharmacist offered drug therapy

management, education, and support specifically to patients in the study group. The goal of this pharmacist-managed process was to empower patients to take an active role in their therapeutic plan, understand the administration method, recognize the importance of adhering to the treatment schedule, manage any adverse drug effects, know what to do in case of a missed dose, learn how to store the medication properly, and receive dietary recommendations. All information were explained to the patients verbally in their mother languages and with written text in Urdu which is annexed.

All the patients in control group were not provided consultation with project pharmacist because the objective of this study was to compare the results of pharmacist intervention in optimizing response in treatment of HCV patients with non-pharmacist involved patients.

Pharmaceutical Care Plan for Chronic Hepatitis C Patients

Subjective data such as patient name, gender, age, weight, presenting complaints or symptoms, smoking, dietary history, medication history, immunization history, socioeconomic history, family history, compliance, and allergy, if any, were included in the pharmaceutical care plan profile created using the SOAP format for chronic hepatitis C patients.

Objective data such as liver biopsy (liver cirrhosis, fibrosis), soft or non-soft abdomen, blood counts (platelets, hemoglobin, and WBC), and biochemistry (ALT, anti-HCV, and HCV RNA by PCR).

These Performas were given to each patient, and the researcher gathered first-hand data on the pharmacological treatment of hepatitis C patients (dosage, frequency, method of administration, occurrence and management of adverse medication reactions, etc.).

Patient Counseling

The following items were discussed verbally and in writing by the researcher with the patients who were part of the study group.

- Patients were encouraged to give Interferon injections in the evening whenever feasible in order to increase their tolerance.
- Patients were advised to take two 500 mg acetaminophen pills before to the injection in order to reduce the risk of some Interferon side effects.
- It was recommended that patients take any missed doses as soon as they remembered. If the

next dose is almost due, they should forgo the missed dose and take the medication at that time. To make up for the missing dose, they shouldn't take more medication.

- Patients were cautioned against sharing toothbrushes, razors, or needles, as well as against engaging in unprotected intercourse.
- Patients were told to only give subcutaneous injections of interferon alfa-2a.
- To guarantee proper hydration, particularly during the start of treatment, patients were instructed to consume six to eight full glasses of water each day.
- Patients were advised not to inject Interferon alfa-2a if it included particles or looked discolored. The vial should be lightly swirled if mixing is required, but not shaken.
- Patients were advised against reusing needles or syringes and to dispose of all used needles and syringes in a proper, puncture-resistant disposal container. They should not stop using this medication without first consulting their doctor or pharmacist.
- Patients were instructed not to freeze Interferon alfa-2a and instead to keep it in the refrigerator between 2 and 8 degrees Celsius.

Follow up Performa for Chronic Hepatitis C Patient for early Detection of ADRs

A follow-up plan was established to monitor side effects, drug-drug interactions, adverse drug reactions, and the prognosis of patients with chronic Hepatitis C. The researcher regularly completed a performance assessment for all patients in both the study and control groups at weeks 0, 4, 8, 12, 16, 20, and 24, either in the hospital during medication administration, via telephone, or during home visits.

During each visit, the pharmacist identified, recorded, and counseled patients (excluding those in the control group) on managing drug-related issues. The pharmacist highlighted that the benefits of therapy generally outweighed the inconvenience of adverse events, and educated patients on coping strategies. For instance, patients experiencing influenza-like symptoms were advised to get plenty of rest, stay well-hydrated, and take paracetamol (not exceeding 2 g/day). Hematological issues were addressed with dose adjustments, while gastrointestinal problems were managed with specific dietary recommendations. The pharmacist also encouraged adherence to drug therapy.

Detection, Monitoring and Management of Drug Induced Problems

The followings were most commonly encountered ADRs. It may be pointed out here that these symptoms usually disappear if the drug/s was/were discontinued according to the parameters given under each heading.

- Patients with fatigue, headaches, and fever were advised to obtain enough sleep, drink enough of water, and take acetaminophen orally in divided doses of less than 2 grams per day if their fever lasted longer than 24 to 48 hours.
- Patients with insomnia were advised to avoid stimulants like caffeine at night and to limit their fluid intake to prevent waking up to use the restroom. The non-habit-forming diphenhydramine (Benadryl), 25–50 mg taken orally at bedtime as needed, was used to treat the patients.
- The Hospital Anxiety and sadness Score (HAADS), a questionnaire with 14 items that is annexed, was used to evaluate patients who complained of sadness, irritation, confusion, difficulties concentrating, and tension.
- For each interview, patients were asked to select one response from a list of four options for the Hospital Anxiety and Depression Scale. They were not permitted to ponder these issues for too long and were encouraged to respond right away. The Performa was then evaluated in accordance with the guidelines, and the degree of anxiety and depression was ascertained using the following standards. Fluoxetine (20 mg orally daily), a selective serotonin reuptake inhibitor, was used to treat patients with abnormal status [4].
- Patients with alopecia were comforted that if interferon is withdrawn, hair usually grows back gradually to nearly pre-treatment levels.
- In order to treat skin rashes, patients who complained of fine, red, reticular rashes, particularly on the arms and trunks, were referred to a physician. Topical treatments included moisturizing lotions, low-dose steroid creams (such as 1% hydrocortisone or triamcinolone), and diphenhydramine. Patients were instructed to switch injection sites if a skin rash appeared at the injection locations.
- Patients who developed anemia (Hb < 10g/dl) had their ribavirin dosage lowered to 600 mg per day, and those whose hemoglobin was less than 8.5 g/dL were stopped taking ribavirin [5].
- For Neutropenia, the patients developing neutropenia with interferon, dosage was reduced

(to 1.5 MIU) when the absolute neutrophil count fell below $750/\text{mm}^3$, and suspended interferon for neutrophil counts below $500/\text{mm}^3$ [6].

- For Thrombocytopenia, the patients developing thrombocytopenia, interferon dosage was reduced (to 1.5 MIU) when the absolute platelet count fell below $80000/\text{mm}^3$, and suspended interferon for platelet counts below $50000/\text{mm}^3$ [7].
- For Visual Changes, the patients were advised to perform a baseline eye exam evaluated by an ophthalmologist. Treatment changes were made in consultation with the ophthalmologist based on the findings observed [8].
- The patients were advised to maintain their weight by eating smaller meals more frequently, eating a diet low in fat and high in carbohydrates, and maintaining sufficient nutrition.
- For disturbances of the digestive system The most frequent adverse effect of anti-HCV medications is nausea. The patients were instructed to take Ribavirin tablets with food and to utilize lemon drops. 5 mg of prochlorperazine (1-2 tabs, bid or tid) was administered to the patients.
- Patients with anorexia were encouraged to consume smaller meals more frequently.
- Patients with diarrhea were advised to eat cooked rice and bananas instead of cola, coffee, or tea. Two tablets of diphoxylate/atropine (Lomotil) 2.5 mg/0.025 mg were administered to the patients no more than four times each day.

Evaluation of Pharmaceutical Care Indicators

The evaluation of pharmaceutical care indicators was conducted using the Pharmaceutical Care Indicator Form, following the format set by the World Health Organization (WHO, 2014). This form presents the facility's services in terms of the following indicators:

- Percentage of patients reporting symptoms.
- Percentage of patients categorized by gender.
- Percentage of patients reporting adverse drug reactions (ADRs).
- Average dispensing time per patient.
- Average consultation time per patient (calculated based on the time spent by the physician, consultant, and researcher).
- Percentage of patients aware of the dosage frequency of their medications.
- Percentage of patients knowledgeable about drug administration.

- Percentage of patients informed about proper drug storage.
- Percentage of patients understanding their disease.
- Percentage of patients knowledgeable about managing ADRs.
- Percentage of patients aware of how to handle missed doses.
- Percentage of adherence rates among patients.
- Percentage of patients achieving a virological response at the end of treatment (ETR).
- Percentage of patients attending the Hepatitis Clinic from various distances.

Statistical Analysis

To validate our results, we performed a statistical analysis of the data in relation to our objectives. We utilized the Z-test to compare the proportions between the control and study groups, as the sample size exceeded 30.

Decisions were based on the P-value: if $p < 0.05$, the results were considered significant; if $p > 0.05$, they were deemed non-significant. For data analysis, we employed MINITAB 15.

RESULTS AND DISCUSSION

It was shown that those between the ages of 30 and 50 are more likely to have chronic Hepatitis C. Under 25, the sickness is less prevalent. This result of a bimodal distribution is consistent with earlier research. According to the report, 35% of women and 65% of men have chronic Hepatitis C.

This study pointed out that Chronic HCV patients receiving Interferon $\alpha 2a$ and Ribavirin had a complaint of adverse drug reactions including fatigue, fever, different degree of nausea and vomiting, diarrhea, Depression, insomnia, anemia, neutropenia, thrombocytopenia, alopecia, and skin rashes [9].

Pharmaceutical care indicators covers, awareness about storage of Interferon vials, administration time, vial deterioration, awareness about not to shake vial before use, knowledge about the management of missed dose, management of ADRs like fever, fatigue, Insomnia, Alopecia, and awareness about Hepatitis C (Table 1). Chronic Hepatitis C is linked to significant morbidity, mortality, and a substantial socioeconomic burden. Recent advancements in treatment regimens, including interferon α and ribavirin, have led to increased sustained virological response (SVR) rates. However, the longer duration of therapy and its often unfavorable

tolerability profile can affect patient adherence. These challenges highlight the need for enhanced efforts to optimize the diagnosis, treatment, and evaluation of Hepatitis C patients for disease progression and adverse drug reactions (ADRs). The primary goal of therapy is to achieve viral eradication and reduce disease-related complications such as fibrosis, cirrhosis, and hepatocellular carcinoma [10-12]. The overall virological response (VR) rate in our investigation was 58%. Idrees' trial, which included patients of all genotypes, revealed a VR of 67% in contrast. Since 91% of Hepatitis C patients in Pakistan are non-genotype 1, both studies, which were carried out in Pakistan, discovered that the majority of patients were non-genotype [13, 14].

In our study, Virological Response at the end of treatment (58%) is comparable to Idrees study (67%). The high rate of adherence to drug treatment may be due to consultation provided by the project pharmacist to the patients in study group regarding therapeutic plan, administration method, need for adherence to treatment schedule,

the management of ADRs, the management of missed dose, storage of medication and dietetic recommendations. The data was then analyzed with respect to pharmaceutical care indicators and a comparison between patients who received pharmacist consultation and patients who did not receive it. There was significant difference observed between study and control groups regarding awareness about storage of Interferon vials, awareness about administration time, awareness about vial deterioration, awareness about not to shake vial before use, knowledge about the management of missed dose, knowledge about management of ADRs like fever, fatigue, knowledge about management of ADRs like Insomnia, knowledge about management of ADRs like Alopecia, awareness about Hepatitis C [15, 16]. These statistically significant improved results in study groups as compared to control group are due to researcher consultation provided to study group patients one by one verbally as well as in the form of written Performa regarding all these parameters on monthly basis.

Table 1: Comparison of pharmaceutical care indicators in study and control group

Description	Study Group n=90	Control Group n=15	P value	Significance Level P < 0.05
%age of patients knowing about dosage frequency of drugs	92.6%	87%	0.547	NS
%age of patients knowing about storage of drugs	97.1%	63%	0.004	Sig
%age of patients knowing about administration route of drugs	92.5%	72%	0.108	NS
%age of patients knowing about administration time	95.3%	55%	0.001	Sig
%age of patients knowing about vial deterioration	92%	37%	0.000	Sig
%age of patients knowing not to shake vial	91.5%	22%	0.000	Sig
%age of patients knowing about management of missed dose	85%	45%	0.000	Sig
%age of patients knowing about management of ADRs like Fatigue, Fever and Headache.	92.5%	52%	0.003	Sig
%age of patients knowing about management of ADRs like Insomnia	91.3%	22%	0.000	Sig
%age of patients knowing about management of ADRs like Alopecia.	91.6%	14%	0.000	Sig
%age of patients knowing about basic information about Hepatitis C	97%	65%	0.015	Sig
%age of Adherence Rate in HCV patients	89%	80%	0.412	NS
%age of HCV patients achieved Virological Response	71%	53%	0.196	NS

Both groups of patients demonstrated a strong awareness of drug dosage frequency, with no significant differences between them. This may be attributed to the simplicity of the dosage regimens. Additionally, there was no statistically significant difference in patients' awareness regarding the route of administration. This could be because patients were required to administer injections at home with the assistance of a qualified dispenser, who was knowledgeable about the administration route for interferon injections. As a result, awareness of this parameter largely depended on the dispenser's knowledge. Both groups also showed similar improvements in medication adherence and virological response.

Average dispensing and consultation time per patient was 2.15 ± 0.05 and 17.2 ± 2.59 minutes. Increased consulting time results from the comprehensive collection of patient histories using a dedicated pharmaceutical care plan structured in SOAP format at the beginning of their visit to the Hepatitis Clinic. This approach saves valuable time for consultants, allowing them to focus more effectively on other critical aspects of patient care, such as counseling on disease parameters, diagnosis, prevention, complications, drug dosing, and drug utilization.

CONCLUSION

The researcher in this study set up a follow-up plan to record compliance and any adverse drug reactions. This procedure need to be a crucial

component of the treatment plans for these patients. By using an early detection system, this would not only enhance patients' quality of life but also lower the likelihood that adverse drug reactions would manifest. Patients who received pharmacist counsel (study group) and those who did not (control group) differed significantly, according to the study. Pharmacists are ideally positioned to enhance patient treatment and reduce the incidence of adverse drug reactions (ADRs) and drug interactions as part of a multidisciplinary care team. They can identify and address potential areas for improvement in medication use. Pharmacists assist patients with managing adverse effects, ensuring drug compliance, understanding their disease state, providing medication information, and achieving overall treatment goals. These efforts have contributed to increased treatment success in patients with hepatitis C (HCV).

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