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Review Article

Pharmacist Interventions and Medication Adherence of *H. Pylori*-Infected Patients: A Review of Randomized Controlled Studies

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ABSTRACT

The *Helicobacter pylori* (*H. Pylori*) eradication regimen challenges patient medication adherence. Pharmacists play an essential role in supporting medication adherence to achieve treatment efficacy. This review aimed to evaluate the effect of pharmaceutical interventions on medication adherence in patients with *H. Pylori* infection taking eradication regimens. The literature was reviewed using Scopus, ScienceDirect, PubMed, and Google Scholar. Keywords included adherence, pharmacist intervention, *H. Pylori*, and eradication regimen. We collected original articles published in English from January 2002 to December 2022 describing pharmacist interventions to improve medication adherence in adult patients with *H. Pylori* infection We . assessed adherence rates before and after the intervention. Two independent researchers extracted relevant data for the inclusion criteria and assessed the methodological quality of studies using the Joanna Briggs Institute Critical Appraisal Checklist Tools. A total of 413 articles were retrieved, of which six were eligible for review. The most common pharmacist intervention strategy was a combination of patient education with oral and written information provided. The findings suggest that pharmacist interventions support the improvement of medication adherence and highlight the role of pharmacist interventions in enhancing overall health outcomes. Further studies must assess the long-term effects and clinical outcomes of pharmacist interventions.

***Keywords*:** *H. Pylori*, Eradication regimen, Pharmacist, Adherence

Introduction

Helicobacter pylori (*H. pylori*) belongs to the genus *Helicobacter*, divided into gastric and non-gastric (enterohepatic) *Helicobacter* species, where both species have a high level of organ specificity. More than half of the population in developed countries have been infected with *H. pylori*, and the infection rates vary from country to country. There is a reversal correlation between the prevalence of infection and the human development index, making *H. pylori* one of humankind's most common bacterial infections.[1]

The increased prevalence of *H. pylori*, associated with decreased eradication rates and the aggregation of its complications to epidemic proportions, has emerged as a significant economic burden, evoking a growing demand to investigate the impact of pharmacist counseling on patient medication adherence and *H. pylori* eradication rates.[1]

Some clinical pharmacy fundamentals are recognizing, answering, and prohibiting drug-related complications. Drug-related complications are 'an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcome'.[2] Pharmacists contribute to drug therapy optimization through several indirect and direct measurements. For instance, they are requested to determine the number of drug-related complications, evaluate patients' health outcomes, and apply interventions to enhance the health outcome.

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A prospective, randomized, controlled study demonstrated H. pylori patients who were subjected to clinical pharmacist intervention to have a significant increase in medication adherence compared to patients in the control group with 92.1% versus 23.7%, P<0.001, respectively. Furthermore, the eradication rate was higher in the intervention group than in the control group, with 94.7% versus 73.7%, P = 0.02, respectively.[3] On the other hand, a study conducted on H. pylori-infected patients, where the intervention group was subjected to pharmacist intervention, revealed no significant difference in medication adherence between the intervention and non-intervention groups. However, this could have been attributed to the short-term therapy regimen used in this study; it was suggested that patients tend to adhere to long-term therapy more than short-term therapy.[4] In addition, other studies have documented pharmacist interventions not to improve patients' medication adherence, H. pylori eradication rates, or dyspepsia symptoms.[5]

The eradication rate among symptomatic *H. Pylori*-infected patients consuming the standard triple therapy of 500 mg clarithromycin twice daily, 1 g amoxicillin twice daily, and 20 mg omeprazole twice daily for 14 days was 61.9%, which is lower than the observed international rates (70-85%),[6,7] Several reasons, including patient non-adherence to eradication regimens, are believed to contribute to these poor eradication rates. Unfortunately, medication adherence assessments and patient awareness interventions to enhance adherence are not yet available among clinical and pharmaceutical care procedures. Poor medical staff and patient knowledge accounted for about 70% of poor adherence[8]. Currently, there needs to be more research addressing patient medication adherence with *H. pylori* treatment in Jordan. Moreover, there is a growing demand to address patients' medication adherence in Jordan, which is affected by six factors: pharmacist counseling, treatment duration, treatment complexity, regimen adverse effects, patient characteristics, and patient knowledge regarding *H. pylori* infection. However, no systematic review has been explicitly published regarding the effectiveness of pharmacist interventions on *H. Pylori* eradication regimen adherence. To address this gap, this review aimed to show the effectiveness of pharmacist interventions in

treatment adherence in patients with *H. Pylori* infection receiving eradication regimens.

Method

The present article reviewed the published literature using Scopus, ScienceDirect, PubMed, and Google Scholar. The search strategy used keywords related to adherence, pharmacist intervention, eradication regimens, and *H. Pylori* infection. The main goal of the review was to increase awareness regarding the vital role of pharmacists in patient treatment plans and to address different strategies that the pharmacist could implement to improve medication adherence among *H—pylori-infected* patients.

The relevant articles were identified based on the title, index term, and abstract. We reviewed full-text articles if they met the following inclusion criteria: Patients: adults, outpatients, and patients with *H. Pylori* (≥ 18 years) receiving eradication regimens; Exposure: pharmacist intervention promoting adherence to eradication regimens; Outcome: quantitative patient adherence rate before and after the intervention; Study type: randomized controlled trial (RCT); Published in the English language; Published in the period 2002–2022; Accessible as full-text articles (Figure 1).

Articles were excluded if the intervention description needed to be clarified and if they were reviews, letters to the editor, editorials, or commentaries. Data were extracted from eligible articles, including the lead author, year of publication, country, research design, follow-up duration, sample size, adherence measurement method, intervention description, control group, parameters measured, and study results.

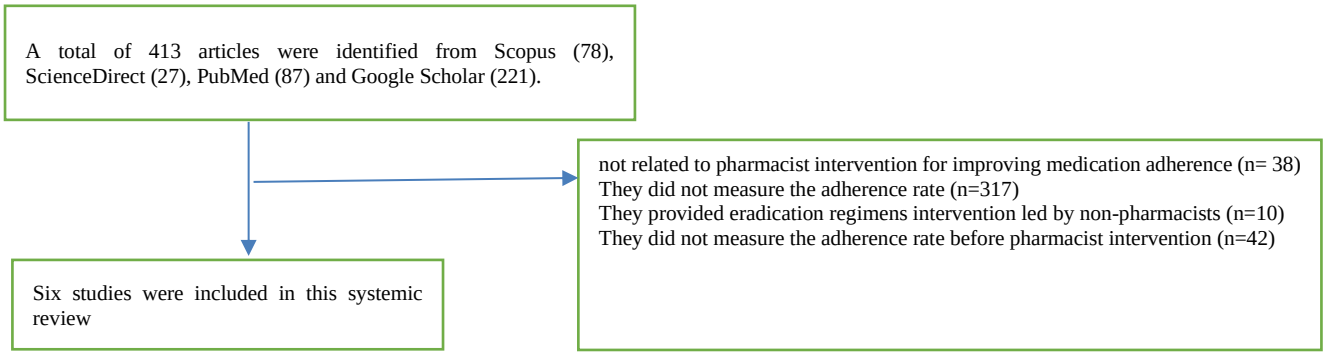

Figure 1: The flowchart of the selection process

Result and Discussion

A total of 413 articles were identified from an online database. We excluded articles because they were not related to pharmacist intervention for improving medication adherence (n=38), they did not measure the adherence rate (n=317), they provided eradication regimen intervention led by non-pharmacists (n=10), or they did not measure the adherence rate before pharmacist intervention (n=42). Six research articles on pharmacist interventions to improve adherence in patients with *H. Pylori* taking eradication regimens met all inclusion criteria for this review. One RCT study was not blinded and did not explain the data analysis. Meanwhile, three non-randomized experimental studies did not use a control group. The study did not give information on the validation score and the reliability test of the measurement tools used.

All studies were published in English between 2002 and 2021 and were conducted in India,[9] Jordan,[10] Northern Ireland,[11] China,[12,13] and Portland.[5] Several studies used an RCT single-centered study. [5,10,13] One study used a single-center before–after study design.[9]

Most studies used face-to-face educational interventions combined with written information. [5,9,13] A study used weekly telephone-based follow-ups. [5,9,13] The pharmacist's education to patients included patient treatment,[5,10,13] information on the drug's side effects and their management, current therapeutic regimen,[5,9-13] the importance of adherence,[5,9-13] risk of non-adherence,[5,9-13] and when a patient refers to a doctor.[10,11] In addition, most studies involved the role of pharmacists in identifying drug interactions or drug–drug-related problems and collaborating with responsible doctors when therapeutic changes were needed.[5,10-13] The studies in this review followed patient adherence by asking them directly[9,10,13] and allowing the patient to call the pharmacist to obtain information and support about managing side effects (Table 2). The duration of the intervention varied from 14-30 days, and three studies reported monitoring the intervention during the treatment period.[9,10,13] The measured outcome parameters varied between studies. Measuring adherence was the primary outcome in all studies. Other assessed products included the eradication rates of *H. Pylori*,[5,9-13] improved patient knowledge regarding the diseases,[10,11] medication side effects,[12,13] and patient satisfaction.[5,9] The researchers used various adherence measurement methods, including structured questions,[5,11] pill count,[8] and the Morisky Green Levine Scale.[9,10,13]

Pharmacist interventions significantly improved the mean daily adherence in the intervention group (P=0.01);[9] the *H. pylori* eradication rates of the reeducation group and control group by pre-protocol (PP) analysis and intention-to-treat (ITT) analyses were 78.7% (59/75) and 55.4% (41/74) (P=0.003).[12] The symptoms after treatment were significantly lower in the reeducation group (1.1 ± 0:9) when compared with the symptoms after treatment in the control group (2.0 ± 1:2) (P<0.001).[12] Furthermore, the pharmacoeconomic evaluation indicated that counseling and follow-up reduced the direct costs of *H. Pylori* eradication.[11] Adverse events occurred in 9 intensive follow-up group patients and 12 in the control group (P=0.488).[13]

The research limitations in most studies were that the same pharmacists delivered both interventions and may have mixed some elements of the counseling treatments. However, some contamination between treatments cannot be ruled out. Also, using the blister packs for dispensing medicines may have increased compliance in both groups. [5,10,11] Furthermore, the follow-up needed to be standardized according to the recommendation of trust-based patient education.[13] Most studies had a small sample size,[2,3,5,6] in addition to single-center studies.[5,9-13]

Pharmacists are essential to the gastroenterology service team because of their expertise and specialized knowledge of GI therapy. The vital role of pharmacists is to maximize treatment benefits and minimize toxicity. [14] This review describes the characteristics and evaluates the impact of pharmacist interventions on adherence to *H. Pylori* eradication regimens in patients with *H. Pylori* infection. The challenge of assessing pharmacist interventions with different strategies provides mixed results and makes it difficult to identify the most influential role of pharmacists. However, we summarized some findings to guide future studies (Table 1). The eradication regimens most assessed in studies are quadruple therapy[5,13] and standard triple therapy.[9-11]

The studies used a variety of adherence measurements because there is no gold standard. The Morisky method is an objective method that can minimize patient manipulation and be used in most studies to assess treatment adherence. Additionally, an open cap indicates that the drug is being taken, making it challenging to track medication ingestion.[15,16] Pill count is another objective measurement method that was used in

two of the studies. On the other hand, a self-reported questionnaire is a subjective method that tends to overestimate patient bias because of recall memory. However, this method is simple, inexpensive, and provides real-time feedback, so it is used more often in clinical settings. [16] The different approach to adherence measurement in these studies affects the adherence threshold. Determining a uniform adherence threshold is necessary to estimate the adherence level and provide better evidence accurately[17].

The most common pharmacist intervention in this review was patient education by providing written and oral information. Patient education is one of the integrated roles of pharmacists in outpatient clinic settings. [14] It is widely reported that patients need adequate knowledge of their health conditions and medications. Some patients need to understand the role of their medication in their treatment,[14] whereas others need to understand the nature of their disease and the importance of medication adherence.[18] Likewise, some patients think about medication consumption only when it is required. To improve the medication adherence of such patients, adequate education and awareness regarding their disease, treatment, and the importance of medication adherence are required.[19] Some studies suggested that healthcare providers could subject patients to sufficient education regarding their disease and treatment. [20] Adolescent patients with little knowledge of their disease and a medication reported poor adherence, whereas patients who received education regarding their condition and medications reported good medication adherence. However, patients who understand the life-long consequences of their disease might demonstrate poor commitment. [21]

It was suggested that the most common causes of poor adherence are poor patient involvement in the treatment process and poor knowledge regarding their disease and therapy.[22] For instance, a cohort multicenter randomized study among *H. pylori*-infected patients revealed that improving patients' knowledge of their disease and treatment in an intervention group resulted in an enhanced eradication rate compared to the control group, suggesting that patient knowledge is one of the components of successful *H. pylori* eradication.[23]

A study investigating poor medication adherence predictors among hypertensive patients revealed the lack of knowledge to be one of the significant predictors of medication non-adherence.[23] Similarly, a study performed among hypertensive patients showed that low knowledge and confidence in the benefits of the medications resulted in poor medication adherence. [24] Consequently, increased patient knowledge among patients with hyperlipidemia enhanced medication adherence and, subsequently, the control cholesterol level.[24] Furthermore, a study conducted among patients consuming chronic medications established a significant positive relationship between patients' knowledge and their medication adherence (correlation coefficient, (r)=0.357, P<0.001).[25]

Recognizing, answering, and prohibiting drug-related complications are fundamental in clinical pharmacy. Drug-related complications are 'an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes'.[26] Pharmacists contribute to drug therapy optimization through several indirect and direct measurements. For instance, they must determine the number of drug-related complications, evaluate patients' health outcomes, and apply interventions to enhance the health outcome. A prospective, randomized, controlled study demonstrated that *H. pylori* patients subjected to clinical pharmacist intervention significantly increased medication adherence compared to patients in the control group (92.1% versus 23.7%, P<0.001, respectively). Furthermore, the eradication rate was higher in the intervention group than in the control group (94.7% versus 73.7%, P=0.02, respectively). [11] On the other hand, a study conducted on *H. pylori*-infected patients, where the intervention group was subjected to pharmacist intervention, revealed no significant difference in medication adherence between the intervention and non-intervention groups. However, this could have been attributed to the short-term therapy regimen used in this study; it was suggested that patients tend to adhere to long-term therapy more than short-term therapy.[3,27] In addition, other studies have documented that pharmacist intervention did not improve patients' medication adherence, *H. pylori* eradication rates, or dyspepsia symptoms.[5]

The limitation of this review is that research on pharmacist interventions for *H. Pylori* eradication regimen adherence is limited. In addition, the differences in study design, method of measuring compliance, and follow-up duration between studies resulted in pharmacist interventions needing to be more directly comparable. The impact of pharmacist interventions on physiological parameters or health outcomes was limited. Additionally, this review includes only articles published in English, so there is a potential for publication bias.

Conclusion

This review shows that pharmacists support medication adherence improvement in adult patients with *H. Pylori* infection by taking eradication regimens. Pharmacist interventions to improve medication adherence generally included patient education by providing written and oral information. Further studies are needed to assess pharmacist interventions' long-term effects and clinical outcomes. Finding new and innovative interventions is also necessary to increase the efficiency and cost-effectiveness of pharmacist interventions.

Conflict of Interest

The authors declare no conflict of interest.

Table 1: Descriptions of pharmacist interventions

Author, year	Country	Study design	Observation period	Sample size	Adherence measurement
Aleena *et al*., 2020	India	Before–after, single centered	14 days.	88	Morisky, Green, and Levine's (MGL) adherence scale.
Shoiab et al., 2018	Jordan	RCT, single-centered	14 days.	100	Morisky, pill count
Al-Eidan *et al.*, 2002	Northern Ireland	Prospective, RCT, single-centered	14 days	76	Pill count, a structured questioner
Chen *et al.*, 2020	China	Prospective, RCT, single-centered	14 days	196	Pill count
Stevens, Victor J *et al*; 2002	Portland	Prospective, RCT, single-centered	90 days	325	Structured questioner
Luo *et al.*, 2020	China	Prospective, RCT, single-centered	14 days	222	Morisky

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Table 2: Components of pharmacist interventions

Author, Year	Pharmacist intervention	Component of intervention	Control group description	Outcome measure	Result
Francis A, 2020	Pharmaceutical care service consists of a combination of written, oral information (face-to-face)	The patients will be counseled regarding drug administration, drug-related problems, and infection. They were also provided with written instructions in leaflets. Eighty-eight patients were analyzed.	Patients in the control group were given traditional instructions.	Adherence	Eighty-four patients had a good adherence of 95.5%, but the other 4.5% did not fully comply with the physician's order. After the first week of standard triple therapy, increased compliance to a mean score from 2.193±0.1301 to 3.5227±0.0704 in the second week. The medication adherence scores significantly increased along with patient counseling.
Shoiab AA, 2018	Pharmaceutical care service consists of a combination of written, and oral information (face-to-face and Weekly telephone-based follow-up)	Intervention patients received their medicine via the hospital pharmacy and were counseled (and follow-up) by the hospital pharmacist	Patients in the control group were given traditional instructions.	Adherence	A statistically significant ($P < 0.05$) association was found between Pharmacist counseling and medication adherence, and Pharmacist counseling was a good predictor for medication adherence.
Al-Eidan FA, 2002	Pharmaceutical care service consists of written and oral information (face-to-face) and Weekly telephone-based follow-up.	Intervention patients received their medicine via the hospital pharmacy and were counseled (and follow-up) by the hospital pharmacist	Patients in the control group were given traditional instructions.	Adherence	Intervention patients exhibited a statistically significant improvement in medication compliance (92.1% vs. 23.7%; $p<0.001$)
Chen Y,2021	Patient education by a clinical pharmacist (face-to-face, written information, and Weekly telephone-based follow-up).	The intervention patients received the details of the drug administration, and possible adverse effects were informed in detail before therapy, including the dosage, frequency, course of medications, and potential adverse effects, such as bitter taste and melena. Meanwhile, we set the reminder on days 3, 14, and 40 (3 days before the UBT) counted from the first day of treatment in the database's follow-up	Patients in the control group were given traditional instructions.	Adherence	Adherence was 96.9% (95/98) in the intensive follow-up group and 85.7% (84/98) in the control group. Semi-automatic intensive follow-up contributed to a higher eradication rate and adherence to H. pylori treatment.

		system.			
Luo M, 2020	Patient education by a clinical pharmacist (face-to-face, written information, and using WeChat, a social media platform, as a patient reminder tool	Patients in the intervention group received traditional instructions and patient reminders through WeChat.	Patients in the control group were given traditional instructions.	Adherence	Patients in the intervention group had significantly better disease-related knowledge, medication adherence, and H pylori eradication rates than those in the control group (P < .05).
Stevens VJ, 2002	Patient education by a clinical pharmacist (face-to-face and written information)	Intervention patients received longer adherence counseling sessions and a follow-up phone call from the pharmacist during drug treatment	Patients in the control group were given traditional instructions.	Adherence	additional counseling by pharmacists did not affect self-reported adherence to the treatment regimen, eradication rates, or dyspepsia symptoms but did increase patient satisfaction.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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