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A Pilot Study Evaluating the Impact of an Algorithm-Driven Protocol on Guideline-Concordant Antibiotic Prescribing in a Rural Primary Care Setting

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Abstract: Approximately 2.8 million cases of bacterial antimicrobial resistance (AMR) infections result in over 35,000 deaths annually in the U.S. AMR is driven largely by inappropriate prescribing of antibiotics, especially in clinics serving rural communities or underserved populations. Antibiotic Stewardship Programs (ASPs) improve prescribing practices, but many rural clinics lack fully functional ASPs. This pilot study evaluated the impact of an algorithm-driven protocol on antibiotic prescribing in a rural primary care setting. We conducted a pre–post quasi-experimental study at a Federally Qualified Health Center (FQHC), focusing on upper respiratory infections, urinary tract infections, and sexually transmitted infections. Eligible patients were enrolled in the study during their primary care visits. The primary outcome was the frequency of guideline-concordant treatment, analyzed using descriptive statistics and Chi-square tests. Among 201 patients (101 pre-intervention, 100 post-intervention), the pre-intervention group consisted of 77% females and 47% African Americans, while the post-intervention group consisted of 72% females and 46% African Americans. The intervention was associated with a 12.6% decrease in the number of antibiotic prescriptions discordant with clinical guidelines (37.6% to 25%) from the pre- to post-intervention periods. This corresponded to an odds ratio of 0.55 (95% CI: 0.30–1.01, $p = 0.054$). Although not statistically significant at $\alpha = 0.05$, this numerical decrease suggests potential benefits of algorithm-driven protocols in improving antibiotic stewardship in resource-limited settings. Longer study periods may further elucidate these benefits.

Keywords: antibiotic stewardship program; rural health; underserved population; antibiotics; pharmacy

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1. Introduction

Each year in the United States, approximately 2.8 million cases of antimicrobial-resistant bacterial infections result in over 35,000 deaths [1]. A significant driver of antimicrobial resistance (AMR) is the inappropriate prescribing of antibiotics, particularly in outpatient settings, where over 50% of prescriptions are deemed unnecessary or inappropriate [2–4]. This issue is especially pronounced in clinics serving rural or underserved populations [5,6].

Fortunately, antibiotic stewardship programs (ASPs) have been shown to significantly improve antibiotic prescribing [7–9], yet they remain largely absent in clinics serving rural communities or underserved populations. Despite the Centers for Disease Control and Prevention (CDC) recognizing inappropriate antibiotic prescribing as a significant issue in these communities—contributing to antimicrobial resistance (AMR) and *Clostridioides difficile* infections—the full extent of the problem remains inadequately understood [10]. A 2020 survey of Vizient member hospitals found that while 88% of inpatient institutions had functional ASPs, only 7% of ambulatory practices implemented them, most of which were in urban areas [11]. Given the limited healthcare access and resources in rural settings, the prevalence of ASPs in these communities is likely even lower. This gap highlights the urgent need for targeted strategies to curb antibiotic misuse and overuse in rural and underserved populations.

Several randomized controlled trials have demonstrated that strategies such as point-of-care testing, communication skills training, clinical decision support, and individualized audit-and-feedback for providers can effectively reduce unnecessary antibiotic use in primary care clinics [12–16]. However, these strategies often require substantial technical resources that may not be readily available or sustainable in resource-limited settings, such as clinics serving rural communities or underserved populations. Understanding these challenges is crucial to developing feasible and effective antimicrobial stewardship programs (ASPs) tailored to these environments.

To gain insight into the perspectives of both patients and clinicians regarding the implementation of ASPs in such settings, we conducted a survey study in a primary care center serving rural communities and underserved populations. The findings revealed that both patients and healthcare providers expressed openness to the integration of ASPs, highlighting a willingness to adopt stewardship initiatives despite existing resource constraints [17,18]. Furthermore, as part of this endeavor to improve antibiotic prescribing in resource-limited clinics, we evaluated the impact of integrating pharmacist-led medication therapy management with an ASP in a resource-limited clinic. The study revealed a 63.69% reduction in antibiotic prescriptions per 1000 patients over several weeks, suggesting that a pharmacist-led ASP is associated with a significant reduction in antibiotic use in a primary care center serving patients residing in rural or underserved communities. However, a limitation of the study is its pre–post design, which may limit the ability to establish causality [19].

Building on findings from our prior studies and acknowledging the resource constraints faced by rural clinics, we hypothesized that a low-tech approach—specifically, a simplified algorithm-driven antibiotic protocol—could effectively improve antibiotic prescribing practices in rural or underserved settings.

Thus, the objective of our pilot study was to evaluate the impact of an algorithm-driven protocol on antibiotic prescribing in a clinic serving rural or underserved communities.

2. Methods

2.1. Study Design

This was a pre–post, quasi-experimental study aimed at evaluating antibiotic prescribing practices in a rural healthcare setting. We developed and implemented an algorithm targeting the most prevalent infectious diseases observed in our Federally Qualified Health Center (FQHC): upper respiratory infections (URIs), urinary tract infections (UTIs), and sexually transmitted infections (STIs). Due to the significant challenges and ethical concerns associated with conducting randomized clinical trials in rural or underserved communities—particularly the ethical dilemmas of withholding potentially beneficial intervention from a control group in resource-limited settings—a pre–post design was chosen for this study to ensure

that all eligible participants had access to the intervention. This study was approved by the Florida A&M University Institutional Review Board (IRB).

Data collection for the pre-intervention period was conducted from November 2023 to January 2024, while the post-intervention period occurred from March 2024 to May 2024, coinciding with patient visits. To ensure that individual patients were not re-enrolled during multiple visits, the medical record numbers of all enrolled patients were documented for both the pre- and post-intervention periods. This approach maintained the integrity of the dataset by preventing duplicate entries.

2.2. Setting and Prior Intervention

The study was conducted at a major local healthcare clinic designated as a Federally Qualified Health Center (FQHC). These federally funded, nonprofit health centers serve medically underserved populations, providing care on a sliding fee scale based on financial need. In 2023, the clinic served 53,824 patients, accounting for approximately 120,818 medical visits. Of these, 56% were covered by Medicaid, 20% were uninsured, 16% had private insurance, and 7% were enrolled in Medicare.

The clinic collaborates with four community pharmacies, all of which participate in the 340B program, ensuring access to affordable medications. Additionally, these pharmacies offer pharmacist-led home health services accredited by the Accreditation Association for Ambulatory Health Care (AAAHC) and provide telehealth services. At the time of the study, the clinic lacked an established antibiotic stewardship program (ASP).

2.3. Intervention

The intervention consisted of educational sessions for all healthcare providers, focusing on antibiotic stewardship and the implications of antibiotic resistance, using guidelines and materials provided by the Centers for Disease Control and Prevention (CDC). This educational session was conducted by a pharmacy resident under the supervision of a clinical pharmacist. A simplified antibiotic prescribing algorithm was developed based on Infectious Diseases Society of America (IDSA) and CDC-recommended strategies for the management of URIs, UTIs, and STIs (see Supplementary Materials for the simplified algorithm). This algorithm emphasized appropriate dosing, frequency, and duration and was distributed to all providers to encourage adherence to evidence-based prescribing practices.

2.4. Study Population

The study included adult patients at least 18 years old who presented with symptoms consistent with infectious diseases, such as fever, cough, or dyspnea, and who were diagnosed by primary care providers with upper respiratory infections (URIs), urinary tract infections (UTIs), or sexually transmitted infections (STIs). Pediatric patients under the age of 18 were excluded from the analysis, although care was provided to these patients during the study period.

2.5. Enrollment

Patients who met the inclusion and exclusion criteria were identified during their primary care visits. During these clinic visits, a pharmacy resident informed eligible participants about the study at the time of enrollment and obtained verbal consent. However, patients were not informed whether they belonged to the pre-intervention or post-intervention group. Data were collected for both the pre- and post-intervention periods.

2.6. Outcomes

The primary outcome of the study was to evaluate the change in the proportion of patients receiving guideline-concordant antibiotic prescriptions before and after the

intervention. For this study, "guideline-concordant treatment" was defined as adherence to IDSA or CDC-recommended dosing strategies, including appropriate therapy duration, dosing frequency, and strength. Non-concordance was characterized by any deviations in these parameters. Diagnoses were further categorized into UTI, URI, and STI groups for analysis.

2.7. Data Collection

To assess the impact of the intervention, patient demographics, diagnoses, and prescription details were recorded in an Excel database. For each prescription, we documented the dose (strength), frequency, and duration. To further evaluate prescribing accuracy, prescription concordance was assessed in relation to patients' renal function and documented allergies. Data were collected during the pre- and post-intervention periods to evaluate changes in antibiotic prescribing patterns and identify potentially inappropriate prescriptions. Of note, in this study, neither the researchers nor the pharmacy resident assessed the accuracy of the diagnoses. Instead, all prescription evaluations were based solely on the diagnoses documented in the electronic health record by the prescribing clinician.

2.8. Statistical Analysis

To assess the impact of the intervention, antibiotic prescriptions for eligible patients during the post-intervention period were compared to those for eligible patients during the pre-intervention period. Descriptive statistics were reported as counts and percentages to summarize patient demographics at the time of their primary care visits. To assess whether the intervention was associated with a significant change in guideline-concordant antibiotic prescribing, a Chi-square test for independence was conducted. This test compared the proportions of guideline-concordant prescriptions between the pre- and post-intervention periods, as these groups were independent. The odds ratio and 95% confidence interval for potentially inappropriate antibiotic prescriptions will be reported comparing pre- and post-intervention periods. A priori, statistical significance was defined as $p < 0.05$ using a two-tailed test. This analysis was conducted with IBM SPSS Statistics version 29.0.2.0 (20).

3. Results

A total of 201 patients participated in this pilot study, with 101 patients in the pre-intervention group and 100 patients in the post-intervention group. Among those in the pre-intervention group, 77% of the participants were female, compared to 72% in the post-intervention group. Regarding racial demographics, 47% of the pre-intervention group identified as African American, and 41% identified as White. In the post-intervention group, 46% were African American, and 33% were White. Additional demographic details are presented in Table 1.

Following the intervention, the proportion of patients receiving potentially inaccurate antibiotic prescriptions—defined as deviations from guideline-concordant recommendations—decreased by 12.6%, from 37.6% in the pre-intervention group to 25.0% in the post-intervention group. Chi-square analysis indicated a numerical decrease approaching statistical significance ($\chi^2 = 3.72$, $p = 0.054$). The odds ratio (OR) from pre- to post-intervention periods was 0.55 (95% CI: 0.30–1.01). Table 2 presents all types of errors categorized by the type of infectious disease.

Table 1. Adult Study Participants Characteristics.

Demographics	Pre-Group (N = 101)	Post-Group (N = 100)
Gender		
Female	77 (76.2%)	72 (71.3%)
Male	24 (23.8%)	28 (27.7%)
Race/Ethnicity		
African American	47 (46.5%)	46 (45.5%)
White	41 (40.5%)	33 (32.7%)
Hawaiian	1 (1.0%)	2 (2.0%)
Hispanic	1 (1.0%)	3 (3.0%)
Alaskan	0 (0.0%)	1 (1.0%)
American Indian	0 (0.0%)	1 (1.0%)
Unknown	11 (11%)	14 (13.9%)
Age		
18–24	18 (17.8%)	23 (23.0%)
25–34	33 (32.7%)	27 (27.0%)
35–44	21 (20.8%)	16 (15.8%)
45–54	13 (12.9%)	18 (18.0%)
55–64	12 (11.9%)	12 (12.0%)
65 and older	4 (4.0%)	3 (3.0%)
Unknown	0 (0.0%)	1 (1.0%)
Insurance		
Private	33 (32.7%)	33 (32.7%)
Medicare	7 (7.0%)	7 (7.0%)
Medicaid	27 (27.0%)	27 (27.0%)
Uninsured	34 (33.7%)	34 (34.0%)
Diagnosis		
Chlamydia	12 (11.9%)	8 (8.0%)
Chlamydia/Trichomonas	1 (1.0%)	0 (0.0%)
Gonorrhea	7 (7.0%)	5 (5.0%)
Gonorrhea/Trichomonas	2 (2.0%)	1 (1.0%)
Trichomonas	17 (16.8%)	13 (13.0%)
Syphilis	3 (3.0%)	2 (2.0%)
Urinary Tract Infection	20 (19.8%)	16 (16.0%)
Pharyngitis	23 (22.8%)	24 (24.0%)
Sinusitis	16 (15.8%)	20 (20.0%)
Gonorrhea/Chlamydia	0 (0.0%)	2 (2.0%)
Gonorrhea/Chlamydia/Syphilis	0 (0.0%)	1 (1.0%)
Urinary Tract Infection/Trichomonas	0 (0.0%)	1 (1.0%)
Pharyngitis/Trichomonas	0 (0.0%)	1 (1.0%)
CAP	0 (0.0%)	2 (2.0%)
Upper Respiratory	0 (0.0%)	4 (4.0%)

Table 2. The number of patients with at least one prescription that is discordant with clinical guidelines—before and after intervention.

Type of Discrepancy	Pre-Intervention (N = 101)	Post-Intervention (N = 100)
All [Irrespective of diagnosis]	38 *	25 *
All—Duration	23	10
All—Wrong ABX	17	12
All—Strength	2	1
All—Frequency	2	1
All—ABX not recommended	9	6
UTI (All Patients)	19/20	4/17
UTI Duration	15/20	3/17
UTI Wrong ABX	4/20	2/17
UTI Strength	1/20	0/17
UTI Frequency	2/20	1/17
UTI ABX not recommended	0/20	0/17
URI (All Patients)	16/39	13/49
URI Duration	6/39	4/49
URI Wrong ABX	4/39	2/49
URI Strength	0/39	1/49
URI Frequency	0/39	0/49
URI ABX not recommended	7/39	6/49
STI (All Patients)	4/35	7/42
STI Duration	3/35	3/42
STI Wrong ABX	1/35	4/42
STI Strength	1/35	0/42
STI Frequency	0/35	0/42
STI ABX not recommended	1/35	0/42

Note: A single patient may have more than one type of prescription discrepancy. ABX: antibiotics. * (χ^2 = 3.72, OR 0.55 [95% CI: 0.30–1.01], p = 0.054).

4. Discussion

In this pilot study, we observed the potential benefits of implementing an algorithm-driven protocol to improve antibiotic prescribing in clinics with limited resources to fully adopt antimicrobial stewardship programs (ASP). Following the protocol's introduction, there was an improvement in guideline-concordant prescribing practices. Although the reduction in inappropriate prescriptions (12.6%) did not reach statistical significance during the study's short duration, the numerical decrease suggests that such interventions can positively influence prescribing behavior. In a similar study conducted in an urgent care setting, Lee et al. (2022) observed significant improvements after implementing outpatient antimicrobial stewardship guidelines [20]. Their intervention, which included provider education and pocket guides, increased guideline-concordant prescribing from 50% to 70% ($p < 0.001$) and reduced the duration of antibiotic prescriptions for UTIs from 7 days to 5 days ($p = 0.007$). These findings align with our hypothesis, suggesting that targeted interventions, even with minimal resources, can enhance antibiotic stewardship. Extending the duration of our study could provide a clearer understanding of the long-term benefits, but the observed results underscore the potential role of algorithm-driven protocols in improving prescribing practices in resource-limited settings.

While prescribing practices for urinary tract infections (UTIs) improved, discrepancies persisted in guideline adherence for upper respiratory infections (URIs) and sexually transmitted infections (STIs). These results suggest that while the intervention was beneficial for certain conditions, targeted, condition-specific strategies may be necessary to align prescribing practices with recommended guidelines across all infectious disease categories. The small sample size and short study duration likely limited our ability to fully observe the intervention's impact.

4.1. Implications for Public Health

Our study is significant as it contributes to the growing body of literature on antimicrobial stewardship in rural primary care settings. It also emphasizes the vital role primary care practices play in influencing the rate of AMR through their antibiotic prescribing practices. Yau et al. (2021), in their narrative review, collated evidence of the correlations between prescribing patterns in rural primary care centers and increased AMR. For instance, azithromycin use was associated with nasal carriage of *S. pneumoniae* and *S. aureus* strains resistant to macrolides [21–23]. Similarly, Hare et al. identified a dose–response relationship between azithromycin use and the carriage of macrolide-resistant *S. pneumoniae* and *S. aureus* [22]. Furthermore, Costelloe et al. emphasized this connection, demonstrating that multiple or prolonged antibiotic courses, particularly with amoxicillin and trimethoprim, are linked to higher AMR rates [21,24]. These findings underscore the urgent need for optimized antibiotic stewardship in rural primary care settings to reduce AMR and preserve the efficacy of treatments.

Implementing antibiotic stewardship programs (ASPs) in rural or underserved communities offers a valuable opportunity to reduce the spread of antibiotic-resistant organisms. Our experience provides a practical model for ASP implementation in resource-limited settings, demonstrating that even small-scale interventions can drive meaningful changes. With sustained efforts, we anticipate that this tailored approach will prove both sustainable and impactful in improving antimicrobial use in such settings.

4.2. Strengths and Limitations

The strength of our study lies in the use of evidence-based, algorithm-driven strategies tailored to the unique needs of a resource-limited clinic. However, our findings must be interpreted in light of the study's limitations, including the small sample size and short duration, which may have contributed to the lack of statistically significant differences observed, potentially leading to a type II error. These factors limit the generalizability of our results. Additionally, the inherent limitations of the pre–post study design, such as its inability to account for unmeasured confounding variables or external events that may have influenced outcomes during the study period, further impact the robustness of our findings. However, given the constraints of our setting, the pre–post design was the most practical choice to ensure inclusivity and avoid excluding individuals. Despite these limitations, our study provides meaningful insights for those aiming to implement and adapt ASPs in rural or resource-constrained environments, contributing to the broader understanding of effective strategies to address antimicrobial resistance in these settings.

4.3. Future Directions

In this study, we did not assess the appropriateness of antibiotic selection but focused solely on evaluating the concordance of prescribed antibiotics with clinical guidelines based on the documented diagnosis. Future studies will aim to evaluate the effect of the algorithm on the appropriateness of antibiotic selection. As we continue this study, we will further refine our intervention to improve antibiotic prescribing practices and document the number of providers who used the simplified algorithm in practice through survey.

We anticipate that as we extend the study's duration and increase the sample size, we will be able to more effectively evaluate the long-term outcomes and the sustainability of the intervention. Additionally, as this current study does not have a control group, future studies should consider conducting cluster analyses involving multiple rural clinics, with some clinics implementing an educational intervention (with the algorithm) while others serve as controls. Our overarching goal is to enhance the implementation and effectiveness of ASPs in resource-limited clinics.

5. Conclusions

This pilot study demonstrates the potential of algorithm-driven antibiotic stewardship protocols in rural and underserved settings. While the observed improvement in guideline-concordant prescribing practices was promising, further research with larger sample sizes and longer study periods is necessary to confirm these findings. Our experience underscores the importance of implementing ASPs tailored to the unique needs of resource-limited settings, with the potential to significantly impact antimicrobial resistance on a broader scale.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/pharmacy13010030/s1: simplified antibiotic prescribing algorithm.

Author Contributions: A.N.O.: Conceptualization, methodology, project administration, writing—original draft preparation, writing—review and editing; A.R.P.: investigation, data curation; S.S.: data curation, formal analysis, writing—review and editing; P.T.E.: formal analysis, writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The Florida Agricultural and Mechanical University Institutional Review Board has approved this study, and this submission has received Expedited Review based on applicable federal regulations. The initial approval date was 2 July 2019 (reference 052-19) and the subsequent approval date was on 10 January 2024, reference 105-23.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data will be made available upon reasonable request following the institutional applicable guidelines and approvals.

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Conflicts of Interest: The authors declare no conflicts of interest.

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Review

The Mentorship Blueprint: A Comprehensive Review for the Development of Programs in Pharmacy Education

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Abstract: Background: Mentorship has benefits for students and faculty, helping to support their professional development, connectedness, and career endeavors. While the value of mentorship programs is well documented in the literature, there is less practical guidance and few compiled resources to start a program. This paper reviews different mentorship practices in pharmacy education and provides a list of strategies to develop high-functioning mentorship programs or groups. **Methods:** A review of the literature was conducted through PubMed and other databases. If the titles and abstracts met the initial criteria for relevance to the topic, the complete article was reviewed in the context of the inclusion and exclusion criteria. Included articles focused on mentorship, mentorship programs, mentorship development, mentoring faculty or students, or mentoring in the workplace. **Results:** Twenty-three studies were included in the final review. Summaries and key points from the studies were reviewed and discussed. The advantages of mentorship programs include increased social connection, goal setting, and professional development. Challenges include increased time commitments and difficulty in determining objective markers of success. Critical components have been extracted from the literature, and key resources and templates have been provided to aid in mentorship program development. **Conclusions:** This review summarizes the pharmacy mentorship literature and provides user-friendly tables to quickly locate resources to build a mentorship program in pharmacy education.

Keywords: mentorship programs; pharmacy mentorship; student mentorship; faculty mentorship; mentorship resources

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1. Introduction

Mentorship has been defined as "a professional, working alliance in which individuals work together over time to support the personal and professional growth, development, and success of the relational partners through the provision of career and psychosocial support" [1]. Mentorship helps future generations of students and faculty to flourish in their profession. Studies have shown that effective mentorship results in growth for both students and faculty in their careers [2–4].

Supporting and developing quality employees through enhanced professional development is critical for institutions to perform at their peak. Offering this development through mentorship allows for learning in both directions (mentor to mentee and mentee to mentor) as both parties gain new perspectives from each other. While many studies are available that describe mentorship programs, a succinct summary and practical guide with examples to develop a full mentorship program would be beneficial [5].

Mentorship can be provided in a variety of formats and can range from personalized one-on-one mentorship to mentorship groups of various sizes with multiple mentors or mentees [6]. One-on-one mentorship can include random assignments in some programs, or the process could be highly personalized based on established relationships or the completion of personality assessments. In addition, mentorship offerings can range from in person to remote, and meetings can vary in terms of frequency based on the preferences of the mentor and mentee [7]. Generally, the mentor is a seasoned veteran who can help more junior colleagues in terms of career and life goals, although other mentorship models use a near-peer or layered learning approach where a more senior faculty/student or trainee mentors a junior faculty/student or trainee [8].

Individual mentor–mentee pairings (or dyads) have a long history and help to achieve goals with a simple design. Most research is focused on the mentor–mentee relationship; however, new formats of mentoring have appeared more frequently in the last few decades [1]. Group mentoring (or triad mentorship) provides multiple vantage points and perspectives for a mentee and allows a layered approach through multiple levels of mentorship. A triad approach allows for increased synergy and networking but can be difficult to schedule and may create competition or adverse relationship dynamics within the group [9].

In pharmacy education, mentorship typically occurs between new faculty and experienced faculty, between faculty and students, or through student-to-student peer mentoring. For example, faculty applying for tenure and/or promotion may leverage mentorship to help to develop goals and timelines to achieve their desired outcomes [6,10]. More experienced faculty also benefit from mentorship when moving into new leadership positions [6]. Offering mentorship support for faculty at all levels can help retention, as well as enhancing skills that lead to more productive teaching and research [6]. Indeed, previous research has shown an increase in scholarly activity and grant funding for faculty who received mentorship [6]. Mentorship programs also strengthen collegiality and positive cultures in the workplace [6], leading to enhanced relationships linked to positive well-being and career outcomes [11,12].

From a student perspective, mentorship offers opportunities to learn from pharmacists or others who are completing a pharmacy program. As mentioned before, mentorship can enhance well-being and provides an opportunity for students to network with faculty or their peers, which could improve their job prospects in the future. Some research has shown that mentorship increases communication, leadership, and professionalism, which are all important components of a student's development into a pharmacist [2,13]. Additionally, research suggests that mentorship can improve academic success [14].

From the institution perspective, declining enrollment at many colleges has made developing relationships with students especially important as a means to increase belonging and retention [15]. Successful mentorship models support social connection through peer-to-peer or faculty-to-student engagement [16–18] and serve as an opportunity to enhance retention through improved well-being and social connection.

Notwithstanding the benefits for individuals and institutions, developing a mentorship program can be daunting. Fortunately, a helpful checklist highlights the key features for the development of a faculty mentorship program [5]. We expand on this work by adding the literature on student mentorship programs and collating example templates and summary information [5]. In addition to reviewing the different mentorship practices in pharmacy education, this paper outlines evidence-based strategies to develop high-functioning mentorship programs for students and faculty.

2. Materials and Methods

A comprehensive literature review was conducted using Google Scholar, EBSCOhost (via the University of Findlay Library), and PubMed. These databases were selected for their extensive coverage of research across academic disciplines. The search terms utilized were mentoring, education, pharmacy, mentors, students, faculty, academic success, academic failure, mentorship, college, higher education, doctorate programs, mentorship program development, mentorship programs, academic achievement, and mentoring practices.

If the titles and abstracts met the initial criteria for relevance to the topic, the complete article was reviewed in the context of the inclusion and exclusion criteria. Specifically, the article had to include pharmacy-related information about mentorship, mentorship programs, mentorship development, mentoring faculty or students, or mentoring in the workplace. Articles were excluded if they included students in postgraduate PhD/residency/fellowship training, clinical settings, or mentorship in other disciplines besides pharmacy. No timeframe restrictions were used, and all duplicate articles were removed. Categorization was completed based on the article focus, and descriptive counts of the number of articles included in each category were determined.

3. Results

The initial search yielded 1630 articles, and 23 articles met the criteria for inclusion in the study—13 focused on student mentorship (Table 1) and 10 focused on faculty mentorship (Table 2). Setting goals and expectations was cited as an important recommendation when establishing relationships between mentors and mentees. Additionally, several studies identified concerns about the time commitment needed and the unsuccessful pairing of some mentors and mentees. Many of the student-focused studies showed benefits, either through improved performance or student satisfaction. Table 2 highlights the references and corresponding descriptions for faculty mentorship programs in pharmacy. Many studies indicated that faculty were satisfied with the program offerings, although logistical hurdles and scheduling served as barriers. Overall, most participants liked the social connection established. Defining expectations early in the process and offering training for mentors were viewed as important components of mentoring programs.

Table 1. Mentoring programs focused on students.

Mentoring Focus	Summary of Results	Key Takeaways
References that Evaluated Student Growth and Development		
Pharmacist-to-student mentorship Rahal et al. [2]	Clinical mentors helped students to develop communication and leadership skills, recognize career opportunities, manage challenges, implement theoretical knowledge, and interpret constructive feedback.	Students who experienced mentoring felt motivated to learn, inspired to follow their goals, and an improved sense of well-being.
Resident-to-student mentorship Nisly et al. [8]	Students rated their resident mentors as knowledgeable, stating that they provided valuable feedback.	This mentorship program allowed residents to enhance their mentorship abilities while students received feedback on their presentations (patient case scenarios).
Pharmacist-to-student mentorship Waghel et al. [13]	A practitioner-to-student mentoring program was well received. Discussions on interviewing and career stories were activities that were well received. Time limitations and scheduling were the most cited challenges.	Providing stories of career experiences from practitioners can be beneficial to students. This provides another avenue for experiential learning.

Table 1. *Cont.*

Mentoring Focus	Summary of Results	Key Takeaways
Lecturer-to-student mentorship Jegede et al. [14]	Mentor relationships with lecturers improved the academic performance, study habits, and self-confidence of students.	Mentorship with lecturers benefits students academically through role modeling and support.
Peer-to-peer student mentorship Raub et al. [19]	In one program, 77% of students felt that mentorship aided in their professional growth, and 76% of senior mentors believed that having a previous student mentor aided in becoming efficient mentors themselves.	A peer mentorship program may aid in student growth and development.
Peer-to-peer student mentorship Etzel et al. [20]	The majority of respondents (71%) thought that the program positively aided in the transition to pharmacy school, although no significant improvement in retention was found.	Mentorship programs may provide a benefit for students transitioning into pharmacy programs.
Faculty-to-student mentorship Lahiri et al. [21]	Both students and faculty perceived benefits from the structured faculty advising program—faculty felt more engaged and students felt more supported, resulting in a 30% improvement in advising satisfaction.	The majority of participants appreciated the value of the revised advising program and meeting opportunities to build relationships and long-term connections.
Peer-to-peer student mentorship Sin et al. [22]	The peer mentoring program improved satisfaction and engagement.	When students are effectively paired together in a mentoring program, it allows for growth personally, professionally, and academically.
Faculty-to-student mentorship Arya et al. [23]	Preceptor involvement can be critical to student development, especially in a mentorship role. It is important to provide feedback to students, as well as understand the expectations of the student and institution.	Students need feedback for growth. Setting goals and expectations can help both the mentor and mentee to grow as part of mentorship.
Peer-to-peer student mentorship Brown et al. [24]	In this program, 74% of the mentees and 64% of the mentors had a positive experience.	Pairing students based on gender and similar hobbies can help a mentorship program to succeed.
References that Focused on Developing a Mentorship Program		
Peer-to-peer student mentorship Asal et al. [16]	This study highlights several elements of mentorship based on 3 separate programs at colleges of pharmacy. Major elements found were selecting mentors and mentees based on surveys and providing mentorship coaching and support.	Mentor support is needed to help facilitate successful pairings. Utilizing surveys to find good matching between individuals is helpful.
Faculty-to-student mentorship Rowe et al. [18]	More students than faculty mentors (86% to 62%). benefitted from a mentorship program focused on setting goals, fostering resilience, and career exploration. Ineffective matching of mentor–mentee pairs and communication were cited as challenges.	Shared goal setting is key to developing successful faculty–student relationships in mentorship programs.
Faculty-to-student mentorship Witry et al. [25]	Focus groups identified that mentees held high expectations for the mentors (engaged, similar interests, etc.), even though time constraints hindered these interactions.	Establishing expectations for mentors and mentees is critical for the success of the program.

Table 2. Mentoring programs focused on faculty.

Author	Results	Discussion
Faculty-Focused References—Faculty Development		
Eiland et al. [3]	In a team-mentoring program for junior faculty, 94% of mentees found the teams helpful, and 90% requested no changes to their mentor team. Importantly, 75% of participants stated that the mentorship approach helped them to achieve a promotion.	The top areas in which junior faculty stated that they improved with assistance from the mentor teams were APPEs (clinical teaching), promotion, and scholarship.
Hennessey et al. [26]	A mentoring program designed to help faculty to become course coordinators led to a higher mean course grade and student evaluation scores compared to the prior five years.	This program allowed for a quicker and easier transition for faculty to become course coordinators.
Eiland et al. [27]	Most participants were satisfied with a mentorship program organized by a professional organization (AACP). Career goal development, work/life integration, and difficult work situations were the most frequently discussed topics.	This nationwide mentoring program for pharmacy faculty allowed mentees to address areas such as career development and research. A unique feature was utilizing a professional organization as a platform for mentorship, rather than home institutions.
Jackevicius et al. [28]	In one program, 96.4% of faculty felt that mentorship developed their abilities and aided in their success as faculty.	The majority of mentors provided insights into time management, what to prioritize, and how to create work/life balance.
References Focused on Development of Faculty Mentorship Programs		
Metzger et al. [4]	In this program, an overview of mentor characteristics helped participants to understand the matching process and expectations. Assessment examples were provided to evaluate mentees, mentors, and the overall program.	In creating a new faculty mentorship program, an institution must consider its mission, resources (from a cost and workload perspective), and size.
Law et al. [5]	Checklists help to form a structured mentorship approach and may include aspects such as mentorship pairing, training, resources, and evaluation.	Successful mentoring requires flexibility, mentor training, and regular assessment.
Biehle et al. [17]	The women involved in a peer mentoring circle enjoyed the group, finding support, mentorship, and a safe sounding board to discuss issues related to their professional lives. The circle created topic lists for each monthly meeting. Challenges included scheduling, time commitments, online format logistics, and efforts needed to develop trust.	Recommendations for the creation of a peer mentoring circle included having gender-exclusive circles, selecting members from different institutions, establishing trust in the circle, and allowing mentees to specify the topics and their needs.
Kinney et al. [29]	One study found high percentages of satisfaction for mentees (80%) and mentors (86%).	There is no single method of structuring a mentorship program. Some qualities of a successful program included clearly defined goals, defined program outcomes, and the support of the organizing institution.
Shields et al. [30]	A review of AACP affinity groups found that a focus on both mentor and mentee needs is critical for success. Mentorship connections provide sources of support and empathy. Preferences in matching were also used.	Mentor programs often fall short in creating a foundation of trust and authenticity in the matched pair if they do not account for the needs and goals of the mentee (e.g., help with promotion, job responsibilities, work/life balance, etc.). Setting expectations, training mentors and mentees, and aligning goals are critical for success.
Minshew et al. [31]	In this program, strengths included the structure and relationships developed. Challenges included time and mentor–mentee matching, even though the 2014 Pairs checklist [5] was utilized.	The program strengths coincided with the AACP Joint Council Task Force on Mentoring recommendations. Resources must be provided to ensure a successful program, particularly incentives for the mentors, such as protected time or stipends.

4. Discussion

Mentoring confers several benefits to its participants, including enhanced professional skills, structured networking, and improved markers of achievement [16]. Indeed, Jackevicius et al. reported that 96.4% of mentees felt that a mentorship program aided in their success as a faculty member [28]. Additionally, 86% of students in one study found mentorship beneficial [18], although other studies did not reach this level of agreement. Many articles support the idea of mentorship to combat social isolation, although challenges should also be considered when developing a new program and recruiting mentors and mentees (Table 3).

Table 3. Advantages and challenges with mentorship programs.

Advantages	Challenges
Improved markers of success (promotion, etc.) [3,6,10]	Time commitment and scheduling [31]
Professional development for all participants [2,13]	Mismatched goals, expectations, or personalities [32]
Possible increased retention of both students and faculty through increased relationship building [33]	Mentoring skills take time to develop [34]
Improved well-being and social connection [16–18,33]	Markers for success may be difficult to measure

Table 4 highlights the critical components and key themes identified in our review, including (1) formal training for mentors (2) the need for authentic communication and engagement through setting clear goals and expectations, (3) the careful selection of teams, and (4) appropriate input from institutional stakeholders to tailor the mentorship program design. Since mentors are less likely to perceive a benefit from the relationship [18], it is especially critical to highlight the value of serving in this role and the opportunity to serve others and learn something new. Additional financial or time incentives may also be helpful [31]. Mentees, on the other hand, are more likely to recognize mentorship as an opportunity to grow professionally and improve their chances for career success. To maximize the mentorship process, it is imperative to thoughtfully match the mentors and mentees to align their personalities and communication preferences. Goal setting is also important at the mentor and mentee level to ensure that expectations are aligned and progress is made. Mentorship teams should take time to write down shared goals and regularly evaluate them to stay on track. Several resources mentioned an additional program component—the necessity to train mentors so that they are well prepared to guide mentees and offer support. This training could take several forms, from informal to formal, but some training or resource guide is essential to support mentors and establish clear expectations for their role [4,5,17]. When starting a mentorship program, institutional leaders should consider the end goals of the program and establish appropriate metrics for the evaluation of success [30]. Table 4 lists example resource kits to help to train mentors, set expectations, and choose the best mentorship style for a program [4,5].

Table 4. Critical components and example resources for mentorship programs.

Critical Component	Guidance and Resources
Define characteristics of the mentorship program [31,35] See the references below for example mentoring programs: Reference [31] Reference [35]	• Define group size or one-on-one mentoring (see reference [35] for menu of options) • Secure stipends or protected time to incentivize mentors (see reference [31])

Table 4. *Cont.*

Critical Component	Guidance and Resources
Carefully select mentorship pairings or teams Consider a survey to match individuals [16,18,36–38] See the references below for example surveys and worksheets to help in selecting mentor-mentee pairs: Reference [18] Reference [36] Reference [37] Reference [38]	- Incorporate assessments of personality types or communication styles to ensure better matching. Provide templates to optimally match the goals and passions of both mentors and mentees. Templates in the literature include the following • Surveys to match mentors and mentees (see reference [36]); • Mentor and mentee self-assessments (see references [37,38]).
Provide training to mentors and mentees [5,16,30,31,39–44] See the references below: Reference [39] Reference [40] Reference [41] Reference [42] Reference [43] Reference [44]	- Provide a guidebook and training at the beginning of the mentorship program (see references [39–44] for examples) - Provide articles focused on mentorship, including the following: • Example questions to start the process of mentorship (see reference [40]); • A list of tips for effective mentorship (see references [39,42]).
Set goals at beginning of program to establish expectations [4,30,45–49] See the references below for examples of expectation and goal setting documents: Reference [46] Reference [47] Reference [48]	- Program level goals should include intended outcomes and an evaluation plan (see references [46–48] for example SMART Goals) - Mentoring pairs or teams should ensure the following: • Communicate on the frequency of meetings and any special scheduling needs; • Develop a list of topics for discussion throughout the program (see reference [47]); • Set an agenda for each meeting; • Establish SMART goals for intended outcomes and agree on measurements for success (see reference [48]).

4.1. Practical Application

Establishing a new mentorship program can be a large task, but taking time to reflect on the intended mission and key aspects of the program while learning from the experiences of others may increase the likelihood of success [34]. As outlined in Table 4, the collective literature on pharmacy mentorship programs suggests the following features. First, determine the purpose of the program and define the structure and participants. Evidence is conflicting regarding whether one-on-one or group mentoring is most effective, which leaves flexibility for the institution to meet the needs and preferences of the stakeholders [1].

The next critical step is to invite participants and implement a survey to assess the specific goals and outcomes desired by these participants. Determining who will participate in the mentorship program and how they will be selected is an important step, and the literature suggests that taking the time to understand what each individual is hoping to achieve will result in higher rates of program success [30]. Some research also supports stipends, protected time, or other incentives to encourage active mentor involvement [31]. Programs can assess additional factors like personality types and communication styles through surveys, as highlighted in Table 4. These available tools could be modified to meet institution-specific needs. During this step, it is also critical to train mentors and mentees and set shared expectations for communication and the overall program (see Table 4 for examples of goal setting documents and training) [5,16,30].

Finally, the developers of a mentorship program should formally evaluate its effectiveness and assess whether programmatic and individual goals were met. Participants

should be surveyed on their perceptions of the program and what quality improvements should be made for future iterations. Defined metrics for evaluation that align with the goals of both the mentors and mentees are important to ensure satisfaction. Some relevant metrics identified in the literature include career advancement, satisfaction with the overall mentorship, the quality of the relationship, progress in building resilience, the number and quality of activities performed, retention, and the achievement of the stated personalized goals [4,5,13,18,20]. Additional markers for success may include how well an individual adjusts to a new institution or leadership position [26]. This could be measured by how quickly they become independent in their new role [26]. The consistent use of formal surveys and evaluation tools also allows for data comparison to evaluate changes and successes over multiple iterations of the program [4].

Several barriers exist when starting a mentorship program, including the most obvious—the significant time commitment for mentors but also mentees [13]. Some strategies may mitigate this to an extent, such as creating agendas for each meeting to maintain focus and matching mentorship teams with similar preferences regarding meeting times and frequencies. Using technology like meeting scheduler tools or remote conferencing platforms to help with the scheduling logistics can also be beneficial [17]. This challenge also further supports the recommendation to provide incentives for mentor involvement [31].

4.2. Limitations

This review and blueprint for mentorship programs possesses several notable limitations. First, we limited the eligibility to the pharmacy education literature, which excluded results from valuable mentorship programs in other fields.

Second, having tangible end products or markers can be difficult to measure with mentoring activities. Therefore, it is important to evaluate programmatic goals after each program offering to ensure that mentorship programs fulfil their purpose [18,29]. This is especially useful if a concrete marker like a faculty promotion or student postgraduate placement is not relevant.

4.3. Key Takeaways

- Mentorship supports connectedness and professional growth for both mentees and mentors.
- Critical factors like setting goals, providing training, choosing teams thoughtfully, and assessing the effectiveness of mentorship relationships are all important in providing a quality mentorship program.
- Challenges in implementing a mentorship program include time commitments, scheduling, poor communication between mentors and mentees, and mismatched goals.
- Many resources and templates already exist to support mentorship program development.

5. Conclusions

This paper provides an in-depth review of both student- and faculty-centered mentorship programs in pharmacy education. Mentorship improves satisfaction and career advancement, especially when the mentoring program is supported by structured training and expectation/goal setting. This review summarizes the pharmacy mentorship literature and provides a list of resources to help to build a quality mentorship program for students or faculty.

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Project Report

Experiences in a Clinical Innovation Pharmacy Fellowship: A Novel Model of Ambulatory Care Training and Practice Advancement

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Abstract: The University of Utah Clinical Innovation Fellowship models novel partnerships between third-party payers, clinical practices, and academia. While healthcare costs continue to increase unabated and physician burnout leads to provider shortages, this fellowship focuses on both crises by training pharmacists to establish new practices in ambulatory clinic spaces using funding provided by third-party payers. Not only does this fellowship represent a future in which pharmacists are able to address third-party payers' need to reduce healthcare costs and clinics' need to address provider shortages, it also successfully trained fellows to pursue jobs in ambulatory care and academia. Payers, clinics, providers and patients all expressed a high degree of satisfaction with the work of the fellows. In multiple clinics where fellows established new pharmacy services, those services led directly to new job approvals funded by the clinics themselves. The purpose of this paper is to serve as a model by which fellowship programs elsewhere can be designed, as well as to show that partnerships between ambulatory clinics, payers, and pharmacists are both sustainable and beneficial to all parties including, most importantly, the patients who receive better care for their complex chronic disease states. While this paper is descriptive in nature, work is ongoing to objectively measure the impact of the fellows on patients, providers, and third-party payers. A sampling of outcomes is presented, describing the impact of the pharmacist fellows' efforts to improve medication management in primary care. Even with limited objective measures of success, we are able conclude that over the past 3 years, the fellowship has accomplished its aim of preparing fellows for future roles in ambulatory care, practice design, and academia while also demonstrating that a funding model aligning payers, clinics, and academia is sustainable.

Keywords: ambulatory care; fellowship; leadership; practice development

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1. Introduction

In response to the growing crises of physician shortages and escalating healthcare costs [1–3], and in an effort to advance practice within the state, faculty at the University of Utah College of Pharmacy created the Clinical Innovation Fellowship. It is already known that pharmacists integrated in the primary care setting can reduce provider burnout by sharing the workload, improving providers' ability to prescribe medications for chronic

diseases, increasing patients' capacity to meet health goals, and improving the overall management of patients [4]. In this way, it was hypothesized that the creation of the Clinical Innovation Fellowship at the University of Utah would meet the needs of and provide proactive solutions for healthcare systems and primary care providers at a critical junction between payers, health systems, and a college of pharmacy. Additionally, it was hypothesized that the creation of the fellowship could also create a novel path of continued training for postgraduate year 1 (PGY1) trained pharmacist trainees. Organizations like the American College of Clinical Pharmacy (ACCP) recognize the need for more specially trained pharmacists that provide high-quality patient care, along with the challenges of expanding pharmacy residency programs to train more of these pharmacists [5,6]. As more pharmacists pursue specialty training [7], there is a need to create novel training methods, such as this fellowship, to meet this demand.

This fellowship is designed to create solutions to these problems by establishing sustainable pharmacy services in an ambulatory care setting. A pharmacist in this fellowship role serves as a connection between patients, their providers, and the payer. By serving all three parties, a pharmacist is uniquely positioned to impact the quality and cost of healthcare, all while supporting providers who are overburdened and burnt out. Further, pharmacists are provided with the skills needed to advance pharmacy practice throughout their careers by completing the fellowship. This paper describes the development of the Clinical Innovation Fellowship by the University of Utah and provides a template for others to develop their own programs.

2. Materials and Methods

2.1. Program Description

The Clinical Innovation Fellowship has three primary objectives: (1) establish ambulatory care pharmacy services at a large multi-specialty clinic and through this gain experience in ambulatory care pharmacy and practice development/innovation, (2) determine/describe the value of pharmacy services in the ambulatory care setting by collecting data before and during the implementation of comprehensive medication management (CMM), and (3) gain competence in the four pillars of academia including scholarship, ambulatory care practice, professional service, and teaching. The fellowship is designed as a one-year training program for an individual who has completed a PGY1 residency and has experience in the ambulatory care setting. Founded in 2020, this fellowship includes one fellow position per year and involves partnerships with the University of Utah College of Pharmacy, third-party payers, and private practice sectors to provide innovative ambulatory care pharmacist services in novel settings. While similar residencies or fellowships have been developed [8], this is the first that we are aware of that involves a relationship with third-party payers. By involving payers, this fellowship differentiates itself from other programs via its ability to create sustainable pharmacist positions that generate revenue for clinics using payer funds. The fellow, in turn, gains valuable skills in practice by developing pharmacy services in new arenas to advance the profession. While "fellowship" is a broad term used to describe various pharmacy practice and research programs, a fellowship provides the flexibility needed for the novel collaboration between a payer, private clinics, and a college of pharmacy. The fellowship directors designed a series of suggested objectives for the program, with the flexibility to adjust these based on the fellow's areas of interest.

2.2. Fellowship Design

While the fellowship was designed to be flexible to meet the individual fellow's professional goals and interests, the fellow must meet the objectives of the fellowship to graduate. These objectives are organized into five domains: Practice, Scholarship, Teaching,

Service, and Professional Development. Specific activities the fellow could expect to participate in were then assigned to each domain, creating a well-rounded experience that prepares the fellow for a variety of career paths in pharmacy practice and academia. Table 1 gives an overview of the expected activities required to graduate from the fellowship and a more detailed list of activities completed by each resident can be found in Appendix A (Table A1).

Table 1. Overview of activities required for fellowship graduation.

Domain	Requirement
Practice	Clinical skills enhancement in established practice experience (1 day/week)
	Clinical practice development at new site (3 days/week)
Scholarship	Submit 1 grant proposal
	Conduct 1 primary research project, concluding with poster and manuscript submission
	Give 1 state-level CE presentation
	1 CoP presentation on research project(s) to faculty/staff
	Submit 2 presentation for consideration at national conferences
	Submit 3 different manuscripts, which could include: • Primary fellowship project • Project in collaboration with other faculty • Smaller-scale project in collaboration with other pharmacy learners (e.g., help mentor PGY1 or pharmacy student research project)
Teaching	Serve as a coursemaster for a class or specific class module
	Serve as facilitator for weekly small-group classroom sessions for pharmacy students for 1 semester
	Give 3 lectures to pharmacy students
	Precept and plan rotation experiences for pharmacy students at established practice site
Service	Formal membership on a CoP committee (e.g., Curriculum Committee)
	Other optional tasks • State organization committee involvement • National organization committee involvement • Volunteering as a preceptor at a student-run free clinic • Student organization precepting
Professional development	Participate in 2 meaningful development programs that correspond to one of the 4 pillars of academia. Examples include: • Professional teaching seminar • Enrolled in graduate-level course on biostatistics • Enrolled in graduate-level course on teaching in higher education • Institutional professional development courses • Institutional leadership courses • CoP grant-writing workshops • Attend 1 national conference
	Leadership discussions with fellowship directors

Abbreviations: CE = Continuing Education, CoP = College of Pharmacy.

2.3. Practice Experience

To accomplish the above, fellows were placed at a primary care practice that had not had pharmacists before. The primary care sites chosen were staffed by a multidisciplinary team including a physician, advanced practice clinicians such as the physician's assistants and nurse practitioners, as well as medical residents and medical students. These clinicians were trained in various fields including internal medicine, pediatrics, family medicine, and internal medicine/pediatrics. The fellow's role throughout the fellowship would be to establish pharmacist services in that environment. Before establishing a new practice, the fellow worked at a University of Utah primary care clinic, which already had established pharmacist services. This clinic served as a model upon which the fellow could base their own practice. After a sufficient onboarding period at the clinic, flexible to the needs of the fellow, they would begin spending 3 days per week establishing their new clinical practice. To continue to develop clinical skills and gain experience in a successful practice, the fellow would continue to serve as the pharmacist at the University clinic once per week. This clinical time also allowed the fellow to experience a layered learning model, as this clinic frequently hosted both medical and pharmacy learners.

2.4. Other Learning Domains

One day per week, the fellow completed various projects aligned with their interest areas that fulfilled the fellowship's objectives. This day is referred to as an "academic day" and was utilized in whatever way best served the productivity of the fellow. Unlike residencies, additional weekend/evening staffing was not included in the fellowship. Figure 1 shows an example of the weekly design of activities.

Monday	Tuesday	Wednesday	Thursday	Friday
Clinical Practice Development	Clinical Practice Development	Academic Day	Clinical Practice Development	Longitudinal Practice Experience

Figure 1. Weekly schedule of the day-to-day activities of the fellow.

2.5. Fellowship Oversight

The fellowship directors, both of whom have a combined 18 years of practice development and academic experience, served as coaches and mentors to the fellows as they established their new practices. They also created tailored learning experiences in the other fellowship domains based on the interests of the fellow. A shared administrative model for the two directors was created in order to leverage the strengths, interests and relationships of each director. Directors engaged the fellow in mentoring meetings every other week and practice site visits at least twice throughout the year. Additional meetings could be accommodated at the request of the fellow or fellowship directors as needed. Because the two fellowship directors shared a primary care practice site at the University of Utah, the oversight of this longitudinal practice was split between the directors. Once a quarter, a more formal evaluation was conducted between both directors and the fellow to discuss in, greater detail, the achievements, progress, and opportunities for growth/improvement in the fellowship.

2.6. Program Funding

The funding for the fellowship position, housed within the College of Pharmacy, was a 50–50 model between the school and the payer. This way, the College of Pharmacy would bear the responsibility of hiring, paying and performing various human resource functions for the fellow each year while the payer, in addition to providing 50% of the

funding, could focus on identifying and providing the fellow with lists of patients most in need of pharmacy services. In this agreement, the payer recognized the benefit of implementing a clinical pharmacist in their primary care practice and received this benefit at a discounted rate as they provided only part of the position's funding and the fellow's salary was less than that of a clinical pharmacist post-training. Ultimately, the payers were investing in a strategy that was improving patient care for at-need populations. However, all stakeholders recognized that an improvement in financial and clinical outcomes likely could not be observed in the scope of a 1-year fellowship due to the nature of the training program. The selection of the payer partner was based on long-standing relationships and the interest of each payer's leaders. Fellowship directors also negotiated a practice site that had a high percentage of patients covered by the third-party payer, with a particular focus on private practices not affiliated with major health systems. Ultimately, practice sites interested and engaged in value-based models became the ideal sites for fellows to develop pharmacy services. Additionally, the fellow provided a unique contribution to teaching, precepting, and scholarship for the College of Pharmacy. No funding was provided by the clinic where the fellow was placed to establish pharmacist services; however, the clinic played a critical role by serving as a pilot site.

2.7. Fellowship Assessment

The outcomes of the fellowship were based on the interest of the individual fellow, their ability to gather data, and the abilities and interests of the practice site and payer. The goal of the fellowship was to create added value for all parties and evolved from year to year through a process of collaboration and continuous program improvement. For this reason, samples of a variety of the outcomes describing the impact that the participating fellows had on their clinical practice locations and the career success they have enjoyed post-fellowship will be presented in this paper. Some outcomes that will be discussed include the medication therapy problems (MTPs) identified by the Pharmacy Quality Alliance (PQA), provider satisfaction, patient satisfaction, practice site sustainability, and fellow job placement upon graduation.

The PQA criteria for MTPs were used in order to promote the consistent categorization and coding of MTPs and the related actions to resolve the MTPs [9]. The framework builds upon categorizing each actionable MTP into one of four categories of MTPs (in order of preference; I = Indication, E = Effectiveness, S = Safety, and A = Adherence). Then, an intervention (Outcome) is associated with each MTP. If multiple MTPs were identified for a single drug, only the highest level/preference MTP was coded.

Patient and provider satisfaction were measured after one year of the fellowship via a validated survey and qualitative assessment of provider interviews. The specific methodology and results of this study have been published previously [10]. Provider satisfaction was determined via interviews, similar to the method used by Funk et al. [11]. Meanwhile, patient satisfaction was assessed via a validated patient satisfaction survey developed and validated by Moon et al. [12].

Practice site sustainability was measured based on whether the pharmacist position started by the fellow was supported, formally created, and funded beyond the duration of the fellowship. This was tracked in order to show value to the payer and practice site, and to measure whether the pharmacy practice could grow and be sustained in private practice.

The job placement of the graduating fellow was measured in terms of whether the graduating fellow found employment upon graduation. This was tracked in order to show that this unique training model could result in trainees that are qualified, in a competitive market, for jobs in ambulatory care pharmacy.

3. Results

At the time of publication, three fellows have successfully graduated from the fellowship program over the three years it has been offered. All three fellows had already completed a PGY1 residency, although each entered the fellowship with different residency experiences.

In one academic year of the fellowship, a fellow identified 1106 individual MTPs. In order of priority, Indication made up 79 (7%) of the MTPs, with 21 (2%) attributable to "unnecessary drug therapy" and 58 (5%) attributable to "needs additional medication therapy". Effectiveness made up at least 9% of the MTPS, with 98 (9%) attributable to "effectiveness". Similarly, Safety made up at least 10% of the MTPS, with 112 (10%) attributable to "adverse medication event". The majority of the MTPs identified fall into the final category of Adherence, with 443 (40%) related to "adherence" and 176 (16%) related to "cost". Regrettably, 198 (18%) MTPs were unable to be coded due to there not being enough detail in the tracking mechanism. The tracking of MTPs also reflects the growth of the fellow as a pharmacist over the course of the fellowship, with an individual fellow documenting 20 MTPs during the first month at the practice site and 163 MTPs in the final month.

Previously published findings showed that the fellow, as an embedded clinical pharmacist providing comprehensive medication management (CMM) at a private primary care clinic, had a positive impact on both provider and patient satisfactions [9].

The fellowship was able to meaningfully advance the practice of pharmacy locally after the first year of the program, resulting in a full-time pharmacist position being fully funded by the clinic. Two of the three fellowship positions resulted in full-time pharmacist positions being created to fill the role being left by the fellow upon graduation. During their fellowship, the individuals delivered a high level of patient care through the use of collaborative practice agreements, allowing them to manage chronic disease states requiring considerable amounts of provider follow-up, such as diabetes and hypertension. Based on the fact that positions were created for these pharmacists upon fellowship completion, they provided significant value to the practice site that was worthy of funding the role of a full-time pharmacist.

All of the fellows were employed as full-time ambulatory care pharmacists, practicing in primary care, immediately after graduating from the fellowship. One of the fellows was hired at a private clinic, while the other two fellows were hired at academic medical centers, directly competing with postgraduate year 2 (PGY2) trained pharmacists for their positions. Upon graduation, in addition to competing in a highly competitive local ambulatory care pharmacist job market, the fellows were uniquely qualified for these positions through the development experiences they likely would not have experienced through traditional pharmacy residencies.

4. Discussion

The strengths of the experience include the novel funding mechanism that requires buy-in from payers, which is a more financially feasible model of funding pharmacist positions than positions funded entirely by a clinic, given the low to non-existent revenue that a pharmacist historically generates. In addition to providing a unique experience via the establishment of new pharmacist services, the fellowship also provided training for fellows that enabled them to compete with other pharmacists trained in ambulatory care for jobs within a clinic. The most similar type of learning environment to this fellowship is a PGY2 ambulatory care pharmacy residency. When compared to a PGY2 ambulatory care residency program, this fellowship has some distinct advantages and disadvantages. The advantages include a greater ability to customize experiences to the individual fellow's

interest, a greater focus on research and academia than a residency allows, and the enhanced independence of the fellow in gaining experience and initiating pharmacy services in a novel setting. The disadvantages include a lack of a formal accreditation, which may be viewed negatively by potential employers, a reduced focus on precepted clinical training, and the challenge of integrating a non-traditional learner into a health-system that is organized around resident learners (e.g., preceptor schedules, co-resident socializing, etc).

The fellowship also provided significant exposure to academia. At the time of submission, one fellow is employed by a Physician Assistant program at a School of Medicine teaching pharmacotherapy and leading the development of new student-run clinics. Upon hire, the hiring faculty specifically cited the experience the fellow gained within the College of Pharmacy, as well as their experience teaching, publishing, grant-writing, and serving on various committees, as making them a qualified and desirable candidate for the position. Another fellow is an adjunct faculty member at a College of Pharmacy, which they attribute directly to their academia experience within the fellowship program.

Finally, the payers and value-based companies involved in the funding of the fellowship also benefited from the better management of their most costly patients, further showing that our novel funding model is a mechanism by which pharmacists moving forward may fill a significant gap in our healthcare delivery system.

There are some weaknesses in this evaluation of the fellowship program. Most notably, we do not have specific data to report regarding patient/provider satisfaction (other than that which is already published [10]), its impact on healthcare costs from the payer perspective, or an objective measure of the reduced burden on primary care providers by adding clinical pharmacy support. While this is a significant limitation in the evaluation of this fellowship, there are some key findings that signal satisfaction from the parties involved. The Clinical Innovation Fellowship still maintains a high level of investment among the funders (payers and the College of Pharmacy), and the work of the fellows led to the creation of new pharmacist positions funded by the clinics they were placed in, signaling support from clinic leadership as well. While these subjective measures indicate that this fellowship was a successful endeavor, future evaluations of the fellowship will focus on data collection over a longer period of time, using objective measures, to justify its existence. Specifically, in addition to patient and provider satisfaction and a quantitative analysis of the fellows' work, future iterations could focus on reducing the number of provider visits and other objective drivers of primary care provider (PCP) burnout.

5. Conclusions

The Clinical Innovation Fellowship was developed to explore the novel relationship between pharmacists in primary care, colleges of pharmacy, and insurance payers to create sustainable solutions that justify the cost of their services and improve access to safe and effective medication use. The fellows effectively identified and managed medication therapy problems, had a positive impact on both patient and provider satisfaction, created jobs for ambulatory care pharmacists, and trained additional pharmacists that were qualified for the same roles as traditionally PGY2 trained pharmacists.

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Appendix A

Table A1. Elements of the fellowship completed by each individual fellow.

Domains and Experiences	Fellow 1	Fellow 2	Fellow 3
Practice	• University of Utah Primary Care • Granger Medical Clinic	• University of Utah Primary Care • Granger Medical Clinic	• University of Utah Primary Care • Intermountain Health Primary Care
Scholarship	• 1 Grant submission • State level CE presentation • CoP presentation on research project • National Presentation • National Presentation and Preceptor's Conference abstracts submission • 1 Article published • 1 Manuscript published	• 1 Grant submission • 2 State level CE presentation • CoP presentation on research project • National presentation submission • Primary project (Granger) • Tenure/Research Faculty project • Smaller-scale project(s)	• State level CE presentation • CoP presentation on research project • Poster Presentation at a national meeting • 1 Manuscript: Pending
Teaching	• Integrated therapeutics lecture at college of pharmacy • Recitation facilitator • Delivered 5-6 CoP Pharmacy lectures Precepted 9 APPE students and 2 PGY1 residents	• Recitation Facilitator • Foundations of Patient Centered Care CoP lecture • Advanced therapeutics debrief • Community Practice CoP lecture • Skills Lab precepting • Precepted Students and PGY1 residents	• Co-coursemaster elective at Utah College of Pharmacy • Foundations of Patient Centered Care CoP lecture • Skills lab precepting • Integrated therapeutics lecture CoP lecture • Recitation facilitator at CoP • Precepted Students and PGY1 residents
Service	• CoP Assessment committee • Local organization Board • National Committee Research Committee	• CoP Admissions Committee • Precepting at local student run clinic	• CoP Curriculum Committee • Precepting at local student run clinic

Table A1. *Cont.*

Domains and Experiences	Fellow 1	Fellow 2	Fellow 3
Professional Development	• Attended 2 national meetings • Attended 1 national webinar series • Completed 1 national Teaching seminar	• Completed 1 national teaching seminar • University of Utah Trainer Essentials Course • Completed a Biostats course	• University of Utah Trainer Essentials Course • Attend 1 national meeting • Completed a Teaching in Higher Education Course

Abbreviations: CoP = College of Pharmacy.

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Development of Chronic Kidney Disease Screening Integrative Care Model Led by Community Pharmacists

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Abstract: Background: The prevalence of chronic kidney disease (CKD) is rising, increasing demand for renal replacement therapy (RRT). Community pharmacies, as accessible healthcare hubs, can play a pivotal role in CKD prevention. This study aimed to develop care models for community pharmacies to optimize medication use, encourage behavior modification, and promote self-management among at-risk individuals. Methods: Conducted between June 2017 and July 2018, this study utilized an action research approach. Microalbuminuria was assessed using urine dipsticks, and pharmacists applied behavioral change and self-management support (SMS) strategies to slow CKD progression. Participants were categorized by albuminuria levels and enrolled in pharmacist-led care programs, with follow-up assessments at weeks 0 and 12. Results: Of 521 participants screened, 57% tested positive for albuminuria. For these individuals, serum creatinine testing and referrals to primary care were initiated. Self-management behavior assessment (S1) scores significantly improved ($p = 0.024$). Key factors associated with urine albumin levels included age < 60 years (OR = 0.44), diabetes (OR = 3.69), hypertension (OR = 2.01), BMI < 27.5 kg/m^2 (OR = 0.42), eGFR $\geq$ 60 mL/min/1.73 m^2 (OR = 3.34), lower systolic (OR = 0.55) and diastolic blood pressure (OR = 0.34), and fasting plasma glucose < 126 mg/dL (OR = 0.29). Conclusions: Community pharmacist-led albuminuria screening effectively supports CKD prevention and enhances self-awareness within communities.

Keywords: action research; community pharmacy; self-awareness; microalbuminuria; renal disease; screening program

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1. Introduction

Chronic kidney disease (CKD) is one of the most common noncommunicable chronic diseases, with a prevalence of 17.5% in Thailand [1]. The number of Thai CKD patients undergoing renal replacement therapy (RRT) increased from 58,385 in 2012 to 69,528 in 2013, 78,044 in 2014, and 85,848 in 2015 [2]. The three leading causes of CKD in Thailand are diabetes, hypertension, and urinary tract obstruction, which account for 38.57%, 30.71%, and 3.74% of cases, respectively [3].

A survey in Thailand found that more than one-third of the general population with diabetes was unaware of their diagnosis, while 44.7% of those with hypertension were unaware of their condition [4]. This lack of self-awareness increases the risk of developing complications, which is likely to escalate each year [5]. In 2017, the National Health Security Office (NHSO) proposed a concept for the control and prevention of the severity of diabetes and hypertension that included three components: (1) Primary prevention focuses on protecting the general population from disease by screening for risk factors, changing behavior, and providing appropriate knowledge and guidance. (2) Secondary prevention is the prevention of patients with diabetes and hypertension from developing renal and eye complications or stroke. It involves the necessary laboratory evaluations, supporting access to medications, and improving the quality of medical services. Both medication therapy and continuous drug monitoring are essential components of disease prevention. (3) Tertiary prevention focuses on the prevention of patients with complications caused by diabetes and hypertension, mortality, or disability by providing CKD clinics and renal replacement services to patients with end-stage renal disease [6].

Accredited community pharmacies in Thailand are part of the public health service system and can provide patient care services, including (1) screening for diabetes and hypertension, (2) improving the quality of medication management, and (3) participating in the modification of drug behavior and healthcare [7]. Accredited community pharmacies that participate in the National Health Insurance System offer comprehensive primary prevention services, such as chronic disease screening, smoking cessation, and medication therapy management (MTM). Additionally, a health prevention program (PP) is offered to patients in community pharmacies as well. These services demonstrate that accredited community pharmacies are easily accessible as screening resources for the public [6].

The current ESC and ACC guidelines emphasize the critical role of comprehensive kidney function assessment, which includes both serum creatinine-based estimated glomerular filtration rate (eGFR) and albuminuria evaluation across various aspects of cardiovascular risk management. The ESC 2021 Guidelines on Cardiovascular Disease Prevention recommend the routine measurement of the urine albumin-to-creatinine ratio (UACR) in hypertensive patients, highlighting its value for detecting early renal damage and refining cardiovascular risk stratification [8]. These guidelines also advocate for regular eGFR assessments as part of a holistic approach to identify and manage CKD.

Similarly, the ACC/AHA 2017 Guidelines on Hypertension recognize albuminuria as a key marker of target organ damage and support the use of both eGFR and UACR testing to guide treatment decisions and monitor disease progression [9]. The dual assessment of eGFR and UACR allows for a more accurate identification of CKD, enabling timely interventions to mitigate cardiovascular and renal complications.

Furthermore, the ESC 2019 Guidelines on Diabetes, Pre-Diabetes, and Cardiovascular Diseases underscore the importance of albuminuria screening in patients with diabetes as an indicator of elevated cardiovascular risk. These guidelines recommend regular assessments of both UACR and eGFR to facilitate the early detection of CKD, guide therapeutic strategies, and reduce the likelihood of complications [10].

The 2015 public health service guidelines for CKD patients prior to RRT recommend annual CKD screening for high-risk individuals to facilitate early diagnosis [11–13]. However, a kidney screening service is not yet available in accredited community pharmacies in Thailand presently. Therefore, this study aimed to (1) develop high-quality kidney screening protocols for accredited community pharmacies, (2) develop a protocol for transferring patients with chronic proteinuria to higher-level service units, and (3) manage medication use, modify behavior, and promote self-management to slow the progression of CKD in at-risk individuals or those with proteinuria.

2. Materials and Methods

2.1. Study Design

This study adopted an action research approach and consisted of three phases: phase 1—developing a practical care model; phase 2—care model implementation; and phase 3—evaluation. This study was approved by the Ethics Committee for Human Research (HE602167), Khon Kaen University, Thailand. Explicit informed consent was obtained from all participants.

2.2. Setting

This study was conducted in Mueang District, Khon Kaen Province, Thailand, in 2017. The district encompasses an area of 953.4 square kilometers and has a population of 382,156 [14].

2.3. Participants

2.3.1. Participants in the Development and Implementation of the Program

The primary target population for this intervention was a network of 13 accredited community pharmacies in Khon Kaen municipality that were registered with the Khon Kaen Provincial Public Health Office.

2.3.2. Participants in CKD Screening

The target population for this study was individuals aged at least 18 years who visited the pharmacy network of accredited community pharmacies and provided informed consent to participate.

Inclusion criteria:

(1) Age $\geq$ 18 years with at least one of the following: (1) diabetes, (2) hypertension, (3) systemic infections such as pyelonephritis or endocarditis, (4) cardiovascular disease, (5) recurrent upper urinary tract infections, (6) gout or elevated serum uric acid levels, (7) regular use of non-steroidal anti-inflammatory drugs (NSAIDs) or nephrotoxic medications, (8) decreased renal mass or unilateral kidney, congenital or acquired, (9) family history of CKD, (10) detected kidney stones or urinary tract stones, (11) three or more kidney cysts detected.
(2) Age $\geq$ 60 years without comorbidities.

Exclusion criteria:

(1) Blood creatinine test results obtained within one year prior to study participation, as documented in the patient's medical record or laboratory certificate.
(2) Inability to communicate or hearing impairment without supervision, and autoimmune disease that can cause kidney disease.

2.4. Program

2.4.1. Program Development

To develop the CKD care model, the content validity index (CVI) was calculated to ensure the validity of the instruments used in the study. A panel of five experts in pharmacy practice, public health, and behavioral sciences evaluated the content of the self-management behavior assessment (S1) and the self-care ability assessment (S2) forms. These experts were selected based on their extensive experience in instrument development and validation. A CVI evaluation form was provided to each expert. This form included criteria such as relevance, clarity, simplicity, and comprehensiveness of each item in the questionnaire. Experts rated each item on a 4-point Likert scale, where 1 = not relevant, 2 = somewhat relevant, 3 = quite relevant, and 4 = highly relevant. The item-level CVI

(I-CVI) was calculated as the proportion of experts rating an item as either 3 or 4. The scale-level CVI (S-CVI) was derived by averaging the I-CVI scores across all items. Based on these evaluations, the CVI was 0.93 for the self-management behavior assessment (S1) and 1.00 for the self-care ability assessment (S2), indicating excellent content validity. Additionally, piloting was conducted in a subset of community pharmacies before the main study to assess the feasibility, usability, and clarity of the guidelines. Feedback from this pilot phase informed the final version of the model. Consistent terminology for the questionnaires and assessments is ensured throughout the manuscript to improve clarity and alignment.

Thereafter, we purposively selected 13 accredited community pharmacies. We first conducted a literature review to develop a preliminary screening model. We then brainstormed with selected pharmacists to develop guidelines for the screening, referral, behavior modification, and self-management of high-risk individuals. Finally, we presented the model to 13 pharmacists from 13 accredited community pharmacies to obtain feedback to improve the model for practical implementation.

Following the implementation of the model, the researchers convened a focus group meeting with pharmacists to reflect on the operational guidelines. The discussion covered the implementation of guidelines, tools used, problems encountered, factors influencing feasibility, practical and non-practical activities, and reasons for non-adherence to the plan. The goal of the meeting was to reach a consensus on how to improve the CKD screening program and develop a reusable care model. Model components and interventions were established based on the inputs and objectives of the stakeholders, and are shown in Figure 1 and Table 1.

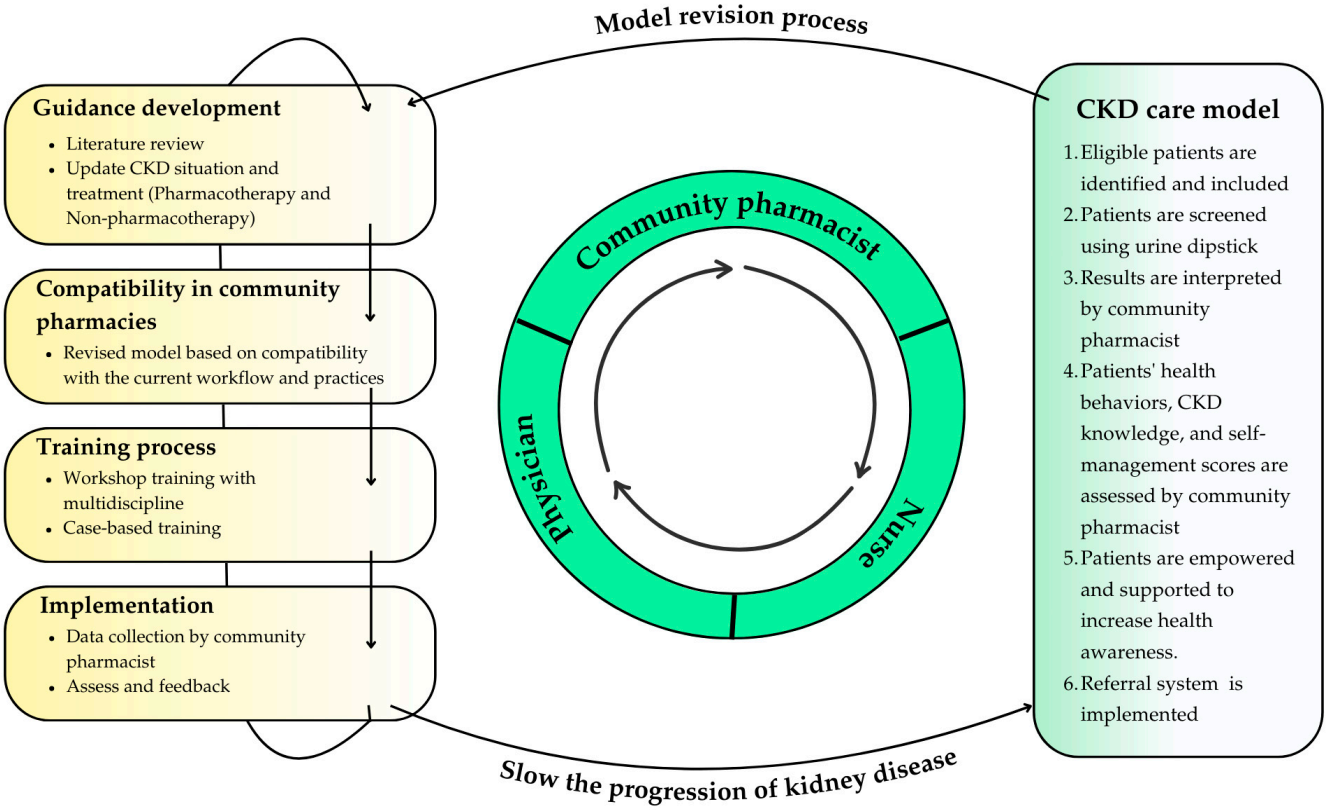

Figure 1. Model components and intervention in accredited community pharmacies.

Table 1. Activities to establish CKD care model in community pharmacies.

Activity	Method	Team Member	Output
Review and update situation	Literature review of knowledge on preventing and slowing down chronic kidney disease	Nephrologist (n = 1) Nurse (n = 2) Community pharmacist (n = 10)	Educational and screening guidance
Design collaboration among accredited community pharmacies	Draft the program to fit with the relevant guidelines and current situation	Community pharmacist (n = 13)	A draft of the collaborative program for CKD care model
Review and draft screening program	Participants' group discussion (1st)	Community pharmacist (n = 13)	A revised care model for CKD screening
Agreement among team member	Participants' group discussion (2nd)	Community pharmacist (n = 13)	Establishment of the CKD care model
Work plan	Participants' group discussion (3rd)	Community pharmacist (n = 13)	Data collection methods and forms related to the outcomes
Training and assessment of screening program	Workshop training	Community pharmacist (n = 13)	Trained team members for the CKD care model

2.4.2. Program Implementation

The first CKD care model was implemented at accredited community pharmacies in July 2017. Pharmacists from accredited community pharmacies participated in a training workshop on the CKD screening program. Pharmacists who completed the training workshop activities and passed the assessment were certified to implement the model. Certified pharmacists conducted the care model on specific dates, scheduling screening, follow-up, and encouragement visits for the included participants. Pharmacists provided CKD screening programs daily during pharmacy operating hours. All at-risk individuals underwent a self-care assessment, received an education package, and took a follow-up albuminuria test at week 12. If urine results at week 0 were positive, the confirmed glomerular filtration rate (GFR) was required.

The pharmacists reviewed the patient's self-management support (SMS) score, which was derived from a validated questionnaire designed to assess the patient's self-management capabilities and knowledge regarding kidney disease. A standardized cutoff score was utilized to determine whether the patient required additional support to independently slow kidney disease progression. Specifically, patients scoring below 50% on the SMS questionnaire were categorized as needing further intervention. In addition to the SMS score, the pharmacists assessed the patient's self-care ability using a separate self-care ability assessment form (S2). This form included a scoring system where a score of less than 5 indicated insufficient self-care abilities, prompting tailored educational or behavioral interventions. While the SMS score provided an overall measure of the patient's self-management readiness, the self-care ability score offered a more specific evaluation of practical self-care capabilities. The two assessments were complementary, enabling pharmacists to identify patients who required additional support and customize their intervention strategies accordingly. In these cases, the pharmacist conducted an intensive follow-up every six weeks to address any identified problems and provided counseling. If further specialized examination was required, the patient was referred to a physician.

2.5. Outcomes

The model outcomes evaluated encompassed patients' knowledge of CKD, as well as metrics derived from the SMS framework. Specifically, this included the assessment of self-management behaviors (S1) and self-care abilities (S2).

2.6. Data Collection

This study employed a three-part questionnaire to gather data, which included the following sections.

1. Demographic data:

Demographic information such as age, gender, level of education, CKD risks, medications, and urine albumin at baseline was collected by community pharmacists.

2. CKD knowledge questionnaire:

This 11-question assessment was used to evaluate participants' knowledge of CKD. The scores are interpreted as follows: "high 8–11 points", "medium 4–7 points", and "low 0–3 points". The questions were developed using guidelines from the Chronic Kidney Disease Outcomes Quality Initiative (KDOQI) and Kidney Disease Improving Global Outcomes (KDIGO), emphasizing fundamental knowledge areas such as kidney function, risk factors, and lifestyle modifications. Categories of "high," "medium," and "low" were based on the scoring thresholds determined during pilot testing, ensuring meaningful differentiation between knowledge levels.

3. The SMS form is divided into two parts:
    (1) The self-management behavior assessment (S1): This 11-item assessment was used to evaluate participants' health behaviors. The scores are interpreted as follows: "good—35–44 points", "fair—23–34 points", "poor—11–22 points". The categories were adapted from validated self-management frameworks that classify behaviors into "good," "fair," and "poor" based on participant responses. These thresholds were determined using prior research on self-care in chronic disease management and feedback from experts during the model development phase.
    (2) The self-care ability assessment form (S2): This was assessed at week 0 and 12. A score of 10 indicates that the participant takes good care of themselves, while a score of 1 indicates that the participant does not and needs thorough attention.

4. Instruments
    (1) Tools to educate and support self-management include a video and poster on CKD developed by CKDNET group.
    (2) A urine dipstick screening tool (Cobas Micral-Test® version 11544039, Roche, Thailand) was used for microalbumin testing. Serum creatinine levels were measured using the Beckman Coulter LX20 PRO analyzer with the modified Jaffe method, and the results were used to calculate estimated glomerular filtration rate (eGFR) based on the CKD-EPI equation. The following guidelines were applied for patient follow-up and management:
        - If the urine dipstick test results were negative for albuminuria, patients were scheduled for follow-up testing at week 12.
        - If the urine dipstick test results were positive for albuminuria with an eGFR < 60 mL/min/1.73 m^2, patients were followed up again at week 12 and referred to a primary care unit (PCU) for evaluation and treatment by a physician.
        - If the urine dipstick test results were positive for albuminuria with an eGFR $\geq$ 60 mL/min/1.73 m^2, patients were scheduled for repeat testing at week 12.

2.7. Data Analysis

Demographic data were analyzed using descriptive statistics (means ± SDs or percentage) where appropriate. For outcomes that were compared pre- and post-intervention (average scores of behaviors, knowledge, and SMS), the Wilcoxon signed-rank test was used to analyze the data. The chi-square test was used to analyze categorical variables. Significance levels were set at 0.05.

To screen factors potentially associated with urine albumin level, a univariable analysis was conducted. Variables with a p-value < 0.25 were included in the subsequent binary logistic regression analysis [15]. The binary logistic regression model was then employed to assess the relationships between the identified factors and urine albumin levels. The results were interpreted using odds ratios (ORs) and their corresponding 95% confidence intervals (CIs), with statistical significance defined at a threshold of $p < 0.05$. Data were managed and analyzed using Stata version 14 software (StataCorp, College Station, TX, USA: Serial number: 401506248924).

In terms of sensitivity and specificity analysis, the reference standard for classifying patients into CKD and non-CKD groups was defined based on clinical guidelines. CKD was identified by the presence of albuminuria $\geq$ 30 mg/dL and/or a sustained eGFR < 60 mL/min/1.73 m^2 across two measurements taken at least 12 weeks apart. Non-CKD was defined as the absence of albuminuria and an eGFR $\geq$ 60 mL/min/1.73 m^2. These criteria were applied to classify participants before evaluating the diagnostic performance of the urine dipsticks.

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the urine dipstick screening tool were calculated by comparing the results of the dipstick tests to this reference standard. The effectiveness of a diagnostic test is determined by its sensitivity and specificity. There are four possible outcomes for a test [16]:

- True positive (TP) refers to individuals who have the disease and the test correctly identifies them as positive (accurate test result).
- False positive (FP) refers to individuals who do not have the disease, but the test incorrectly identifies them as positive (inaccurate test result).
- True negative (TN) refers to individuals who do not have the disease and the test correctly identifies them as negative (accurate test result).
- False negative (FN) refers to individuals who have the disease, but the test incorrectly identifies them as negative (inaccurate test result).

The sensitivity and specificity values can then be calculated using the following formulas:

$$\text{Sensitivity} = \frac{\text{True positive (TP)}}{\text{True positive (TP)} + \text{False negative (FN)}} \quad (1)$$

$$\text{Specificity} = \frac{\text{True negative (TN)}}{\text{True negative (TN)} + \text{False positive (FP)}} \quad (2)$$

3. Results

In this model, we used albumin urine dipsticks as screening tools in 18 accredited community pharmacies. Urine screening was performed according to Roche company's instructions. The participants were informed about the CKD video and data sheets. The screening care model is illustrated in Figure 2. At-risk individuals with positive albuminuria upon first-time screening were referred to a partner's laboratory office to confirm their serum creatinine level. Individuals with positive albuminuria at week 12 were referred to 11 PCUs around the municipal area using a universal pharmacist referral form (PhRF).

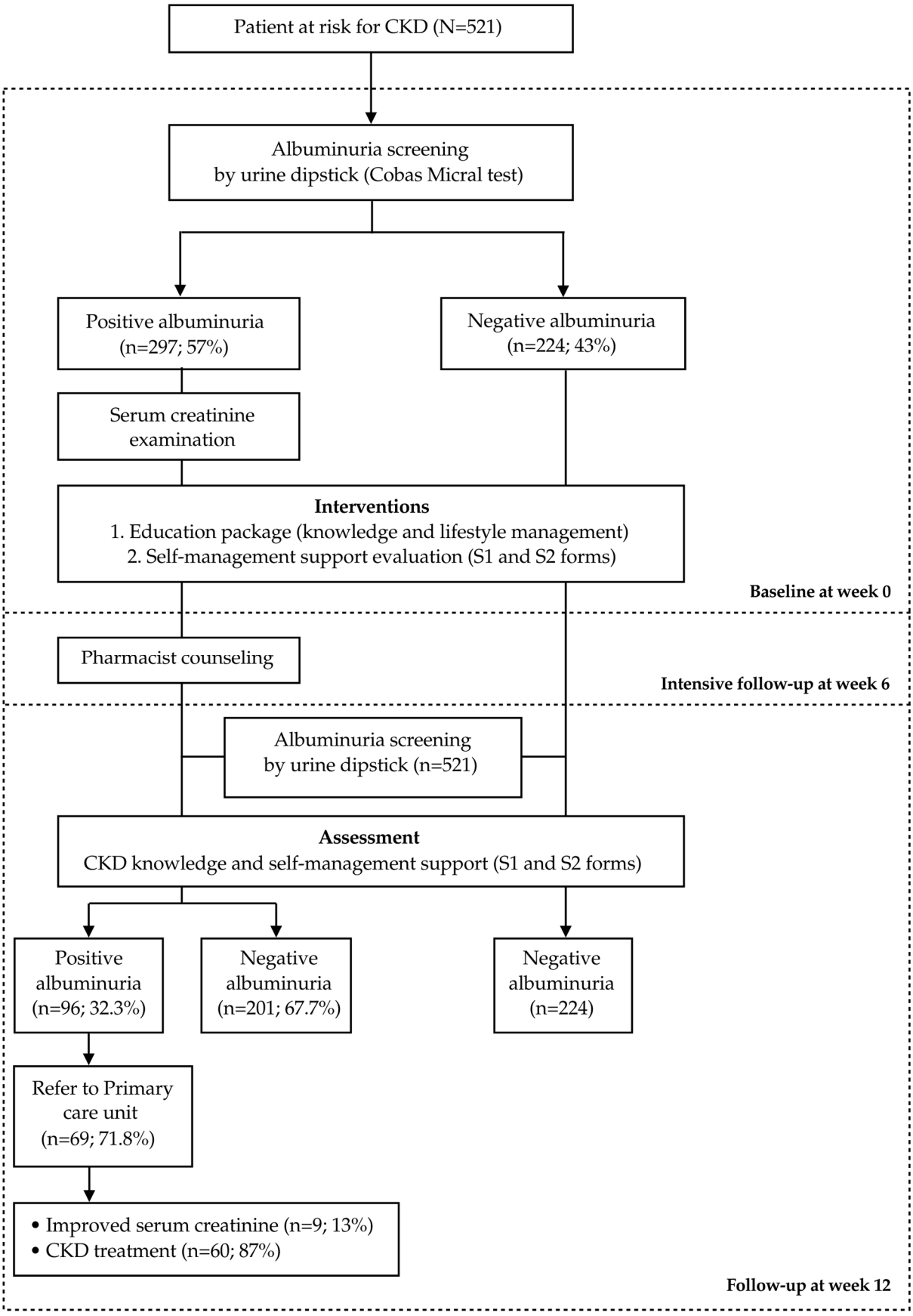

Figure 2. CKD care model for accredited community pharmacies.

3.1. Demographics of Participants

The screening results demonstrated that 521 patients were at risk of CKD; 68.7% were female, with a mean age of 54.81 ± 12.11 years. The study participants had a history of taking NSAIDs or nephrotoxic agents (43.6%). Of 521 participants, 297 individuals tested positive for albuminuria at week 0. At week 12, 96 patients tested positive for albuminuria. The demographic data of the participants are shown in Table 2. The characteristics of hypertension, diabetes, or taking nephrotoxic agents, especially NSAIDs, can lead to albuminuria. More than 70% of the positive albuminuria group could not delay kidney progression with lifestyle modification alone. Patients with heart failure, diabetes, and hypertension managed their kidney function through medication, achieving a notable shift to the negative albuminuria group by week 12. Notably, approximately 12% of patients used antihypertensive medications other than ACE inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), 10% used antidiabetic drugs, and 9% used HMG-CoA reductase inhibitors, such as simvastatin or atorvastatin.

Table 2. Demographic data of included participants.

Baseline Characteristics	Number of Participants (%) or Mean ± SD
Gender (N = 521)	
Female	358 (68.7)
Male	163 (31.3)
Age (Years)	54.81 ± 2.11
Level of education (N = 521)	
Primary school	180 (34.6)
High school/Certificate	101 (19.4)
Undergraduate	47 (9.0)
Not defined	193 (37.0)
CKD risks (N = 521) [a]	
Diabetes mellitus	121 (23.2)
Hypertension	135 (25.9)
Older than 60 years of age	132 (25.3)
Received NSAIDs or nephrotoxic agents	241 (46.3)
Family history of CKD	46 (8.8)
Others	53 (10.2)
Medications (N = 521) [b]	
Antihypertension	90 (17.3)
Antidiabetes	77 (14.8)
Statins	63 (12.1)
Antiplatelets	42 (8.1)
Antidepressants	5 (1.0)
Alpha-adrenergic blockers	10 (1.9)
ACEIs/ARBs	54 (10.4)
Anti-thyroid drugs	6 (1.2)
NSAIDs	22 (4.2)
Uric-lowering drugs	7 (1.3)
Chemotherapy	1 (0.2)
Iron supplements	65 (12.5)
Herbal medicines	23 (4.4)
No medications	306 (58.7)

Table 2. *Cont.*

Baseline Characteristics	Number of Participants (%) or Mean ± SD
Urine albumin at baseline (N = 521)	
Negative (0 mg/dL)	224 (43.0)
Positive (20, 50, 100 mg/dL)	297 (57.0)

Remark: [a] Participants have more than one risk factor. [b] Participants have more than one medication.

3.2. CKD Knowledge Score

Most participants were unaware of the role of alcohol consumption and/or smoking. Only 45% were aware of the benefits of weight loss in slowing kidney disease progression, and a few participants were taking diabetes medication. Hypertension is a leading cause of kidney failure. However, after receiving education about CKD from a pharmacist, participants' self-awareness of CKD improved, with the average score increasing significantly from 6.43 ± 2.34 to 8.06 ± 1.06 ($p < 0.005$) (Table 3).

Table 3. CKD knowledge score (N = 521).

CKD Knowledge Score	Week 0 Correct Answer (%)	Week 12 Correct Answer (%)	*p*-Value
1. The kidneys are organs responsible for excreting water and removing waste products from the body.	383 (73.5)	517 (99.2)	0.020
2. The kidneys help balance mineral salts and pH in the body.	322 (61.8)	498 (95.6)	0.017
3. Diabetes and hypertension do not cause kidney disease.	279 (53.6)	476 (91.4)	<0.005
4. People with normal kidney function do not leak protein in their urine and blood waste levels are within normal range.	337 (64.7)	499 (95.8)	<0.005
5. Very salty foods cooked with monosodium glutamate (MSG) cause kidney deterioration faster.	382 (73.3)	513 (98.5)	0.021
6. Drinking alcohol has a reduced effect on kidney function.	243 (46.6)	396 (76.0)	0.006
7. Smoking does not affect kidney function.	172 (33.0)	358 (68.7)	0.007
8. Weight loss can help slow down kidney degeneration.	235 (45.1)	449 (86.2)	<0.005
9. Herbal medicine, Chinese medicine, and herbal pills will help slow down kidney deterioration.	265 (50.9)	455 (87.3)	0.007
10. The use of painkillers or medications does not impair kidney function.	295 (56.6)	450 (86.4)	0.004
11. Taking medication to treat diabetes and high blood pressure causes kidney deterioration.	71 (13.6)	327 (62.8)	<0.005
Total score (11 points) mean ± SD	6.43 ± 2.34	8.06 ± 1.06	<0.005
High (8–11 points)	201 (38.6)	421 (80.8)	<0.005
Medium (4–7 points)	194 (37.2)	99 (19.0)	<0.005
Low (0–3 points)	126 (24.2)	1 (0.2)	<0.005

3.3. Self-Management Support (SMS) Score

3.3.1. Self-Management Behavior Assessment (S1) Form

The evaluation of self-management behaviors aimed at mitigating kidney disease progression was conducted using the -S1 form. The study found that the first three low-grade behaviors that contributed to kidney disease progression were consuming low-flavor or bland foods (most patients preferred to eat processed foods), exercising at least 30 min per day or three days per week, and consuming fresh, organic vegetables. All health behavior scores were not different between positive albuminuria or negative albuminuria at week 0. After 12 weeks of follow-up, all study participants scored significantly higher on the behavior assessment ($p = 0.024$) (Table 4). In the negative albuminuria group, the behavior score increased significantly ($p = 0.042$).

Table 4. Self-management behavior assessment (S1) score (N = 521).

Self-Management Behavior Question	Week 0 (Mean ± SD)	Week 12 (Mean ± SD)	*p*-Value
1. You consume food and beverages that are high in sugar, such as candy, cookies, fruit syrups, smoothies, and soft drinks.	2.82 ± 0.95	2.79 ± 0.99	0.781
2. You eat food that is tasteless or less salty.	2.54 ± 1.03	2.73 ± 0.95	0.032
3. You consume food that has been artificially flavored or processed in a way that alters their original state.	2.87 ± 0.89	3.07 ± 0.91	<0.005
4. You drink more than eight glasses of water each day.	3.14 ± 1.12	3.31 ± 1.03	<0.005
5. You consume fresh, organic, or home-cultivated plant-based food.	2.79 ± 1.09	2.78 ± 1.09	0.990
6. You obtain six-eight hours of sleep per night and experience minimal nocturnal awakenings.	3.24 ± 0.96	3.26 ± 1.03	0.681
7. You are able to effectively cope with and manage stressful situations.	3.16 ± 0.95	3.16 ± 0.92	0.990
8. You incorporate herbal therapies into your medication regimen under the supervision of your healthcare provider.	3.37 ± 1.07	3.52 ± 0.97	0.042
9. You self-medicate without consulting a healthcare professional.	3.38 ± 0.81	3.57 ± 0.78	0.011
10. You engage in moderate-intensity physical activity for at least 30 min per day on most days of the week.	2.58 ± 1.10	2.66 ± 1.23	0.260
11. You are a tobacco user.	3.78 ± 0.75	3.73 ± 0.84	0.831
Total score (44 points)	33.68 ± 4.20	34.58 ± 4.34	0.024
Good level (35–44 points), Number of participants (%)	193 (37.0%)	216 (41.5%)	0.152
Fair level (23–34 points), Number of participants (%)	250 (48.0%)	229 (44.0%)	0.224
Poor level (11–22 points), Number of participants (%)	78 (15.0%)	76 (14.6%)	0.931

3.3.2. Self-Care Ability Assessment (S2) Form

A self-care ability assessment form was also used (S2). To assess the impact of self-care on kidney disease progression, we evaluated participants' self-care capabilities at baseline and after 12 weeks of receiving guidance on self-care for kidney disease. At baseline, participants rated their self-care capabilities as moderate, with specific areas of focus including chemical food control, food control, eating fresh, non-toxic vegetables, and exercise. After 12 weeks of receiving guidance, participants' self-care scores increased in all areas (p = 0.068) (Table 5).

Table 5. Self-care ability score (N = 521).

Self-Care Ability Question	Week 0 (Mean ± SD)	Week 12 (Mean ± SD)	*p*-Value
1. I am able to manage my intake of sugary food and beverages to protect my kidney health.	6.58 ± 2.44	7.17 ± 2.18	0.004
2. I am able to manage my intake of sodium to protect my kidney health.	6.52 ± 2.53	7.17 ± 2.27	<0.005
3. I am able to control various flavored food for kidney health.	6.98 ± 2.49	7.28 ± 2.27	0.011
4. I maintain adequate hydration to support my kidney health.	7.91 ± 2.28	8.71 ± 1.81	<0.005
5. I consume fresh, organic plant-based food to support my kidney health.	7.02 ± 2.71	7.24 ± 2.74	0.08
6. I obtain 6–8 h of sleep per night to support my kidney health.	7.25 ± 2.52	7.32 ± 2.37	0.667
7. I employ effective stress management strategies to maintain my mental and emotional well-being.	7.52 ± 2.38	7.75 ± 2.36	0.962
8. I avoid medications or herbs that can affect the kidneys.	7.80 ± 2.58	8.54 ± 2.12	<0.005
9. I engage in regular physical activity to support my kidney health.	6.55 ± 2.77	7.47 ± 2.44	<0.005
10. I am a non-smoker.	8.57 ± 2.70	8.85 ± 2.22	0.071
Total score (100 points)	75.84 ± 13.13	77.34 ± 12.72	0.068

3.4. Logistic Regression Analysis of Urine Albumin Levels

To identify factors associated with urine albumin levels, we employed a univariate analysis and selected variables with a p-value < 0.2 for inclusion in the logistic regression analysis. The results of the univariate analysis are presented in Appendix A.

The logistic regression analysis elucidated several significant determinants of positive albuminuria among the study cohort. Participants aged < 60 years demonstrated significantly lower odds of positive albuminuria compared to their counterparts aged ≥ 60 years (OR: 0.44, 95% CI: 0.31–0.72, $p < 0.005$). Clinical conditions, particularly diabetes (OR: 3.69, 95% CI: 2.30–6.03, $p < 0.005$) and hypertension (OR: 2.01, 95% CI: 1.33–3.04, $p < 0.005$), emerged as robust predictors, exhibiting a strong association with increased odds of albuminuria. Conversely, protective factors included a lower BMI (<27.5 kg/m^2, OR: 0.42, 95% CI: 0.28–0.67, $p < 0.005$), better renal function (eGFR ≥ 60 mL/min/1.73 m^2, OR: 3.34, 95% CI: 1.16–9.86, $p = 0.030$), lower systolic blood pressure (OR: 0.55, 95% CI: 0.38–0.83, $p < 0.005$), lower diastolic blood pressure (OR: 0.34, 95% CI: 0.23–0.55, $p < 0.005$), and fasting plasma glucose < 126 mmHg (OR: 0.29, 95% CI: 0.19–0.57, $p < 0.005$). Moreover, no current use of pain relievers or NSAIDs (OR: 1.50, 95% CI: 1.41–1.98, $p = 0.040$) and self-management behavior support scores of at least 50 points (OR: 2.04, 95% CI: 1.13–3.82, $p = 0.020$) were significantly correlated with increased odds of albuminuria. However, variables including sex, CKD knowledge, health behavior CKD scores, and MTM did not exhibit statistically significant associations (Table 6).

Table 6. Logistic regression analysis of urine albumin level (N = 521).

Variables	Urine Albumin Level		Adjusted OR	*p*-Value
	Positive Albuminuria	Negative Albuminuria		
Sex				
Male (n = 163)	101	62	1.29 (0.90–1.92)	0.160
Female (n = 358)	198	160	1	
Age				
<60 years (n = 389)	206	183	0.44 (0.31–0.72)	<0.005 *
≥60 years (n = 132)	93	39	1	
Diabetes				
Yes (n = 121)	96	25	3.69 (2.30–6.03)	<0.005 *
No (n = 400)	203	197	1	
Hypertension				
Yes (n = 135)	94	41	2.01 (1.33–3.04)	<0.005 *
No (n = 386)	205	181	1	
Systemic infection				
Yes (n = 2)	2	0	3.69 (0.18–78.28)	0.390
No (n = 519)	297	222	1	
Regular use of NSAIDs or nephrotoxic medications				
No (n = 280)	180	100	1.81 (1.38–2.17)	<0.005 *
Yes (n = 241)	119	122	1	
Decreased renal mass or unilateral kidney, congenital or acquired				
Yes (n = 2)	2	0	3.72 (0.18–78.28)	0.400
No (n = 519)	297	222	1	
BMI				
<27.5 kg/m^2 (n = 391)	141	178	0.42 (0.28–0.67)	<0.005 *
≥27.5 kg/m^2 (n = 121)	78	43	1	

Table 6. *Cont.*

Variables	Urine Albumin Level		Adjusted OR	*p*-Value
	Positive Albuminuria	Negative Albuminuria		
Current use of pain relievers or NSAIDs				
No (n = 381)	229	152	1.50 (1.41–1.98)	0.040 *
Yes (n = 140)	70	70	1	
eGFR				
<60 mL/min/1.73 m^2 (n = 30)	26	4	3.34 (1.16–9.86)	0.030 *
≥60 mL/min/1.73 m^2 (n = 398)	279	145	1	
Systolic blood pressure (SBP)				
<140 mmHg (n = 291)	149	142	0.55 (0.38–0.83)	<0.005 *
≥140 mmHg (n = 175)	114	61	1	
Diastolic blood pressure (DBP)				
<90 mmHg (n = 319)	156	163	0.34 (0.23–0.55)	<0.005 *
≥90 mmHg (n = 147)	107	40	1	
Fasting plasma glucose (FPG)				
<126 mg/dL (n = 203)	108	95	0.29 (0.19–0.57)	<0.005 *
≥126 mg/dL (n = 94)	73	21	1	
Hemoglobin A1C (HbA1C)				
<7% (n = 17)	14	3	0.52 (0.12–2.33)	0.410
≥7% (n = 68)	61	7	1	
Health behavior CKD score				
≥35 points (n = 193)	112	81	1.01 (0.73–1.49)	0.820
<35 points (n = 328)	187	141	1	
CKD knowledge score				
≥8 points (n = 201)	114	87	0.91 (0.67–1.37)	0.810
<8 points (n = 320)	185	135	1	
Self-management behavior support score				
≥50 points (n = 465)	282	183	2.04 (1.13–3.82)	0.020 *
<50 points (n = 47)	20	27	1	
MTM [a]				
Yes (n = 137)	88	49	0.12 (0.006–1.86)	0.808
No (n = 8)	8	0	1	

Remark: [a] MTM: medication therapy management., * *p*-value < 0.2 for inclusion in the logistic regression analysis.

3.5. Sensitivity and Specificity of Urine Dipsticks

Based on Table 7, this study found that the sensitivity and specificity of urine dipsticks were 96.8% and 45.7%, respectively. The positive predictive value (PPV) and negative predictive value (NPV) were calculated as 10.4% and 99.6%, respectively.

Table 7. Sensitivity and specificity of urine dipsticks.

Screening Results	Characteristics in Population		Total
	CKD	Non-CKD	
Positive albuminuria	31 (TP)	266 (FP)	297
Negative albuminuria	1 (FN)	223 (TN)	224
Total	32	489	521

4. Discussion

This study developed CKD screening and pharmacy self-care support models to help patients at risk of CKD, a criterion selected based on the described guidelines [11–13]. These care models aim to slow the progression of CKD to end-stage renal disease (ESRD). However, leakage of other proteins may also be associated with a patient's condition, which could affect the study. The problems encountered in developing a care program include documents and screening equipment, number of participants, education of pharmacists, and patient follow-up.

Previous studies have screened and referred people at risk of CKD in pharmacies, focusing on people aged 40 years or older who have not been diagnosed with CKD. Using a combination of the Kidney Disease Self-Screening Questionnaire (KIDs) and urine protein screening, 241 patients at risk were identified and referred to PCUs. However, this preliminary study was conducted in only one pharmacy and had limited coordination with cooperative service units [17–19]. While the study identified patients with CKD through screening, it also found problems with the referral and tracking of treatment outcomes.

This study was an action research project that aimed to develop a network of screening programs to prevent kidney disease. In collaboration with 13 accredited community pharmacies in the municipal district of Khon Kaen Province, Thailand, this study aimed to provide CKD risk screening and albuminuria testing by community pharmacists. There is evidence of pharmacists successfully providing counseling services to improve patient's CKD awareness. The results showed that the patient's satisfaction was high [20].

Screening with urine dipsticks had different sensitivity and specificity values than those reported by the manufacturer. While urine dipstick screening is a useful tool for stimulating patients to modify their behaviors by recognizing their urinary protein leakage, it cannot be used to diagnose CKD. This study is an important contribution to the literature on kidney disease screening, as it raises self-awareness among people at risk. However, it is important to note that the study had a small number of patients who tested positive and were referred to PCUs (n = 69, 71.8%). Additionally, only 13% (n = 9) of the referred group showed an improvement in serum creatinine..

This study, which developed a risk screening protocol for community pharmacies, was an action research study that used both reactive and proactive approaches. Summary and group meetings were necessary to identify problems and improve the guidelines for real-world use. This is consistent with Cha'on et al.'s study [21], which developed guidelines for CKD care in primary care settings. A key consideration for developing successful clinical guidelines is to ensure that they are clear, concise, and easy to implement in real-world settings. The guidelines should also be compatible with existing components of the service and subject to feedback for improvement. For example, the use of a pharmacist referral form (PhRF) has advantages because it provides essential information about the patient, including their insurance status, medical information, reason for referral, and the pharmacist's contact number. This form is also familiar to medical staff, which can reduce confusion and facilitate the referral process. If the patient does not agree to receive care at the PCU, the pharmacist can continue to follow up on their medication use and recommend behavioral changes at the pharmacy.

The findings of this study reveal that pharmacists regarded the CKD service as efficient, user-friendly, and significantly beneficial for their patients. However, a notable challenge identified was the lack of patient engagement in disease prevention efforts, compounded by a limited understanding of CKD among the population. Furthermore, pharmacists highlighted the importance of interprofessional collaboration, particularly between pharmacists and general practitioners, as a key determinant of the scope and success of pharmacy practice in preventive care. Customer acknowledgment of the pharmacist's role in disease

prevention was also perceived as a critical factor influencing the service's impact and acceptance [20].

A systematic review examining patient attitudes found that they were more receptive to the availability of medicine-related services than health promotion or screening services, but those who experienced these pharmacy services were highly satisfied with them [22]. In a recent Australian atrial fibrillation screening study, pharmacists perceived combining screening with other established services, such as medication reviews, as an alternative approach to improve service uptake [23]. Similarly, in this qualitative study, pharmacists observed an improvement in the patients' response to the CKD service when it was integrated with other professional services.

Jane et al. (2019) [24] demonstrated that self-management processes and concepts are effective strategies for empowering individuals with risk factors or chronic diseases to effectively manage their conditions. This study assessed the impact of a self-management intervention against three dimensions: risk factors and prevention, self-management, and outcome. This study found that the intervention was effective for improving short-term outcomes, such as knowledge and behavior changes. However, this study only measured short-term outcomes, and did not assess long-term outcomes, such as health status, quality of life, or healthcare costs. The researchers recommend further studies to assess long-term outcomes [25,26].

The logistic regression analysis identified several factors associated with positive albuminuria. Participants aged < 60 years had lower odds of albuminuria than those $\geq$ 60 years, consistent with studies linking age-related renal and vascular decline to albuminuria [27,28]. Diabetes and hypertension strongly predicted albuminuria, as these conditions cause microvascular damage and glomerular hyperfiltration [29,30], while lower BMI was protective, aligning with findings that obesity accelerates kidney damage [31]. Better renal function (eGFR $\geq$ 60 mL/min/1.73 m^2) reduced albuminuria risk, highlighting the role of preserved filtration capacity [32]. Lower systolic and diastolic blood pressure were protective, underscoring that blood pressure control is important [33]. Elevated fasting plasma glucose increased albuminuria risk, reflecting glycemic control's critical role in kidney health [34]. Regular NSAID use increased albuminuria odds, consistent with NSAID-induced renal damage [35]. However, the current use of NSAIDs exhibited lower odds; this point is surprisingly opposed to the current knowledge. This might be due to the short-term use of NSAIDs, as the long-term effects may not have been presented.

Participants with higher self-management behavior support scores exhibited increased odds of albuminuria, contrasting findings from previous studies [36,37]. This association may stem from prior participation in CKD health awareness programs provided by public health practitioners, potentially influencing their inclusion in this study and increasing the likelihood of identifying positive albuminuria cases. Variables like sex, CKD knowledge, health behavior scores, and MTM were not significantly associated with albuminuria, reflecting mixed findings in the literature.

We investigated pharmacists' perspectives on self-management among patients with chronic conditions and explored the feasibility of establishing pharmacist-led self-management initiatives. Our findings suggest that an effective model for chronic disease management should actively involve patients with stable conditions in self-management practices, thereby preventing health deterioration and reducing healthcare costs. Fiona et al. [38] emphasized that the role of pharmacists should extend beyond medication-related responsibilities to encompass broader participation within the primary healthcare system. The previous study suggested that primary care organizations are associated with perceived self-management support. Team-based primary care has been associated with the provision of more patient-centered care [39].

To facilitate the development of pharmacist-led self-management programs, the authors highlighted the importance of government support in expanding pharmacists' roles in health services. This could be achieved through fostering public–private partnerships with community pharmacists and implementing measures to support this transition. Key recommendations include enabling pharmacists to access electronic health records to enhance the continuity of care and considering the deregulation of certain prescription-only medicines to allow them to be dispensed as pharmacy-only medicines. These measures were identified as critical steps toward gradually establishing pharmacist-led patient self-management within the healthcare system.

This study has several limitations. First, the researchers did not analyze the quality of life of the participants in the screening; therefore, the researchers could not evaluate the relationship of the self-management system to kidney filtration rates and quality of life as part of the study [40]. However, this study found that some topics related to SMS involve avoiding drugs or herbs that affect the kidneys, and non-smoking contributes to a decrease in urine protein levels. Second, this study was conducted in community pharmacies and screened by pharmacists; therefore, we had restrictions on blood sampling, resulting in the need to transfer participants for serum creatinine testing. For further research, screening participants' blood samples should be arranged in cooperation with network medical or laboratory technicians. Third, the collection of urine samples depended on the participants' convenience, being affected by the time of day. This may interfere with the results of this study.

5. Conclusions

Screening people at risk of kidney disease with microalbuminuria dipsticks can help identify new cases earlier and more frequently, increasing the chances of delaying the progression of CKD. All individuals with positive albuminuria results should be referred to a physician for further evaluation. Community pharmacists can provide patients with counseling on medication use and self-care behaviors. For all individuals with negative albuminuria results, further testing, such as a serum creatinine testing, should be recommended at least annually if they have chronic diseases. A well-planned system for referral and communication can help ensure that patients receive continuous and appropriate care.

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Data Availability Statement: The research data are unavailable due to privacy or ethical restrictions.

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Appendix A.

Appendix A.1. Univariate Analysis of Urine Albumin Level

Variable	*p*-Value
Sex	0.005
Age	<0.001
Diabetes	<0.001
Hypertension	<0.001
Systemic infections	0.016
Cardiovascular disease	0.950
Recurrent upper-urinary-tract infections	0.600
Gout or elevated serum uric acid levels	0.449
Regular use of NSAIDs or nephrotoxic medications	<0.001
Decreased renal mass or unilateral kidney, congenital or acquired	0.164
Family history of CKD	0.470
Detected kidney stones or urinary tract stones	0.830
BMI	0.007
Waist circumference (metabolic disease)	0.206
Exercise	0.858
Smoking	0.315
Alcohol consumption	0.546
Unvoid urine	0.883
Drink a small amount of water (<40mL/kg/day)	0.643
Use herbal medicines or traditional medicines	0.329
Current use of pain relievers or NSAIDs	0.074
Current use of dietary supplements	0.325
eGFR	<0.001
Systolic blood pressure (SBP)	0.127
Diastolic blood pressure (DBP)	<0.001
Fasting plasma glucose (FPG)	<0.001
Hemoglobin A1C (HbA1C)	0.086
Serum lipid	0.382
Self-management behavior assessment score (S1)	0.169
CKD knowledge score	<0.001
Self-care ability assessment score (S2)	0.010
MTM	0.005

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Exploration of Challenges and Opportunities for Good Pharmacy Practices in Bangladesh: A Qualitative Study

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Abstract: Background: In 2015, the Directorate General of Drug Administration (DGDA) of Bangladesh accredited model pharmacies (MPs) to enhance the quality of pharmacy services across the country. We examined the challenges and opportunities for pharmacists in MPs, and also explored the perspectives of the pharmacy stakeholders for improving good pharmacy practices (GPPs) in Bangladesh. Methods: In-depth interviews (IDIs) were conducted with graduate pharmacists (Grade A) and diploma pharmacists (Grade B) recruited from a few selected MPs that were included in a previous study. Key informant interviews (KIIs) were conducted with the government and non-government stakeholders who were involved in pharmacy regulations and practices. Trained qualitative researchers conducted IDIs and KIIs using interview topic guides under relevant themes developed by the study investigators. Results: Between February and March 2021, nine Grade A and six Grade B pharmacists and nine government and non-government stakeholders were interviewed. The key challenges, as well as demotivational factors, for Grade A pharmacists were reported to be multiple responsibilities, inadequate salary, poor social status, an unfavorable working environment, long working hours, a lack of recognition, and low respect for their profession. However, Grade B pharmacists expressed job satisfaction, primarily due to working opportunities in reputable pharmacies and learning opportunities. The stakeholders reported a high operation cost of the MPs, a shortage of trained pharmacists, poor salary structures, and a lack of public awareness about the critical roles of the pharmacists in healthcare to be challenges of retaining Grade A pharmacists at the MPs. Addressing the challenges of the pharmacists and revising compensation packages along with strengthening monitoring systems would be important for improving GPPs at the MPs. Conclusions: This study has demonstrated that specifying the roles of the pharmacists, offering competitive packages, conducive working hours, and professional recognition would be imperative for the retention of trained pharmacists at MPs. Implementing regulatory standards and monitoring performance would enhance good pharmacy practices in Bangladesh.

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1. Introduction

The World Health Organization (WHO) has estimated that there are over 2.1 million pharmacists and other pharmaceutical professionals in the world [1]. Before the mid-1990s, the role of pharmacists was restricted to labeling, compounding, and dispensing medicine [2]. Currently, pharmacists play a vital role in healthcare, adopting a patient-centered approach [3], and they are often the first point of contact of a patient with the healthcare system [4]. Pharmacists have to perform several roles, including filling prescriptions, handling orders, checking inventory, maintaining patients' records, counseling patients, etc., and these roles vary from country to country based on the levels of competencies [5,6]. Pharmacists play a very important role in ensuring the proper distribution and use of medicines [7]. It is imperative that pharmacists follow good pharmacy practices (GPPs) in their professional lives, an international standard for all pharmacists set by the WHO [3].

However, pharmacists often face ethical, economic, and legal issues in their day-to-day work, which create a gap between what is expected from them and what is being done. There are concerns about the quality of pharmacy practices, particularly in low- and middle-income countries (LMICs) due to poor regulations and policies [8], albeit limited information is available about the challenges of pharmacists in pharmacy practices in the LMICs. A scarcity of graduate pharmacists in retail pharmacies has been identified in Yemen, coupled with dissatisfaction with the job, poor salaries, and a lack of regulations and standards [9]. A poor working environment and inadequate training and knowledge were reported to be challenges in pharmacy practices in Indonesia [10].

In Bangladesh, it has been estimated that there are around 191,512 registered retail pharmacies [11], and an equal number of pharmacies operate without registration [12]. There are three categories of pharmacists in Bangladesh: (i) the Grade A pharmacists, who have a graduate degree in pharmacy offered by the recognized higher degree institutions, typically universities; (ii) the Grade B pharmacists, who have completed a 3-year Diploma in Pharmacy course offered by the Pharmacy Council of Bangladesh (PCB) under the recognized paramedic institutions; and (iii) the Grade C pharmacists, who have completed a 3-month training course on dispensing medicine jointly offered by the PCB and the Bangladesh Chemist and Druggist Samity (BCDS), an organization of drug dispensers in Bangladesh [11]. The PCB is the governing body in Bangladesh for ensuring quality pharmacy education, capacity building, and registration of pharmacists. The Directorate General of Drug Administration (DGDA) is the government regulatory body for ensuring quality pharmacy practices in Bangladesh. In Bangladesh, independent prescribing rights for pharmacists are limited, except for over-the-counter (OTC) drugs. There are 39 OTC drugs in Bangladesh [13]. As per the law of Bangladesh, any individual having a valid pharmacist registration of Grade A, Grade B, or Grade C can apply for a license from the DGDA to open a retail pharmacy and sell OTC and prescription medicines. These regular pharmacies often operate with less oversight, lack graduate pharmacists, sometimes sell prescription medicines without prescriptions, have an absence of counseling services, and are often run by Grade C pharmacists [14–16].

In 2015, the DGDA launched accreditation programs for two new levels of medicine outlets, the model pharmacy and the model medicine shop, in order to promote good pharmacy practices (GPPs). A model pharmacy (MP) is managed, served, and supervised

by a graduate pharmacist (Grade A) with the support of lower-grade pharmacists, such as Grade B [17]. Between 2016 and 2020, the DGDA inaugurated 274 model pharmacies in Bangladesh to ensure high-quality pharmacy services, requiring the presence of graduate pharmacists and adherence to the strict guidelines for dispensing medicines (e.g., labeling), and the presence of storage, pharmacy-grade refrigerators, air conditioning systems, adequate space (at least 300 square feet), patient counseling services, etc. MPs are designated to promote safe pharmacy practices and prevent the misuse of antibiotics [17,18], whereas ordinary pharmacies are often operated with less oversight, with a lack of graduate pharmacists and an absence of counseling services, and are often run by Grade C pharmacists [12,14]. However, after 2020, many MPs have failed to retain trained pharmacists, which is an important barrier to promoting GPPs [19], albeit challenges faced by the pharmacists have not been explored in Bangladesh. We have explored potential challenges and opportunities for GPPs in the model pharmacies in Bangladesh from the perspectives of pharmacists and the relevant stakeholders.

2. Materials and Methods

2.1. Study Design and Settings

This study was conducted in five districts (Dhaka, Chattogram, Rangpur, Barisal, Khulna), where 56% of MPs were inaugurated by the DGDA. A list of Grade A and Grade B pharmacists was developed by visiting the model pharmacies that were randomly selected from the list of MPs inaugurated by the DGDA. A pharmacist was recruited from the selected MPs if they met the following criteria: (i) have a bachelor's degree in Pharmacy (Grade A) or a Diploma in Pharmacy degree (Grade B), (ii) have a valid registration either as a Grade A or a Grade B pharmacist from the PCB, and (iii) have at least 6 months of working experience in an MP. We purposefully selected from the list of eligible Grade A and Grade B pharmacists to have a good mix of age, sex, location, and duration of employment before inviting them to participate in an in-depth interview (IDI). Simultaneously, an additional list of the government and non-government stakeholders was created in consultation with the DGDA for conducting key informant interviews (KIIs), including those stakeholders who have been involved in regulatory or administrative or human resource development roles for pharmacy practice in Bangladesh, such as representatives of the DGDA, the PCB, institutions offering degrees or a Diploma in Pharmacy, and other relevant organizations.

2.2. Data Collection

IDIs with Grade A and Grade B pharmacists were conducted face-to-face at their duty stations by trained team members following an IDI topic guide (Annex S1 in the Supplementary Materials) that included the participants' general information, attitudes, opinions about the model pharmacy initiative, responsibilities, job satisfaction or dissatisfaction, motivational or demotivational factors, challenges, and opportunities for continuing services in an MP. The IDI topic guide also explored recommendations of the pharmacists for the retention of trained pharmacists in MPs in the long term. A separate interview topic guide (Annex S2, Supplementary Materials) was used for conducting KIIs with the stakeholders to explore their perspectives about the challenges of the model pharmacy initiative, opportunities, and recommendations for retaining Grade A pharmacists in the MPs. Both the IDIs and KIIs were audio recorded following consent.

2.3. Data Analysis

The audio records of each IDI and KII were transcribed line by line in the local language (Bangla) in order to generate a transcript, and the transcript was coded using a code list developed around the interview topic guides by a bilingual researcher (NC) guided by

the Principal Investigator (AN). Atlas.ti (version 7.5) software was used for coding. Codes and sub-codes were used for data extraction. Extracted data were first summarized in Bangla following a thematic approach based on key themes and sub-themes before being translated into English. Any quote of a participant was labeled by the type of interview (IDI/KII), type of the respondent (labeled as 'A' for a Grade A pharmacist, and 'B' for a Grade B pharmacist), and district name (BA for Barishal, CH for Chattogram, DH for Dhaka, RA for Rangpur, and KH for Khulna). A unique interview number was assigned to each participant for de-identification and maintaining data privacy.

The transcripts were analyzed to present the summary results under two broad themes: 'theme i', challenges of model pharmacies, and 'theme ii', opportunities to improve model pharmacies. A few sub-themes were generated as guided by the analyses of the transcripts. The sub-themes under 'theme I' included multiple responsibilities of pharmacists, job dissatisfaction of the pharmacists, demotivational factors, operational costs of model pharmacies, shortage of qualified pharmacists, and low social status. The sub-themes under 'theme ii' included salary and benefits, the role of the pharmacist-in -charge, and monitoring of the MPs. The summary results of the sub-themes of the IDIs were collated to explore the views of the pharmacists about challenges and opportunities extrapolated from their own experiences to draw recommendations for their retention in the MPs. The summary results of the sub-themes of the KIIs were collated to explore the views of the stakeholders about the challenges and opportunities of the pharmacists for improvement.

2.4. Ethics Approval

Ethics approval was obtained from the Ethical Review Committee (ERC) of the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b PR-20142, 15 February 2021) and the National Research Ethics Committee of the Bangladesh Medical Research Council (BMRC). Written informed consent was obtained from each respondent prior to enrolment in the study and before conducting an interview.

3. Results

Between February and March 2021, IDIs were conducted with nine Grade A pharmacists and six Grade B pharmacists, and Table 1 summarizes their socio-demographic characteristics. The age range of the participants was 20–29 years, and they were purposively selected from five districts where 56% of the MPs were established. The majority of Grade A pharmacists were female, and the majority of Grade B pharmacists were male. The length of the jobs of the pharmacists working at a model pharmacy ranged from six months to three years.

Table 1. Characteristics of the pharmacists.

Characteristics		**Grade A (*n* = 9)**	**Grade B (*n* =6)**
Gender	Male	3	6
	Female	6	0
Age group	20–24 years	2	3
	25–29 years	7	3
Location	Dhaka	5	3
	Rangpur	2	2
	Barisal	1	0
	Khulna	1	0
	Chattogram	0	1

Table 1. *Cont.*

Characteristics		Grade A (*n* = 9)	Grade B (*n* =6)
Dispensing experience	6 months–1 year	2	1
	1–2 years	3	3
	2–3 years	2	1
	3 years	2	1
Type of involvement	Employee	9	6

KIIs were conducted with nine government and non-government stakeholders. The majority of the stakeholders were male, with an age range of 31–61 years. The key informants were mostly from Dhaka, where the majority of the pharmacy regulatory agencies were located, and a small number of key informants were recruited from the Khulna district (Table 2).

Table 2. Characteristics of the stakeholders.

Characteristics		Total Number = 9
Gender	Male	8
	Female	1
Age (years)	31–40 years	2
	41–50 years	2
	51–60 years	3
	61 years and above	2
Education	HSC	1
	Bachelor	2
	Master	5
	Doctorate	1
Institution	Directorate General of Drug Administration (DGDA)	3
	Pharmacy owner	1
	Pharmacy Council of Bangladesh (PCB)	1
	Institute of Health Technology (IHT), Mohakhali	1
	Dhaka University	1
	Bangladesh Chemist and Druggist Samity (BCDS)	2
Location	Dhaka	7
	Khulna	2

3.1. Challenges of Model Pharmacies: Perspectives of the Pharmacists

3.1.1. Multiple Responsibilities

Grade A pharmacists reported a wide range of responsibilities in the model pharmacies, including reviewing prescriptions and patient counseling to ensure proper medicine use, and verifying medicines dispensed by the pharmacy staff to ensure alignment with the doctor's prescriptions, with particular attention to antibiotics. Grade A pharmacists also ensured the proper storage of medicines at a proper location, maintenance of the right

temperature, and regular monitoring of both room and refrigerator conditions. Another key responsibility was to supervise the junior staff dispensing medicines to the customers and oversee overall pharmacy operations. Additionally, Grade A pharmacists were responsible for tracking the expiration dates of stock medicines and returning expired medicines to the medicine companies, while procuring new stock. A few Grade A pharmacists reported that they manage the cash counter and measure blood pressure and blood sugar levels in addition to their regular responsibilities in the MP. One Grade A pharmacist stated the following:

> "If needed, I have to help them (other staff at the pharmacy) and observe what they are doing. Sometimes, I also have to manage cash when necessary." (IDI-A-DH-05)

The Grade B pharmacists reported similar responsibilities to that of a Grade A pharmacist, except that some reported that they occasionally performed data entry tasks for which they were not responsible. One Grade B pharmacist stated the following:

> ". . .. . .on top of my other works, I also sometimes perform data entry activities at the pharmacy". (IDI-B-CH-06)

3.1.2. Job Dissatisfaction

The majority of the Grade A pharmacists expressed dissatisfaction with their jobs in the model pharmacies. The key reasons for dissatisfaction were low salaries, negative public perceptions about the pharmacy profession, and a lack of recognition. Additionally, it was perceived by the Grade A pharmacists that they do not get the respect they deserve from the owners of the model pharmacies, which aggravated their dissatisfaction further. Long working hours and no compensation for overtime were reported to be significant reasons for dissatisfaction. Furthermore, owners occasionally insisted on prioritizing selling medicines over providing proper counseling to customers, and they have limited autonomy to make choices that may differ from those of the pharmacy owners.

> "The salary structure is very poor. When I joined here (model pharmacy) initially, they offered me ten thousand takas (equivalent to USD 85) per month. They said this was because I would have fewer duties. I thought this amount was too low, but later I decided that I needed the experience, so I joined. They (model pharmacy authority) said they would increase my salary after three months but they didn't. They didn't keep their word and paid only the initial salaries." (IDI-A-DH-05)

The majority of the Grade B pharmacists reported being satisfied with their job in the model pharmacies. Factors contributing to their satisfaction included working in a reputable pharmacy, maintaining good relationships with colleagues, having opportunities to learn, and improving their skills in dispensing medicines.

> "I am satisfied, because considering the current job market, this is a good job. I do my duty for eight hours and I work in a good institution, which is one of the good companies in Bangladesh". (IDI-B-RA-01)

A few Grade B pharmacists expressed dissatisfaction due to low salaries and insufficient benefits. They also felt that sometimes they had a lack of knowledge about basic pharmaceutical issues, such as a lack of understanding of the generic names of the medicines, which contributed to dissatisfaction for some Grade B pharmacists.

3.1.3. Demotivational Factors

Several factors contributed to the demotivation of Grade A pharmacists to work in a model pharmacy. First, they often felt undervalued in the workplace, and some believed that they did not receive the respect or the recognition of their position from their co-workers or customers or the pharmacy owners that they deserved as holders of a graduate degree in pharmacy. Second, the work environment was described as less conducive in terms of inadequate salaries and an absence of any benefits package, which highly demotivated the Grade A pharmacists from continuing their roles in MPs. Third, job insecurity and limited job opportunities led to demotivation significantly. Fourth, Grade A pharmacists were often recruited as medicine sellers, which did not fall under their professional responsibilities, and this demotivated them to continue working in a model pharmacy. One Grade A pharmacist stated the following:

> "Some of my colleagues treat me as a salesman, and they don't want to understand the role of a pharmacist. They even don't know that a Grade A pharmacist is essential to run a model pharmacy." (IDI-A-DH-05)

A few Grade A pharmacists reported that they were compelled to work on government holidays, which disrupted their work–life balance and left them with little time to spend with their families, which negatively impacted their personal lives. The constant demand for unregulated long working hours contributed to feelings of burnout and dissatisfaction with their jobs at the model pharmacies. In addition, Grade A pharmacists generally believed that very few people truly understood the professional roles of a Grade A pharmacist, and, as a result, the general public often did not show respect toward pharmacists working in medicine outlets. This lack of recognition led to significant challenges in their social lives and even impacted their personal relationships. Some Grade A pharmacists also expressed that they did not consider their pharmacy job to be prestigious enough to meet their career aspirations, which was a demotivational factor.

> "Social status is an issue. For example, if I work for a company (pharmaceutical) I may be treated well as a pharmacist but now I am a shopkeeper. Obviously, a shopkeeper, as a result, I become underrated." (IDI-A-BA-08)

Grade B pharmacists similarly expressed dissatisfaction with their poor salary, inadequate benefits, and low social status as demotivating them to work in a model pharmacy. Further, despite being frontline healthcare providers, there is no provision for health insurance coverage for the pharmacists, which is a driver for demotivation.

> "The bad feeling is, our profession (pharmacist) is closely connected with the health service and we have to work in the frontline but we didn't see any initiative from the government. We don't have any health insurance facility and there is no trust in this profession." (IDI-B-DH-03)

3.2. Challenges of Model Pharmacies: Perspectives of Stakeholders

3.2.1. Operation Cost

Stakeholders have identified several challenges associated with operating model pharmacies in Bangladesh. First, the cost of running a model pharmacy is significantly higher, while the profit margins are relatively low. Second, hiring a Grade A pharmacist is expensive for the pharmacy owners. In addition to hiring a Grade A pharmacist, owners are also required to hire drug sellers, which further increases the operational costs. As a result, it becomes financially difficult for owners to afford a Grade A pharmacist to run an MP.

> "If you want to do all the package practice in an appropriate way, it comes at a cost. The costs of sustaining a Grade A pharmacist are prohibitively high if all the rules of a model pharmacy are to be followed." (KII-DHA-06)

3.2.2. Shortage of Qualified Pharmacists

Most of the stakeholders highlighted the shortage of qualified pharmacists in Bangladesh as a major challenge for operating the model pharmacies. Although the demand for quality pharmacy services is high due to a growing population and increasing healthcare needs, the production of qualified pharmacists is insufficient to meet this demand. As a result, most Grade A pharmacists prefer to work in the pharmaceutical industry, where they get better benefits packages and other opportunities, as opposed to working in retail pharmacies. One stakeholder stated the following:

> "The head of a model pharmacy is Grade A pharmacist and assisted by a Grade B pharmacist. These two types of pharmacists are not adequately produced in our country." (KII-DH-03)

3.2.3. Low Social Status

Stakeholders reported that the low social status of the Grade A pharmacists is a significant concern. When graduate pharmacists join a pharmacy, they are often expected to focus on selling medicines rather than utilizing their professional skills. This misalignment between their training and the actual duties they perform leads to a sense of underappreciation, among both the customers and their own professional communities. This lack of respect and recognition contributes to their dissatisfaction with the role. One of the stakeholders stated the following:

> "The society can think that the (pharmacists) is only working in a pharmacy. A Grade A pharmacist had to take a graduate degree at least. In our country, we have only a few pharmacies where pharmacists have a place for counseling." (KII-KH-02)

Some of the stakeholders also cited that a poor salary structure for the Grade A pharmacists is a major reason for the discontinuation of jobs in MPs. A few stakeholders argued that there is a high turnover of Grade A pharmacists in the model pharmacies because the Grade A pharmacists are lured by the pharmaceutical industry with an offering of better benefits and career opportunities.

3.3. Opportunities to Improve Model Pharmacies: Perspectives of the Pharmacists

3.3.1. Salary and Benefits

There are opportunities to improve the retention of Grade A pharmacists in the model pharmacies by offering competitive salaries and benefits. Most of the Grade A pharmacists suggested that the government could encourage model pharmacy owners to implement a competitive salary structure for the Grade A pharmacists backed by compensation packages and additional benefits, such as transportation and housing allowances, which would, in return, also encourage the model pharmacy owners to retain skilled pharmacists. One Grade A pharmacist stated the following:

> "...Everybody wants to see self-benefit. If there is lesser salary provided in a model pharmacy than a pharmaceutical company why pharmacists would be interested to join in a model pharmacy?" (IDI-A-RA-04)

Grade B pharmacists similarly emphasized the importance of offering competitive salaries to Grade A and Grade B pharmacists to ensure their long-term retention and sustainability in the profession. They also proposed adding more benefits, including

annual salary increments, fixed working hours, festival bonuses, and guaranteed weekends, as well as annual leaves to improve the chances of retention of Grade A pharmacists in MPs.

> "We need a government policy for the pharmacists. Since the government has initiated a model pharmacy and model medicine shop program, there is an opportunity for Grade A and Grade B pharmacists. Therefore, there needs to be a policy for the salary and other facilities for staff. If this happens, pharmacists would show their interests." (IDI-B-CH-06)

3.3.2. Role of Pharmacist-in-Charge

Given the shortage of Grade A pharmacists, it has been explored whether Grade B pharmacists could fill in for Grade A pharmacists when necessary. However, the majority of the Grade A pharmacists indicated that Grade B pharmacists study a three-year diploma course, whose curriculum has comparatively low standards compared to the four-year bachelor's course studied by a Grade A pharmacist. As a result, there is insufficient coverage of pharmaceutical topics in the course curriculum for the Grade B pharmacists. Examples include managing the extensive inventory of medicines and overseeing pharmacy operations, which would require a comprehensive knowledge of pharmacology, which Grade B pharmacists cannot learn from their limited diploma courses. Further, the current operational guidelines for the model pharmacies do not permit Grade B pharmacists to take on the role of a pharmacist-in-charge. As such, Grade B pharmacists are not equipped with adequate knowledge and training to assume the role of a pharmacist-in-charge in a model pharmacy, which is the expected role of a Grade A pharmacist. Therefore, the Grade A pharmacists discouraged the promotion of the role of a Grade B pharmacist to the role of a Grade A pharmacist, and instead advised that the number of graduate pharmacists be increased to facilitate the operations of a high number of model pharmacies in order to improve quality of pharmacy practices in Bangladesh.

> "There is no opportunity to replace Grade A pharmacist by Grade B. I guess, there is no opportunity to run a model pharmacy without a Grade A pharmacist in-charge. Otherwise, those pharmacies will not be considered as model pharmacies. One Grade A pharmacist is essential to run a model pharmacy." (IDI-A-DH-07)

Nonetheless, a few Grade A pharmacists acknowledged that the Grade B pharmacists could potentially assume some limited roles of a pharmacist-in-charge in the absence of a Grade A pharmacist, provided that they acquire proper training and gain adequate experience. On the contrary, the Grade B pharmacists expressed confidence in their ability to take on the role of a pharmacist-in-charge, and the majority of them argued that their qualifications, including the length of their studies and the hands-on training received during an internship, adequately prepare them for taking over the role of a Grade A pharmacist. One Grade B pharmacist stated the following:

> "If you ask about the options of Grade A pharmacists, I should say yes. Grade B pharmacists can manage model pharmacy because they have a 3 years 6 months duration pharmacy course and gain experience by doing an internship in a hospital setting. I don't see any difference regarding the responsibility in the model pharmacy. They can manage various crisis moments and they can provide simple treatments, so I think Grade B pharmacists are capable to assume the role of a Grade A. Grade A pharmacist responsibilities can be easily performed by the Grade B pharmacists." (IDI-B-DH-04)

3.4. Opportunities to Improve Model Pharmacy Services: Perspectives of the Stakeholders

3.4.1. Salary and Benefits

The stakeholders recommended competitive salary structures, ensuring proper recognition and respect for pharmacists, and providing a congenial work environment for the pharmacists in order to foster accountability in pharmacy practices. Some stakeholders highlighted that offering competitive salaries would not only retain pharmacists but also elevate their social status.

> "I believe to retain Grade A pharmacists, their salaries and benefits should be increased. At the same time, the government needs to take initiatives to raise awareness on the importance of qualified pharmacists in managing model pharmacies. Enhancing their economic recognition will also contribute to improving their social status." (KII-DH-06)

3.4.2. Role of Pharmacist-in-Charge

The stakeholders expressed mixed opinions about whether Grade B pharmacists should be allowed to assume the role of pharmacist-in-charge in model pharmacies. Some stakeholders opposed the idea by referring to the limited knowledge of Grade B pharmacists and their scarcity in numbers, which they believe would hinder their ability to meet the demanding task of managing a model pharmacy. However, a few stakeholders recognized the challenges in retaining Grade A pharmacists in this role and suggested improving the Grade B course curriculum to reduce the knowledge and skills gap of the Grade B pharmacists, so that they can take on the role of a pharmacist-in-charge when necessary. However, Grade A pharmacists receive proper training on professional ethics and adhere to them, which is a strong justification for recommending Grade A pharmacists to hold the role of a pharmacist-in-charge in a model pharmacy.

> "The work of Grade A pharmacist cannot be performed by the Grade B pharmacist. Meanwhile, the number of Grade B pharmacists enrolling per year is less, compared to the number of Grade A pharmacists. Actually, there is no chance of substituting Grade A pharmacists. There are a few things that need to be done. One is that they have professional ethics, they have to have a place to practice ethics. Grade A pharmacists do not continue a job in a model pharmacy, because people are not being able to do any unethical practices with them. That's why business is losing, that's why they are not recruiting Grade A pharmacists." (KII- DH-01)

3.4.3. Monitoring of the Model Pharmacies

A few stakeholders recommended conducting regular monitoring of model pharmacies to ensure the presence of qualified pharmacists. This is because some owners do not hire Grade A pharmacists even after securing a model pharmacy license, which represents non-adherence to the model pharmacy standards. Robust monitoring and administrative oversight are recommended by the stakeholders to enforce standardized practices in model pharmacies. Such measures would compel owners to comply with the established guidelines and contribute to sustaining quality pharmacy services.

> "The DGDA has to be strict. They have to check whether the Grade A pharmacists are available at the model pharmacies or not. Whether they are doing their jobs or not. It has been seen that many model pharmacies do not replace the vacancy of a pharmacists with a Grade A pharmacist after departure of the originally recruited Grade A pharmacist." (KII-DH-09)

Additionally, stakeholders suggested maintaining quality standards and offering government support, such as, loan facilities for model pharmacy owners. This financial assistance would enable owners to recruit qualified Grade A pharmacists and strengthen the overall workforce quality in model pharmacies.

4. Discussion

The purpose of this study was to explore the challenges and opportunities for good pharmacy practices in model pharmacies in Bangladesh from the perspectives of pharmacists and other relevant stakeholders. Grade A pharmacists face several challenges that hinder their motivation and job satisfaction. These include juggling multiple responsibilities, receiving inadequate salaries, having a poor social status, working in unfavorable environments with long hours, and experiencing a lack of recognition or respect for their profession. In contrast, Grade B pharmacists reported job satisfaction, primarily due to working opportunities in reputable pharmacies and learning opportunities.

The stakeholders identified the high operational costs, the shortage of trained pharmacists, poor salary structures, and limited public awareness of pharmacists' critical roles in healthcare as the key barriers to retaining Grade A pharmacists at model pharmacies. Stakeholders further recommended revising compensation packages, promoting qualified pharmacists, and strengthening monitoring systems to uphold and enhance the standards of pharmacy practice.

The study revealed that multiple responsibilities tend to impose a burden of workload on Grade A and Grade B pharmacists in model pharmacies, which poses a significant challenge that is similar to that of pharmacists in low- and middle-income countries (LMICs) [20–22]. Job dissatisfaction was highly related to the motivation levels of Grade A and Grade B pharmacists. Those who reported job satisfaction were typically employed in reputable model pharmacies, where they received better salaries and benefits compared to those working in less reputable pharmacies. Salaries and other benefits were also found to be key motivational factors for pharmacists in other LMICs [23]. In contrast, negative social perceptions, poor working conditions, inadequate facilities, lack of respect, and the desire to pursue careers in the pharmaceutical industry were cited as reasons for leaving model pharmacies for Grade A pharmacists.

Stakeholders also highlighted low salaries, poor facilities, low social status, family demands, and unfavorable working conditions as key reasons for the demotivation and discontinuation of Grade A pharmacists. These findings align with previous studies, which identified attractive salaries, opportunities for promotion, and professional recognition as some of the most powerful motivational factors for pharmacists [24,25].

Low social status and professional discontent among Grade A pharmacists present another significant challenge. Limited literatures on healthcare workforce dynamics indicates that professional identity and job satisfaction are closely linked to social recognition and the appropriate utilization of skills [25]. A lack of recognition from society and customers, coupled with a limited scope for professional growth in retail pharmacies, has led many pharmacists to prefer working in the pharmaceutical industry, where the benefits, salary structure, and career prospects are more appealing.

According to the model pharmacy accreditation guidelines, model pharmacies are required to have Grade A pharmacists [17]. Due to the high turnover of Grade A pharmacists, the possibility of shifting Grade B pharmacists to assume the role of pharmacist-in-charge in model pharmacies was explored. There were differences observed regarding the opportunities for making Grade B pharmacists in charge in model pharmacies among Grade A pharmacists and stakeholders and Grade B pharmacists. Grade A pharmacists and stakeholders were opposed to the idea of placing Grade B pharmacists in charge in model

pharmacies, considering the insufficient training and inadequate curriculum of Grade B pharmacists. However, Grade B pharmacists found themselves to be qualified for the position, as they are capable of managing the routine tasks carried out by Grade A pharmacists, such as temperature management, medicine procurement, patient counseling, and staff supervision.

Despite the challenges, the opportunities to improve model pharmacy services in Bangladesh are primarily centered around enhancing salary structures, promoting qualified pharmacists, and establishing a robust monitoring system. A key recommendation made by both Grade A and Grade B pharmacists is to increase salaries and benefits, as competitive compensation is critical for retaining skilled pharmacists. Studies on healthcare workforce retention highlight that job satisfaction is closely tied to both intrinsic factors like professional recognition and extrinsic factors like financial compensation [26]. Studies on regulatory oversight in healthcare have found that consistent monitoring is essential for enforcing compliance and maintaining high service standards [27]. The stakeholders in Bangladesh pointed to the need for a proper monitoring system to ensure compliance with model pharmacy standards and the maintenance of the quality and integrity of pharmacy services.

Both the pharmacists and the stakeholders considered the model pharmacy initiative as a promising approach that could significantly enhance pharmacy practices. This type of accreditation of medicine outlets was found to be scalable and sustainable in Tanzania, as it effectively improved the quality of pharmacy services, ensured better adherence to regulatory standards, enhanced customer trust, and contributed to improved healthcare outcomes [28,29].

5. Strength and Limitations

The first limitation of this study is that the number of MPs was much higher in the Dhaka district, and all key regulatory agencies were located there; hence, the majority of our interviews were conducted in Dhaka, which might have reduced our ability to obtain a much broader perspective on the pharmacists and stakeholders working outside Dhaka. Second, due to a low number of Grade B pharmacists in the professional group, we were unable to increase the number of interviews with Grade B pharmacists. However, this study included a wide mix of pharmacists and stakeholders, including representatives from regulatory bodies, academicians, pharmacy owners, and representatives from medicine sellers' organizations, which rendered a better representation of the pharmacy community in Bangladesh. Further, despite the low number of interviews, we were able to reach data saturation with the IDIs and KIIs of each group. This allowed us to obtain a broader knowledge base on the practical challenges of attaining good pharmacy practices in the MPs and potential opportunities for strengthening model pharmacy initiatives in Bangladesh.

6. Conclusions

This study has highlighted the challenges faced by Grade A and Grade B pharmacists working in model pharmacies. The model pharmacy initiative is a unique and promising effort to promote good pharmacy practices across Bangladesh. However, its success depends on rigorous monitoring, consistent enforcement, and support from the relevant authorities to ensure adherence to established standards. Despite the challenges, the model pharmacy initiative has great potential for further improvements by enhancing regulatory standards and effective implementation and fostering a supportive work environment in MPs for retaining pharmacists. Periodic training, better incentives, and the provision of heightened social value of the pharmacists are essential for empowering the pharmacists to

deliver high-quality pharmacy services and promote better health outcomes for the people of Bangladesh.

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Article

Resentful, Resigned and Respectful: Opioid Analgesics, Pain and Control, a Qualitative Study

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Abstract: Opioid analgesic prescribing has increased significantly with associated concerns about dependence and overdose. This study aimed to explore non-cancer patients' experiences and views of taking opioid analgesics to manage their pain. Twenty-two patients were purposively sampled from English GP practices and participated in semi-structured telephone interviews. Braun and Clarke's thematic analysis was used to generate emerging latent and semantic themes. Patients resented taking opioid analgesics due to tolerance and addiction fears but were resigned to experiencing chronic pain. Control emerged in relation to patients' acceptance of doctors' control over treatment decisions but also patients' attempted self-control over medicine adherence. This involved negatively perceived attempts to control pain but also prevent tolerance and addiction. Non-pharmacological treatments were viewed negatively by patients and addiction awareness arose from various sources. Patients were respectful of doctors but expressed negativity about the lack of addiction warnings, medication reviews and appointments. Family and friends were infrequently mentioned, as was reference to shared decision-making, suggesting patients navigate control over opioids and pain in relatively isolated ways. Patients reported generally negative experiences of opioid use for pain, which provides key insights for health professionals to enhance understanding and the management of such patients.

Keywords: opioid analgesics; chronic pain; qualitative research

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1. Introduction

Chronic pain and the particularly optimal ways to manage it represent ongoing issues in many countries. It is estimated that around 11–20% of people in Europe and the United States (US) may experience chronic non-cancer pain [1], and estimates in the UK suggest this may be even higher, with between a third and half of the population experiencing a type of chronic pain [2]. These are linked to increasingly ageing populations and associated chronic conditions. Opioid analgesics play a significant role in the management of various types of pain, ranging from traditional opiates such as morphine and codeine to more recent semi-synthetic and synthetic opioids such as oxycodone and tramadol. Opioid use in acute, operative and cancer pain is well established and clinically supported, but concerns have been increasingly raised about opioid use in chronic non-cancer pain [3]. Concerns relate to a variety of harms including dependence in particular but also increased risks of overdose and fatalities [4], respiratory depression and hyperalgesia, misuse, abuse and medication-error-related adverse events [5] and sociological concerns about stigma and shame also [6,7]. Exacerbating these concerns have been trends of increased prescribing and

availability of opioids in many high-income countries and more specifically prescribing of higher strength opioids [8–10]. These trends are multifactorial, attributed partly to commercialised healthcare systems influenced by pharmaceutical companies and lobby groups leading to a

> "[. . .] perception, promoted by some pharmaceutical manufacturers and clinical societies, that chronic pain in the general population was under-treated.". [11] p. 2

A deficit in opioid alternatives has also been cited as a contributing factor, with other medications considered ineffective or having excessive side effect profiles, and all these factors have led to opioid analgesics being considered a global issue [10].

Studies have reported both prescribing doctors and affected patients expressing negative experiences surrounding the management of pain and associated outcomes. Doctors have recognised their need to develop prescribing skills, opioid pharmacological understanding and patient communication skills [12,13]. Patients using opioids have unmet needs with regards to pain relief and support in improving quality of life [12]. For other health professionals such as pharmacists, further negativity about opioids and pain management has been reported, relating to over-prescribing and limited clinical guidance [14]. Patients perceive opioids to be potent and associated with addiction and dependence but also express dissatisfaction with alternative therapies [15,16]. A recent meta-ethnography of international qualitative studies exploring patient experiences of opioid use in chronic pain identified themes such as reluctant use, good and bad understanding, problems in the therapeutic alliance, stigma, tapering and withdrawal challenges [1]. This review identified only two studies relating to the UK, where prescribing and use trends may not reflect those in other high-income countries. This study aimed to address this relative lack of understanding and sought to explore the experiences and views of patients in England taking opioids for non-cancer pain, capturing a range of demographics and clinical aspects such as patient location, age, clinical condition, opioid type and also medication dependency status.

2. Materials and Methods

This qualitative study was one phase of a wider study of non-cancer opioid analgesic use among patients in England, which involved an initial cluster sample of patients from 10 GP practices across England. Practices were selected to represent a broad distribution geographically but also in terms of the number of patients registered at each GP practice site (ranging from around 4600 to over 19,000 patients), urban and deprivation, reflecting recognised patterns and variations in opioid prescribing across England [9,17].

Participants in the quantitative phase of the study were invited to complete a postal questionnaire, which included a dependence measure—the Prescription Drug Use Questionnaire Patient version (PDUQp) [18]—and the option to participate in the qualitative interviews presented in this paper. From those who responded, a purposive sample of patients (based on age, sex, GP practice, dependency status and score) was invited to participate in a semi-structured telephone interview. Inclusion criteria included patients currently taking an opioid for analgesic purposes for non-cancer pain for a period of at least 3 months and having the capacity to consent. A qualitative interview guide was developed based on an initial review of the relevant literature and an analysis of quantitative stage questionnaires (see Supplementary Materials). Topics included exploring in more depth patients' conditions and their use of opioid medicines over time and whether patients considered them (and other treatments) to be effective in controlling their pain, their experiences of health and social care services and the impact their opioid use has had upon key aspects of their lives such as relationships, work and other activities. The

telephone interviews were fully audio-recorded with patients' consent from a private university meeting room (using an in-line digital audio-recording device). Audio recordings were then transferred to a secure university digital file store, and then trained university transcribers used them to produce an anonymised written transcript; this was used in the subsequent analysis using Braun and Clarkes' six-stage thematic analysis [19,20] to identify relevant themes. Theoretical saturation was used to determine the final sample size with additional participants being identified and recruited until no new themes emerged from the analysis; interviews were undertaken around January 2018. Coding was undertaken manually using the annotation of paper transcripts and the charting of emerging themes, which were reviewed and revised as the analysis progressed, using the later stages of Braun and Clarke's 6-stage thematic analysis. In particular, active attempts were made to identify not only semantic themes (those more explicit and literally identified within the data) but also latent themes (those that were less literal and reflected more underlying themes).

3. Results

The analysis revealed a range of themes reflecting experiences with healthcare, and doctors in particular, along with experiences of living with chronic pain and the role of various treatments. Three dominant latent themes of resentment, resignation and respectfulness emerged. Patients were resigned to taking opioid analgesics yet resented this fact while appearing implicitly respectful of the clinical decisions of doctors. Contrasting aspects of control also emerged as a further latent and overarching theme: patients relinquished control of medicine initiation and dose titration to doctors while attempting to gain subsequent control over how they consumed and adhered to their opioid medication. The latter was a balance of the perceived threat of dependence with the need to control pain; many of these were captured in one key quote, from Kim and her account of long-term opioid use for post-operative knee pain:

> "[. . .] I think I did get myself off the pills but then I got in so much pain they put me back on again [. . .] and I've always sort of not been good at taking them, I do take them when the doctor says you have to, but when you've been on them for a very long time you think: 'have you been on them too long? Are they doing anything?' And try to wean off." Kim

Each theme is now considered in more detail with illustrative quotes from different patients. As Table 1 indicates, all participants were currently taking an opioid but several reported using other analgesics, and these are captured in the accounts that follow.

Table 1. Summary of participant patient characteristics and relevant clinical details.

Pseudonym	Location	Age	Employment	Current Opioid and Other Medicine	Initially Prescribed by	Pain-Related Condition	PDUQp
Laura	U2C1	60s	Retired	Codeine, co-dydramol	Hospital gastroenterologist	Pain and associated symptoms of Irritable bowel disease	16
Louise	U2C1	60s	Retired	Codeine, gabapentin, amitriptyline, co-codamol	Hospital pain clinic	Osteoarthritis, knee replacement, post-op complications	16
Georgia	U2C1	50s	Retired	Oxycodone, codeine	GP	Back pain	15
Elizabeth	U2C1	40s	Long term sick/disabled	Co-codamol	Nurse prescriber	Renal calculi	14

Table 1. *Cont.*

Pseudonym	Location	Age	Employment	Current Opioid and Other Medicine	Initially Prescribed by	Pain-Related Condition	PDUQp
Mike	U2C1	40s	Self-employed part-time	Co-codamol	GP	Accident at work, then car accident	13
Sylvia	U1A1	70s	Retired	Buprenorphine dihyrocodeine parcetamol	GP and hospital	Accident/pain injury, polymyalgia rheumatica	13
Tony	U1A1	50s	Long term sick/disabled	Buprenorphine	Not disclosed	Accident	12
Dan	U2C1	60s	Retired	Zomorph, co-codamol, co-dydramol	GP and hospital	Accident/fractures	12
Kara		60s	Employed	Tramadol	GP	Back pain	11
Vera	U2C1	80s	Retired	Co-codamol	GP	'Severe arthritis'	11
Kim	U2C1	60s	Long term sick/disabled	Tramadol, co-codamol, gabapentin, amitryptline,	GP	Arthritis, knee operation	10
Clive	U1A1	50s	Long term sick/disabled	Co-codamol	GP	Arthritis 'joint pain-hips, knee, ankles, shoulder'	10
Claire	U1A1	50s	Long term sick/disabled	Co-codamol	Hospital surgeon	Posterior tibial dysfunction	10
Sharon	U1B1	20s	Long term sick/disabled	Co-codamol	GP	Sciatica—Herniated Disk	8
Alice	U1A1	70s	Retired	Morphine	GP	Degenerative disc disease, osteoarthritis/knees, arachnoiditis	7
Katie	U2C1	60s	Long term sick/disabled	Fentanyl	GP	Degenerative lumbar disc disease	6
Jackie	U1B1	70s	Retired	Co-dydamol	GP	Arthritis spine, spondylosis neck	6
John	U1A1	60s	Retired	Co-codamol, Tramadol	GP	Osteoarthritis, rheumatoid arthritis	3
Veronica	U2C1	30s	Employed	Co-codamol	GP	Sciatica after hysterectomy operation	3
Jack	U1A1	60s	Self Employed	Codeine	GP	Back pain	2
Len	U1B1	70s	Retired	Co-codamol	GP	Migraine	1
Flora	U1A1	60s	Retired	Tramadol	Hospital registrar	Rotator cuff injury	1

U1A1: large urban area, major conurbation; U1B1: large urban area, minor conurbation; U2C1: smaller urban area, urban city and town.

3.1. Resigned to Pain

Patients were resigned to experiencing pain, despite the use of opioids, additional analgesics and other therapies. Views about pain varied but most demonstrated stoicism towards pain being unavoidable and only partially treated:

> "I'd like to say I'm on this painkiller and that painkiller and it's doing the job. At the moment nothing's touching it [. . .] I grin and bear it and I shouldn't. I'm not one to complain [. . .]" Dan

Pain was not a static phenomenon and patients with chronic conditions described worsening of pain along with partially predictable fluctuations, for example, after exer-

cise. Controlling pain was challenging with both dependent and non-dependent patients needing to be vigilant about opioid timing to avoid excess pain:

> "I am in a lot of constant pain but at least this sort of takes the edge off it a bit. If I forget to change it [fentanyl patch] and I do know. I am in a lot of pain. I realise I've forgotten to change the patch. But I make sure I've got a thing set on my phone that reminds me to change it every seventy-two hours." Katie

Patients appeared to legitimise their use of opioids by comparing their pain to prior painful experiences such as obstetric pain and migraines. By the pain being more severe than these episodes, this seemed to give their opioid use context and validation. Although some patients reported acute accidents and iatrogenic harm, most patients received a chronic medical diagnosis which initiated their illness narratives and provided further legitimation for opioid use. Also linked to resignation, there was a pessimism about prognoses and the future, often reinforced by doctors:

> "Basically I've got a worn out disc now [. . .] So the doctor has said it is never going to get better. It's just something basically that I've got to kind like live with. So I live with back pain like every single day, but some days it is worse than others." Mike

For a minority of patients, particularly those with more acute conditions, there was more optimism, and patients either reported that they no longer used opioids, or felt that their use might reduce over time.

3.2. Resentment of Medicines

The most explicitly articulated concern for patients was a negativity towards taking any medicines but opioids in particular in the accounts of both non-dependent and dependent patients:

> "I would love to be off the medication. . .absolutely I hate taking them. Absolutely hate it. But I know I can't function without them." Kara

Patients actively resisted consumption of medicines even if it meant they experienced pain, as Len noted about his attempts to control migraines:

> "I am not a good tablet taker. I would prefer to suffer for twenty minutes if you know what I mean and then take a tablet. But if it's. . .I know there's a migraine coming on, I have to take something because I know for a fact it's going to knock me out you know." Len

Most patients reported active attempts to limit opioid doses and even try to stop completely, often accepting higher pain levels in order to reduce dependency risks. Patients were generally knowledgeable about their opioid, reflected by the use of generic and brand names interchangeably, dose and strength specifics and many referring to the 'maximum' dose they typically never exceed in their accounts.

Opioid side effects contributed to resentment, with participants demonstrating well-informed lay knowledge of common complaints. The terms 'dependence' and 'addiction' were explicitly used along with implicit concerns about the loss of therapeutic effects and fears of becoming 'immune':

> "[. . .] I also keep changing them if I can. If I'm on one for quite a long time I'll switch to a different one because I think your body gets used to it." Vera

For several patients, the recognition of being on the maximum strength of an opioid carried anxiety due to the lack of future pain control. The concern that the prospect of addiction instilled varied. Those with experience of withdrawal symptoms or previous

addiction to either alcohol, illicit substances or prescription medications had heightened concerns:

> "So I only take them if I'm actually in pain and it's really, really annoying [. . .]. I was a very, very severe alcoholic. Obviously there's an addiction. . .underlying addiction problem so I'm trying to keep off [medicines] except for my diabetes medicines and my statins." Clive

All patients recognised that opioids have addiction potential; however, some perceived themselves to have non-addictive personalities and were not concerned whereas others, and particularly those who had other previous addictions, considered this a key concern. Opioid addiction awareness came from a range of sources, including prior knowledge, internet searches, social media, general media, friends and family and, for some, medical advice (see Table 2).

Table 2. Influences of the social construction of opioids and addiction.

Negative Depiction	Positive Depiction
Medical advice	Medical advice
Personal experience	Personal experience
Media reporting	
Social media	
Internet	
Celebrity addiction	
Experiences of family and friends	

Often, multiple sources contributed to patients' lay understanding of opioids and addiction, as Clive summarised:

> "The information I've got is via the internet, via the newspapers but I don't tend to believe what the newspapers print. I'd rather double check with the NHS. I do know people do get addicted and are compulsive pill poppers so I've seen that in my dad [and my], girlfriend's mum she used to be a compulsive pill popper" Clive

Family and partners emerged in several patient accounts; some served as cautionary examples as in Clive's case or had commented negatively and had questioned patients' use of opioids as was the case for some friends and work colleagues:

> "My partner doesn't like me taking things like that. She's very against all forms of medication really, generally, especially painkillers. But that's just her, that's just her opinion." John

Despite patients' relatively informed knowledge of opioid strengths and dosages, many did not have concomitant pharmacological insights. Several patients noted that it was only from hearing about their medicines in the media that they had become aware they were taking opioids:

> "Well I knew opioids were addictive but I just didn't realise until it was on the news. I didn't realise that the fentanyl was an opioid [. . .] I know what opioids are like cocaine and stuff like that." Katie

Several patients had actively attempted to either reduce the dosage or completely cease opioids with some reporting withdrawal symptoms which, particularly when linked to embodied physical effects, heightened their addiction concerns. Withdrawal symptoms varied and included flu-like symptoms, headaches, restlessness, shaking, insomnia and nausea. In some cases, doctors appeared to confirm and legitimise such experiences:

> "[. . .] when I was poorly in the hospital and sort of fidgety and twitching and this particular doctor said well it's obvious because you've stopped codeine for four days." Laura

Drowsiness was most often mentioned, however, and several patients reported this being an increasing problem with stronger opioids and tramadol in particular. Several patients also reported the associated impact this had on their work and productivity:

> "I never took tramadol while I was at work. I just tried to manage on the codeine because obviously tramadol makes me very drowsy [. . .] so yeah it was just trying to balance what kept the edge off the pain enough to be able to do my job really." Claire

Tramadol was viewed particularly negatively, and several patients recounted how it had been discontinued by prescribers due to adverse side effects. Despite the frequency of musculoskeletal conditions, there was a surprising lack of reference to NSAIDs and paracetamol. Some patients reported non-opioid analgesics helped control pain and other symptoms like insomnia; however, they were often regarded as being ineffective:

> "I. . .the GP decided that I'd been on things quite long enough, and they changed them all so I has something else. . .yes I mean I was on paracetamol and you might just as well throw them in the bin, [. . .] they have got no effect whatsoever." Sylvia

This quote also illustrated the recurrent description of patients appearing to passively accept medical decisions in the correction of 'I' to 'the GP', which will be considered later in terms of 'respect' for doctors.

3.3. Other Treatment Options

A further factor that appeared to substantiate the previous two themes of resignation to pain and resentment to taking medicines was the perceived lack of effective opioid alternatives. Patients identified several non-opioid treatment options; some viewed these positively, yet overall, they were viewed negatively (Table 3). Some patients attributed this to a lack of perceived benefit while others reported logistical issues such as referral/appointment delays which caused some to give up trying to access such services. Sharon described her request for alternative analgesia; however, as will later be described, doctors retained control over this decision, and Sharon appeared to accept their input:

Table 3. Alternative treatment options.

Treatment	Positive Aspects	Negative Aspects
Physiotherapy	Few but some short-term benefits	Made symptoms worse, long waiting list, lack of any benefit, low motivation to continue
Acupuncture	Fear	None reported
Non-opioid analgesics	Non-addictive	Tolerance, concerns, side effects and contra-indicated
Pain clinic	Improved pain	Waiting lists
Self-management	Prevented exacerbations of pain, linked to maintaining mobility	Cost (of equipment), required motivation
Psychological therapies	None reported	Patronizing and not effective

> "I asked my new GP. I said 'Could I get something stronger?' She said 'I am so sorry Sharon' she went, 'but we can't. We can't give you something stronger'; [she] talked about physiotherapy [and] I did one session and it were absolutely

> brilliant. It eased the pain for a couple of weeks but then I was back to the same pain again. So really it were just to be honest it were a waste of time doing that really." Sharon

There appeared to be variation in which patients were referred to a pain clinic. Some patients reported being reviewed by the clinic as a positive experience; however, others reported this service not being made available to them.

Patients expressed being 'stuck' on opioids with alternatives failing to manage their pain. This lack of pain control led to a minority of patients increasing their opioid quantities as was the case with Georgia and Veronica. Alice illustrates the concerns surrounding addiction and lack of alternatives:

> "Well you know, my only concern is that I'm addicted to it and I know I will be after this length of time, but what is the alternative? [. . .]. All the alternatives I've had have never done anything at all, so at least this keeps my pain level just to a stage." Alice

3.4. Respectful of Doctors

Doctors were referred to repeatedly throughout patient's accounts, the majority being general practitioners with others including hospital consultants and those involved in pain clinics and acute admissions. A key finding that emerged was implicit descriptions of patients accepting both opioid and non-opioid medical treatment passively and appearing respectful of doctors overall. However, there was criticism, with issues regarding difficulty obtaining appointments, a lack of continuity of care and medication reviews, conflicting information being given by different doctors and a perceived lack of warning about opioids and addiction overall. Overall, patients were implicitly respectful toward doctors and particularly their decisions about medicines. This was shown by their acceptance of medical paternalism and the use of the pronominal 'they' to generalise doctors, as Kara illustrated in her account of having medicines changed:

> "I was on tramadol and then they put me on to, what was it, pregabalin, yes because the tramadol just didn't seem to be touching and then it was the pregabalin and that that helped, [. . .] but then I don't know if I got immune to that as well [. . .] and then eventually this other doctor changed pretty much all of them so I'm just coping with those." Kara

This account contained elements that were typical of many patients, including lay references to tolerance—being 'immune'—and reflecting a passive acceptance of doctors' authority. Patients' accounts did vary and ranged from some accepting doctors' decisions, even when expressed as recommendations, to challenging and criticising them. However, across all patients, there was still an overarching acceptance of doctors' decisions. Sylvia recounted instances where doctors made errors but countered them with repeated examples of her compliance and trust in doctors, as these two contrasting quotes illustrate:

> "[. . .] under no circumstances was I to have gabapentin whether it was to do with medication I was on already, I don't know, but anyway the stupid doctor you know gave me gabapentin and I tell you my ankles swelled [. . .]" Sylvia

> "[. . .] you go to the GP or you are in hospital, you come out the doctor writes a prescription out for you, so you automatically think that it is safe [. . .] and you think they know what they are doing when the give you a prescription [. . .]" Sylvia

As the above illustrates, examples of perceived poor medical practice were reported, and accounts of iatrogenic harm arose, for example, relating to post-operative pain. Infre-

quent examples of shared decision making were reported and often related to GPs giving a choice of medications, as Flora described:

> "Actually he gave me the choice. He said 'You can have, I can give you, a tramadol or I can give you'—I can't remember what the other tablet was [. . .] I said 'I've heard of tramadol a friend of mine takes it and she finds it very good so I'll try the tramadol' [. . .]. That was how I actually first came to take it and nobody's reviewed it with me since [. . .]." Flora

This quote illustrates the influence of others in relation to opioid decision making, but also about the subsequent lack of medication review. Veronica felt that this lack contributed to her escalating use of codeine at doses significantly higher than recommended:

> "No, I feel angry in a way because they could have stopped it a long time ago. And I think if they'd reviewed me more regularly they could have probably picked up before even I did, but there was an issue. I mean because by the time I'd picked it up, I was going to go into withdrawal. And then I had no support when I was going through withdrawal either." Veronica

For other patients, reviews were reported and appeared to involve relevant discussions about opioids, but this was less common and in examples such as Mike's below, may have been related to his frequent contact with his GP:

> "[. . .] when I went in for a review [. . .] she said you are not a red flag alert to us really because she said there are some people she said that like take thirty to forty Solpadeine a day with an addiction. And I was actually in shock. I was just like wow. I said I've never gone past eight a day." Mike

Many patients expressed negativity about the lack of warning about possible addiction given, and at times, conflicting medical advice. For some, this led to anger about not being able to make an informed decision about their medicine:

> "I felt like the doctor should have said you maybe come addicted or what the problems could have been and then I might have said 'No I'm not taking them. I'll take an alternative'. [. . .] nobody seems to tell you things these days about. . . not just tablets, but you have to find a lot of information out yourself." Kara

Other healthcare professionals were rarely mentioned, for example there was brief mention of community pharmacists; however, pharmacists did not appear to represent a significant professional group, except as being the route to opioid supply.

4. Discussion

Overall, patient experiences of opioids varied greatly. There were overriding reports of resignation to being in pain alongside strong resentment to requiring opioid medications to only partly relieve pain. Patients appeared to respect and accept the decisions of doctors to initiate or change their treatment, including opioid-based and alternative treatments, while maintaining a broadly negative opinion as to whether their pain could be ameliorated. Unfortunately, the support available to patients requiring analgesia varied widely based on these patient narratives. This included inconsistencies regarding who was referred to pain clinics, the extent of information that was provided to patients about what medicines they were prescribed and warnings about addiction and tolerance risks. In response to concerns about tolerance and addiction, patients attempted to exert control over their own use of opioids, often reporting trying to take them less frequently or only when in pain. This highlights the complexity of the relationship between patients and their opioid analgesia and the various ways they relinquish and retain control. Figure 1 illustrates key themes and where they relate to the respective patient or doctor domains and overlaps. As the

figure shows, there were few examples of a genuine relationships and joint decision making between doctors and patients.

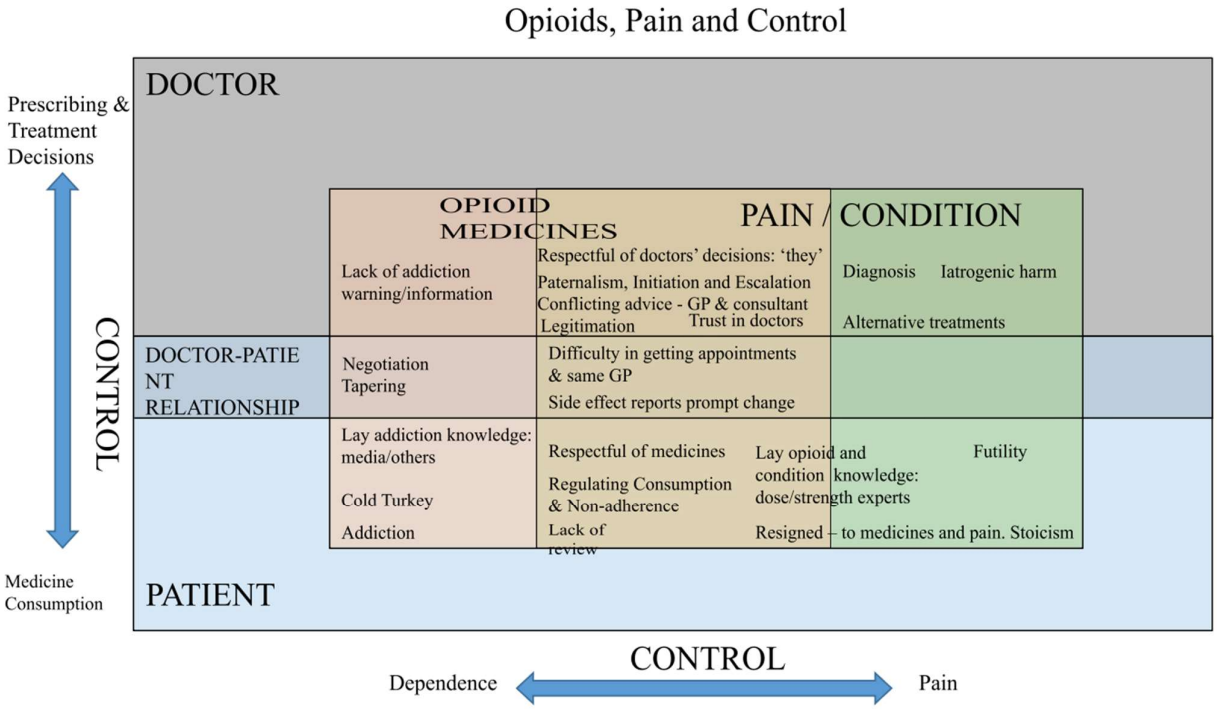

Figure 1. Summary of the relationship between patients and doctors.

5. Comparison with Existing Research

This study highlighted the largely negative experiences and attitudes patients had towards pain management, often describing perceived futility regarding attempts to control pain. This attitude has been documented in prior qualitative studies and meta-ethnographies also describing patients returning to medical professionals with ongoing pain despite increasing doses of analgesics [1,12].

A proportion of patients enrolled in this study emphasised the lack of information regarding opioids they were given prior to taking them. Although some patients demonstrated a high level of opioid-based knowledge, some highlighted the perceived lack of warnings regarding addiction and tolerance they received which may have altered their decision to commence opioids. This lack of patient awareness regarding opioids and their risk is seen in other literature, also extending to a lack of awareness of support available for those suffering from dependence [21]. The need for patient education is also implied by efforts, both in the UK and internationally, to educate the general public about potential opioid candidates [10].

Concerningly, patients in this study also reported a perceived lack of support after commencement on an opioid, for example, a lack of medication review appointments. This finding was echoed in other studies reporting patients remaining on opioid prescriptions without sufficient follow-up or clear treatment plans, in some cases resulting in patients using opioids for longer than necessary, increasing addiction risk [21].

A major barrier to opioid use reduction was reported to be a lack of suitable analgesic alternatives, and within this study, this added to patient anxiety due to concerns regarding what could alleviate their pain once high-dose opioids became ineffective due to tolerance. This lack of suitable alternatives has been reported in other studies that also reference it as a catalyst for long-term opioid prescribing [1,10,12].

5.1. The Role of Doctors in Opioid Analgesic Dependence

A key emerging concern from patients in this study was that whilst they appeared to be respectful of doctors in terms of accepting their prescribing decisions, negativity did emerge in relation to several key issues, including a perceived lack of sufficient addiction or dependence warning given to patients, a lack of review or monitoring of their opioid prescribing and difficulty obtaining appointments and continuity of care. In relation to providing warning, this was arguably related to the other issue, summarised in Figure 1, of the doctor–patient relationship and the lack of emerging examples where this appeared to involve shared decision making and communication. Similar themes and concerns have emerged in previous qualitative research involving opioid analgesic patients and GPs in England [12] and a meta-ethnography of pain patients [22]. For McCrorie et al. [12], a concern about 'locating control' and differing doctor and patient perspectives was identified. Evidence does appear to suggest opioid medication reviews are undertaken, and Song and Foell [23], for example, reported an audit of opioid analgesic prescribing, and reviews were documented in 85.7% of cases, but the quality of such reviews could not be assessed. RCGP guidance materials [24] also suggest the need for appropriate monitoring as part of the prevention of misuse and dependence and specifically describe what should be involved in 'discussions with patients', and in particular, ensuring patients are given sufficient information and warning about dependence.

5.2. The Role of Pharmacies in Opioid Analgesic Dependence

There was surprisingly little mention of community pharmacies by participants in this study. Indeed, the role of pharmacists and pharmacy staff seemed to be considered as one of supply with little clinical input; although, there was one passing reference to a pharmacist reviewing a patient's medication. This differs from the wider policy and research context in which the role of both community and primary care (GP practice) pharmacists in managing chronic pain patient medication has been researched, and evidence suggests there could be clinical benefit from pharmacist involvement. Bennet et al. [25] undertook a systematic review of pharmacist-delivered educational interventions in chronic pain management, which included four studies in a meta-analysis. The findings demonstrated a reduction in average pain intensity (0.5 on a 0 to 10 scale), a reduction in adverse effects by more than 50% and an improvement in satisfaction with treatment (1 point on a 0–10 point scale). Community pharmacies would appear to be an obvious location to deliver an educational intervention, given that people attend regularly to collect prescriptions, and there is a documented lack of treatment satisfaction in the current model of care, which was noted in this study and elsewhere. A Canadian study [26] found patient satisfaction with pain treatment was low, particularly around the provision of information regarding treatment and medication. That study concluded community pharmacists could extend their role to improve the management of chronic non-cancer pain. In a GP practice setting, an exploratory trial by Bruhn et al. [27] indicated that pharmacist medication review (with or without pharmacist prescribing) could reduce pain intensity and improve mental wellbeing in patients with chronic pain. Several evidence reviews have also identified opportunities for pharmacists to contribute to opioid stewardship, leading to beneficial outcomes in areas such as education and medication therapy adjustments [28,29]. In England, there are community pharmacy services such as the New Medicines Service (NMS), which allows pharmacists to undertake reviews on certain medicines when they are initially prescribed, but none of the current eligible conditions for NMS would cover opioid analgesics. There was also a Medicines Use Review (MUR) service, which had been argued to be of relevance to managing opioids [30], but this service was discontinued in England in 2021. It should also be noted that pharmacists are increasingly undertaking prescribing in several countries,

and this research hopefully provides insights for pharmacists who may be involved in the prescribing of opioids and the management of pain.

6. Strengths and Limitations

This study had key strengths in linking patients' self-reported quantitative opioid use and providing additional insights linked to dependency status and experience, with no obvious patterning of experiences or views linked to whether patients were dependent or not according the PDUQp definition. Purposive sampling captured a range of different demographic characteristics across a number of GP practices in England. Interviews were by telephone, and this may have impacted the establishment of rapport in the interviews but were preferred by participants. The interviews were conducted around January 2018 and reflected the prescribing trends and service provisions in England at that time and may not reflect current practices. However, they remain a powerful and important insight into patients with chronic pain taking opioid medicines.

7. Conclusions

This paper reveals that patients have complex relationships with opioids. This study offers further evidence of problematic opioid use and of patients resigned to pain, resenting opioid medicine consumption, but being respectful of doctors and managing in relatively isolated ways. Different aspects of control also emerged, which were located in medical authority but also patient autonomy with a contested overall balance in relation to this. There are several implications for clinical practice and policy in relation to the need to increase awareness of opioid addiction risks among the public, as numerous other studies have found, to improve the appropriate prescribing and also deprescribing, improve the reviews on opioids as well as associated reviews on the management of non-cancer chronic pain more generally and increase awareness on how shared decision-making can be achieved between patients and various health professionals. This in turn suggests important opportunities for other health care professionals to do more and to review their relationships and communications with patients on opioid analgesics to improve their experiences.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/pharmacy13010025/s1, Examples of Qualitative Interview Questions.

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Article

University Pharmacy Clinic: Preventing Errors and Enhancing Lives Through Expert Medication Management

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Abstract: The University of Otago School of Pharmacy Clinic serves as a model for innovative medication management, tackling critical medication-related problems (MRPs) to enhance patient outcomes and advance pharmacy education. This study evaluated the clinic's impact, examining 456 patient consultations over four years, with a focus on MRPs such as dosing errors, non-adherence, and inadequate monitoring. Using the DOCUMENT classification system, pharmacists identified 754 MRPs and issued 836 recommendations, primarily related to medication adjustments and monitoring. Patients reported significant improvements in health-related quality of life, as measured by the SF12V2 survey, with notable gains in mental and physical health metrics. This outcome highlights the clinic's dual role in optimising patient care and providing pharmacy students with experiential learning opportunities. By integrating hands-on training within a supervised clinical environment, the clinic addresses workforce shortages and reinforces the value of pharmacist-led interventions. The findings advocate for university-based clinics as pivotal hubs for resolving MRPs through interprofessional collaboration, targeted interventions, and innovative technologies such as telepharmacy. The study underscores the need for expanded roles for clinical pharmacists in healthcare policy and practice, showcasing their potential to prevent medication errors, enhance lives, and reshape the future of pharmacy education and patient care.

Keywords: medication-related problems (MRPs); pharmacist-led interventions; health-related quality of life (HRQoL); university-based clinics; experiential pharmacy education

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1. Introduction

In the ever-evolving landscape of healthcare, medication management is crucial for ensuring optimal patient outcomes and enhancing the overall quality of care. As the complexity of therapeutic interventions increases, so does the need to identify and resolve medication-related problems (MRPs), which are essential for patient safety. Clinical pharmacists, with their specialised expertise in pharmacotherapy, are pivotal in this process. Their role extends beyond merely dispensing medication—they are key healthcare team members, addressing MRPs and optimising medication regimens to improve patient health outcomes [1–3].

To address the shortages of clinical pharmacists, the University of Otago School of Pharmacy Clinic has developed a dedicated hub where expert clinical pharmacists provide patient-centred care focused on identifying and resolving MRPs [4]. Located on the University of Otago campus, the clinic serves a diverse patient population, offering specialised medication management services tailored to various healthcare needs. Whether patients self-refer or are referred by other healthcare professionals, the clinic provides a

range of services, including comprehensive medication reviews, medication reconciliation, deprescribing consultations, chronic disease management support, vaccinations, adherence counselling, and ongoing support to maintain effective medication regimens. For example, pharmacists assist patients with complex polypharmacy by optimising their medication regimen, providing smoking cessation programmes, and offering individualised education on managing conditions such as diabetes and hypertension—all at no cost to the patient.

The clinic is not just a teaching facility but a space where learning and practice converge. With dedicated patient interview spaces and the involvement of undergraduate pharmacy students in each consultation, the clinic provides invaluable hands-on experience. These clinical placements allow students to apply their academic knowledge in real-world settings, deepening their understanding of healthcare complexities and honing the competencies required to deliver high-quality patient care. By immersing students in the practical challenges of patient care, the clinic supports the ongoing evolution of the pharmacy profession.

Tackling challenges like funding, patient involvement, and integration into national healthcare systems is essential for sustainable success. Funding constraints may impact staffing and operational capacity, while patient involvement remains vital to ensure consistent participation and adherence to pharmacist recommendations. Additionally, incorporating pharmacist-led clinics into national healthcare frameworks necessitates policy adjustments and collaboration with primary care providers. This study will add to the existing body of evidence by showing how a university-led pharmacist clinic can effectively tackle medication-related issues, improve patient health outcomes, and enhance healthcare efficiency. This research will provide valuable insights for policymakers and healthcare leaders considering the wider implementation of pharmacist-led services by assessing intervention outcomes and pinpointing barriers such as funding limitations and issues with patient involvement.

MRPs remain a significant challenge in healthcare due to their association with increased hospital admissions, adverse drug events, and healthcare costs. Studies indicate that MRPs contribute to nearly 30% of hospital admissions in older adults, highlighting their widespread impact [5]. These problems, which can arise from medication errors, adverse reactions, drug interactions, or non-adherence to prescribed regimens, pose serious risks to patient health. The Pharmaceutical Care Network Europe (PCNE) defines an MRP as "an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes". This definition underscores the importance of identifying and addressing MRPs to ensure safe and effective medication use [1].

The Australian PROMISE II trial systematically classified these medication-related issues using the DOCUMENT classification system. This system was further refined in the PROMISE III trial, enhancing the accuracy and effectiveness of MRP categorization [2,3]. University-led pharmacy clinics in Australia and the United Kingdom have demonstrated positive outcomes in medication management, student training, and reducing medication-related problems (MRPs) [6]. These international examples highlight the potential for pharmacist-led interventions to improve healthcare systems across different regions.

The primary aim of this study was to explore the impact of university clinic pharmacists in preventing medication errors and enhancing patient quality of life through the identification and resolution of MRPs. By analysing data collected during School of Pharmacy clinic consultations, we sought to quantify the prevalence and types of MRPs encountered, evaluate the interventions to prevent these errors, and assess the subsequent improvements in patients' health-related quality of life.

2. Materials and Methods

2.1. Study Participants

Ethical approval was obtained from the University of Otago Human Ethics Committee.

All patients visiting the School of Pharmacy Clinic between July 2019 and 30 June 2023 were included in this study; there were no exclusion criteria. Patients were informed that any research utilising their data would only proceed with approval from an ethics committee. They were reassured that any published research would not disclose any personally identifiable information. Despite efforts to recruit patients from diverse populations by advertising and promoting the clinic in various medical centres and local community groups, the pharmacists did not exclude patients based on these criteria. Consequently, the sample may not sufficiently represent New Zealand's population.

Patients were scheduled for a comprehensive medication review with one of three clinic pharmacists. The consultation length varied based on the patient's needs, typically lasting up to an hour to thoroughly review medical history, current medications, and any relevant symptoms.

2.2. Data Collection

Before the consultation, patients completed a consent form, which included voluntary demographic information, contact details, and consent to a pharmacy student's presence during the consultation. For phone or Zoom consultations, verbal consent was obtained. The form also gathered details on the patient's usual pharmacy, general practitioner, any special needs (e.g., hearing, visual impairment, language difficulties), exposure to COVID-19, and present symptoms.

Patients were then offered a validated survey using the Your Health and Well-Being Short Form 12 Version 2 (SF12V2). One month later, a follow-up survey was conducted to monitor health status or adjust medication regimens as needed. Patients completed a satisfaction questionnaire and, upon providing feedback, were entered into a draw for an NZD 50 gift card.

All data were recorded on the REDCap web platform, streamlining survey management. The clinical pharmacists made therapeutic recommendations and advised on lifestyle modifications or other non-pharmacological interventions to enhance health outcomes. These recommendations were communicated to the patient and/or GP through electronic methods (email or patient management system) or paper-based methods (letter) to resolve MRPs. The uptake of the recommendations was not assessed as it fell outside the scope of this study; this is a recognised limitation.

2.3. Data Collection Tools

Clinical pharmacists retrospectively reviewed a subset of patient charts (n = 103) and classified them according to the DOCUMENT classification system for MRPs. The data were recorded and stored in Excel and REDCap on a secure University server.

Although the study included 456 patients, only 103 patient charts were analysed in detail due to resource constraints and the need for a representative subset for in-depth evaluation. This approach ensured the analysis was thorough while maintaining the study's validity.

1. The DOCUMENT MRP classification system is a widely used tool for systematically identifying and categorising medication-related problems (MRPs) like adverse reactions, drug interactions, dosing issues, and non-adherence. It provides a structured framework for clinical pharmacists to evaluate and document MRPs, ensures consistency, and allows for precise intervention, optimising patient outcomes. Unlike other tools that may focus solely on adverse drug reactions or compliance, MRPs offer a holistic framework for addressing a broad spectrum of medication issues. Inter-rater reliability was validated through a cross-evaluation process where multiple independent raters classified a subset of MRPs, and Cohen's kappa statistic was used to measure agreement between raters, confirming their consistency and reliability.

2. The SF12V2 health survey, a shorter version of the SF-36, assesses health-related quality of life by evaluating physical and mental health. It covers eight key health areas and combines scores into two summary measures: the Physical Composite Score (PCS) and the Mental Composite Score (MCS). It was selected for its brevity and reliability in capturing physical and mental health metrics, making it well-suited for this study's objectives.

2.4. Data Analysis

Descriptive statistics characterised patient demographics and baseline treatment. MRPs were assessed using the DOCUMENT classification system, with frequencies reported as percentages. Medicine frequency was analysed using Anatomical Therapeutic Chemical (ATC) codes.

SF12V2 survey scores for physical and mental health were analysed for mean and standard deviation, with a one-month follow-up assessing changes over time. The minimum clinically important difference (MCID) was set at 0.5 times the standard deviation, and Cohen's effect size (d) quantified observed changes. Statistical analyses were performed using R version 4.1.2/R Studio (2023.03.0).

3. Results

3.1. Study Population

The study included 456 individuals: 225 males, 222 females, and 9 unspecified. The average age was 68 years (SD 14.18). Ethnically, most were New Zealand European/Pakeha (89%). Most referrals were self-referrals (35%), followed by other healthcare providers (19%). Detailed demographics are shown in Table 1.

Table 1. Demographic details from the Pharmacy Clinic data.

Characteristics	Count (*n* = 456)	%
Gender		
Male	225	49
Female	222	49
Missing	9	2
Age, Mean (SD)	67.89 (14.81)	
<25	6	1
25–34	13	3
35–54	47	10
55–64	73	16
65+	289	63
Missing	28	6
Ethnicity [1]		
New Zealand European Other/Pakeha	407	89
Māori	12	3
Pacific	8	2
Asian	5	1
Referrals *		
Self-referral	159	35
From general practitioners	36	8
From hospital	74	16
From pharmacist	9	2
From other healthcare providers	87	19
From nurse	11	2

[1] Respondents can select more than one ethnicity, so results may add up to more than 100%. * 80 unknown sources for referrals to the clinic and/or follow-up cases.

3.2. Medicine-Related Problems (MRPs)

A review of 103 medication charts revealed 754 MRPs (Table 2). Common issues included non-laboratory monitoring (16%) and patient requests (16%). Other problems included medicine supply and quality issues (8%), dosing errors (too high: 3%; too low: 4%), adherence issues (underuse: 4%; erratic use: 1%), undertreated (9%) and untreated conditions (4%), and potential adverse reactions (1%). Laboratory monitoring was needed for 10% of patients.

Table 2. Medicine-related problems (MRPs) (*N* = 754) identified from the 103 reviewed patients.

Code	Category	Sub-Category	Number (% of Category)	Number (% of Total)
D	Drug selection	Duplication	15 (1.98)	129 (17.10%)
		Drug interaction	11 (1.45)	
		Wrong drug	5 (0.66)	
		Incorrect strength	1 (0.13)	
		Inappropriate dosage form	1 (0.13)	
		Contraindications apparent	1 (0.13)	
		No indication apparent	18 (2.38)	
		Other drug selection problem	77 (8.8)	
O	Over- or underdose	Prescribed dose too high	19 (2.51)	63 (8.35%)
		Prescribed dose too low	27 (3.71)	
		Incorrect/unclear dosing instructions	1 (0.13)	
		Other dose problem	16 (2.12)	
C	Compliance	Under use by patient	28 (3.71)	58 (7.69%)
		Overuse by patient	1 (0.13)	
		Erratic use of medication	9 (1.19)	
		Intentional drug misuse	1 (0.13)	
		Difficulty using dosage form	0 0	
		Other compliance problem	19 (2.51)	
U	Undertreated	Condition undertreated	69 (9.15)	114 (15.11%)
		Condition untreated	33 (4.37)	
		Preventative therapy required	4 (0.53)	
		Other undertreated problem	8 (1.06)	
M	Monitoring	Laboratory monitoring	76 (10.07)	203 (26.92%)
		Non-laboratory monitoring	123 (16.31)	
		Other monitoring problem	4 (0.53)	
E	Education or Information	Patient requests drug information	121 (16.04)	176 (23.34%)
		Patient requests disease management advice	45 (5.96)	
		Confusion about therapy or condition	0 (0)	
		Demonstration of device	0 (0)	
		Other education or information problem	10 (1.32)	

Table 2. *Cont.*

Code	Category	Sub-Category	Number (% of Category)	Number (% of Total)
N	Not classifiable	Clinical interventions that cannot be classified under another category	2 (0.26)	2 (0.26%)
T	Toxicity or ADR	Toxicity/ADR	9 (1.19)	9 (1.19%)

Adapted from Williams et al. (2012) [3], the original table included the description of Category, Sub-category, described by the DOCUMENT system with the number and percentage of categories and the moderate to high clinical significance of the PROMISE III results, while this table included the number and percentage of categories of pharmacy clinic data. Co-morbidities, medication use, and patient characteristics, such as age, may also influence the occurrence of DRPs.

3.3. Recommendations

Pharmacists issued 836 recommendations (Table 3). The most frequent were changes in medications (23%), non-laboratory monitoring (15%), and laboratory monitoring (12%). Other recommendations included dose adjustments (increase: 5%; decrease: 3%), changes in therapy (2%), referrals (14%), and educational or information provision (24%). In two cases, no recommendation was deemed necessary.

Table 3. Recommendations described by the DOCUMENT system (*N* = 836).

Recommendation		Sub-Category (%)	Category (%)
A change in therapy	Dose increase	44 (5.26)	296 (35.40)
	Dose decrease	23 (2.75)	
	Drug change	191 (22.84)	
	Drug formulation change	3 (0.35)	
	Drug brand change	0 (0)	
	Dose frequency/schedule change	18 (2.15)	
	Prescription not dispensed	0 (0)	
	Other changes to therapy	17 (2.03)	
A referral required	Refer to prescriber	101 (12.08)	118 (14.11)
	Refer to hospital	5 (0.59)	
	Refer to medication review	0 (0)	
	Other referral required	12 (1.43)	
Provision of information	Education/counselling session	100 (11.96)	198 (23.68)
	Written summary of medications	21 (2.51)	
	Commence dose administration aid	0 (0)	
	Other written information	77 (9.21)	
Monitoring	Monitoring laboratory test	97 (11.60)	222 (26.55)
	Monitoring: non-laboratory	125 (14.95)	
Other	No recommendation necessary	2 (0.24) *	
	Total	836 (100.0%)	

* Not included in the recommendation analysis. Adapted from Williams et al. (2012), the original table included the recommendations described by the DOCUMENT system [3].

3.4. Medicines Implicated in MRPs

In the review of 103 patient charts, 925 medications were assessed, averaging about 9 per chart. The most frequently implicated drugs were cholecalciferol, paracetamol,

atorvastatin, omeprazole (each 5%), and aspirin (3%). Other drugs included ibuprofen, bisoprolol, salbutamol, cilazapril, levothyroxine, metoprolol (2% each), and various others, comprising 1% of the total, as shown in Table 4.

Table 4. Top 10 ATC medicines groups classified.

ATC CODE	Description	Frequency of Drugs (*N* = 925)	Total, %
A11CC05	Vitamin D and analogues	Cholecalciferol (48)	5.18
N02BE01	Anilides, analgesics, other analgesics, and antipyretics	Paracetamol (48)	5.18
C10AA05	Lipid-modifying agents/HMG co a reductase inhibitors	Atorvastatin (46)	5.00
A02BC01	Proton pump inhibitors	Omeprazole (43)	4.64
N02BA01	Analgesic and antipyretics	Aspirin (26)	2.81
M01AE01	Anti-inflammatory and antirheumatic products, non-steroids	Ibuprofen (20)	2.16
C07AB07	Beta-blocking agents, selective	Bisoprolol (18)	1.94
R03AC02	Drugs for obstructive airway disease/adrenergic inhalants	Salbutamol (15)	1.62
C09AA08	Agents acting on the renin–angiotensin system/ace-inhibitors, plain	Cilazapril (14)	1.51
H03AA01	Thyroid therapy	Levothyrozine (14)	1.51
C07AB02	Beta-blocking agents, selective	Metoprolol (14)	1.51
C09CA06	Cardiovascular system/agents acting on the renin–angiotensin system	Candesartan (13)	1.40
N02BF01	Analgesics and antipyretics	Gabapentin (13)	1.40
MO4AAO1	Antigout preparations/preparations inhibiting uric acid production	Allopurinol (11)	1.18
C03CA01	Diuretics/high-ceiling diuretics/loop diuretics	Furosemide (11)	1.18
C02CA04	Antihypertensives/antiadrenergic agents, alpha-adrenoreceptor antagonists	Doxazosin (11)	1.18
N06AX16	Antidepressants	Venlafaxine (11)	1.18
	Total drugs prescribed	925	100

3.5. SF-12V2 Survey Results

Patients showed improved health-related quality of life one month after clinical pharmacist reviews. General health scores increased, indicating better self-reported health. Physical functioning slightly declined, from 44.77 to 43.98, suggesting a minor decline in performing physical tasks. The Role Physical (RP) score, which measures how much work and other activities were accomplished, increased, indicating an improvement in the participants' ability to complete tasks. The Body Pain (BP) scores also improved, suggesting a reduction in the participants' pain level. The mean energy level increased, and participants' ability to cope with physical or emotional issues also improved, as indicated by the increase in average calmness and depression (MH) score. Overall, these changes reflect a positive impact on patients' health and well-being.

3.6. Physical Composite Score and Mental Composite Score

The results in Table 5 indicate that the mean physical composite score in SF-12V2 at baseline was 32.42 (SD19.44), which increased to 36.08 (SD19.29) after one month. SF-12V2 scores range from 0 to 100, with higher scores indicating better health status. Similarly, the mean mental composite score at baseline was 44.08 (SD18.59), which increased to 48.86 (SD17.74) after the one-month follow-up period. These findings suggest a notable improvement in both physical and mental health over the one-month period (Table 6).

Table 5. SF-12V2 health survey results (*N* = 97).

Domain	Mean Score (SD)	Mean Score (SD) After 1 Month Follow-Up	*p* Value	Effect Size Cohen's d
General Health (GH)	44.66 (24.08)	48.85 (22.91)	0.027	0.18
Physical Functioning (PF)	44.77 (36.28)	43.98 (38.34)	0.6937	0.03
Role Physical (RP)	49.95 (29.29)	54.40 (28.90)	0.17	0.14
Body Pain (BP)	55.34 (32.57)	57.71 (30.98)	0.3426	0.07
Vitality (VT)	40.23 (27.13)	45.75 (24.51)	0.0007538	0.30
Social Functioning (SF)	67.08 (37.55)	72.22 (28.04)	0.412	0.08
Role Emotional (RE)	67.02 (27.83)	74.18 (25.54)	0.007467	0.25
Mental Health (MH)	64.78 (21.66)	67.52 (19.93)	0.1566	0.13

GH = health; PF = moderate_activities + climbing_stairs; RP = accomplish_less + work_other_activites; BP = pain; VT = energy; SF = physical_emotional; RE = accomplish_less_emotion + activities_less_carefully; MH = calm + depressed.

Table 6. Physical and mental scores (*N* = 97).

Scores	Pre-Visit (SD)	Post-Visit (SD)	Change	MCID ($0.5 \times SD^{+}$)	Effect Size (d)
P score	32.42 (19.44)	36.08 (19.29)	−3.66	9.68	0.18
M score	44.08 (18.59)	48.86 (17.74)	−4.78	9.08	0.26

MCID formula is taken from Norman et al. [7]. + denote pooled standard deviation. Effect size (d) Cohen's d was calculated using (post pscore − pre pscore)/pooled SD.

The summary scores in Table 6 demonstrate a significant change in both the Physical (PCS) and Mental Health scores. Specifically, 39% of respondents exhibited an improvement in their PCS, with 22% achieving a change that exceeded the MCID of 9.68. Moreover, 45% experienced a positive change in MCS, with 33% achieving a change that surpassed the MCID value of 9.08. The effect size for the PCS was 0.18, indicating a small effect, while for the MCS, it was 0.26, indicating a small-to-moderate effect. The observed decline in physical discussion could be attributed to the advanced age and multimorbidity of the study population, natural disease progression, or other underlying health conditions not directly addressed by pharmacist interventions

4. Discussion

This study aimed to explore the impact of university clinic pharmacists in preventing medication errors and enhancing patient quality of life. The study demonstrates the important role of clinical pharmacists in addressing medication-related problems (MRPs) that persist despite regular interactions with general practitioners (GPs) and community pharmacists. By identifying significant MRPs and providing targeted recommendations to patients' GPs, clinic pharmacists enhanced patients' quality of life, making pharmacy clinics accepting self-referrals and practitioner-based referrals an ideal setting for resolving these issues.

4.1. Key Clinical Findings

The study found that the most common of the 745 identified MRPs were related to medicine selection, monitoring issues, and patient requests for information. This echoes findings from similar studies in Australia and the Netherlands, highlighting the ongoing need for focused medication management to address these frequent problems [8,9].

The study also revealed that 8% of medication-related problems (MRPs) were linked to medication non-adherence, including underuse, overuse, and improper use. This finding aligns with international research, which has shown that non-adherence can lead to adverse outcomes, and highlights the need for strategies to simplify medication regimens [10,11]. Additionally, 23% of MRPs identified in this study involved patient education, emphasising the importance of empowering patients with knowledge about their medications to prevent non-adherence and improve outcomes.

Clinical pharmacists are ideally placed to help with these errors, as seen in the 836 recommendations, which are primarily related to monitoring and medication adjustment. Previous studies have demonstrated the effectiveness of such pharmacist-led interventions in improving compliance and mitigating drug-related risks [12,13].

The SF12V2 survey results showed a significant improvement in physical and mental health one month after the intervention, suggesting that even brief pharmacist-led interventions can have a meaningful impact on patient well-being.

4.2. Implementing These Findings into Routine Practice

The study's findings advocate for continued collaboration between pharmacists and other healthcare professionals to optimise patient care and outcomes. Given the current workforce and funding shortages for clinical pharmacists in New Zealand and internationally, university-based clinics could effectively serve as hubs for managing MRPs and implementing interventions. This can be achieved through collaboration, technology-driven solutions, targeted interventions, resource optimisation, and advocacy [14,15].

Collaboration is crucial in distributing the workload effectively, particularly in university-based clinics. These clinics offer a unique environment where pharmacy students, interns, and residents can be integrated into the clinical workflow under the supervision of experienced pharmacists. By involving these learners, the burden on clinical pharmacists is reduced, allowing them to focus on more complex tasks while students gain hands-on experience in medication management and patient care. This approach not only enhances the students' educational experience but also contributes to the overall efficiency and effectiveness of the clinic. Research shows that involving pharmacy students in clinical settings can significantly aid in managing medicine-related problems [6,16]. By providing these opportunities, university clinics can become hubs for both patient care and professional development, ensuring that resources are used efficiently even in the face of workforce and funding challenges.

This research highlights that University clinics should focus their efforts on high-risk patients, such as those with multiple chronic conditions or recent hospital discharges, ensuring that limited resources are used effectively. Standardised protocols for MRP management can streamline processes and allow even less experienced staff or students to contribute meaningfully [17]. Technology, such as telepharmacy and Clinical Decision Support Systems (CDSS), can extend the reach of clinical pharmacists and improve efficiency. Despite being geographically separated, telepharmacy would enable remote consultations and follow-ups, while CDSS helps prioritise critical cases by identifying potential MRPs like drug interactions or high-risk patients [18,19].

4.3. Study Limitations

One of the primary limitations of this study is the potential bias introduced by the self-referred patient population. Patients who actively seek pharmacist-led medication reviews may be more engaged in their healthcare, leading to an overrepresentation of individuals with higher adherence to prescribed therapies. This could impact the generalisability of the findings to broader patient populations who may not actively seek such services.

Another key limitation is that the study was conducted within a single university-affiliated pharmacy clinic. While this setting provides a controlled environment for assessing pharmacist interventions, it limits the ability to extrapolate the results to other clinical settings, such as community pharmacies or hospital-based pharmacy services. Future studies should consider multicentre trials to evaluate the effectiveness of pharmacist-led interventions across diverse practice settings.

Lastly, the study did not account for long-term patient outcomes beyond the follow-up period, making it difficult to assess the sustained impact of pharmacist interventions on medication-related problems and health outcomes. Further research should focus on longitudinal studies to track patient progress over extended periods.

4.4. Policy Implications

The results of this study carry significant implications for healthcare professionals and policymakers alike. The evidence suggests that university-based clinical pharmacists' interventions, particularly in identifying and addressing medication-related problems (MRPs), can significantly improve both physical and mental health outcomes.

Incorporating these pharmacist-led strategies into routine healthcare practice is not only beneficial but essential. However, sustainable funding models need to be established, either through government reimbursement schemes or partnerships with private healthcare providers. This would enable pharmacist-led clinics to expand their services without financial barriers. Advocacy for the role of clinical pharmacists in university clinics is crucial in securing support and funding while also necessitating further studies that demonstrate the substantial impact pharmacists have on patient outcomes and, likely, healthcare costs.

Additionally, there is a need to develop standardised metrics for assessing the impact of clinical pharmacists on MRPs and patient outcomes to ensure their contributions are consistently recognised and valued. Regulatory frameworks should adapt to acknowledge pharmacists as essential healthcare providers capable of delivering primary care services. This may include expanding pharmacist prescribing rights and integrating their services into national healthcare strategies.

Finally, policies should encourage interdisciplinary collaboration between pharmacists, general practitioners, and allied healthcare professionals. Establishing clear referral pathways and shared decision-making models would strengthen the integration of pharmacist-led services into mainstream healthcare systems, ultimately improving patient outcomes and reducing healthcare costs.

5. Conclusions

In summary, clinical pharmacists in university clinics play a critical role in managing medication-related problems, significantly improving patient outcomes. Their specialised knowledge, collaborative approach, and patient-centred focus make them indispensable healthcare team members. As the healthcare landscape continues to evolve, the role of clinical pharmacists should be further integrated and expanded to maximise their positive impact on patient care.

Several actionable steps should be considered to scale the university clinic model to other settings or healthcare systems. Firstly, creating standardised protocols for pharmacist-led interventions can facilitate their implementation across various clinical environments. These protocols should be adaptable to different healthcare settings, ensuring consistency in service delivery while allowing for flexibility based on local needs.

Additionally, fostering partnerships between universities, healthcare institutions, and policymakers can facilitate knowledge exchange, training opportunities, and research collaborations. Establishing networks for sharing best practises and evaluating outcomes across multiple sites will contribute to the ongoing evolution of pharmacist-led clinics.

Lastly, targeted workforce development initiatives, including training programmes for pharmacy students and continuing education for practising pharmacists, will help them to obtain the necessary skills and competencies for expanding these models beyond academic settings.

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Abbreviations

The following abbreviations are used in this manuscript:

MRPs	Medication-related problems
PCNE	Pharmaceutical Care Network Europe
PROMISE	Program of Research on Medication Issues and Solutions Evaluation
DOCUMENT	Drug-related problems Outcomes and Categorisation and Utility Evaluation in Clinical Tools
SF12V2	Short-Form 12 Version 2 (Health Survey)
PCS	Physical Composite Score
MCS	Mental Composite Score
ATC	Anatomical Therapeutic Chemical (classification system)
CDSS	Clinical Decision Support Systems
GP	General Practitioner
MCID	Minimum Clinically Important Difference
ADR	Adverse Drug Reaction

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Review

Targeting Amyloid Pathology in Early Alzheimer's: The Promise of Donanemab-Azbt

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Abstract: Objective: The purpose of this review is to examine the potential role of donanemab-azbt in the treatment and management of early-stage Alzheimer's disease (AD), with a focus on its efficacy, safety, and clinical relevance based on data from key clinical trials. Data Sources: A comprehensive literature search of PubMed was conducted using relevant keywords such as "donanemab", "Alzheimer's disease", "Kisunla", "TRAILBLAZER clinical trials", and "amyloid-related imaging abnormalities (ARIA)". Additional data were extracted from clinical trial records (clinicaltrials.gov), conference abstracts, and product monographs. Study Selection and Data Extraction: Only English-language studies conducted in human populations were included. Clinical trials and peer-reviewed studies detailing the efficacy, safety, and mechanistic insights of donanemab-azbt were prioritized. Data Synthesis: Key findings from the TRAILBLAZER series of clinical trials highlighted the potential of donanemab-azbt in slowing cognitive and functional decline in early-stage AD: (1) TRAILBLAZER-ALZ (Phase 2): This trial focused on participants with intermediate levels of tau protein. Results demonstrated a statistically significant slowing of cognitive and functional decline. (2) TRAILBLAZER-ALZ 2 (Phase 3): A large-scale, randomized, double-blind, placebo-controlled study confirmed the efficacy of donanemab-azbt in reducing amyloid plaque accumulation and cognitive decline. Key results included a 35% slowing of decline on the Integrated Alzheimer's Disease Rating Scale (iADRS) and a 36% slowing on the Clinical Dementia Rating-Sum of Boxes (CDR-SB). Additional secondary outcomes showed improvements in activities of daily living and reduced risk of disease progression. (3) TRAILBLAZER-ALZ 3: This ongoing trial is evaluating donanemab's potential in delaying or preventing Alois Alzheimer in cognitively normal individuals with amyloid plaques, broadening the scope of early intervention strategies. (4) TRAILBLAZER-ALZ 4: A head-to-head comparison with aducanumab revealed superior amyloid plaque clearance with donanemab. (5) TRAILBLAZER-ALZ 5: Currently recruiting, this trial aims to evaluate safety and efficacy across diverse populations with varying tau levels and comorbidities. (6) TRAILBLAZER-ALZ 6 (Phase 3b): This trial investigates modified dosing regimens to reduce ARIA while maintaining efficacy, particularly in populations with genetic risk factors like ApoE ε4 homozygotes. Relevance to Patient Care and Clinical Practice: Donanemab-azbt represents a promising treatment option for patients with early-stage AD. It specifically targets and reduces amyloid beta plaques, a hallmark of the disease, potentially slowing progression and preserving cognitive function. However, its administration requires careful patient selection, including genetic testing for ApoE ε4 status, to mitigate risks of ARIA. Furthermore, the findings emphasize the importance of close monitoring during treatment. Conclusions: Donanemab-azbt offers a new avenue for managing early-stage AD, showing promise in reducing amyloid burden and slowing cognitive decline. While its efficacy and safety have been demonstrated in clinical trials, further research is essential to validate long-term outcomes, assess effectiveness across

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diverse populations, and refine dosing strategies to minimize side effects. With continued investigation, donanemab-azbt could significantly impact the clinical landscape of AD treatment.

Keywords: Kisunla; donanemab-azbt; Alzheimer's disease; TRAILBLAZER-ALZ 2,3,4,5,6; amyloid; ARIA

1. Introduction

Alzheimer's disease (AD), the most common cause of dementia, is a progressive neurodegenerative disease characterized by two key pathological features in the central nervous system (CNS): extracellular amyloid plaques derived from amyloid-beta peptides and neurofibrillary tangles formed from aggregated and hyperphosphorylated tau proteins [1]. Tau is a microtubule-associated protein that stabilizes the structural framework of neurons and facilitates intracellular transport. In AD, tau becomes hyperphosphorylated, detaches from microtubules, and aggregates into neurofibrillary tangles, disrupting normal neuronal function. Similarly, amyloid-beta (Aβ) is a peptide formed by the cleavage of the amyloid precursor protein (APP) through beta- and gamma-secretase enzymes. While Aβ is typically regulated and cleared in healthy brains, in AD, its excessive production and impaired clearance lead to the formation of amyloid plaques, a hallmark of the disease. Brain imaging studies in both early and late-onset AD reveal significant disruptions in Aβ homeostasis, which appears to initiate tau pathology. In the early stages, Aβ is believed to facilitate the spread of tau, contributing to cortical neurodegeneration. As the disease progresses, tau neurofibrillary tangles and Aβ plaques accumulate concurrently in the cortical regions of the brain, highlighting a dependency of tau pathology on Aβ levels [2].

Over 55 million people worldwide are living with dementia, with more than 60% residing in low- and middle-income countries. According to the World Health Organization, there are nearly 10 million new cases of dementia every year [2]. In the United States, an estimated 6.9 million Americans aged 65 and older currently have AD [3]. This number is projected to rise to 13.8 million by 2060 unless medical breakthroughs are made to prevent, slow, or cure AD [4]. Clinically, AD is characterized by memory loss, confusion, poor judgment, language disturbance, visual complaints, agitation, withdrawal, and hallucinations. Furthermore, the progress of the disease into the late stage is marked by loss of brain function leading to infection, pneumonia, dehydration, poor nutrition, and possibly death [5]. Research studies have shown that 75–87% of people with AD develop impairments in cough/and swallowing. Dysphagia increases the risk of sarcopenia, lower body mass, and various degrees of malnutrition [6]. This increases the risk of aspiration pneumonia leading to infections and hospitalizations [7].

AD can be broadly categorized into dominantly inherited familial AD (FAD), early-onset AD (EOAD), and late-onset AD (LOAD), each with distinct genetic and clinical characteristics. FAD, a rare form of AD caused by mutations in the amyloid precursor protein (APP), presenilin 1 (PSEN1), or presenilin 2 (PSEN2) genes, accounts for less than 1% of all cases. It typically manifests early, with an average age of onset of around 46.2 years and cases reported as early as the 20s [8].

EOAD is diagnosed in individuals younger than 65 years and, while slightly more common than FAD, comprises fewer than 5% of pathologically confirmed cases. EOAD often presents atypically and follows a more aggressive progression compared to other forms of AD [9]. Additionally, individuals with Down syndrome who have a partial or full trisomy of chromosome 21, which includes the APP gene, almost universally develop AD

pathology by age 40. Most exhibit clinical symptoms by age 50, and a majority progress to dementia by age 65 [10,11].

LOAD, the most prevalent form of AD, is generally sporadic but influenced by genetic risk factors. The apolipoprotein E (APOE) gene, particularly the APOE4 allele, plays a significant role in disease risk. A single copy of the APOE4 allele increases the odds of developing AD by approximately threefold, while homozygosity for APOE4 raises the odds twelvefold [11]. The APOE4 allele is also linked to increased susceptibility to vascular dementia, Lewy body dementia, and traumatic brain injury, as well as AD pathology in individuals with Down syndrome [12].

Beyond APOE, additional genetic risk factors for LOAD, including TREM2, ADAM10, and PLD3, have been identified through genome-wide association studies. These genes are implicated in processes such as cholesterol metabolism, immune response, endocytosis, and the regulation of APP and tau proteins, furthering our understanding of AD pathogenesis [13,14]. Ongoing research into these and newly discovered genetic factors continues to offer valuable insights into the mechanisms underlying the development and progression of AD.

Pathologically, the main microscopic feature of extracellular amyloid plaques and intracellular neurofibrillary tangles was first observed over a century ago [15]. Amyloid plaques, initially described by Alois Alzheimer as "miliary foci" are formed by the extracellular accumulation of Aβ40 and Aβ42 peptides resulting from the aberrant processing of amyloid precursor protein by β- and γ-secretases. These processes create an imbalance between production and clearance of amyloid peptides [16]. The resulting 4 kDa peptides fold into beta-pleated sheet structures, which are highly fibrillogenic.

There are numerous types of nonvascular amyloid deposits described, but diffuse plaques and dense core plaques are the most prevalent in AD pathology [17]. Diffuse plaques, which initially form in the neuropil, show weak staining with amyloid-binding dyes such as thioflavin S and Congo red. They often lack argyrophilia on Bodian silver staining and are not associated with significant microglial or astrocytic activation. Dense core plaques, on the other hand, exhibit compact, radiating amyloid deposits that intensely stain with amyloid-specific dyes and are associated with more fibrillogenic forms of Aβ [18].

A subset of dense core plaques, referred to as neuritic plaques (NPs), contains tau-positive dystrophic neurites and is linked with synaptic loss, activated microglia, and reactive astrocytes [19]. While diffuse plaques generally lack neuritic components, diffuse neuritic plaques may appear in advanced stages of AD. There is ongoing debate as to whether diffuse plaques represent early stages in the development of neuritic plaques or are part of pathological aging. Additionally, plaques exclusively composed of dense cores without neuritic elements, termed "burnt-out plaques", are often observed in later stages. Neuritic plaques with dense amyloid and tau-positive neurites are believed to have the strongest association with neuronal loss and cognitive decline in AD [20]. Figure 1A–C below represent diffuse plaques, dense core plaques, and cored neuritic plaques described above.

We shed light on the different types of plaques due to the fact that there are new studies that have identified different roles of these plaques in AD. According to a study using animal models, it was noted that fewer dense core plaques seem to be more detrimental to the disease progression [21].

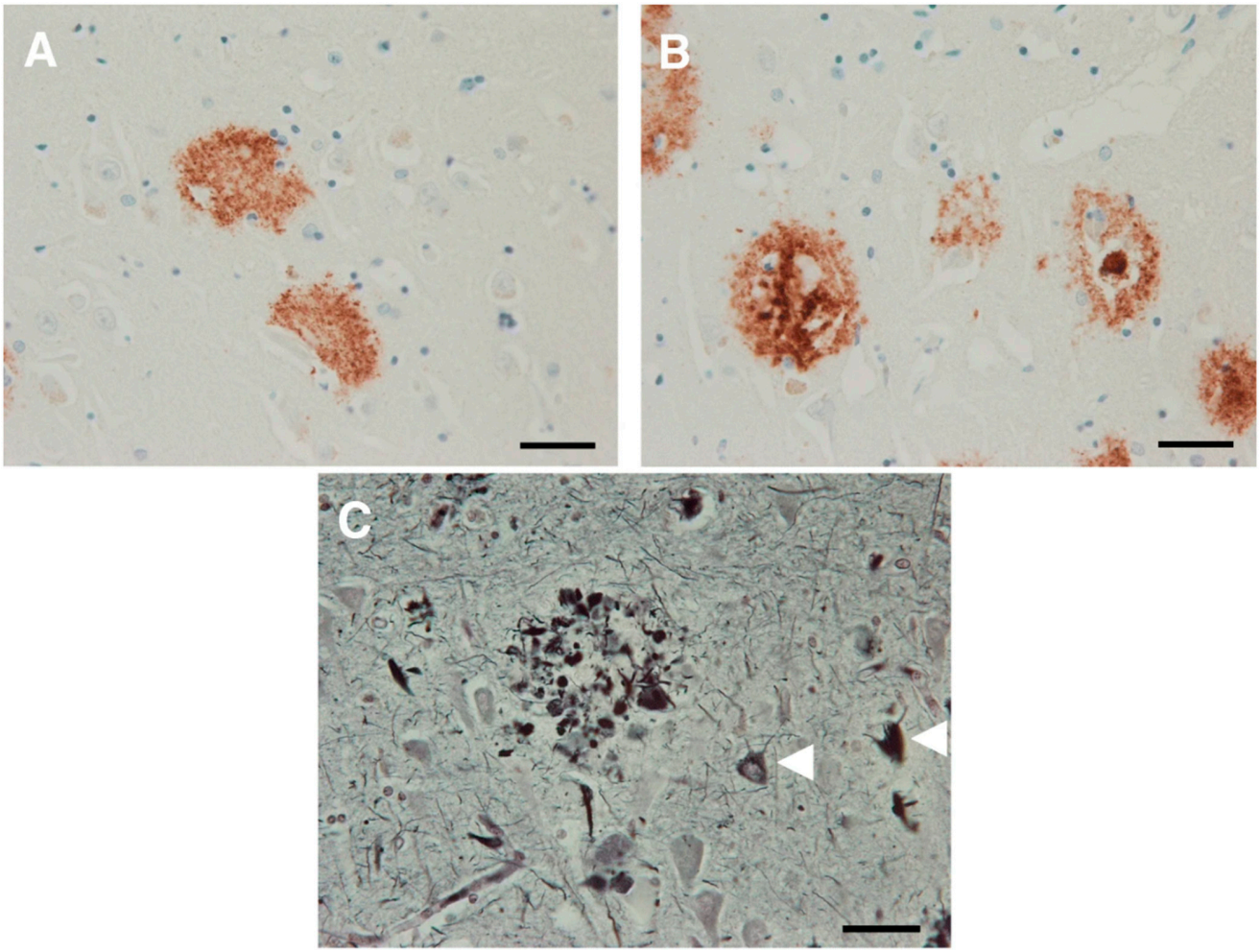

Figure 1. Alzheimer Senile Plaques. Immunohistochemistry of affected Alzheimer's tissue using antibodies directed against Ab peptides. (**A**): Diffuse plaques (**B**): Dense core (**C**): Neuritic plaques. Neuritic AD plaques are readily observed using Bielchowsky silver staining as shown above pointed by the white triangles. Image courtesy to *Molecular Neurodegeneration* volume 14, Article number: 32 (2019) [15].

1.1. AD Treatment Landscape

The treatment landscape for AD has evolved significantly over the past few decades. Initially, therapeutic options were limited to cholinesterase inhibitors (e.g., donepezil, rivastigmine) and the NMDA receptor antagonist memantine, which provided modest symptomatic relief without altering disease progression [22]. Recent advancements have introduced anti-amyloid monoclonal antibodies designed to target amyloid-beta plaques, a hallmark of AD pathology. Aducanumab was the first of these agents to receive FDA approval, aiming to reduce amyloid-beta accumulation in the brain. Subsequent developments include lecanemab and donanemab, both of which have demonstrated efficacy in slowing cognitive decline in early AD by targeting amyloid-beta aggregates [23].

Lecanemab was developed by Eisai and Biogen Inc. Tokoyo, Japan. and was approved by the Food and Drug Administration (FDA) in July 2023 and donanemab-azbt which was developed by Eli Lilly and Company, Indianapolis, IN was FDA approved in July 2024 [24,25].

1.2. Mechanism of Action

Donanemab and lecanemab are both humanized monoclonal antibodies targeting Aβ proteins. Their mechanism of action differs in terms of the specific forms of Aβ they target and their subsequent effects.

Donanemab-azbt is a humanized immunoglobulin-1 (IgG1) monoclonal antibody that binds specifically to an N-terminal pyroglutamate-modified form of amyloid-beta at position 3 (pGlu3-Aβ). Upon binding to the modified Aβ plaques, donanemab facilitiates their removal through microglial-mediated phagocytosis, a process where immune cells in the brain engulf and degrade the plaques [26].

Lecanemab targets soluble amyloid beta protofibrils, which are the precursors to the insoluble amyloid plaques. By binding to these protofibrils, lecanemab promotes their clearance, thus reducing the formation of amyloid plaques in the brain [27].

Compared to lecanemab and donanemab, aducanumab involves selectively binding to both soluble and insoluble forms of Aβ aggregates, including oligomers and fibrils, facilitating their removal and potentially mitigating neurodegeneration [28].

In summary while both donanemab and lecanemab aim to clear the Aβ plaques present in AD, they do so by targeting different forms of Aβ: donanemab focuses on established plaques, whereas lecanemab targets soluble protofibrils to prevent plaque formation [29].

Please refer to Figure 2 for an illustration of the mode of action.

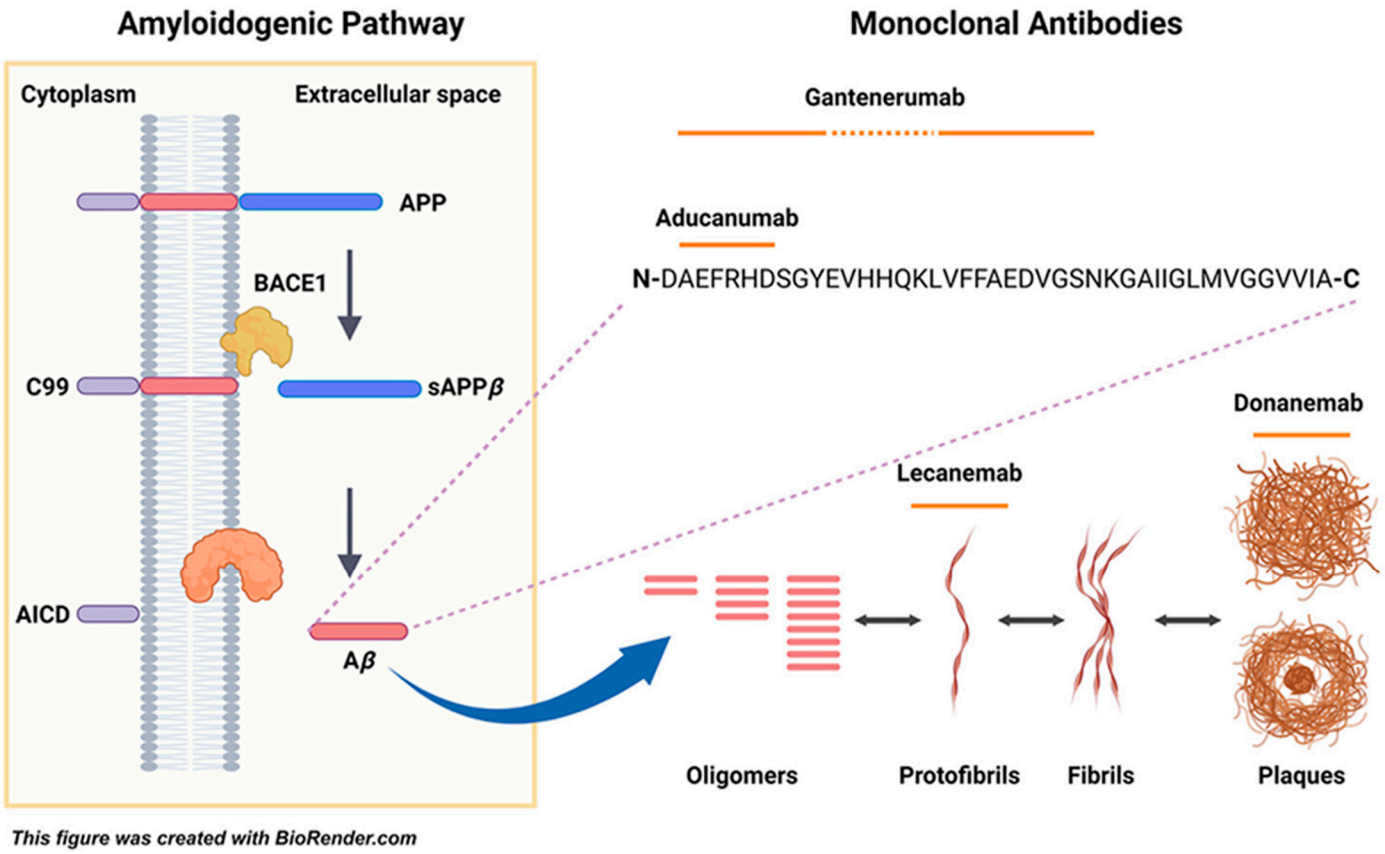

Figure 2. Molecular Targets of Anti-Amyloid Monoclonal Antibodies. Processing of APP and production of Aβ. APP is initially cleaved by α-secretase in the Non-amyloidogenic pathway, yielding two fragments: sAPPα and C83. The late is cleaved by the γ-secretase complex, creating the p3 and AICD peptides. In the Amyloidogenic pathway, β-secretase (BACE1) cleaves APP to produce the sAPPβ and C99 fragments. A linear epitope formed by the amino acids 2–7 of Aβ increases aducanumab's affinity towards aggregates of fibrils Lecanemab recognizes Aβ protofibrils with much higher affinity than monomers. Credit to: Acta Pharmaceutica Sinica B Volume 14, Issue 7, July 2024, Pages 2795–2814 [30].

2. Pharmacokinetics and Pharmacodynamics

The pharmacokinetic (PK) profile of donanemab was characterized through a population PK analysis involving participants with AD. This analysis incorporated data from individuals with mild cognitive impairment or mild to moderate dementia due to AD from a phase Ib study, as well as participants with early symptomatic AD from the TRAILBLAZER-ALZ study [31].

The analysis revealed that donanemab has a terminal elimination half-life of approximately 11.8 days. Body weight and antidrug antibody titer were found to impact donanemab exposure; however, these factors did not significantly affect the pharmacodynamic response. Maintaining a donanemab serum concentration above 4.43 μg/mL was associated with amyloid plaque reduction. The time to achieve amyloid plaque clearance varied depending on baseline amyloid levels, with higher baseline levels associated with fewer participants achieving amyloid clearance. The majority of participants achieved amyloid clearance by 52 weeks of treatment [31].

No clinical studies have been conducted to evaluate the pharmacokinetics of donanemab in patients with renal or hepatic impairment. However, due to its degradation pathway, dose adjustments are not necessary for patients with renal or hepatic impairment [32].

Additionally, the analysis indicated that APOE ε4 carriers were four times more likely than noncarriers to experience amyloid-related imaging abnormalities with edema or effusions (ARIA-E) by 24 weeks, irrespective of donanemab serum exposure.

Dosing and Administration: The treatment regimen includes an initial dose of 700 mg administered via intravenous infusion every 4 weeks for 3 doses, followed by 1400 mg IV every 4 weeks until amyloid plaques are significantly reduced on amyloid PET imaging. Infusions are delivered over 30 min, and dilution is performed with normal saline (NS) to a final concentration of 4 to 10 mg/mL. Based on the package insert, once the medication is diluted, the solution should be used immediately, or it may be stored in the refrigerator at 2 °C to 8 °C (36 °F to 46 °F) for up to 72 h, or at room temperature (20 °C to 25 °C [68 °F to 77 °F]) for up to 12 h including the duration of the infusion [33].

3. Efficacy and Clinical Trials

The efficacy and safety of donanemab-azbt was assessed in a series of clinical trials. Below is an expanded discussion of these trials.

TRAILBLAZER-ALZ: The TRAILBLAZER-ALZ phase 2 study targeted individuals with early symptomatic AD, particularly those with intermediate levels of tau protein accumulation in the brain. The study demonstrated that donanemab treatment led to a reduction in the rate of cognitive and functional decline [34].

TRAILBLAZER-ALZ 2: was a large-scale, randomized, double-blind, placebo-controlled trial that assessed the safety and efficacy of donanemab. Participants were stratified based on their tau protein levels. The study's primary analysis population (n = 1182), composed of individuals with intermediate tau levels and clinical symptoms of AD, showed significant findings. In this group, the primary endpoint, the Integrated Alzheimer's Disease Rating Scale (iADRS), demonstrated a 35% reduction in the rate of decline ($p < 0.0001$). Additionally, a key secondary endpoint, the Clinical Dementia Rating-Sum of Boxes (CDR-SB), indicated a 36% reduction in decline ($p < 0.0001$) over an 18-month period. Further prespecified secondary analyses revealed that 47% of participants receiving donanemab experienced no decline on the CDR-SB at one year, compared to 29% in the placebo group ($p < 0.001$). Moreover, 52% of participants in the donanemab group completed the treatment course by one year, with 72% completing it by 18 months, primarily due to achieving amyloid plaque clearance. At 18 months, individuals on do-

nanemab showed 40% less decline in performing activities of daily living (as assessed by the Alzheimer's Disease Cooperative Study–Instrumental Activities of Daily Living Inventory or ADCS-iADL, $p < 0.0001$). Finally, donanemab-treated participants had a 39% lower risk of progressing to the next stage of the disease compared to those on placebo (measured by the CDR-Global Score, Hazard Ratio = 0.61, $p < 0.001$) [35].

This study was followed by the ongoing TRAILBLAZER-ALZ 3.

TRAILBLAZER-ALZ 3: aims to evaluate the potential to delay or prevent AD in cognitively normal individuals with amyloid plaques but no symptoms. It is part of a broader effort to investigate early intervention strategies. The trial will provide crucial data on the efficacy of amyloid-targeting treatments in the preclinical phase of AD. TRAILBLAZER-ALZ 3 highlights the growing emphasis on early detection and intervention in AD management. If successful, it would support the use of donanemab not only as a treatment for early symptomatic AD but also as a preventive therapy in high-risk individuals. This could shift clinical practice toward more proactive management strategies, emphasizing biomarker screening and early therapeutic intervention to delay or prevent the onset of symptoms, potentially reducing the overall burden of AD [36].

3.1. TRAILBLAZER-ALZ 4

Donanemab was studied in a head-to-head trial with aducanumab in TRAILBLAZER-ALZ 4 where 37.9% donanemab-treated vs. 1.6% aducanumab-treated participants achieved amyloid clearance ($p < 0.001$). In the intermediate tau subpopulation, 38.5% donanemab-treated vs. 3.8% aducanumab-treated participants achieved amyloid clearance ($p = 0.008$). These results suggest that donanemab may be more effective at clearing amyloid plaques in AD patients, potentially leading to better clinical outcomes [37].

3.2. TRAILBLAZER-ALZ 5

TRAILBLAZER-ALZ 5 focuses on evaluating safety and efficacy in broader populations, including those with varying tau levels and comorbidities. It is an ongoing Phase 3, double-blind, placebo-controlled clinical trial designed to assess the safety and efficacy of donanemab in individuals with early symptomatic AD, specifically those in the prodromal stage or with mild dementia due to AD, who exhibit brain tau pathology. The trial aims to enroll participants aged 60 to 85 years who have demonstrated gradual and progressive changes in memory function over at least six months, possess a Mini-Mental State Examination (MMSE) score between 20 and 28, and have confirmed tau pathology via brain imaging [38].

Participants are randomly assigned to receive either intravenous infusions of donanemab or a placebo. The study's primary objective is to evaluate the efficacy of donanemab in slowing cognitive and functional decline, as measured by the Integrated Alzheimer's Disease Rating Scale (iADRS). Secondary objectives include assessments of safety, changes in amyloid and tau levels, and other cognitive and functional measures.

TRAILBLAZER-ALZ 6 (Phase 3b) results were presented in 2024. It highlighted a modified titration regimen that reduced amyloid-related imaging abnormalities with edema/effusion (ARIA-E) while maintaining plaque removal efficacy. This was particularly effective for individuals with genetic risk factors (APOE4 homozygotes). Interim results from TRAILBLAZER-ALZ 6 indicated that the modified titration dosing regimen led to a significant reduction in the occurrence of ARIA-E compared to the standard dosing regimen. Specifically, there was a 41% reduction in the relative risk of ARIA-E in the modified dosing group. Safety profiles were comparable across both groups, with no new safety signals identified. The frequency of infusion-related reactions in the modified titration arm was similar to that of the standard dosing arm. The findings from TRAILBLAZER-ALZ 6 suggest

that implementing a modified titration dosing regimen of donanemab may enhance the safety profile of the treatment by reducing the risk of ARIA-E, without compromising its efficacy [39].

A summary of the clinical trials is listed in Table 1.

Table 1. Summary of Donanemab Clinical Trials.

Key Clinical Trials Name [34,35,40–43] Drug Studied	Number of Participants	Age Range (yr)	Phase	Location	Identifier
TRAILBLAZER-EXT Donanemab	94	60–90	II	Canada USA	NCT04640077
TRAILBLAZER-ALZ Donanemab	272	60–85	II	Canada USA	NCT03367403
TRAILBLAZER-ALZ 2 Donanemab/Placebo	1736	60–85	III	Global	NCT04437511
TRAILBLAZER-ALZ 3 Donanemab/Placebo	2196	65–80	III	Japan, Puerto Rico, USA	NCT05026866
TRAILBLAZER-ALZ 4 Donanemab/Aducanumab	148	50–85	III	USA	NCT05108922
TRAILBLAZER-ALZ 5 Donanemab/Placebo	Actively recruiting	60–85	III	Global	NCT05508789
TRAILBLAZER-ALZ 6 Donanemab/Placebo	800	60–85	III	Global	NCT05738486

4. Safety and Tolerability

Donanemab-azbt common adverse reactions included ARIA-E or Amyloid Related Imaging Abnormalities with Edema, ARIA-H (Amyloid Related Imaging Abnormalities with Hemosiderin Deposition) microhemorrhage, ARIA-H with Superficial Siderosis, allergic and infusion related reactions, and headache. The treatment group experienced a 10% or higher incidence than the placebo group. This drug is contraindicated in patients with a known severe hypersensitivity to donanemab-azbt or any of its excipients. The drug carries a black box warning regarding ARIA (Amyloid-Related Imaging Abnormalities), which can manifest as either edema (ARIA-E) or hemosiderin deposition (ARIA-H). This typically occurs early in treatment and is often asymptomatic, but it can be serious and life-threatening. Significant intracerebral hemorrhages greater than 1 cm have been observed in patients using this medication. To prevent this, providers should perform APOE ε4 testing on patients before starting treatment with donanemab, as patients who are APOE ε4 homozygotes—about 15% of AD patients—are at a higher risk of developing ARIA, including symptomatic, serious, and severe radiographic ARIA, compared to heterozygotes and non-carriers [44].

Due to the risk of developing ARIA, it is recommended to obtain a baseline brain magnetic resonance imaging (MRI) before initiating treatment, and before the 2nd, 3rd, 4th and 7th infusion. Making recommendations for patients who develop ARIA depends on clinical symptoms and radiographic severity [45].

Other than ARIA, studies reported infusion-related reactions in 9% of patients treated with donanemab compared to 0.5% of patients on placebo. These reactions occurred mainly within the first 4 infusions and the signs included: chills, erythema, headaches, nausea/vomiting, difficulty breathing, sweating, and low blood pressure. The manufacturer

recommends reducing or discontinuing the infusion if clinically indicated. Pre-treatment with acetaminophen, antihistamines, or corticosteroids may be considered [46].

5. Comparison with Existing FDA-Approved Medications

Cholinesterase inhibitors include donepezil approved for all stages of AD, galantamine, and rivastigmine for mild to moderate AD. These drugs work by increasing the amount of acetylcholine to improve the cognitive symptoms. NMDA receptor antagonist such as memantine is approved for moderate to severe AD. This drug helps to reduce the excitotoxicity related to an increased activation of glutamate receptors. The limitations of these two classes of drugs are that they only help to manage the symptoms of the disease, without tackling the underlying causes of AD. In addition, cholinesterase inhibitors' side effects include sleep disturbances, nausea, vomiting, diarrhea, muscle weakness, headache, and dizziness [47]. NMDA receptor antagonist side effects include confusion, headache, dizziness, and constipation. The above small molecule drugs target either acetylcholine levels or excitotoxicity, while the new recently developed amyloid-targeting therapies address amyloid plaques for potentially disease modifying therapies.

Amyloid-targeted therapies include lecanemab, aducanumab, and the newly approved donanemab. These drugs aim to inhibit the aggregation of amyloid-beta plaques in the brain. Among these, aducanumab was removed from the market in November 2024 based on a business decision by Biogen [48].

Currently, no direct head-to-head clinical trials are comparing small-molecule AD drugs like memantine and donepezil with monoclonal antibodies such as donanemab or lecanemab. However, indirect comparisons through meta-analyses and systematic reviews provide some insights into their relative efficacy and safety profiles.

Clinical studies showed that donanemab and lecanemab were significantly superior to placebo in efficacy in Clinical Dementia Rating sum of boxes (CDR-SB) [49]. A systematic review conducted by Terao, et al. stated the incidence of ARIA-E to be 36% and 35% in the two included trials of aducanumab, 12.6% and 9.9% in the two included trials of lecanemab, 26.7% and 24% in the two included trials of donanemab. ARIA-H: 19% and 20% in the two included trials of aducanumab, 17.3% and 6.8% in the two included trials of lecanemab, 22.1% and 19.7% in the two included trials of donanemab. Please refer to Table 2 for a comparison of donanemab and lecanemab [49].

Table 2. Comparison of the Amyloid Target Therapy.

Drug Name [25,50]	Dosage	Administration	Frequency	Cost	Mechanism of Action
Donanemab-azbt (Kisunla)	Initial: 700 mg every 4 weeks for 3 doses; Maintenance: 1400 mg every 4 weeks	IV infusion over 30 min	Once every 4 weeks	$32,000 per year	Humanized monoclonal antibody targeting insoluble N-truncated pyroglutamate amyloid beta
Lecanemab (Leqembi)	10 mg/kg body weight	IV infusion over 1 h	Once every 2 weeks	$26,500 per year	Humanized monoclonal antibody binding to soluble and insoluble toxic amyloid-beta protofibrils

6. Place in Therapy and Clinical Recommendations

Donanemab-azbt is a promising treatment recommended for adults' patients with early symptoms of AD, including mild cognitive impairment (MCI) or mild dementia (mini-mental state examination (MMSE) of 21–26 with confirmed abnormal amyloid. This drug works by removing the amyloid beta plaques (a key feature in AD) that formed in the brain of AD patients; therefore, adequately slowing functional and cognitive declines. In therapy, donanemab-azbt can be considered as first-line for this particular category of patients. It is recommended that candidates for this drug have no underlying bleeding condition, no transient ischemic attack (TIA), stroke, seizure in the past 12 months, no malignancies within 3 years of screening, and no underlying conditions that may cause cognitive impairment. Other underlying conditions that may cause cognitive impairment include vitamin B12 deficiency, depression (except those with Geriatric Depression Scale or GDS > 7), and substance abuse within 2 years. Since there is a need for brain MRI, patients eligible for this medication should have no brain magnetic resonance imaging (MRI) contraindication [51].

Economic and Quality-of-Life Considerations

Table 3 below from Eli Lilly and Company represents the total cost of treatment with donanemab-azbt after 6, 12, and 18 months. Out-of-pocket expenses like the duration of treatment, monthly clinical visits for IV infusion, imaging (PET scan, MRI), and any additional clinic fees will vary based on each patient's insurance plan. The cost of a single vial is $695.65. The first 3 doses consist of 2 vials (700 mg) followed by 4 vials (1400 mg) doses after.

Table 3. Cost of treatment with Donanemab-azbt in the United States [52].

Length of Treatment	6 Months	12 Months	18 Months
30 min infusion	6	13	19
Course of therapy cost	$12,522	$32,000	$48,696

7. Conclusions

Donanemab-azbt is a monoclonal antibody used for early stages of AD. Clinical studies have shown that donanemab is effective in slowing cognitive and functional decline by reducing and targeting amyloid-beta plaques, which are essential to the pathophysiology of AD [53]. According to the findings of the TRAILBLAZER-ALZ 2 trial, donanemab-azbt can dramatically lower the buildup of amyloid plaque, which may change how the disease progresses for patients who are still in early stages. Donanemab-azbt carries a black box warning for ARIA therefore, genotype testing for APOE ε4 along with monitoring are recommended. Long-term research on the efficacy and safety of donanemab-azbt is ongoing and is essential to evaluate future directions in treatment recommendations.

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A Physicochemical Stability Study of Pembrolizumab Vial Leftovers: Let Us Stop Pouring Good Money Down the Drain

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Abstract: Background: Pembrolizumab is a monoclonal antibody (mAb) approved for treating Non-Small Cell Lung Cancer (NSCLC), melanoma and lymphomas. Commercialized in single-size (100 mg/4 mL) vials, the pembrolizumab solution contains no preservative. As such, the manufacturer recommends using pembrolizumab vials only once, and thus, to rapidly dispose of any unused portion. Thus, appreciable amounts of this costly product are wasted. Objective: To evaluate the physical, chemical and microbiological stability of pembrolizumab vial leftovers stored at room temperature or at 4 °C, 7 and 14 days after first vial puncturing. Methods: Following pH assessments, submicronic aggregation and turbidity of pembrolizumab were measured by dynamic light scattering (DLS) and spectrophotometry, respectively. In addition, SE-HPLC (size-exclusion high-performance liquid chromatography), IEX-HPLC (ion exchange HPLC) and peptide mapping HPLC served to respectively evaluate aggregation and fragmentation, distribution of charge and primary structure of pembrolizumab. Incubation at 37 °C for 48 h of pembrolizumab vial leftovers on blood agar plates was used to determine their microbiological stability. Results: Physical, chemical and microbiological stability of pembrolizumab leftovers was demonstrated for at least two full weeks. Conclusions: These results argue forcefully in favor of allowing prolongation of pembrolizumab vial leftovers usage well beyond a single day.

Keywords: pembrolizumab; vial leftovers; stability

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1. Introduction

Pembrolizumab (Keytruda®) is an IgG4/κ isotype monoclonal antibody (mAb) designed to sit on the PD-1 (programmed cell death 1) receptor. In doing so, it prevents both its ligands, PD-L1 and PD-L2, from interacting with the receptor [1]. As a key immune checkpoint, the PD-1 pathway may be stimulated by cells in the immediate vicinity of the tumor to escape activated T-lymphocyte immune control. Pembrolizumab, by blocking this pathway, promotes efficient T-lymphocyte function, thus favoring tumor regression [2]. In the United States and Canada, pembrolizumab is currently approved for treating many subtypes of cancers, including melanoma, Non-Small Cell Lung Cancer (NSCLC), classical

Hodgkin and primary mediastinal large ß-cell lymphomas; head and neck, esophageal, gastric, urothelial, cervical, biliary tract and bladder cancers; hepatocellular, renal, endometrial and cutaneous squamous cell carcinomas; as well as Triple-Negative Breast Cancer (TNBc) [3,4]. In advanced NSCLC patients, when compared to docetaxel or platinum-based chemotherapy, pembrolizumab was shown to increase both overall and progression-free survival [5,6]. Moreover, when compared to a number of chemotherapeutic agents, such as paclitaxel and carboplatin, pembrolizumab performed better in safety, overall survival and progression-free survival [7]. In addition, when used for melanoma and compared to ipilimumab-based treatment, pembrolizumab was shown to increase progression-free survival [8].

Pembrolizumab is marketed in single-use vials containing no preservatives, as an undiluted solution (100 mg/4 mL) to be further diluted in saline before intravenous infusion. Such an injectable product containing no preservatives is, thus, considered as 'High-risk' by the USP (United States Pharmacopeia) [9], essentially as a microbiological precaution. Indeed, the USP considers that 24 h at room temperature is the maximum microbiological BUD (Beyond-use Dating) for 'High-risk' products, such as most monoclonal antibodies (mAbs). Consequently, the manufacturer (Merck Sharpe & Dohme, Rahway, NJ, USA) recommends discarding any unused portion left in the vial and administering pembrolizumab solution quickly after it is prepared. In the event the solution is not infused immediately, it must be discarded after 6 h at room temperature or after 96 h under refrigeration [3,4].

Although the therapeutic efficacy of pembrolizumab has been shown, it comes at a price, which is very high. In Canada (including the province of Québec [10]) the acquisition cost is CAD 4400.00 (USD 3212.00) per 100 mg vial (100 mg/4 mL) or CAD 1100.00/mL [11]. The pan-Canadian Oncology Drug Review (pCODR) has determined that treating a single patient on a 2 mg/kg every 3 weeks dosing regimen can cost as much as CAD 140,029.00 per year or CAD 8237.00 per 28-day course of treatment [11]. A pembrolizumab dose of 2 mg/kg was initially approved in 2014 by the FDA and in 2015 by Health Canada [3,4]. As the years went by, a flat dose of 200 mg was also approved in both countries for all pembrolizumab's indications [3,4]. At first, the flat dosing option was well received by clinicians, as being much more convenient, while suggesting the end of product wastage. However, it was soon realized that this 'one size fits all' practice was exposing most patients to higher than needed doses, considering that the better efficacy of such doses has never been proven [11]. Thus, when thinking about it, flat dosing is for most patients a form of wastage that still inflates the final treatment costs. It was, therefore, established that using pembrolizumab 2 mg/kg is a fair clinical practice that turns out to be more cost-effective while making no compromise on efficacy [11].

In fact, the cost of pembrolizumab wastage goes beyond imagination, reaching hundreds of millions of dollars yearly worldwide [12]. Of note, Canadian provincial healthcare systems are not escaping from this tsunami of expenses. A retrospective analysis of melanoma and NSCLC patients in all six British Columbia Cancer Regional Centres performed for fiscal years 2017 and 2018 [11] showed the amplitude of the problem. In this study, a total of 2948 pembrolizumab doses were administered for treating 202 patients with NSCLC and 182 others with melanoma. Without any vial sharing (using vial leftovers to treat other patients), the amount of drug wasted by these six BC Cancer Treatment Centres while treating those 384 patients was measured at CAD 6,682,460.40. With optimal (and theoretical!) vial sharing, the amount of drug saved was estimated at CAD 3,207,600.00, which is appreciable but still leaving a whopping CAD 3,474,860.40 in losses, and still representing 15.25% wastage of the total product despite optimal 100 mg vial sharing assumptions.

Apart from drug dosing, other factors increase the costs of mAbs such as pembrolizumab, including single-use vials and same-day administration practice, cancellation

from patients for any given reason, and even no-shows [12–14]. However, the current 'single-use vials' and 'same-day administration' practice is, by far, the leading contributing factor to the overall wastage of mAbs [15]. For instance, in a large cancer treatment center such as our own, the high number of patients treated with pembrolizumab for NSCLC, along with tight drug administration scheduling, allow efficient vial sharing and minimize drug wastage. Yet, despite all these vial usage-optimizing efforts, our pharmacists have evaluated that pembrolizumab wastage reached a total of 92 mL for the fiscal year 2022–2023, which is equivalent to 23 full vials of undiluted pembrolizumab (Keytruda® 100 mg/4 mL). With an acquisition cost of CAD 4400.00 per vial, this represents at least CAD 101,200.00 yearly, or a CAD 8433.33 average monthly loss for our institution only, on this single product! (personal communication).

Interestingly, most of the concerns raised by mAb manufacturers to justify the single-use of vials and rapid discarding of leftovers are based on potential threats of a microbiological nature [3,4]. Yet, a number of studies have demonstrated that numerous extensively used, preservative-free mAbs remain highly stable even after dilution in saline or as undiluted vial leftovers way over 24 h [15–19], provided that they were handled under appropriate aseptic settings, which are required and tightly controlled in any cancer treatment center. In addition, in any cancer treatment center. Thus, once aseptic conditions are applied, the overall stability of mAbs mainly depends on their intrinsic physicochemical properties.

Although it has been marketed in the US since 2014 and in Canada since 2015, data on pembrolizumab's physicochemical stability, specifically in the form of undiluted vial leftovers, are still very scarce [16]. Interestingly, a recent study by Arnamo et al. [20] showed that by using size exclusion chromatography (SE-HPLC) and dynamic light scattering (DLS), pembrolizumab vial leftovers are stable from a physicochemical standpoint for at least two weeks when kept refrigerated. They also showed the biological stability of these vial leftovers by use of an Enzyme-Linked Immuno-Sorbent Assay (ELISA). However, this study provided no data on microbiological stability whatsoever. The present study was, therefore, aimed at complementing the study of Arnamo et al. [20] by evaluating the physicochemical stability of pembrolizumab vial leftovers using further sets of new experiments using other additional assays and by providing the first evidence suggesting microbiological stability of these leftovers when stored at either room temperature or 4 °C on Days 0, 7 and 14 after first puncturing.

2. Methods

2.1. Pembrolizumab Samples

Unopened Keytruda® vials (pembrolizumab 100 mg/4 mL, Merck Canada Inc., Kirkland, QC, Canada), lot numbers A102541, A102193 and X012124, were obtained from the Pharmacy Unit of our hospital. A total of 3 punctures (only once on Day 0, 7 and 14) were performed aseptically in each vial with an 18 G × 1" needle syringe.

2.2. Visual Inspections

In a sterile hood, before handling vials on Days 0, 7 and 14, inspection was performed to look for suspended particles, turbidity, signs of formation of aggregates or gas or any colour change, as described previously. This inspection was always performed by the same person using the naked eye without background. The vials were protected from sunlight at all times, as described previously [21].

2.3. Turbidity

A UV-VIS 1800 spectrophotometer (Shimadzu, Columbia, MD, USA) was used to measure the turbidity of pembrolizumab solution samples in triplicates at room temperature.

Ultraviolet (UV) absorbance of samples was obtained at two wavelengths, 280 nm ($A_{\lambda 280}$) and 350 nm ($A_{\lambda 350}$), and used to calculate the aggregation index (AI) using this formula, as described previously [21].

$$\mathrm{AI} = \frac{A\lambda 350}{A\lambda 280 - A\lambda 350} \times 100$$

When AI is under 10, it means there are no soluble aggregates. Pembrolizumab 100 mg/4 mL vial leftovers were diluted in demineralized water (filtered at 0.22 µm) at 1 mg/mL (final concentration) to take into account the detection capacity of the apparatus.

2.4. Dynamic Light Scattering (DLS) to Assess Aggregation of Submicronic Particles

At different time intervals, pembrolizumab's hydrodynamic diameter was compared by dynamic light scattering (DLS), as described previously [21]. DLS serves to detect aggregates of 1 nm–10 µm size. Samples of pembrolizumab vial leftover solution (100 µL) were tested at 25 °C in triplicates on a Zetasizer apparatus (Malvern, UK). The Z-average calculated by the instrument is defined as the intensity-weighted averaged hydrodynamic diameter. The polydispersity index (PDI) was also evaluated. When representative population of pembrolizumab particles had no deviation superior to 1 nm from their normal mean hydrodynamic diameter, the solution was considered stable and monodispersed (PDI smaller than 0.1 means less than 10% change in mean normal diameter and no aggregation).

2.5. pH Measurements

A pH meter was used to measure the pH of pembrolizumab undiluted vial leftovers in triplicates, as described previously [21]. The Day 0 value was used to compare the pH of pembrolizumab leftovers at Day 7 and Day 14. A variation smaller than half a unit (0.5) of pH from Day 0 value was considered to show stability of the pH of the solution.

2.6. Size-Exclusion High-Performance Liquid Chromatography (SE-HPLC) to Assess the Aggregation of Pembrolizumab

SE-HPLC was used to determine (in triplicates) the aggregation of pembrolizumab in solution, as described previously [21]. An SIL-20ACHT automatic sample injector, an SPD-20A UV detector and an LC-20AT pump (Shimadzu, Columbia, MD, USA) were used at 25 °C. An isocratic method was performed at 0.6 mL/min using a buffer solution A of 0.2 M potassium phosphate buffer with 0.25 M potassium chloride, pH 6.2 [22]; aXBridge Premier Protein SEC 250 Å column with its guard column was used (Waters, Mississauga, ON, Canada). Each pembrolizumab solution sample was diluted to 1 mg/mL in the buffer solution A and filtered. Thereafter, 25 µL of pembrolizumab (1 mg/mL) was injected into the system. Pembrolizumab's peak areas were obtained at a wavelength of 280 nm using UV absorbance, and Day 0 data were considered as reference values. The EZ Start software package version 7.4 from Shimadzu was used to collect and analyze the chromatograms. USP <129> monograph criteria [22] were applied to assess pembrolizumab stability.

2.7. Ion Exchange HPLC (IEX-HPLC) to Assess Pembrolizumab's Charge Distribution

Deamidation-induced variations in charge distribution of pembrolizumab's main, acidic and basic species were assessed by IEX-HPLC, according to criteria of USP <129> monograph [22].

IEX-HPLC was used to perform analyses in triplicates at 30 °C in a gradient mode, as described previously [21]. Two mobile phases (A and B) were composed of 0.02 M MES (4-morpholineethanesulfonic acid, Millipore Sigma, St. Louis, MO, USA), pH 6.2, and 0.5 M of NaCl was added to the mobile phase B. BioResolve SCX mAb column and SCX mAb VanGuard FIT guard column (both from Waters, Milford, MA, USA) were used to perform this gradient method at a flow rate of 0.4 mL/min. Each pembrolizumab solution sample

was diluted (1 mg/mL) by use of the mobile phase A, filtered before the transfer into the HPLC vial, and then injected (50 microliters) into the system. The gradient conditions used are summarized as follows:

Time	%B
Initial	0%
6	0%
12	6%
36	12%
51	18%
52	100%
53	0%
68	0%

Pembrolizumab's peak areas were obtained at a wavelength of 280 nm by UV absorbance, and Day 0 data were considered as reference values [23].

2.8. Peptide Mapping HPLC to Determine the Primary Structure of Pembrolizumab

Peptide mapping HPLC was used to determine the primary structure of pembrolizumab, as described previously [21]. Samples of pembrolizumab solution (100 mg/4 mL) were diluted to 1 mg/mL with a digestion buffer made of 50 mM NH_4HCO_3, pH 7.8 (Millipore Sigma). Fifty microliters (50 µL) of this diluted solution (in duplicates) were further diluted in an extra volume (10 µL) of the digestion buffer [23]. To enhance the enzymatic digestion, a solution of 0.1% Rapigest® reagent (Waters) was added to the diluted samples. The diluted samples were heated at 80 °C for 20 min to denature the antibody (pembrolizumab). After this step, the denatured samples were cooled down on a bench for a few minutes [23]. The reduction step consisted of adding 1 µL of 0.22 M dl-dithiothreitol (DTT, Millipore Sigma) to all denatured samples, which were then mixed and warmed at 37 °C for 60 min. All reduced samples were then mixed with 1 µL of 0.66 M iodoacetamide (IAA, Millipore Sigma) incubated in darkness for 30 min at RT [23]. The alkylated samples were then digested in 1.5 µg of trypsin (Promega, Madison, WI, USA). The digested samples were then agitated and warmed at 37 °C overnight (for 18 h) [23]. The enzymatic reaction was stopped with a solution of 25% trifluoroacetic acid (TFA, Millipore Sigma). The preparation was then agitated and warmed at 37 °C for 30 min [23]. After this incubation, the digested pembrolizumab samples were centrifugated at 13,000 rpm for 10 min at RT, and approximately 50 µL of the supernatants were used for HPLC analysis [23].

2.9. HPLC Analyses

These analyses were performed, as described previously [21], at 40 °C. Two mobile phases (A and B) were prepared by adding trifluoroacetic acid (0.1%) in water (A) or (B) in acetonitrile (Fisher Scientific, Whitby, ON, Canada) to be used later in gradient mode. The specific conditions of the gradient were as follows:

Time	%B
Initial	0.5%
2	0.5%
62	50%
65	95%
66	95%
80	0.5%

An XSelect Premier CSH C18 130 Å column with its guard column (both from Waters) was used for this gradient method at a flow rate of 0.5 mL/min. Samples as triplicates of 25 µL each were injected into the system. Peaks of pembrolizumab were obtained by UV absorbance detection at two wavelengths: 214 and 280 nm. The Day 0 chromatograms of pembrolizumab peptide mapping served as baseline and reference values. The USP <1055> monograph [24] criteria were used to evaluate the stability of pembrolizumab.

2.10. Microbiological Stability Assessment

Pembrolizumab vial leftovers' microbiological stability was evaluated, as described previously [21,25,26]. Briefly, all pembrolizumab (100 mg/4 mL) solution samples (100 µL) were aseptically withdrawn from pembrolizumab vials and inoculated on plates containing 5% blood agar, as triplicates. These plates were placed in an incubator for 48 h at 37 °C before detection of colonies and counting. All this work was conducted while fully complying with the ISO 14644-01 norm in effect at the Pharmacy Department of IUCPQ-UL [26].

2.11. Statistical Analyses

The GraphPad Prism software, version 10.2.2 (La Jolla, CA, USA), was used to perform statistical analyses. Two-way repeated measures ANOVA or Student's paired *t*-test were used to compare data. All parameters were presented as mean ± SD, and p values < 0.05 were considered statistically significant.

3. Results

3.1. Physicochemical Stability Assessment

No evidence of colour changes, gas formation, turbidity, suspended particles or formation of large aggregates were ever noticed after visual inspection. Tables 1 and 2 show the data acquired from pembrolizumab vial leftovers on Days zero, seven and fourteen, when they were stored at either room temperature or in a refrigerator at 4 °C. All data were compared as Day zero vs. Day seven or as Day zero vs. Day fourteen.

There was no difference in turbidity after 7 or 14 days at both storage temperatures (room or 4 °C). As seen in Tables 1 and 2, the aggregation index (AI) stayed highly stable and far below 10 at all times, ruling out the presence of visible or subvisible soluble aggregates at any given time.

With a variation of less than 1 nm at any given time, the mean hydrodynamic diameter of pembrolizumab stayed well within acceptance limits at either room temperature or at 4 °C. The polydispersity index (PDI) has never reached 0.1 at any moment at either room temperature or at 4 °C. Pembrolizumab vial content was considered as a monodispersion, implying the absence of submicronic aggregation, further demonstrating stability of the solution throughout all the experiments at both room temperature and 4 °C.

With a deviation of less than 0.5 unit at all times, the pH of undiluted pembrolizumab vials remained stable at both room temperature and 4 °C. Indeed, all values remained within the acceptable pH range (5.2–5.8) throughout all experiments.

SE-HPLC experiments with pembrolizumab vial leftovers revealed four peaks: the first representing the oligomers of pembrolizumab, the two main peaks illustrating the well-characterized monomeric and dimeric forms of pembrolizumab [1], and a fourth peak of pembrolizumab fragments (a seen in Figure 1 and its inset). These peaks were observed in all samples. At all times and at either room temperature or 4 °C, the AUC (area under the curve) of the monomeric and dimeric peaks of pembrolizumab accounted for nearly all (>99%) of the AUC of all peaks put together (Tables 1 and 2). As a result, this left a very small portion of the total AUC representing the two remaining peaks of oligomers and fragments of pembrolizumab. These two combined have never reached 0.5% of the total

AUC at either room temperature or 4 °C, showing that pembrolizumab did not aggregate or fragment, thus, again, demonstrating high stability.

Table 1. Pembrolizumab (100 mg/4 mL) stored at RT (room temperature). All mean ± SD.

Parameters		Day Zero	Day Seven	Day Fourteen	Statistics
Turbidity	Aggregation index (AI %)	0.1288 ± 0.0479	0.1428 ± 0.0195	0.1110 ± 0.0179	Non-significant
Dynamic light scattering (DLS)	Size (nm)	11.31 ± 0.05	11.27 ± 0.06	11.11 ± 0.13	Non-significant
	Polydispersity index (PDI)	0.077 ± 0.004	0.071 ± 0.006	0.070 ± 0.008	Non-significant
pH	Units of pH	5.55 ± 0.01	5.54 ± 0.03	5.54 ± 0.02	Non-significant
SE-HPLC			Variants (%)		
	Oligomeric	0.09 ± 0.02	0.09 ± 0.01	0.09 ± 0.02	Non-significant
	Dimeric	6.29 ± 0.05	6.58 ± 0.02	6.68 ± 0.06	Non-significant
	Monomeric	93.44 ± 0.03	93.14 ± 0.02	93.05 ± 0.05	Non-significant
	Fragmental	0.18 ± 0.01	0.18 ± 0.00	0.18 ± 0.00	Non-significant
IEX-HPLC			Variants (%)		
	Acid peaks	18.0 ± 1.0	17.7 ± 1.4	17.3 ± 0.1	Non-significant
	Main peak	64.8 ± 1.1	64.8 ± 1.3	65.2 ± 0.1	Non-significant
	Basic peaks	17.2 ± 0.1	17.5 ± 0.2	17.5 ± 0.1	Non-significant
Microbiological assay	Colonies	Absent	Absent	Absent	

Table 2. Pembrolizumab (100 mg/4 mL) refrigerated at 4 °C. All mean ± SD.

Parameters		Day Zero	Day Seven	Day Fourteen	Statistics
Turbidity	Aggregation index (AI %)	0.1346 ± 0.0855	0.1550 ± 0.0138	0.1138 ± 0.0216	Non-significant
Dynamic light scattering (DLS)	Size (nm)	11.21 ± 0.15	11.35 ± 0.05	11.45 ± 0.04	Non-significant
	Polydispersity index (PDI)	0.067 ± 0.013	0.076 ± 0.014	0.085 ± 0.009	Non-significant
pH	Units of pH	5.64 ± 0.13	5.65 ± 0.13	5.67 ± 0.11	Non-significant
SE-HPLC			Variants (%)		
	Oligomeric	0.06 ± 0.02	0.06 ± 0.02	0.08 ± 0.02	Non-significant
	Dimeric	6.08 ± 0.31	6.33 ± 0.27	6.49 ± 0.36	Non-significant
	Monomeric	93.66 ± 0.32	93.43 ± 0.27	93.24 ± 0.36	Non-significant
	Fragmental	0.19 ± 0.00	0.18 ± 0.00	0.19 ± 0.01	Non-significant
IEX-HPLC			Variants (%)		
	Acid peaks	16.6 ± 3.2	17.7 ± 0.7	16.8 ± 0.2	Non-significant
	Main peak	65.7 ± 2.6	64.7 ± 0.5	65.4 ± 0.2	Non-significant
	Basic peaks	17.7 ± 0.5	17.6 ± 0.3	17.8 ± 0.1	Non-significant
Microbiological assay	Colonies	Absent	Absent	Absent	

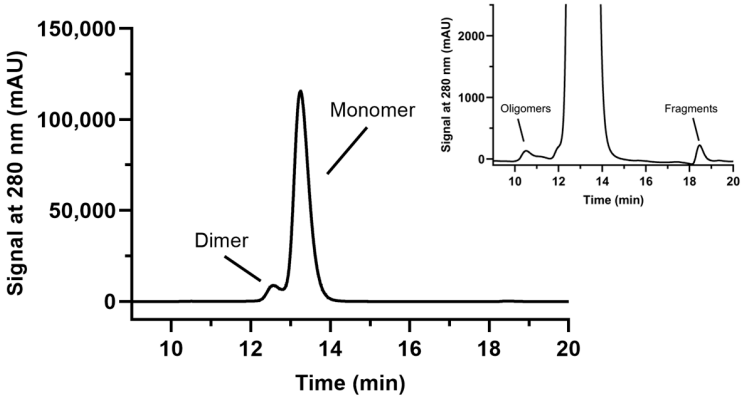


Figure 1. SE-HPLC elution profile of dimeric and monomeric pembrolizumab. Oligomers and fragments are magnified in inset.

IEX-HPLC chromatograms displayed pembrolizumab's distinctive peaks: the principal species, a number of pembrolizumab acid species and a smaller set of pembrolizumab basic species (as seen in black as upward peaks of Figure 2A). All these pembrolizumab species (principal, acid and basic) remained constant in terms of relative proportions at any given time and at either room temperature or 4 °C (Tables 1 and 2 and downward peaks (in red) of Figure 2A + panels B and C of Figure 2).

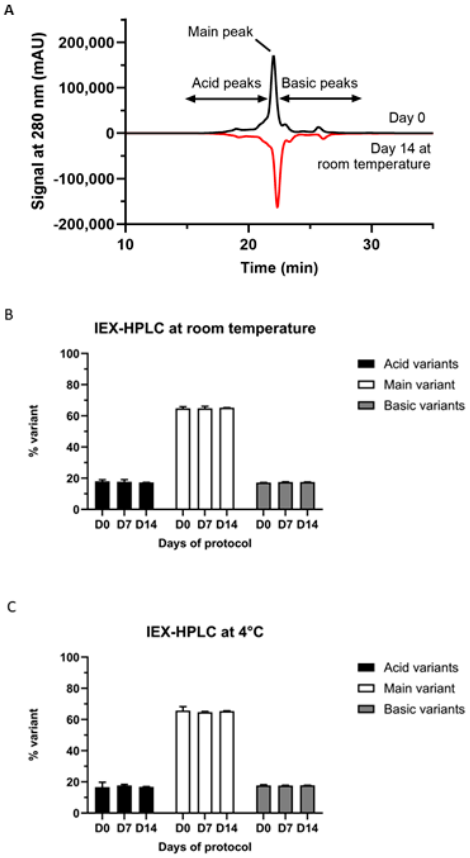
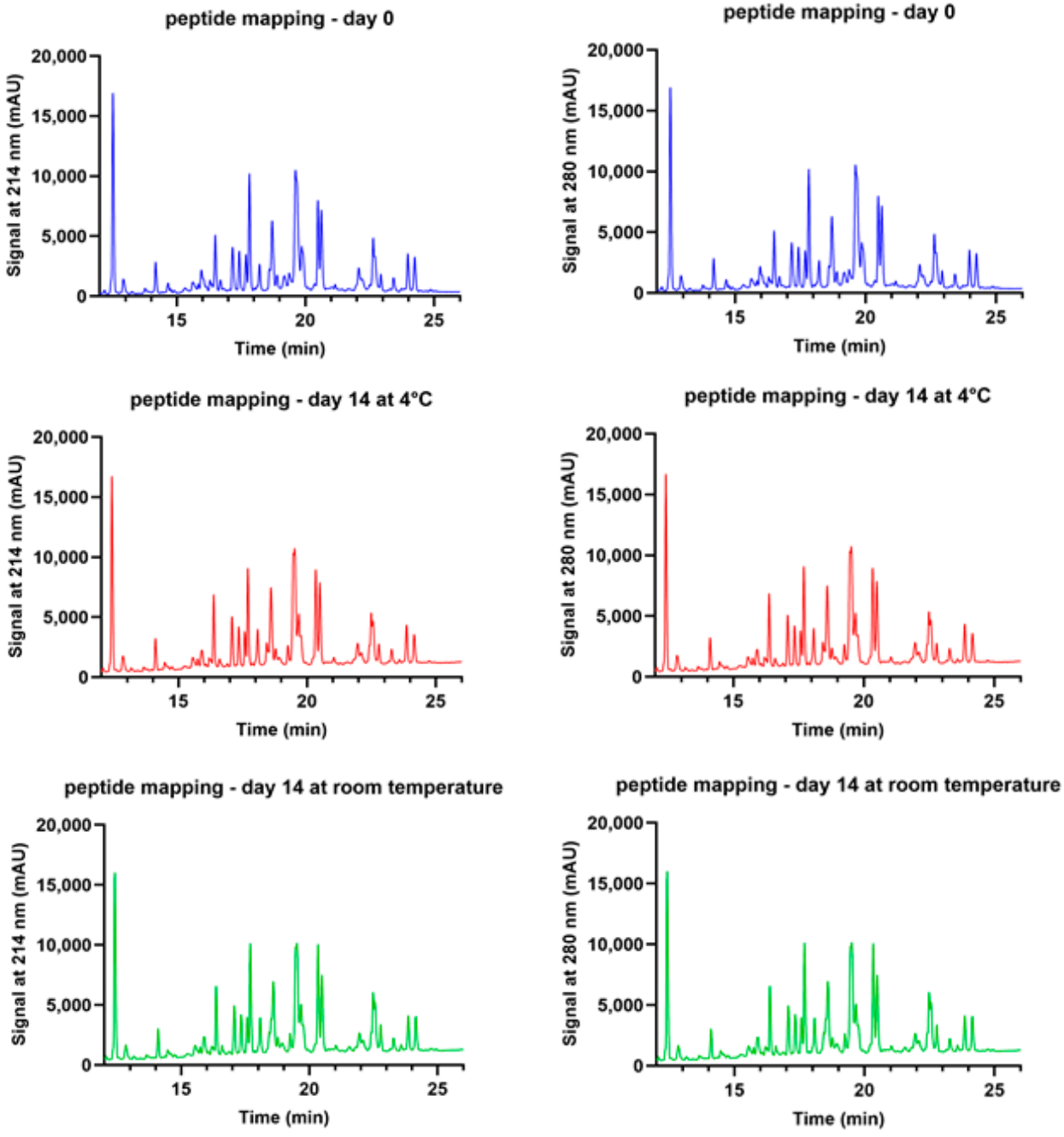


Figure 2. (**A**) IEX-HPLC elution profile of pembrolizumab. A number of peaks of the respective isoforms of pembrolizumab (main, acid and basic) are represented by the black tracing, with Day zero respective proportions. The same data are shown on Day fourteen at RT by the tracing in red. (**B**) Respective percentage of pembrolizumab's same isoforms at Days zero, seven and fourteen with storage at RT. (**C**) The same data as in panel B but with vials stored at 4 °C.

Chromatograms generated in peptide mapping experiments (Figure 3A,B) revealed that at two different wavelengths (214 and 280 nm), pembrolizumab's primary structure was not affected at all when vial leftovers were stored for as long as 2 weeks at either room temperature or at 4 °C. Indeed, all pembrolizumab chromatograms obtained at either 214 or 280 nm are nearly superimposable.



(**A**) (**B**)

Figure 3. (**A**). Peptide mapping chromatograms obtained by HPLC at 214 nm of pembrolizumab vial leftover solutions on Day zero (upper panel, blue) and on Day fourteen when refrigerated at 4 °C (middle panel, red) or at RT (lower panel, green). (**B**). Peptide mapping chromatograms obtained by HPLC at 280 nm of pembrolizumab vial leftover solutions on Day zero (upper panel, blue) and on Day fourteen when refrigerated at 4 °C (middle panel, red) or at RT (lower panel, green).

3.2. Microbiological Stability Assessment

All pembrolizumab leftover samples, withdrawn from the vial on Day 0, 7 or 14 and incubated in triplicates at 37 °C during 48 h on blood agar plates tested negative for any bacterial or fungal growth.

4. Discussion

Pembrolizumab vial leftovers' physicochemical stability, as a function of time and storage temperature, was thoroughly tested. When stored at either room temperature or 4 °C and handled aseptically, as recommended, pembrolizumab vial leftovers were shown to remain highly stable from a physicochemical standpoint for a minimum of 14 days. Moreover, the microbiological assay performed on these pembrolizumab vial leftovers showed no bacterial or fungal growth, suggesting microbiological stability as well.

Neither turbidimetry, DLS nor SE-HPLC showed physical instability. No pembrolizumab corpuscle with a larger hydrodynamic diameter was ever detected, ruling out nucleation, a phenomenon generally occurring before aggregation [15]. In addition, SE-HPLC experiments have shown that the relative percentages of the main peaks (monomeric and dimeric pembrolizumab) or of the remaining peaks (representing pembrolizumab oligomers and fragments) hardly ever changed at all, thus demonstrating that aggregation or fragmentation of pembrolizumab has not happened, even after two full weeks of storage at either room temperature or 4 °C. Moreover, the relative percentages of pembrolizumab main component, as well as acidic and basic variants, remained virtually unchanged over time, as shown by IEX-HPLC experiments, thus, again, confirming the remarkable stability of pembrolizumab vial leftovers up to two full weeks when stored at either room temperature or 4 °C.

Potential protein degradation and site-specific assessment of chemical reactions, such as oxidation or deamidation of pembrolizumab, was performed by peptide mapping HPLC. Pembrolizumab's primary structure was not affected by 14 days of storage at either room temperature or 4 °C. This did not come as a surprise, as changes in the proportion of pembrolizumab's main variant were way too small (<1.6%, as measured by IEX-HPLC [15]) to detect any noticeable modification of the primary structure.

Pembrolizumab's microbiological stability was also suggested in all vial leftover samples tested. Indeed, whether the samples were from vial leftovers stored at RT or in a refrigerator at 4 °C for 7 or 14 days, no bacterial or fungal growth (including yeasts) of any kind was ever observed in any blood agar culture plates when they were incubated for 48 h at 37 °C.

This is in perfect agreement with a similar study with durvalumab [21] and with a recent study [16] showing that from a microbiological standpoint, it is acceptable to extend storage and to further use monoclonal antibody leftovers, as the overall risk of contamination is very low (0.05%), even in multi-punctured vials. As an additional convincing example, Das et al. [18] have not seen any infection or inflammation in the eyes of their 221 consecutive patients when receiving a total of 973 intravitreal injections of bevacizumab, even without prior aliquoting of vial leftovers, and thus, after hundreds of direct withdrawals from these vials. In fact, their vial leftovers were shown to remain sterile for at least a week when kept refrigerated.

Numerous studies from around the world have shown that mAbs, provided that they are kept in appropriate conditions and adequately handled by qualified people, should be considered far more stable than previously thought and specified in the official monographs of their respective manufacturers [16–19,27–31]. Indeed, it has even been shown that mAbs have to be exposed to high temperatures for an extended period of time to observe relevant physicochemical alterations [32]. The present report is in agreement

with all these studies. In fact, we demonstrated physicochemical stability of undiluted (100 mg/4 mL) pembrolizumab vial leftovers for at least two weeks when conserved at either room temperature or 4 °C. Our microbiological data suggest stability as well over the same period and in the same storage conditions. The current study also corroborates similar results concerning pembrolizumab's physicochemical stability as an admixture solution in saline IV infusion bags [20,31] or as vial leftovers, such as recently described by Arnamo et al. [20]. Yet, of utmost importance, the present study is the first to suggest that pembrolizumab vial leftovers might be stable for at least two weeks, from a microbiological standpoint, when stored at either room temperature (RT) or at 4 °C. The present study also reinforces Arnamo's physicochemical stability data by adding IEX-HPLC data confirming the stability of pembrolizumab and both its acidic and basic variants, as well as demonstrating the stability of pembrolizumab's primary structure by peptide mapping HPLC. A possible limitation of the present study is that we did not assess the biological stability of pembrolizumab vial leftovers. However, by using flow cytometry and ELISA testing, pembrolizumab's biological stability after dilution and storage in saline bags at either 1 or 4 mg/mL was shown by Acramel et al. [33] to reach one full week at room temperature and four full weeks at 4 °C, which was also recently corroborated by Arnamo et al. [20]. Another potential limitation of this study is the potential instability risks that might come from the progressive increase in interfacial contact of the pembrolizumab solution with glass over time (less solution in the vial relative to the same contact surface).

Indeed, glass delamination is a phenomenon known to happen with injectable drug solutions stored for several months, including some biologics such as antibodies. This can lead to the generation of both visible and subvisible particles. Delamination results from the chemical attack on the glass surface. In fact, glass attack, in this case, mostly results from ion exchange or dissolution. Ion exchange happens when water manages to diffuse into the glass, leading to the exchange of H+ with alkali ions. On the other hand, dissolution is mainly caused by hydroxide ions (OH-) attacking the glass silicate backbone. Overall, these two mechanisms could lead to the formation of a leached layer, potentially detaching from the glass surface.

Yet, the data presented in the present paper do not suggest that increased interfacial contact with glass is a relevant issue with pembrolizumab vial leftovers. Indeed, the assays we used to evaluate the progressive formation of visible and subvisible particles (visual inspection and spectrophotometry) did not show any relevant formation of such particles. More importantly, our ion exchange chromatography (IEX-HPLC) data showed that the relative proportion of pembrolizumab and both its acidic and basic variants did not change over a period of 14 days at either 4 °C or RT. Glass leaching due to ion exchange is, thus, not considered to be of any relevance in the case of pembrolizumab vial leftovers.

5. Conclusions

The long-standing single-use vial and same-day administration clinical practice associated with pembrolizumab should be revised. Indeed, these new sets of data show that pembrolizumab vial leftovers could be safely administered at least 14 days after the first product withdrawal from the vial. This would, therefore, offer the possibility of reallocating vial leftovers to other patients within the next few days instead of discarding them on a daily basis. This would further optimize the usage of the product and reduce wastage to nearly zero. Allowing later usage of pembrolizumab vial leftovers that, for any given reason, cannot be infused to other patients within the same day would, therefore, lead to huge savings by eliminating costly wastage.

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Systematic Review

Medication Non-Adherence in Inflammatory Bowel Disease: A Systematic Review Identifying Risk Factors and Opportunities for Intervention

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Abstract: Inflammatory bowel disease (IBD) is treated with medications to induce and maintain remission. However, many people with IBD do not take their prescribed treatment. Identifying factors associated with IBD medication adherence is crucial for supporting effective disease management and maintaining remission. Quantitative and qualitative studies researching IBD medication adherence between 2011 and 2023 were reviewed. In total, 36,589 participants were included in 79 studies. The associated non-adherence factors were contradictory across studies, with rates notably higher (72–79%) when measured via medication refill. Non-adherence was lower in high-quality studies using self-report measures (10.7–28.7%). The frequent modifiable non-adherence risks were a poor understanding of treatment or disease, medication accessibility and an individual's organisation and planning. Clinical variables relating to non-adherence were the treatment type, drug regime and disease activity. Depression, negative treatment beliefs/mood and anxiety increased the non-adherence likelihood. The non-modifiable factors of limited finance, younger age and female sex were also risks. Side effects were the main reason cited for IBD non-adherence in interviews. A large, contradictory set of literature exists regarding the factors underpinning IBD non-adherence, influenced by the adherence measures used. Simpler medication regimes and improved accessibility would help to improve adherence. IBD education could enhance patient knowledge and beliefs. Reminders and cues might minimise forgetting medication. Modifying risks through an adherence support intervention could improve outcomes.

Keywords: inflammatory bowel disease; medication non-adherence; medication non-concordance; medication non-compliance; medication non-persistence; systematic review

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1. Introduction

Inflammatory bowel disease (IBD) refers to the chronic inflammatory diseases of Crohn's disease (CD) and ulcerative colitis (UC). Worldwide, there were 4.90 million IBD cases in 2019 [1], an almost 50% increase since the 1990s. Historically, IBD has been most prevalent in developed regions; however, recently there has been a rapid rise in incidence within the Middle East, Asia, and South America.

These incurable conditions are associated with an excessive immune response leading to unpredictable disease course, impacting quality of life and causing long-term consequences such as gut damage and colorectal cancer [2]. The most frequently reported

symptoms in remission are fatigue, chronic pain, incontinence and extra-intestinal manifestations such as arthritis. Diagnostic examinations are typically reported as "painful" and "stressful" by patients [3]. Medication therapy aims for "tight control" of inflammatory activity and to induce and maintain symptomatic, endoscopic and histological remission whilst reducing the risk of sequalae [4]. Some medications also decrease the incidence of colorectal cancer, e.g., mesalazine. However, the protective effect requires strict adherence. High non-adherence prevalence (up to 72%) has been reported across a range of IBD drugs and healthcare systems [5]. Non-adherence to IBD medications can significantly impact treatment outcomes, with studies associating it with increased risks of disease flare [6] and a reduced quality of life [7]. Non-adherence in IBD leads to high healthcare and societal costs [8–10].

Researching and understanding adherence is complex. Defining, measuring and identifying patients with a high possibility of non-adherence, as well as understanding and supporting medication adherence, is a challenge [11]. A combination of determinants have been found to influence non-adherence, including patient-related and healthcare-related factors [12]. Yet typically, studies have investigated only a one or two of these individually.

This is mirrored throughout healthcare, across multiple health conditions. Several theories have been proposed as to why people are non-adherent to their medication, with recognition that some factors can be modifiable and can be addressed. This includes health psychology and cognitive behavioural theories [13] (health belief model, social cognitive theory, and theory of planned behaviour) which consider an individual's cognition as a key behaviour change factor. Alternatively, biopsychosocial models attribute various physical and psychosocial influencers to explain non-adherence [14].

Knowing why a person with IBD is non-adherent would enable the development of tailored and effective interventions to improve self-management and adherence in this chronic condition, whilst reducing costs. Previous work has considered either adherence, non-adherence or related concepts in IBD individually or focussed upon specific medication types [12,15]. Earlier scoping and systematic reviews identified the complexity of related factors on non-adherence across a range of conditions [16,17], yet a comprehensive systematic review focussed upon IBD is lacking. This piece will build upon previous reviews of all IBD medication non-adherence terms over an extended time period. The aim of this review is to systematically explore and synthesise the available evidence of both modifiable and non-modifiable factors associated with non-adherence in people with IBD. This will help to identify both modifiable targets for health interventions to enhance and maintain adherence and non-modifiable targets which should be clinically monitored and supported wherever possible to minimise non-adherence.

2. Materials and Methods

Search strategy

Six electronic databases were searched systematically in November 2023. Published articles from peer-reviewed journals relevant to the review's aims were identified. The reference lists of the included studies were searched for appropriate papers. A combination of terms relating to adherence and IBD was used to search the databases. A full list of search terms, adapted for each database, is presented in Supplementary Table S1a,b. Retrieved studies were exported into EndNote (Version 20) and transferred to the Covidence (Version 2) reference management software. Bias was minimised through two reviewers (K.K. and C.N.) screening 50% each of the titles and abstracts of retrieved papers for eligibility, according to pre-determined inclusion criteria. Reviewers were assigned full-text papers for data extraction, with K.K. performing double data extraction. Any disagreements were resolved through discussion with a third reviewer (W.C.D.). A flow diagram

(Supplementary Figure S1) reports the study selection process and provides reasons for inclusion and exclusion as suggested by the PRISMA-P guidelines [18]. The protocol was registered in PROSPERO [CRD42021240056].

Inclusion Criteria

All papers in English, published from 2011 to November 2023, where the majority of participants were ≥16 years old, with a diagnosis of IBD and prescribed one or more medication for IBD, were included. A cut-off of 12 years was considered extensive for the previous literature, whilst considering contemporary, relevant IBD medications. Papers were excluded if the study population were all children/young people (<16 years old), not living with IBD or not prescribed medication for IBD. Bias was minimised through conducting a thorough review of available published literature. Peer-reviewed papers of qualitative or quantitative study design were included investigating factors associated with adherence and non-adherence in adults living with IBD. Grey literature was not considered due to the volume of papers identified within the specified period. Intervention studies, reviews/protocols or conference abstracts were excluded from this review, as were papers not written in English.

As the review's aim was to investigate factors associated with any type of non-adherence, where papers reported adherence, outcomes were reversed to non-adherence to ensure meaningful comparisons. When studies used alternative terms to describe not taking medication as prescribed (compliance/non-compliance, concordance/non-concordance and persistence/non-persistence), these were also included. When studies differentiated between persistence/non-persistence or discontinuation and non-adherence, the study was only included if non-adherence/adherence was reported separately as a primary outcome (See Supplementary Figure S1).

Analyses

Most studies included were quantitative and did not control for potential confounders, presenting only univariate (one variable) or bivariate (two variables) data analysis. Due to the need to control for other factors within a model, the increased likelihood of larger samples being used in multivariable analysis (MVA) and the large number of studies found overall, only factors significant in MVA were considered most likely related to non-adherence. If methods were stated as multiple linear regression, multiple logistic regression, multivariate analysis of variance (MANOVA), factor analysis, cluster analysis or multivariable analysis, we included this as MVA. If data were stated as being statistically significant at univariate or bivariate analysis, but non-significant at MVA, this was also reported.

Quality Appraisal

The Critical Appraisal Skills Programme (CASP) tools were used to assess the quality of both qualitative and quantitative papers. Qualitative studies were appraised using the CASP checklist for qualitative data [19]. For quantitative papers, in line with the CASP tool recommendations [20], a CASP scoring system was not used and a systematic rating system was devised for quality rating by the research team. Each quantitative study was given a total base score of "three"; one point was subtracted if the study did not use a reliable, recognised adherence measure and one point was subtracted if authors did not specify the use of a form of MVA. This resulted in scores of three (high), two (medium) or one (low). If study reporting was unclear and/or with limited data, the study was reviewed again by reviewers and scores amended. No studies were excluded based on quality.

3. Results

A total of 7596 papers were identified from six databases and the reference lists of the included studies. After screening titles and abstracts, 384 papers remained with full-text eligibility screening. A total of 79 papers were identified for the review, undergoing data

extraction. Studies were conducted between 2011 and 2023, across the world, including Europe (32 studies), North America (20 studies), South America (4 studies) Asia (18 studies), and Oceania (3 studies). Two studies conducted their research multi-nationally [8,21]. While many included single sites (38 studies) based within general or tertiary hospitals settings, some were multi-site (32 studies) or not site-specific (9 studies, e.g., online).

Demographics of participants

In total, 36,589 participants were included, ranging from 7 to 6048 per study (Supplementary Table S2). Ages ranged from 15 to 81 years, although not all studies reported this clearly. Most studies had both male and female participants, except three which had 100% female participants [22–24]. The race or ethnicity of participants was reported by one study only [25].

Most studies did not present smoking or alcohol use and for those which did, participants were largely non-smokers.

Most participants were in full-time employment. Education levels were mixed. When relationship status was reported, participants were mainly married, in a relationship/currently partnered and/or living together with their partner.

Studies categorised the disease type as either UC, CD, IBD, IBD unclassified (IBDU), indeterminate ulcerative colitis (IUC) and unknown, with 2 not reporting the disease type (2.53%) and 34 investigating both CD and UC (43%). A total of 4 studies (5.1%) investigated exclusively CD, whereas 19 (24.1%) focussed on UC. Eighteen studies also categorised IUC or IBDU (22.8%). Two studies did not distinguish between IBD types [8,26].

Time since diagnosis was frequently reported, ranging from 0.1 years to 51 years. A variety of medication classes, routes, regimes and doses were presented, with almost a third included all medication types (27 studies, 34.2%), and 11 (13.9%) not stating this.

Study design

Sixty-six studies (83.5%) were quantitative and ten (12.7%) used mixed methods [9,27–35]. The remaining three (3.8%) were qualitative [36–38], with data analysis following grounded theory principles to develop themes and associated links in one study [37]. Forty-six studies (58%) were cross-sectional design, through online or face to face questionnaires at a single centre. The remaining study designs were either prospective (10), longitudinal (2), retrospective (12), observational (5), cohort (1) or interviews/focus groups (3). The study length was from 1 month to 13 years. Fifteen studies did not report the length of data collection (see Supplementary Table S3).

The p values considered as significant were typically <0.05, with either univariate or a range of multivariate analyses conducted.

A theoretical framework was used by nine studies (11.4%) to explain adherence, their choice of an adherence measure or their findings.

Quality appraisal rated most studies as medium in quality (36) or high (35), and eight were of low quality. Several studies presented unclear reporting of their results [11,22,27,39–41].

Measuring and Categorisation of Non-adherence

The 79 studies used a wide variety of definitions and tools to measure non-adherence. Consequently, a huge range from 4.3% to 88.9% in non-adherence is presented in Figure 1, alongside alternative classifications (when a study used multiple tools for measuring adherence, an overall non-adherence value was calculated). Very few studies found non-adherence to be under 20%.

Cut-offs for defining adherence/non-adherence were dependent upon the adherence measure used. The most popular cut-off was 80% adherence, whereby non-adherence was taken as the use of equal to [42] or less than 80% of the prescribed medication [3,43,44]. Alternatively, good adherence was defined as taking >80% of the prescribed doses [44].

Similarly, if the medication possession ratio (MPR) was ≥80% for an aminosalicylate (5-ASA) treatment, this was frequently rated as good adherence [2].

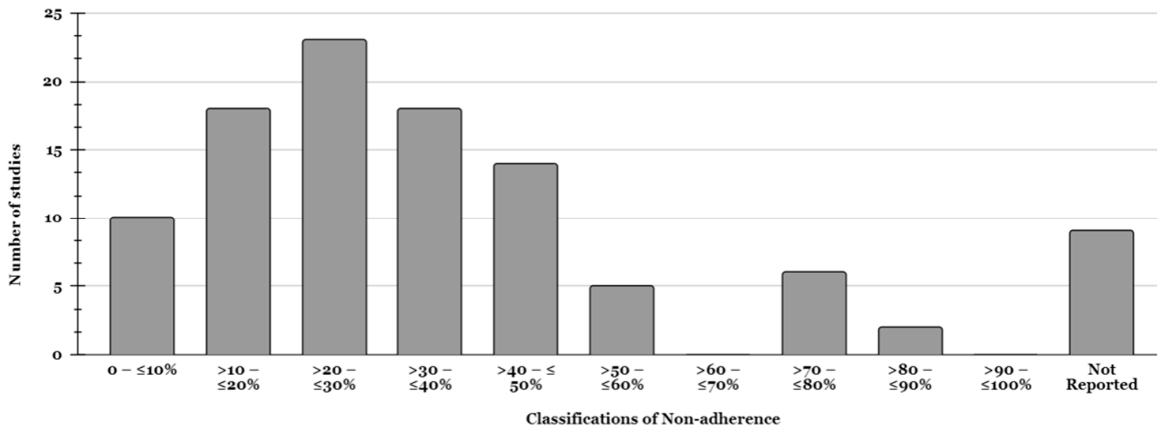

Figure 1. Rates of non-adherence. (Note: The range of non-adherence (4.3–88.9%) reflects variations in study populations, adherence definitions and measurement methodologies).

Sub-group analysis of high-quality, multi-centre studies with over 100 participants showed distinct differences between non-adherence rates through validated self-report questionnaires (10.7–49.8%) and medication possession ratios (72–79%).

Typically, 21–30% of participants were non-adherent to their medication. Ten (12.7%) papers did not report any non-adherence/adherence rates or anything similar [28,36,41,45–50] or were vague in their categorisation, such as "not good adherence" (7%) [51] or "partial non-adherence" at 20% [52] or 18% [26]. Some authors were consistent in their use of terms, such as "low", "medium" or "high" non-adherence/adherence, yet studies varied in their definition of these terms, sometimes with minimal or no definition. For example, "low adherence" referred to both 3% [52] and 49.8% [53] in different studies, whereas "inadequate" adherence in one study included all participants answering "rarely," "sometimes," "often" or "always" when asked "How often do you miss medication intake"? [29].

The classification of taking or not taking medication as prescribed was most commonly referred to as "adherence" or "non-adherence" (see Supplementary Table S4). However, not taking medication as prescribed was occasionally defined as "poor adherence" [21] or "low adherence" [39,52–55], amongst other descriptors.

Table 1 shows the measures of non-adherence reported. Typically, quantitative tools were used. The Morisky medication adherence scale (MMAS) was utilised in 26 studies and author-designed, non-validated questionnaires in 17. Scores on the MMAS often ranged between 4 and 6 out of 8 and were considered as a self-report of "good" adherence. Scoring for validated measures was in line with the recommended guidelines. For example, scoring 4–16 out of a possible 20 in the four studies using the medication adherence scale.

Report Scale-4 (MARS-4) [6,45,57,58] was used to assess non-adherence to medication [56]. The MARS-5 [40,48,59,60] and 10-item scale [52] were also used, as well as one MARS scale unspecified [56]. Additional measures included monitoring of therapeutic drug levels [25], medication possession ratio in 14 studies (MPR; percentage of prescribed medication dispensed to a patient during a specific period/over a period of refill intervals) [23,56] and persistence evaluated over one year after an index prescription [2]. Pill counts over varying time periods [42,82], e.g., two months [42], were used in two studies. Sub-group analysis of high-quality studies showed non-adherence ranged from 21.7 to 49.8% when using the validated MMAS measure, whereas this ranged from 10.7 to 28.7% with the MARS measure. Qualitative studies also used a variety of tools to elicit medication concerns [37].

Table 1. Quantitative measures of non-adherence.

Measures of Non-Adherence	Version	Studies
Self-report: medication adherence report scale (MARS)	Not specified 4 5 10-item scale	[56] [6,45,57,58] [40,48,59,60] [52]
Self-report: Morisky medication adherence scale (MMAS)	Non-specific (4 items) Non-specific (6 item) Non-specific (8 item) For IBD patients (8 item)	[33,49,50,61–65] [21] [6,9,39,41,54,55,66–69] [11,25,46,53,70–72]
Self-report: Medication adherence (non-validated)	(23 items)	[3]
Self-report: Visual analogue scale (VAS)	Not reported	[24,73,74]
Self-report: QUOTE-IBD questionnaire	Non-standardised multiple-choice test with open-ended questions	[27]
Self-report: study's own questionnaire	E.g. individual questions, Likert scale, ordinal scale	[9,22,28,29,31,32,41–43,47,51,69,75–80]
Self-report: verbal	Amount/dose of treatment or incidents taken or missed within a specific time period	[33,42,44,81–83]
Medical records	Reviewed by researchers	[42,44,77]
Pill count	(Short-term measure of adherence)	[42,82]
Medication possession ratio (MPR) *	% of prescribed medication dispensed to a patient during a specific period	[2,7,23,34,35,69,71,84–90]
Proportion of days covered (PDC)	Number of any oral 5-ASA drug on hand during a 1-year period (different to MPR).	[90]
Blood tests (thiopurine levels)		[25,26]
Other		[34,60,91–93]
None reported		[36]

Key: * The medication possession ratio (MPR) is the proportion of medication supply dispensed, presuming that the previous prescription was not filled within the first and last dispensed date [94,95]. Adherence using MPR is usually defined as ≥80%, and non-adherence <80%.

Strongest and most consistent associations with non-adherence

Knowledge and understanding of IBD and its treatment had the strongest and most consistent associations with non-adherence, with 92% in the reviewed quantitative studies being significant. Accessibility, organisation and planning were positively correlated with significant results in 80% of investigations using quantitative studies. Qualitative studies also emphasised the impact of forgetting, poor medication availability and disorganisation as the main modifiable non-adherence causes.

Modifiable treatment-related factors (such as treatment type, route and regimens) were frequently discussed in quantitative and qualitative studies; most were positively associated with non-adherence.

Modifiable psychological factors were also significantly positively associated with non-adherence in 72% of investigations.

Several non-modifiable patient demographics were reported in quantitative studies. Most significant was living in poor residential areas, associated with a reduced life quality and socioeconomic status [8,20,25,32,45,48,81]. Finance, medication and increased care cost difficulties were found to be frequently associated with non-adherence risks [7,25,32,34,44,67,77,85], along with the demographics of age, disease activity and sex.

Factors associated with non-adherence

Within categories associated with non-adherence, specific non-modifiable and modifiable factors were identified throughout the literature. The findings were often contradictory, with minimal agreement, and will be discussed in greater detail.

Unless otherwise stated, the findings presented are significant under MVA, presented in categories and as individual factors in Table 2 and summarised in the text. The non-adherence risk generally increased with the greater number of significant risk factors experienced [80].

Table 2. Factors associated with non-adherence/low adherence in studies using multivariate analysis (mva), multiple logistic regression or factor analysis.

Categories	Individual Factors Associated with Non-Adherence/Low Adherence	Relationship	Studies
Age	Younger age (15–29 years)	+	[2,25–27,31,53,56,65,67,70,72,78,88,90]
		–	No studies
		NS	[6,30,54,55,71,73,75] [58] (specific age range not stated) [53] (males, <40 years)
	Early middle age (30–45 years above)	+	[2,27,70,90] [53] (significant for all patients <40 years (p = 0.034), yet in terms of sex only females significantly associated <40 years (p = 0.002))
		–	No studies
		NS	[40,55,75] [53] (not significant in males <40 years) [58] (specific age range not stated)
	Late middle age (46–60 years above)	+	[2,90]
		–	No studies
		NS	[55,75] [58] (specific age range not stated)
	Older age (61 years+)	+	[28] (older patients had less recall, rating themselves non-adherent)
		–	[54,55]
		NS	[58,75] (specific age range not stated)
	Increased feeling of being between adolescence and adulthood	+	[57]
		–	No studies
		NS	No studies
Age at Diagnosis	Younger age at diagnosis (Up to 29 years)	+	[74,84]
		–	No studies
		NS	[25,72]
Sex	Female	+	[2,11,62,90] [59] (in UC) [83] (in whole population and CD, but not UC) [53] (in terms of sex, only females <40 years old)
		–	No studies
		NS	[27,30,75]
	Male	+	[53,67]
		–	No studies
		NS	No studies

Table 2. *Cont.*

Categories	Individual Factors Associated with Non-Adherence/Low Adherence	Relationship	Studies
Race	African–Caribbean descent	+	No studies
		−	No studies
		NS	[25]
Diagnosis	Crohn's disease	+	[26,54,60,89]
		−	No studies
		NS	[6,8,33,75,93]
	Ulcerative colitis	+	[11]
		−	No studies
		NS	[8,75,93]
	IBD unclassified	+	No studies
		−	No studies
		NS	[8,26]
	Distal involvement (ulcerative colitis)	+	[59]
		−	No studies
		NS	No studies
	Perianal/perineal disease	+	[93]
		−	No studies
		NS	No studies
	Length of time since diagnosis	+	[57] (increased time since diagnosis) [78] ("short" diagnosis duration, ≤5 years) [32] ("long" diagnosis duration, 6–15 years) [83] ("long" diagnosis duration, 6–15 years with whole population and UC, but not CD)
		−	[33] ("long" diagnosis duration, 6–15 years)
		NS	[75] ("short" diagnosis duration, ≤5 years) [54,55,75] ("long" diagnosis duration, 6–15 years)
	Disease activity	+	[74,86,93] (active disease/not in remission); [66] (lower relapse probability) [57] (inactive disease/in remission) [44] (absence of physical bleeding)
		−	[33] (having at least one relapse in past 12 months)
		NS	[25,26,72] (active disease/not in remission) [11,25,66] (inactive disease/in remission) [74] (being in pain/discomfort)
	Aminosalicylates	+	[11,30,31,70,71,78]
		−	No studies
		NS	[8]
	Thiopurines	+	[44] (no concomitant use of thiopurines)
		−	No studies
		NS	No studies

Table 2. *Cont.*

Categories	Individual Factors Associated with Non-Adherence/Low Adherence	Relationship	Studies
Treatment	Biologics	+	[73] (intravenous/self-administering biologics) [75] (greatest non-adherence in combination therapy of biologic and immunomodulator, then infliximab, then adalimumab) [87] (intravenous/self-administering biologics only within 1st 12 months of treatment) [6] (intravenous/self-administering biologics; greatest non-adherence in adalimumab (43%), then infliximab (8%)) [88] (self-administering biologics only) [57] (not using biologics)
		–	No studies
		NS	[8] (self-administering biologics only) [89] (intravenous and self-administering biologics) [11] (not using biologics)
	Steroids	+	[86] (prescribed steroid script) [2] (not using steroids)
		–	[8] (prescribed steroid script)
		NS	[32]
	Antibiotics or topical steroids	+	[31] (either)
		–	No studies
		NS	No studies
	Immunosuppressants	+	[3] (not using immunosuppressants)
		–	No studies
		NS	[32]
	Biologics/immunosuppressants	+	[90] (no use of biologics/immunosuppressants within 12 months post-index date)
		–	No studies
		NS	No studies
	Dose	+	[66,79,82] (frequent/multiple-daily dose, e.g., ≥3 times daily) [33] (regimen of 40 mg adalimumab every other week as opposed to 40 mg every week) [90] (starting multiple daily dosing of either: balsalazide, mesalamine-delayed release (Asacol) or sulfasalazine) [44] (less frequent/fewer daily medications; <8 daily tablets)
		–	[33] (frequent/multiple-daily dose; regimen of 80 mg every other week, as opposed to 40 mg every other week)
		NS	[75] (less frequent/fewer daily medications—monotherapy) [90] (starting once-daily regime: "Multi-Matrix System" mesalamine/Lialda)

Table 2. *Cont.*

Categories	Individual Factors Associated with Non-Adherence/Low Adherence	Relationship	Studies
	Ongoing/lengthy treatment	+	[62,82]
		–	No studies
		NS	No studies
	Pill-burden (e.g., problem with dosing time regimen, high pill frequency or pill size)	+	[47] (time of dosing or pill size)
		–	No studies
		NS	[30]
	Route	+	[28] (subcutaneous rather than oral) [90] (not using rectal 5-ASA) [78] (topical medication)
		–	No studies
		NS	[32] (topical medication)
	Presence of adverse/side effects	+	[30,56]
		–	No studies
		NS	[66]
	Induction treatment	+	[90] (no history of switching from induction medication) [6] (anti-TNF induction)
		–	No studies
		NS	No studies
	Care perspectives	+	[9,11,30,72] (negative relations/poor communication with HCP)
		–	[29] (perception of easy contact with gastroenterologist)
		NS	[29,40] (negative relations/poor communication with HCP) [8,52] (lack of trust in gastroenterologist) [29,30,40] (poor patient satisfaction)
Healthcare	Care experienced	+	[66] (lack of treatment information from clinical team) [27,40,90] (no specialist/tailored care/follow-up by GP) [66] (lack of physician reinforcement regarding importance of treatment adherence) [65] (≤1 month between outpatient clinic appointment) [7] (frequent emergency care) [7,86] (frequent inpatient hospitalisation) [83] (no history of IBD related surgery, CD patients) [7] (fewer all-cause healthcare appointments)
		–	No studies
		NS	[9] (lack of/poor treatment information from clinical team) [9] (lack of involvement in prescribing) [8] (frequent inpatient hospitalisation) [29,31,93] (no history of IBD related surgery)

Table 2. *Cont.*

Categories	Individual Factors Associated with Non-Adherence/Low Adherence	Relationship	Studies
	Medication-taking behaviour close to timing of clinic visits	+	[82]
		–	No studies
		NS	No studies
General Health	Receiving treatment for other chronic condition	+	[66] (use of treatment for other chronic condition/s) [29] (use of treatment for other chronic condition/s when prescribed 5-ASA for IBD); [84] (not prescribed other chronic treatment)
		–	No studies
		NS	[55] (use of treatment for other chronic condition/s)
	Having a disability certificate	+	No studies
		–	No studies
		NS	[29]
	Comorbidities	+	[66]
		–	No studies
		NS	No studies
Habits	Smoking	+	[3,29,54] (current smoker) [53] (male only current smoker)
		–	[67] (current smoker) [54] (non-smoker)
		NS	[73,74,88,93] (current smoker) [89] (current smokers with CD)
	Alcohol consumption	+	[53] (whole population)
		–	No studies
		NS	[58] [53] (females only)
	Prescribed narcotic use (at time of biologic initiation)	+	No studies
		–	No studies
		NS	[89]
Diet	Frequently eating alone	+	[71]
		–	No studies
		NS	No studies
	Frequently missing a meal	+	[79]
		–	No studies
		NS	No studies
	Not storing treatment near to where meals are eaten	+	[42]
		–	No studies
		NS	No studies
	Use of nutritional supplements	+	No studies
		–	[31]
		NS	No studies

Table 2. *Cont.*

Categories	Individual Factors Associated with Non-Adherence/Low Adherence	Relationship	Studies
Finance	Healthcare/pharmacy prescription costs	+	[7] (lower UC pharmacy prescription patient costs and/or overall higher healthcare costs for patients)
		–	No studies
		NS	[66] (higher healthcare cost perception for patient appointments/treatment)
	Income/socioeconomic status	+	[25] (lower socioeconomic status)
		–	[41] (higher income)
		NS	[32] (higher socioeconomic status)
	Having public/non-commercial insurance	+	[88–90]
		–	No studies
		NS	No studies
Living Location	Country of residence (UK instead of Australia)	+	No studies
		–	[8]
		NS	No studies
	Living in north-east, south or west America	+	[90]
		–	No studies
		NS	No studies
	Living in mid-west America	+	No studies
		–	No studies
		NS	[90]
	Poor residential area/Poor QoL	+	[8,63,66] (reduced/poor quality of life) [26,41] (living in a poor residential area)
		–	No studies
		NS	No studies
Employment	Employment type	+	[11] (employed)
		–	[70] (self-employed)
		NS	[30] (permanent employment)
	Professional constraints	+	[56] (demanding jobs) [73] (work rhythms/constraints relating to treatment)
		–	No studies
		NS	No studies
Education	Educational level	+	[59] (lower educational level) [58,70] (higher educational level)
		–	No studies
		NS	[32,78] (higher educational level)
	Combined higher educational, occupational and socioeconomic status	+	[32]
		–	No studies
		NS	No studies

Table 2. *Cont.*

Categories	Individual Factors Associated with Non-Adherence/Low Adherence	Relationship	Studies
Social support + Relationships	Being single	+	[70]
		–	No studies
		NS	[93]
	Poor/low social support	+	[30] (received, emotional, tangible) [57] (informational)
		–	No studies
		NS	[57] (received, emotional, tangible)
	Having friends	+	[59] (dealing with friends when experiencing CD)
		–	No studies
		NS	No studies
Psychology	Treatment beliefs/perceptions/concerns	+	[30,66] (belief treatment is ineffective) [74] (belief treatment is ineffective in CD) [8,56,69,71] (belief there is no/little need for treatment/scepticism) [40] (negative beliefs about medication and poor patient satisfaction) [72] (lower perceived competence with treatment regime) [11,74] (lower perceived control over disease) [44] (negative beliefs about taking aminosalicylates: susceptibility, severity, benefits, barriers and cues to action) [47,69] (side effect concerns) [58] (adverse effect concerns)
		–	[58] (belief there is a need for treatment)
		NS	[65,78] (belief treatment is ineffective) [44] (belief for no/little need for treatment/scepticism) [9] (lower perceived competence with treatment regime) [30] (lower perceived control over disease) [66] (side effects and efficacy concerns) [71] (potential for harm of medication in general concerns) [6,8] (potential adverse effects concerns)
	Illness beliefs	+	[6] (shorter timeline perception/perceptions of IBD as an acute episodic disease) [59] (shorter perceived illness duration in CD; "perceptions that CD will end too soon") [74] (shorter perceived illness duration in UC) [6] (illness identity)
		–	No studies
		NS	[6] (illness consequences)
	Depressive symptoms/antidepressant use/ psychiatric history	+	[25,58,66,67,74,92] (depressive symptoms/antidepressant use) [30] (patient-reported diagnosis and/or depression score from HADS)
		–	No studies
		NS	[89] (history of psychiatric disease in CD) [88] (comorbid psychiatric disease with IBD, e.g., depression and/or anxiety)

Table 2. *Cont.*

Categories	Individual Factors Associated with Non-Adherence/Low Adherence	Relationship	Studies
	Mood and attitude	+	[74] (low influence of disease on mood) [56] (indifferent attitude/less bothered regarding treatment benefit) [6] (stronger emotional response/negative emotions resulting from IBD)
		–	No studies
		NS	[73] (low influence of disease on mood) [72] (feeling stressed) [11] (lower sense of coherence)
	Anxiety	+	[30,58,73,74]
		–	No studies
		NS	No studies
	Negative religious coping (questions, doubt and strain around sacred matters with the divine, oneself and others)	+	[46]
		–	No studies
		NS	No studies
Accessibility, Organisation and Planning	Forgetting/disorganisation	+	[40] (forgetfulness) [30,71] (missing scheduled appointments)
		–	No studies
		NS	[63] (forgetfulness/carelessness)
	At weekends	+	[82]
		–	No studies
		NS	No studies
	Not keeping medications accessible when due	+	[42]
		–	No studies
		NS	[67]
	Not being as careful when taking medications	+	[9]
		–	No studies
		NS	No studies
	Lower priority for medications	+	[47]
		–	No studies
		NS	No studies
	Fewer cues to action (e.g., reminders to take medication)	+	[44]
		–	No studies
		NS	No studies
	Not using adherence tools (e.g., dosette boxes, alarms)	+	[42]
		–	No studies
		NS	No studies

Table 2. *Cont.*

Categories	Individual Factors Associated with Non-Adherence/Low Adherence	Relationship	Studies
Knowledge and Understanding	Poor/inadequate disease/ treatment knowledge	+	[11] (poor understanding of IBD as a disease) [59] (poor understanding of specifically CD) [74] (poor understanding of specifically UC) [58,65] (poor treatment knowledge) [66] (having inadequate information about treatment)
		−	No studies
		NS	No studies
	Poor recall of medical information	+	[28]
		−	No studies
		NS	No studies
	Internet use	+	[41] (not keen on using internet)
		−	No studies
		NS	No studies
	Being an information seeker/ having high curiosity	+	[31] (being an information seeker)
		−	No studies
		NS	[30] (having high curiosity)
	Patient organisation membership	+	[73]
		−	[8]
		NS	No studies
Alternative treatments	Complementary and alternative medicine (CAM) use	+	[63]
		−	No studies
		NS	[75]

Abbreviations: GP: general practitioner (family doctor); HADS: Hospital Anxiety and Depression Scale; HCP: Healthcare professionals; QoL: quality of life; UK: United Kingdom. Key: + = positive association with non-adherence; − = negative association with non-adherence; NS: non-significant association with non-adherence on MVA/factor analysis; blank cells = data not reported; [70]: age younger than 40 years old.

Demographics (non-modifiable):

Age

Twenty-four studies reported on age with MVA. There were 15 positive associations with age and non-adherence, 3 mixed (positively and/or negatively associated and non-significant age group dependent), and only 6 non-significant associations in different studies. Participants within the ages of 15–29 years were most likely to be non-adherent, while those ≥61 years had greater likelihood of being adherent. Similarly, being below 60 years was also found to be associated with lower adherence compared to over 60 years [2].

Age at diagnosis

Four studies explored age at diagnosis in relation to adherence, with mixed findings. Two studies [74,84] found that people being diagnosed at a younger age (up to 29 years), were more likely to non-adhere. Yet, two other studies [25,72] reported non-significant results.

Sex

Eleven studies analysed the associations of sex with non-adherence. Females were more likely to be non-adherent in seven studies [2,11,53,59,62,83,90]. One study reported only females with UC showing higher non-adherence [59], whereas another found this for CD [83]. Females under 40 years old [53] had greatest risk for non-adherence. In contrast,

males were significantly more adherent [2]. However, contradictory findings were also presented in two studies [53,67] with non-adherence higher in males.

Race

Race was only reported in one study [25]. Non-adherence was most common in participants of African–Caribbean descent, although this was not significant.

Diagnosis (non-modifiable):

Twenty-two studies reported mixed results regarding diagnosis.

Disease type

Eleven studies explored the type of IBD. Four found CD to be associated with non-adherence [54,60,89,91], yet five reported this as non-significant [6,8,33,75,93]. Three studies found UC was not a significant predictor of non-adherence [8,75,93].

Disease activity

Eleven studies investigated disease activity. Participants with active disease were more likely to be non-adherent in three studies [74,86,93]. The relationship between highly active CD and non-adherence through avoiding infusions was associated with pain, diarrhoea or being admitted as an inpatient and receiving alternative treatment [93]. A negative relationship was reported between active disease and non-adherence in one study [33], yet only in patients experiencing at least one relapse in the past 12 months.

In other studies, participants in remission [6,57], those with a lower probability of relapse [66] or an absence of abdominal symptoms (such as visible bleeding) [72] were most likely to be non-adherent. Yet, six studies found these relationships or being in pain due to IBD to be non-significant [11,25,26,66,72,74].

Disease duration

Participants with a "long" diagnosis duration of between 6 and 15 years were reported to be more adherent than those with a shorter diagnosis in a single study [33]. Contradicting this, three studies [32,57,83] found non-adherence increased with time since diagnosis. Two studies investigated a "short" diagnosis duration of less than 5 years with non-adherence, one finding a significant relationship [78] and the other a non-significant one [74].

General health (modifiable/non-modifiable)

General health was reported by four studies [29,55,66,84], with three modifiable and non-modifiable factors related to non-adherence. The most frequent general health risk factor for IBD non-adherence was taking treatment for another chronic condition [29,66], with one study finding this to only be significant when the IBD medication was 5-ASA. Having comorbidities was also associated with non-adherence in IBD [66].

Conversely, another study found that individuals not prescribed other chronic treatment were at an up to 2.2 times higher risk of non-adherence with their IBD medication than those who were [84].

Treatment (modifiable)

Treatment, including medication type and mode, route, dose, regimen frequency, convenience of administration and adverse effects, was the most investigated modifiable factor, analysed by MVA in 28 studies with 35 positive relationships with non-adherence.

Drug-Class

Frequently associated with non-adherence was being prescribed either aminosalicylates [11,30,31,70,71,78] or biologics [6,73,75,87,88]. Mesalamine was a significant predictor of non-adherence, compared to other drugs [70]. One study reported a non-significant relationship between non-adherence and aminosalicylates [8].

Patients who had never switched from an index aminosalicylate were much more likely to be non-adherent than those who changed ($p < 0.0001$), with up to 76.9% non-

adherence [90]. Patients with no history of switching from any drug type from their index medication were also likely to be non-adherent [90].

Within different mesalamine types, oral Pentasa had the lowest adherence rate (26.4%), whereas adherence to Mezavant once daily was significantly higher (40.9%) than other oral treatments ($p < 0.001$). Only one study reported lower adherence in patients prescribed non-immunomodulators ($p = 0.049$) than aminosalicylates [3]. In this study, despite aminosalicylates having the highest non-adherence rates, this was not significant. In the same study [3], biologics were related to adherent behaviours, supporting other research [57].

Although mixed significant results were also found for biologic medications, if prescribed either biologic/combination biological–immunomodulator therapy, this was the only factor associated with low adherence when starting on anti-TNFs in one study [6] and the single factor correlated with non-adherence in another [75]. Regardless of whether patients were treated with biologics intravenously or subcutaneously [73,75,87,88], this medication increased the non-adherence risk.

Four studies found that the prescribed medication type did not have an impact upon non-adherence, whether these were 5-ASAs, biologics, steroids or immunosuppressants [8,11,32,89] ($p < 0.05$).

Route

Eleven studies investigated the route of administration, with this most frequently relating to higher non-adherence. An uncomfortable medication route, i.e., subcutaneous as opposed to oral treatments [28] or via infusion, was associated with not taking it as prescribed [6,88]. When patients had never used rectal 5-ASAs, this increased their risk of not taking oral 5-ASA medication [90].

Frequency/Regime

Four studies reported the relationship between non-adherence and frequent/multiple medications [33,66,79,82] or long-term treatments [62,82]. This included initiating treatment on multiple daily dosing of either balsalazide, mesalamine-delayed release (Asacol) or sulfalazine [90]. A regimen of 40 mg adalimumab every other week was a predictor for missing medication, as opposed to 40 mg weekly. However, increasing adalimumab to 80 mg every other week was a predictor of improved adherence.

Pill burden (the effort of taking all prescribed drug/s) was a risk for non-adherence in one study [47], yet it was also reported as non-significant [30]. In contrast, when patients were prescribed fewer than eight daily tablets [44], non-adherence was increasingly likely. Yet monotherapy was found to have a non-significant effect on non-adherence [75].

Side effects

Side effects and non-adherence were reported only by three studies, with a positive relationship in two [30,56] and non-significant in one [66].

Future non-adherence

Current non-adherence was found to be an independent predictor for future non-adherence [74].

Healthcare (modifiable)

Healthcare was frequently investigated for its relationship with non-adherence (17 studies), with 18 modifiable risk factors identified [7,9,11,27,30,40,65,66,72,82,83,86,90]. Non-adherence was most likely when patients experienced negative relations and/or poor communication with healthcare providers [9,11,30,72], if no specialist or tailored care was received [27,40,90] or if frequent inpatient hospitalisation or emergency care was experienced [7,86]. Frequent IBD outpatient [65,82] and general health appointments and adherence monitoring were also associated with adherence promotion [7]. The risk of non-adherence significantly increased if a patient received minimal treatment information from their team [66] or the importance of medication adherence was not reinforced [7].

When patients found contacting their gastroenterologist easy, adherence improved [29].

Habits (modifiable)

Modifiable habits were investigated by 11 studies, the most common being smoking—in 10. Four studies found current smoking to be a non-adherence risk factor [3,23,29,54]. In one study, smoking was one of a few significant factors [3]. Smoking highly influenced non-adherence in specific cohort—in patients prescribed thiopurines [29] or oral 5-ASA [23]. Male smokers also showed a significant relationship with non-adherence ($p = 0.018$) [23] whereas females did not, with these all being non-smokers. Similarly, another study found non-smoking participants to be more adherent [54]. Yet, smoking was not significantly associated with not taking medication in five studies [73,74,87,89,93].

Alcohol consumption was investigated by two studies, with mixed findings. Consumption (but not frequency) was related to low adherence ($p = 0.029$) in males [23]. This was not significant in females [23] nor patients overall [58]. Prescribed narcotic use was only explored by one study [89], with non-significant findings.

Diet (modifiable)

Modifiable dietary factors were reported by four studies. Regularly eating alone [71] or missing a meal [79] and not storing medications where meals are eaten [42] were all positive predictors of non-adherence. The use of nutritional supplements protected against non-adherence [31].

Finance (modifiable/non-modifiable)

Eight studies reported that a mixture of modifiable and non-modifiable financial variables increased non-adherence, specifically having public or non-commercial insurance as opposed to private [88–90], lower socioeconomic status [25] or overall higher healthcare costs (including inpatient, outpatient and emergency) [7].

Living location (non-modifiable)

Six studies identified living location as a predictor for non-adherence [8,26,41,63,66,90]. Residing in a socially deprived area and/or reduced life quality significantly predicted non-adherence in all studies that reported this [8,26,41,63,66,90].

Country and areas of residence however had mixed results. Living in north-east, south or west America was positively associated with taking medication [90], whereas living in the mid-west was not significant [90]. Residing in the UK over Australia was negatively associated with non-adherence [8].

Employment (non-modifiable)

Five studies investigated employment. Demanding, busy work constraints relating to treatment increased non-adherence [56,73]. Full-time employment and/or a greater number of working hours were also positively associated with non-adherence [11].

"Permanent employment", however, was not significantly correlated with non-adherence [30], and "self-employment" reduced the risk of non-adherence [70].

Education (non-modifiable)

Five studies reported on education level and its impact upon taking medication [32,58,59,70,78]. Those with a combined higher socioeconomic status, occupational and educational level were more non-adherent, but they were not significant as individual factors in the same study [32].

Social support and relationships (modifiable/non-modifiable)

Five studies investigated social support and relationships [30,57,59,70,93]. Non-adherence was associated with being single [70] or receiving poor social support, whether emotional or tangible [30] or low informational social support [57]. Having to "deal with friends" when living with CD in fact increased the risk of non-adherence, but not in UC [59].

Psychological factors (modifiable)

Psychological health was one of the most frequently modifiable factors investigated, but with contradictory results. Twenty-five studies were carried out, with treatment beliefs, perceptions and concerns explored in seventeen studies. Negative beliefs, mediated by poor patient satisfaction, led to low adherence [40]. When treatment was thought ineffective [30,66,74] or unnecessary by the patient [8,56,69,71], this was also positively related to non-adherence (seven studies). Conversely, when individuals expressed a need for their IBD treatment, this was protective against non-adherence [58]. Disease beliefs were also significantly related to non-adherence—specifically when IBD was perceived as having a short illness duration [6,59,64], with one study finding significance only for participants with CD [59]. A weaker illness identity (fewer IBD associated symptoms) was also a risk for low adherence [6], although the illness perceptions of the daily consequences of living with IBD were not [6].

Treatment concerns, namely side [47,69] and adverse effects [58], predicted low medication adherence (in three studies), regardless of medication type. However, this was non-significant in four studies [6,8,66,71].

When participants expressed a reduced sense of control over their IBD [11,74], lower perceived competence with treatment regime [72] or experienced religious or spiritual struggle using negative coping strategies [46], non-adherence increased.

Nine studies researched depression and poor psychological states, seven of which identified these as significant non-adherence risks [25,30,58,66,67,74,92].

Anxiety was a significant risk for non-adherence in all four studies investigating this factor [30,58,73,74]. When UC had less of an impact on an individual's mood [74] or the patient was indifferent or sceptical regarding treatment benefit [56], these were largely predictive of non-adherence. Experiencing a stronger, negative emotional response to having IBD [6] was also associated with not taking medication as prescribed. Only one study found mood did not influence adherence [73].

Accessibility, organisation and planning (modifiable)

Ten studies reported on personal awareness and planning [9,30,40,42,44,47,63,67,71,82]. Missing scheduled appointments [30,71], having a lower priority for medications [47], not being as careful when taking medications [9] and medication doses at weekends [82] were found to be significant non-adherence predictors. Not using tools such as dosette boxes or cues to action, e.g., alarms or reminders to take medication, whether from family or healthcare providers, was also a risk for non-adherence [42,44]. Mixed evidence was found for forgetting or carelessness and not keeping medications accessible when due, reporting both significantly positive [40,42] and non-significant [63,67] relationships with not taking medication.

Knowledge and understanding (modifiable)

This was investigated by 12 studies, with 10 showing positive associations with non-adherence [11,28,31,41,58,59,65,66,73,74]. Having poor disease or treatment knowledge [11,58,59,65,74] or limited medical information recall [28] was related to non-adherence. Yet one study found this only in UC patients [59] and another only for knowledge of azathioprine [58]. These factors were also related with non-adherence when participants reported poor communication with [39] or inadequate medication information from healthcare professionals [66].

Not being keen on using the internet [41] was a significant risk for non-adherence, whereas having "high curiosity levels" [30] was not.

Patient organisation membership increased adherence in one study [8] and increased non-adherence in another [73].

Alternative treatment (modifiable)

Of two studies investigating alternative and complementary therapies, one found patients seeking holistic health approaches to be more likely to reduce prescribed IBD medication, as compared to those who did not (30% vs. 16%, $p = 0.02$) [63]. Yet individuals using complementary therapies for general health showed similar non-adherence to those using prescribed medications. Complementary therapy use for IBD was also non-significant [75].

Specific cohorts (non-modifiable)

Cohort specific factors investigated included pregnant and post-partum women [22–24,38], with no studies specifically analysing non-adherence risk at the MVA level. However, non-adherence led to a significantly increased likelihood for disease relapse and adverse pregnancy outcomes at the MVA level, particularly in women taking oral mesalamine [24].

Two studies researched non-adherence throughout the COVID-19 pandemic; again, there were none at the MVA level [52]. The greatest non-adherence reason was fear of attending hospital (50% participants), due to the perception of catching infections because of their IBD, being immunosuppressed [77] or having higher medication concerns [52].

Qualitative studies

Thirteen studies presented qualitative data, three were purely qualitative [36–38], and nine predominantly quantitative with free text comments [9,27–35] (Table 3).

Table 3. Design of qualitative studies.

Reference	Qualitative or Mixed Methods	Data Collection Methods
[36]	Qualitative	Focus group
[33]	Quantitative and qualitative	Questionnaire with free text options
[34]	Quantitative and qualitative	Interviews and focus groups
[37]	Qualitative	Interviews and focus groups
[35]	Qualitative section within largely quantitative paper	Data from IBD Spanish database: electronic medical records reviewed
[38]	Qualitative	Social media posts: online with descriptive content analysis conducted
[29]	Qualitative section within largely quantitative paper	Online questionnaire with free text options
[28]	Qualitative section within largely quantitative paper	Recorded consultation with nurse (questionnaire completion pre and post) and 3-week follow-up telephone interview
[30]	Qualitative section within largely quantitative paper	Self-administered questionnaires with free text responses
[31]	Qualitative section within largely quantitative paper	Self-administered questionnaire with free text responses
[32]	Qualitative section within largely quantitative paper	Interviews with questionnaire followed by free text responses
[9]	Qualitative section within largely quantitative paper	Two open-ended questions within a questionnaire. Questionnaire completion via email/during clinic visits and medical records reviewed
[27]	Qualitative section within largely quantitative paper	Multiple choice questionnaire with some open-ended questions

Reported reasons for non-adherence, are presented in themes (Table 4), with direct quotations (Table 5).

Table 4. Qualitative data/free-text analysis/specific reasons reported for non-adherence.

Theme	Reasons for Non-Adherence	Studies
Disease/condition	Feeling better/being in remission	[29,32]
	Feeling unwell/hospitalisation	[33]
	No effect of medication/worsening of disease	[32]
Treatment	Side effects/adverse effects	[29,30,32–34,36–38]
	Complicated/difficult administration mode (pill size/discomfort/pain)	[30,32,34,36,37]
	Too many drugs/frequent drug dosing/regimen	[32,37]
	Pill fatigue	[37]
	Life-long treatment	[32]
	Treatment response time	[37]
	Drug safety	[38]
Healthcare	Distrust/poor confidence in healthcare provider	[38]
	Lack of convincing benefit based on doctor's explanation	[30]
Background and general health	Having an infection	[33,36]
Eating	Fasting	[32]
Finance	Treatment cost	[29,30,32,36,37]
Work/occupation	Not taking treatment to work	[32]
Lifestyle	Busy life	[34,37]
	Change of routine (weekend/vacation)	[37]
	Being in public/social stigma	[37]
	Travel/away from home	[32,33,36,37]
Beliefs	Perception of treatment necessity	[29,37]
	Treatment fear, anxiety and uncertainty	[38]
	Stress/pressure	[38]
	Scepticism about treatment efficacy	[30,37]
	Treatment being disease reminder	[36]
	Disease non-acceptance	[36]
	Intentional non-adherence	[30,33,34]
Forgetting and organisation	Forgetting	[29,30,32,33,36,37]
	Timing/carelessness/disorganised	[30,37]
Accessibility	Treatment accessibility (including through GP/pharmacies/hospitals)	[29,32,33,36]
	Running out of treatment (whilst at home)	[29,32]
	Refill inconvenience	[37]
Knowledge and understanding	Lack of understanding regarding treatment regime	[32]
	Lack of understanding regarding treatment benefits	[37]
"Alternatives" to prescribed treatment	Using "healthier" alternatives	[38]
Pregnancy and pregnancy planning	Infertility	[38] *
	Pregnancy/avoiding perceived harm for current baby	[33,38]
	Avoiding all treatment for their next pregnancy	[38]
Independent research	Information gathered from online sources/online communities	[38]
Non-disclosed	Personal reasons	[38]

Abbreviations: GP: general practitioner/family Doctor. Key: * [38]: Infertility concerns were reported by both male and female participants with regards to taking IBD medications. Note: Ref. [35] collected and analysed qualitative variables, recording these according to the international classification of diseases (ICD), including chronic and psychiatric pathologies, expressed as frequencies (%). However, no demographic, phenotypic factors of the disease or therapeutic regimes were predictors of thiopurine non-adherence. Ref. [64] collected qualitative data regarding information-seeking sources and themes, but not the reasons for non-adherence, and thus not data relevant for the above table.

Table 5. Themes, sub-themes and qualitative quotations for non-adherence.

Theme	Sub-Themes for Non-Adherence	Qualitative Quotations for Non-Adherence
Treatment	Side effects/adverse effects	"Because of fears of side effects." [29]
		"I've had some that make me jerk like a puppet. . .Side effects that you didn't know, didn't need and don't want, and it's so bad for you; you just stop because it's. . . too much." [36]
	Drug safety	"Humira is so new that most Dr's [doctors] don't have a clue when we ask about complications." [38]
	Complicated/difficult administration mode (pill size/discomfort/pain)	"Those ones in the leg, would just, aaaarghh (shudders), and I know it's coming and it was really hard. . . I felt sore. . . taking it all the time." [36]
	Pill fatigue	"That's really the biggest thing. . . I just have to take it in the morning, and then every once in a while, I'm just sick of taking it." [37]
	Too many drugs/frequent drug dosing/regimen	"I take four of one kind twice a day; it would be awesome if that could be reduced down to one pill. . . 'cos by the time you've had three devils. . . you choke on the pill. . . the big horse ones which have a nice coating, but they still get stuck down your throat." [36]
Finance	Treatment cost	"Because medication is expensive." [29]
		"If you get a repeat prescription and you had to go to the GP and they said so that's gonna be $60 or a $100, I would go: I don't have $100 or I have $100 but it makes a kind a financial thing." [36]
Lifestyle	Travel/away from home	"Boxes of medications that's just especially if you're travelling overseas. . . makes for a very bulky parcel, and then there's sometimes you get to your hotel room and you don't have a fridge. . . it's pretty much a nightmare, pretty challenging." [36]
Beliefs	Disease non-acceptance	"So you develop an intense dislike that you have to take them because it makes you angry." [36]
Forgetting and Organisation	Forgetting	"Because I forget." [29]
	Timing/carelessness/disorganised	"I have a terrible memory so may have forgotten and just not realised. . . I take it a couple hours later when I remember." [37]
Accessibility	Treatment accessibility (including through GP/pharmacies/hospitals)	"Because medication is not available in pharmacies." [29]
	Running out of treatment (whilst at home)	"Because I run out of medications before I get a new prescription." [29]
	Refill inconvenience	"When you go to refill it and you've passed the pharmacy hours or something. You just forgot or it wasn't convenient." [37]
		"The week before when you pick up your last repeat, you've got to then email. And sometimes they get it, sometimes they don't. . . or it could be in their spam box." [36]
Pregnancy and Pregnancy planning	Infertility	"My wife and I are most worried about having children soon or in the future but based on my research, you should not try while on the medication. Does anyone know any info on this? Please help!" [38]
	Pregnancy/avoiding perceived harm for current baby	"My doctor now wants me to take Asacol HD and I'm very hesitant to take any medication while pregnant for fear it may cause some kind of issue or birth defect with my baby." [38]
		"Humira has not been fully studied in pregnant women. . . I know of a horror story and pregnancy and humira." [38]

Treatment

The most frequent type of treatment adherence barriers expressed were adverse effects [29,30,32–34,36–38]. Uncertainty regarding drug safety was also common [38].

The administration mode [30,32,34,36,37], including rectal [34], and self-administered subcutaneous injections, was reported as a challenge [36]. Several drugs taken multiple times a day were considered to pose treatment difficulties, resulting in "pill fatigue" [37]. A desire for a "simpler regimen" [36] was often expressed.

Finance

Repeated prescription costs were also reported as a non-adherence reason [29,30,32,36,37].

Lifestyle

Travelling and/or being in public spaces [34] with busy lifestyles were problematic for adhering. This included carrying medications to work [32] or difficulties renewing prescriptions when away from home [32,33,36,37].

Beliefs

Personal opinions regarding treatment necessity often influenced medication discontinuation, altering doses and missing intermittent ones [29,30,33,34,36–38]. Reasons also included non-acceptance of diagnosis, leading to a negative emotional response towards treatment [36].

Forgetting and Organisation

Forgetting was a main reason for not taking medications [29,30,32,33,36,37]. Timing with due treatment or general disorganisation were also adherence barriers [37].

Accessibility

Accessing medications was a common adherence challenge [29,32,33,36,37], as was repeatedly refilling medications [36,37].

Pregnancy and pregnancy planning

Being pregnant and avoiding harm to the baby was a frequent concern of women using a range of medications [33,38]. Women also spoke about safety and uncertainty of teratogenic effects if currently pregnant or planning pregnancy, in addition to fertility concerns from females and males [38].

4. Discussion

This is the most recent comprehensive international review that outlines the complexities and challenges of non-adherence to prescribed medication in IBD today. Between 4.3% to 88.9% of patients were identified to be non-adherent, with at least 30% in most studies and a lack of consensus on defining adherence/non-adherence [28,29,35,87,93]. The large range of adherence cut-offs, depending upon the instrument's purpose [44,86], maximised differences between adherent and non-adherent IBD patients, potentially leading to inaccurate measurement of these concepts. Multiple versions of the same tool to measure adherence made study comparisons difficult.

Individual studies suggest adherence rates differ due to a range of complex, modifiable and non-modifiable factors that could be intentional and/or unintentional [87]. Interestingly, the majority of reviewed studies did not measure "intentional" or "unintentional" concepts or explore the reasoning behind non-adherence. Consequently, a large, inconsistent, often poorly reported and contradictory set of literature exists, making it challenging to draw specific clinical conclusions from this review.

Knowledge and understanding of IBD and its treatment were the most frequent modifiable predictors of non-adherence, with 92% of associations in the reviewed quantitative studies being significant for non-adherence. Low disease knowledge can be influenced by diagnosis uncertainty [29,53], leading to classification bias for patients and research. This review included CD, UC and indeterminate colitis and their range of treatments, which were not wholly comparable. Agreed validated international case definitions for IBD are required to clarity patient understanding whilst minimising the risk of misclassification, impact upon non-adherence and data misinterpretation [23].

Lack of understanding of IBD and medication benefits [8,11,58,59,65,74], common in newly diagnosed patients, can significantly impact non-adherence. Improved patient understanding of the disease and the need for continuous medication requires clear, concise education regarding IBD and its treatment, provided by multidisciplinary teams [56]. If not delivered effectively by specialist clinicians [96], IBD patients may recall only 50% of information from appointments [28]. This can lead to poor adherence soon after the first consultation [48], meaning the reinforcement of key medication messages is critical. Also

vital at the treatment recommendation stage is determining the likelihood of patients taking medication. This will allow the clinician to work through together with the patient to target any challenges or barriers. Socratic questioning to elicit personal circumstances together with Motivational Interviewing techniques such as "How likely are you to take your medication?" and "What would help you in taking it?" have been shown to be particularly effective [97].

The impact of self-education is inconsistent [98], as this review shows it may not facilitate adherence [31]. Patients have a desire for self-teaching surrounding their long-term condition and medication-related knowledge [41]. Internet use is popular to support active learning, promote disease understanding and evaluate medical advice, but has the potential to be inaccurate and/or misleading and may not fully meet patients' expectations, leading to poorer adherence [99]. Furthermore, adherence research using the internet may exclude those without access. Alternatively, when healthcare professionals take time to provide accurate guidance, patients can feel more confident about managing their IBD [72], reducing their anxiety and encouraging more timely follow-ups [100]. Yet, clinicians must remain mindful of knowledge and understanding developing within the same individual through experience, potentially impacting upon adherence changes [47]. This demands a need for personalised educational interventions, rather than generic solutions [43], for adherence promotion [41].

Accessibility, organisation and planning were positively correlated with significant results in 80% of investigations by quantitative studies. Qualitative studies emphasised the impact of forgetting, poor medication availability and disorganisation as the main modifiable non-adherence causes. Lack of routine, busy lifestyles, including full-time employment [11,56,73] and medication regimes interfering with daily activities commonly increase the likelihood of forgetting, leading to non-adherence [29,43,79,82], particularly if lower treatment priority is expressed. Forgetting can be effectively modified with strategies such as setting alarms and placing medication close to traditional reminders (e.g., toothbrush or kettle) [47,56,67,78,101]. Reminders and feedback from healthcare professionals can also be an effective, inexpensive method to enhance clinical practice and medication use [12,17,102]. Memory cues help to prevent a diminished sense of treatment priority [44]. Medication dispensers or pill cases are reportedly strongest at predicting good adherence [42], easily determining whether medication has been taken. Adherence interventions containing such technical components have demonstrated consistent benefits over time [103]. Reward approaches have also shown improvements when combined with these technical strategies, although further research is recommended [104].

Modifiable treatment-related factors were frequently discussed in quantitative and qualitative studies, most were positively associated with non-adherence. IBD has the complexity of multiple medications, supplements and variable regimes, which can significantly impact non-adherence—found in some studies to be almost 90% [105]. Medication side effects [28,29,105] also significantly determine adherence, potentially increasing the use of "complementary and alternative medicine."

IBD treatment administered via various routes [37] may cause discomfort (e.g., injections, rectal medications or oral tablets that are difficult/large to swallow) and may be associated with greater non-adherence risks [47,86], impacting life quality [43]. Yet despite this, some non-adherence data collection tools are designed solely for one medication route and/or type [28]. Furthermore, techniques such as MPR have been identified to have variable calculation methods, significantly affecting adherence estimates [106]. Thus, the validity and verifiability of study results should be interpreted with caution. A variety of methods collecting a combination of adherence barriers and disease activity have

been suggested, although data interpretation gathered from a range of approaches can be challenging, increasing the potential for disagreement.

Non-adherence to oral 5-ASA was frequent in this review [11,30,31,70,71,78], correlating with previous reports [51,65] ranging from 38 to 60% [107]. Prescribed for less severe, more stable disease, this requires minimal monitoring, often leading to greater non-adherence [90]. Patients typically identify quiescent periods with recovery, with a reduced need for treatment [47,56,58,76]. Aminosalicylates are also associated with decreased frequency and dosing, with monotherapy reporting higher non-adherence rates, as opposed to combination therapy [67]. Monitoring adherence using targeted strategies in stable patients is therefore necessary [44].

Other IBD medications taken infrequently (e.g., immunosuppressants) necessitate specific storage and/or require attendance to hospital appointments for administration, raising non-adherence risks [36]. Conversely, multiple inconvenient dosing regimens influence developing routines and habits [43,44,64,86]. Similarly, previous literature reported 30% of patients when asked reasons for non-adherence, answered "*too many pills*" [10]. Despite a long-established inverse relationship between the dosing regimen complexity and non-adherence in IBD [101,108], complicated "three times daily" dosing regimens are still used by many gastroenterologists [64]. To achieve better clinical IBD outcomes, the findings from this review and prior evidence support simplifying daily regimes wherever possible [2,56,68,79].

Patient preferences must be identified in both clinical prescribing and reversed supervision (prospective prescriptions considering individual retrospective medication adherence) [26,43]. For research, specific aims investigating single medication regimes in one chronic disease is encouraged, to more accurately identify non-adherence predictors [53].

Modifiable psychological factors were significantly positively associated with non-adherence in 72% of investigations, supporting previous systematic reviews [16,17]. Depression was the most common, followed closely by anxiety, then patients less bothered about the treatment benefit or their IBD having a lower impact on mood. Depression is a risk in many chronic disease populations [25,26,109,110], frequently associated with stress, "feeling hassled" and significant life events, together possibly contributing to non-adherence and IBD relapse [53,111]. Concerns regarding medication safety and adverse effects regarding long-term maintenance medication [3,10,107] cause further treatment stressors and "adherence barriers" [72].

Purposefully not taking prescribed medication can often be the main reason for intentional non-adherence. Ranging from 70.7 to 97%, it is typically higher than non-intentional non-adherence, associated with treatment doubts when feeling well and/or not experiencing effective action, particularly if an individual considers that the treatment disadvantages outweigh the benefits [44]. This perception of the necessity for medication can be impacted by prior experiences, with the importance of necessity reducing over time [69].

Yet voluntary non-adherence is more challenging to address. These non-adherence difficulties may not be disclosed to healthcare professionals [75], particularly if negative relations exist involving poor communication [9,11,30,72] and a lack of specialist healthcare [27,90]. This review and previous studies and reviews found such modifiable healthcare factors positively associated with non-adherence [16]. To promote good patient–physician relations, reinforcing empathy and leniency is recommended [75]. This helps by avoiding putting patients in a defensive state when asking them to self-report adherence behaviours, achieving honest, reliable answers [75]. Despite this, it is argued that most people report the truth when questioned about their adherence [25,26]. Many studies conclude that the combined use of self-reporting along with a more validated, objective

adherence measurement is appropriate for a greater understanding of non-adherence reasons [25,35,40,42,43,48,77,78,81,82].

Once non-adherence is identified, intervention strategies must actively involve those patients choosing not to take IBD medication as prescribed [78], promoting their awareness of the non-adherence consequences [23,24,53]. When individuals view their medications more positively, they are more likely to adhere to it [30,40]. However, this tailored approach in specialist healthcare with overstretched services could be challenging. To ensure that the care needs of people with IBD are focussed upon [41], a balanced approach with multidisciplinary teams supporting patients to access offline/online resources [81,109], offering accurate, comprehensive and holistic IBD education, will subsequently help to promote knowledge and self-management [53,74].

Several non-modifiable patient demographics were reported in quantitative studies. Most significant was living in poor residential areas, associated with reduced life quality and socioeconomic status [8,25,26,41,63,66,90]. Finance, medication and increased care cost difficulties also indirectly impact psychological stability and adherence [7,25,26,29,30,32,37,86], referred to as "downstream non-adherence consequences" [86], rather than being direct predictors [41]. Further research is warranted to explore these complex contributory factors to non-adherence [30,78].

Age, disease activity and sex were non-modifiable demographics associated with significant non-adherence risks. Yet age and disease activity were also not significant in some studies, supporting the previous inconsistent literature [73]. Younger people do not necessarily prioritise medication use, focussing upon leisure, going out and friendships [23] as opposed to discussing health conditions and concerns with others [107]. The contradictory results for these factors could be attributed to the high levels of heterogeneity in the studies compared. Most specifically, methodological weaknesses were brought about by many smaller, single-site, retrospective studies with lower sample sizes. Additional sub-group analysis of specific data highlighted the limitations of comparing multiple adherence measurements across a range of studies, namely self-report and medication refills. As secondary measures of adherence, medication refills are a popular, relatively straightforward method for avoiding the subjective bias of inaccurate patient recall. However, they have been known to inaccurately estimate adherence and it is impossible to determine whether a patient has accurately taken their medication [112]. The PDC is considered a more accurate, suitable method, focusing on days the patient is "covered" or supplied with medication [113].

Simple, universal interventions for these non-modifiable factors reflect similar outcomes, often producing non-significant improvements in non-adherers [69]. Special care should be taken to increase medication adherence in youngsters with IBD [81], particularly with IBD incidence in adolescents increasing [26]. Younger patients need support to modify their treatment, thought processes on adherence and non-adherence consequences [46]. Simpler drug delivery regimes whilst monitoring patients are beneficial [53], combined with supervised, smooth care transitions to adult services [26].

Specifically, the non-adherence in young females with IBD identified in this review [2,47,53,55,90] is consistent with previous findings [110]. Social embarrassment of IBD and enema use are suggested reasons [27,111]. As IBD patients are largely affected during child-bearing age, females frequently express treatment concerns specific to reproductive journeys, fertility, pregnancy and lactation fears, leading to non-adherence [38,47,114], verified by qualitative data. Previous research shows pregnant women often overestimate the potential harm of their IBD medication, with many of those choosing to breastfeed discontinuing treatment (74%) [115]. Enhancing the quality and quantity of accurate, accessible reproductive health and IBD information available for patients is necessary, as opposed to

potentially seeking limited, non-evidence-based information online [38]. Timely, bespoke reproductive counselling from gastroenterologists, reinforcing importance of adherence before, during and after pregnancy is effective [114]. This close working of clinician and patient in a supported, communicative manner bridges vital information gaps in reproductive health and IBD whilst reducing flare-ups and modifying non-adherence [38].

Strengths and Limitations

The literature for this review spans 12 years, identified from a broad range of extensive databases representing medical, nursing, health, psychology and scientific disciplines, from clinical, academic and research data. With healthcare changing rapidly, variability is huge across the identified studies. The selected period allows a consideration of the unprecedented, life-changing experiences (e.g., COVID-19 pandemic, cost of living crisis) [77] which critically impacted medication use and data collection. However, these times may also limit accuracy and generalisability. Considering such prior practice may be incompatible, opposing current patient care, particularly following the pandemic or immunomodulator use [86].

This international literature review considered a huge variety of factors including healthcare, cultures, insurance, prescribing and medications, clinic and medication accessibility, availability and disease-related knowledge [2,21,29,38,53,76], enhancing generalisability. These must be considered when investigating non-adherence in patients.

Yet, cross-continental comparison of the same medication type incorporates national drug variations due to formulations, prescribing practices, treatment availability, diverse patient-funding of prescriptions and biased patient profiles [21,27,50]. Additional difficulties arise when validated tools are translated into alternative languages, with assorted interpretations. A range of adherence and non-adherence terms being used synonymously across the literature adds further interpretative complexity. Non-adherence rates may also be determined by the adherence measure/s used, which may not be wholly comparable.

The review inclusion criteria were pre-defined but generous, with no design restrictions, resulting in a large quantity of studies, varied patient cohorts and study designs. However, this led to challenges in synthesising data. Overall, a large sample [2,26,29,38,114] more accurately represents the adherence of general populations in real-world clinical settings as opposed to clinical trials. Yet this is limited by minimal demographic data collection [38]. Individually, many studies had the strengths of focussing upon "select cohorts," particularly those who were non-adherent [53], from single centres [9,22,25,26,34,35,37,39,45–47,51,54,55,58,59,61–71,75,77,78,81,83,84,87–89,91,92], typically outpatient or tertiary [3,8,22,24–26,32,35,42–44,46,47,51,52,54,56,58,59,62,63,66,67,69,70,77,78,83,84,87,89,92], with small samples [3,24,28,34,35,40,57,68,81,82,85]. However, such literature may not generate "meaningful" results [26,57]. Future research acknowledges a need for replication with larger, more diverse samples from multi-centres [3,42,81] and extended follow-ups, enhancing representation whilst increasing validity [58].

58%of the reviewed studies were cross-sectional in design [8,9,11,21–23,25,27,28,30–32,39–42,44–47,49–59,61,62,64,66,68,70–72,75–79,81,92], typically at a single timepoint, over short periods, meaning it was impossible to evaluate the suggested strategies for adherence promotion [42]. Longitudinal studies have challenges regarding pharmacy medication records maintaining accuracy and consistency. Studies presenting retrospective research [2,23,26,44] are limited to previous behaviours. To predict future non-adherence and evaluate strategies for adherence promotion, further prospective research is necessary [26,42,82].

A specific study limitation identified from this review and earlier research [114], was the restricted inclusion criteria, with some studies only including participants of a certain diagnosis length [41,50]. This may minimise the influence of disease duration, shown to impact IBD non-adherence [32,57,78,83]. Using only papers published in English

and with methodological differences of selection [2,42,44] restricts the representativeness, generalisability and persuasiveness to community practice.

Biases also arose from the investigation of specific adherence-related factors [81], with some studies failing to report on known risks (e.g., smoking, body mass index, employment or socioeconomic status) [35,53,54] or the reasoning for non-adherence [24].

The analysis of this review was thorough and detailed, considering both qualitative and quantitative studies. Focussing on significance at a multivariate level ensured confounding factors were eliminated, whilst identifying those most likely related to non-adherence.

Finally, a main limitating challenge within all adherence data is the true prevalence rate [26]. Typically, non-adherers are the least likely to participate in research or attend clinics [57,69], potentially masking and underrepresenting their perspectives, trends and behaviours. Moving forward, utilising accurate prescription databases with more clinical data collection may overcome this, comparing responders with non-responders [114].

5. Conclusions

Treatment adherence is a critical component in maintaining remission, alongside other clinical and biological factors. This review has identified many modifiable and non-modifiable factors having mixed relationships with non-adherence in IBD, thus offering an improved understanding of determinants of adherence and non-adherence.

In future practice, multidisciplinary clinicians must collaborate with patients throughout their IBD journey. Firstly, identifying barriers and challenges patients foresee regarding taking their IBD medication through active listening and questioning. Clinicians aware of non-modifiable factors can better identify patients at risk of non-adherence and develop targeted strategies to support them. Problem solving targeting modifiable adherence barriers could reverse and modify active patient decisions of not taking treatment.

Unrealistic modifiable medication fears must be addressed through education to enable clear knowledge and understanding of IBD and treatment. Healthcare professionals should enhance patients' self-management strategies, offering accurate resources for independent learning. Various technical and reward strategies could be suggested to patients to improve their organisation and planning of treatment taking. Ongoing patient monitoring of the psychological and physical impact of IBD with personalised adherence support is required. A "one-size-fits-all" approach must be avoided, as the underlying causes and common barriers may differ considerably, necessitating varied interventions.

For future research, a unified, formalised definition of non-adherence is urgently needed, with consideration of how theoretical models of adherence could inform future research. This will help to further clarify between intentional and non-intentional non-adherence and modifiable and non-modifiable factors. It is critical to utilise a range of measures to help to determine objective, accurate non-adherence rates. Additional qualitative investigations will also identify reasoning behind non-adherent behaviours.

Further investigation of adherence promotion interventions tailored to the most salient non-adherence risk factors including knowledge and understanding of IBD and treatment, accessibility, organisation and planning, forgetting, poor medication availability, treatment-related factors (type, route and regimens) and modifiable psychological factors is also critical. Specifically, further research to minimise forgetting and regarding the impact of reward strategies is warranted.

Informed development and implementation of adherence support programmes will ultimately improve individual health outcomes, quality of life and health-related costs.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/pharmacy13010021/s1, Figure S1: PRISMA flow diagram, selection of studies for systematic review—Supplementary Figure S1 outlines the process of selection for identified, screened and included studies for the systematic review; Table S1a: Key search terms—Supplementary Table S1a presents the full list of key search terms used for the database searching of relevant articles; Table S1b: Search strategy for all databases—Supplementary Table S1b presents the search strategy applied for all databases; Table S2: Patient demographics—Supplementary Table S2 shows the demographical data of participants from the reviewed studies; Table S3: Study design—Supplementary Table S3 presents the study designs of all the studies reviewed; Table S4: Categorisation and measuring non-adherence—Supplementary Table S4 lists the terminology used when describing non-adherence, non-adherence measures, non-adherence cut-offs in quantitative studies and the percentage of non-adherence within each reviewed study.

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Abbreviations

The following abbreviations are used in this manuscript:

CAM	Complementary and Alternative Medicines
CASP	Critical Appraisal Skills Programme
CD	Crohn's Disease
GP	General Practitioner/Family Doctor
HADS	Hospital Anxiety and Depression Scale
HCP	Healthcare Professionals
IBD	Inflammatory Bowel Disease
IBDU	Inflammatory Bowel Disease Unclassified

IUC	Indeterminate Ulcerative Colitis
MARS	Medication Adherence Report Scale
MANOVA	Multivariate Analysis of Variance
MMAS	Morisky Medication Adherence Scale
MPR	Medication Possession Ratio
MVA	Multivariable Analysis
PDC	Proportion of Days Covered
QoL	Quality of Life
UC	Ulcerative Colitis
UK	United Kingdom
VAS	Visual Analogue Scale

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Social Determinants of Health and Medication Adherence in Older Adults with Prevalent Chronic Conditions in the United States: An Analysis of the National Health and Nutrition Examination Survey (NHANES) 2009–2018

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Abstract: Background: The older adult population is rapidly expanding in the United States (US), with a high prevalence of high blood pressure, high cholesterol, and diabetes. Medication nonadherence is prevalent in this population, with less evidence on the influence of social determinants of health (SDoH). Thus, the objective of this study was to identify and prioritize SDoH associated with medication adherence among US older adults with these comorbidities. Method: Using the World Health Organization Commission on Social Determinants of Health and Pharmacy Quality Alliance Medication Access Conceptual Frameworks, publicly available National Health and Nutrition Examination Survey datasets (2009–2018) were cross-sectionally analyzed among respondents aged 65 and older who were diagnosed with study diseases. Data analyses included descriptive statistics, and logistic regression using an alpha level of 0.05. Result: Analyses included 5513 respondents' data. Bivariate analysis revealed significant differences in medication adherence based on several structural (e.g., ethnicity) and intermediary (e.g., disability status) determinants of health. Multivariable analysis revealed significant differences in medication adherence for alcohol consumption ($p = 0.034$) and usual healthcare place ($p = 0.001$). Conclusions: The study findings underscore pertinent implications for public health and policy, with specific SDoH being the most likely to affect medication adherence in common chronic conditions among older adults in the US.

Keywords: medication adherence; social factors; older adults; high blood pressure; high cholesterol; diabetes

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1. Introduction

Improvements in life expectancy have culminated in a population drift toward older adults that is marked by a great prevalence of chronic diseases, often managed by one or more prescription medications [1–4]. Hypertension, high cholesterol, and diabetes are the

prevailing chronic diseases in this population, with 42% of individuals taking five or more prescription medications and a nonadherence rate of 20–60% [5–8].

Disparities in the prevalence of these diseases were reflected among racial minority groups, with significant contributions from medication nonadherence and Social Determinants of Health (SDoH) [9–12]. SDoH are "the environmental conditions where people are born, live, learn, work, play, worship, and age that affect a wide range of health, functioning, and quality-of-life outcomes and risks [13]". However, there have been shortfalls in national concerted efforts to manage SDoH, health disparities, and medication nonadherence concurrently or consistently [13,14].

The Centers for Medicare and Medicaid Services administer adherence-related quality measures for Medicare Part D (prescription medication) insurance policy plans, grading plans on the percent of beneficiaries adherent to hypertension, high cholesterol, and diabetes medications [15]. These plans incentivize pharmacies to drive medication adherence quality measures positively via rebate incentives and by including them in preferred pharmacy networks, ensuring consistent access for patients [16].

Nevertheless, community pharmacists' inability to address SDoH negatively influences adherence-related quality measures among older adult Medicare beneficiaries [17]. Also, the extant literature has not fully delineated the association between SDoH domains and adherence to concurrent medications for hypertension, high cholesterol, and/or diabetes [18]. The studies identified in this review were narrow in scope, focusing on just one specific disease and a less diverse population. Also, a study on SDoH and adherence to antihypertensive medications has highlighted that most SDoH analyses do not prioritize factors such as health behaviors and social resources like housing and food insecurity [19]. Thus, the primary objective of this study was to identify and prioritize SDoH associated with medication adherence among older adults with hypertension, high cholesterol, and/or diabetes in the US. The hypothesis was that structural and intermediate determinants of health were associated with medication adherence. The secondary objective was to estimate self-reported medication adherence while highlighting implications for pharmacy practice and underserved populations.

2. Materials and Methods

2.1. Study Design

This cross-sectional study examined a nationally representative sample of secondary data obtained from the National Health and Nutrition Examination Survey (NHANES) database, which included secondary datasets designed to examine the health and nutritional status of a representative sample of US adults and children [20]. Five biannual data years (2009–2018) were downloaded from the NHANES database Ethical approval was not required for the study and was reported using Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines [21].

2.2. Study Population

The study population for analysis included all respondents from the 2009–2018 NHANES datasets aged 65 and older whose doctors told them to take at least one prescription for hypertension or cholesterol and/or were told they had diabetes. Post hoc power analysis produced a power greater than 99% with an alpha value of 0.05 when the difference in proportions between the groups was 4% or larger.

2.3. Conceptual Framework

Two complementary conceptual frameworks—(1) World Health Organization (WHO) Commission on Social Determinants of Health (CSDH) and (2) Pharmacy Quality Alliance

(PQA) Medication Access—were integrated (Figure 1) to inform and categorize SDoH covariates in the NHANES dataset and minimize selection bias [11,22].

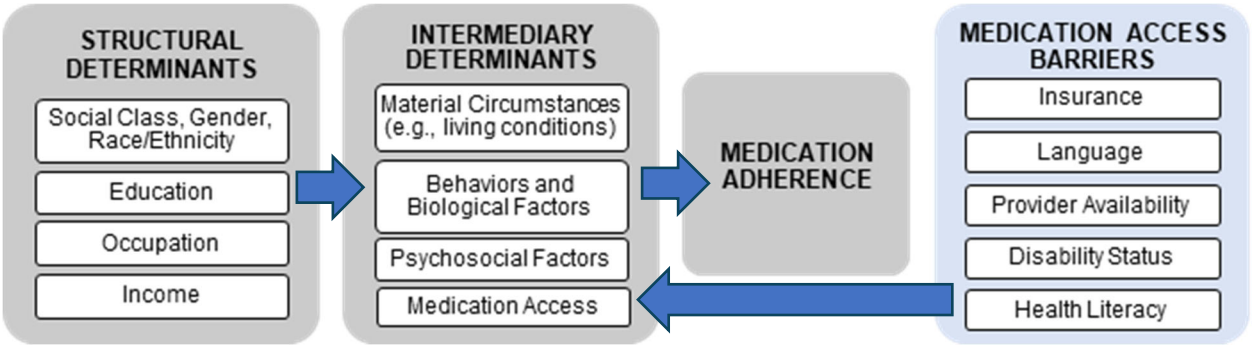

Figure 1. Adeoye-Olatunde et al.'s [23] integrated conceptual framework on social determinants of health and medication adherence. Legend: Blue components: Pharmacy Quality Alliance Framework (PQA) Grey components: World Health Organization Commission on Social Determinants of Health.

Two CSDH elements, structural and intermediate determinants of health, were used for NHANES' individual-level measurement. The framework defines structural determinants as "social determinants of health inequities"; these inequities function through intermediary determinants—material, psychosocial, behavioral, biological factors, and healthcare access—that mediate the effects of structural determinants on health inequities and directly impact health outcomes. Therefore, structural and intermediary determinants were operationalized as SDoH [22]. Healthcare access and health outcome were redefined as medication access and medication adherence, respectively. Finally, the study added barriers to medication access from the PQA Medication Access framework, which were unaddressed in the CSDH framework [11,22].

2.4. Data Variables, Sources, Management and Statistical Methods

Applicable NHANES datasets were combined by study identification number using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA). Those variables needed for analysis (as defined by the conceptual framework) were retained, while all other variables were eliminated from the combined dataset.

All NHANES datasets used, interpretations, computations, and mapping of study variables to conceptual framework determinants are published in the data dictionary, which is available online at https://doi.org/10.6084/m9.figshare.21947018 (accessed on 2 February 2025). The mapping of study variables to conceptual framework determinants is also depicted in the bivariate results table. Notably, the emergency room was included as a usual place for healthcare to align with the predefined response options. While emergency rooms are typically used for emergent care, this categorization reflects the respondent's most frequent source of care, consistent with the survey's intent to capture healthcare utilization patterns. This reflects the lived realities of individuals who may rely on emergency rooms for routine care commonly due to barriers to accessing primary care. Alcohol consumption was categorized as an intermediary SDoH under behavioral and biological factors per the WHO framework. Similarly, age is considered a biological factor that is an intermediary determinant of health.

Descriptive statistics were used to characterize the study population. The study's outcome variable, medication adherence, was dichotomized into "Adherent" and "Not Adherent". Respondents were considered adherent if they responded that they were

currently taking all prescribed medications for each studied disease state they had (i.e., hypertension, high cholesterol, diabetes) [18,24].

Bivariate analyses utilized logistic regression for continuous predictors and Rao-Scott Chi-Square tests for categorical predictors. Multivariable analysis for medication adherence utilized logistic regression. Predictors with *p*-values less than 0.20 in the bivariate analyses were considered predictors in the multivariable analysis [25]. This *p*-value is often used to include variables that have moderate associations with the outcome variable [25]. Multicollinearity effects were reduced by removing OR $\geq$ 2.477 corresponding to a Cohen's d of 0.50. A 5% significance level was used for all tests.

3. Results

A total of 5513 respondents met the study's inclusion criteria. The majority of respondents were 75 years of age or older (46.2%), identified as female (51.7%), Non-Hispanic White (50.6%), and married (54.7%). Hypertension was most prevalent (78.7%), followed by high cholesterol (65.6%) and diabetes (32.8%). Most respondents (79.4%) adhered to (reported taking) prescribed medications for hypertension, high cholesterol, and/or diabetes (Table 1).

After allowing for study adjustments to the Demographic Assessment for Health Literacy (DAHL) [26], the mean health literacy (DAHL) score amongst respondents was 68.4 (standard deviation (SD) = 14.4), indicating marginal to adequate health literacy. The mean household income to poverty ratio was 2.0 (SD = 1.2), indicating a family income at 200% of the poverty level [27]. The mean prescription medication count was 5.2 (SD = 3.1), with a minimum of one and a maximum of 22 medications.

Table 1. Characteristics of the study sample (N = 5513).

Variables (N)	Level	n (%)
Age Group (N = 5513)	65–69 years	1546 (28.0)
	70–74 years	1421 (25.8)
	75+ years	2546 (46.2)
Gender (N = 5513)	Female	2849 (51.7)
	Male	2664 (48.3)
Race [a] (N = 5513)	Other	1593 (28.9)
	Non-Hispanic Black	1128 (20.5)
	Non-Hispanic White	2792 (50.6)
Ethnicity [b] (N = 5342)	Hispanic	1037 (19.4)
	Non-Hispanic	4305 (80.6)
Education (N = 5492)	<High School Graduate	1727 (31.4)
	≥High School Graduate, but not College Graduate	2696 (49.1)
	College Graduate	1069 (19.5)
Alcohol Consumption Category [c] (N = 3899)	Never Drinks	1564 (40.1)
	Light Drinking	2043 (52.4)
	Moderate Drinking	233 (6.0)
	Heavy Drinking	59 (1.5)
Disability Status (N = 5510)	No Disability	3862 (70.1)
	Has Disability	1648 (29.9)

Table 1. *Cont.*

Variables (N)	Level	n (%)
Employment Status [d] (N = 5508)	Not Employed	4717 (85.6)
	Employed	791 (14.4)
Household Balanced Meals (N = 5360)	Could Not Afford	790 (14.7)
	Could Afford	4570 (85.3)
Insurance [e] (N = 5502)	Medicaid	669 (12.2)
	Medicare	4134 (75.1)
	Other	543 (9.9)
	None	156 (2.8)
Interview Language (N = 5513)	English	4941 (89.6)
	Spanish	572 (10.4)
Lower Social Class [f] (N = 4947)	Not Lower Social Class	2945 (59.5)
	Lower Social Class	2002 (40.5)
Marital Status (N = 5509)	Not Married	2494 (45.3)
	Married	3015 (54.7)
Smoking Status (N = 2788)	Does Not Smoke	2279 (81.7)
	Smokes	509 (18.3)
Usual Place for Healthcare (N = 5513)	Does Not Have Usual Place	142 (2.6)
	Has Usual Place	5371 (97.4)
Usual Place for Healthcare Type (N = 5365)	Clinic or Health Center	1101 (20.5)
	Doctor's Office or HMO	3940 (73.4)
	Hospital Emergency Room	105 (2.0)
	Hospital Outpatient	155 (2.9)
	Other	64 (1.2)
Told By Doctor to Take Prescription for High Blood Pressure (N = 4401)	No	61 (1.4)
	Yes	4340 (98.6)
Told By Doctor to Take a Prescription for High Cholesterol (N = 4814)	No	1198 (24.9)
	Yes	3616 (74.6)
Doctor Told You Have Diabetes (N = 5509)	No	3700 (67.2)
	Yes	1809 (32.8)
Overall Adherence (N = 5513)	Not Adherent	1136 (20.6)
	Adherent	4377 (79.4)

Abbreviations: HMO—health maintenance organization. [a] The "Other" race category contains those respondents who did not identify as Non-Hispanic Black or Non-Hispanic White. The "Other" race category included Mexican American [541 (9.8%)], Other Hispanic [496 (9.0%)], Non-Hispanic Asian [385 (7.0%)], and Other Races—including Multiracial [171 (3.1%)]. [b] Ethnicity categories were developed from NHANES race/Hispanic origin categories. The "Hispanic" group included respondents identified as Mexican American or other Hispanic. The "non-Hispanic" group included respondents who were classified as Non-Hispanic White, Non-Hispanic Black, or Non-Hispanic Asian. Respondents identified as Other Race—including Multiracial—were categorized as missing. [c] Alcohol consumption categories were calculated using responses for the number of days alcoholic drinks were consumed annually, the number of drinks consumed on those drinking days, and guidelines from previous literature [28]. [d] Not employed included those reporting that they were not working at a job or business, looking for work, or retired. Those who reported working at a job or business were employed. [e] Respondents with Medicaid as at least one source of health insurance were included in the "Medicaid" category, respondents with Medicare (but not Medicaid) as at least one source of insurance were included in the "Medicare" category, and all other respondents without Medicaid or Medicare were included in the "Other" category. The insurance types included in the "Other" category included private insurance, Medi-Gap, military healthcare, state-sponsored health plans, other government insurance, and single-service health plans. [f] Respondents with annual family incomes of USD 25,000 or less were classified as lower social class.

As shown in Table 2, bivariate analyses of categorical predictors revealed significant differences in adherence to medications based on structural determinants, including ethnicity ($p = 0.038$), gender ($p = 0.009$), and lower social class status ($p = 0.023$), as well as intermediary determinants, including the level of alcohol consumption [28] ($p = 0.004$), disability status ($p = 0.014$), ability to afford balanced meals for the household ($p < 0.001$), insurance ($p = 0.010$), marital status ($p = 0.020$), and whether or not they had a usual place for healthcare ($p < 0.001$). None of the continuous variables in this initial analysis were significant.

Table 2. Bivariate analyses of overall high blood pressure, high cholesterol, and/or diabetes medication adherence with categorical predictors (N = 5513).

				Medication Adherence		
				Adherent	**Not Adherent**	
				N = 4377	**N = 1136**	
Determinant Type	**Determinant**	**Study Variable**	**Level**	**N (%)**	**N (%)**	***p*-Value**
Structural Determinants	Gender	Gender *	Female	2243 (78.7)	606 (21.3)	0.009 [a]
			Male	2134 (80.1)	530 (19.9)	
	Race/Ethnicity	Race *	Black	877 (77.7)	251 (22.3)	0.194
			Other	1259 (79.0)	334 (21.0)	
			White	2241 (80.3)	551 (19.7)	
	Race/Ethnicity	Ethnicity *	Hispanic	798 (77.0)	239 (23.0)	0.038 [a]
			Not Hispanic	3440 (79.9)	865 (20.1)	
	Education	Education *	<HS Grad	1375 (79.6)	352 (20.4)	0.124
			College Grad	865 (80.9)	204 (19.1)	
			HS Grad	2121 (78.7)	575 (21.3)	
	Occupation	Employment Status	Not Employed	3740 (79.3)	977 (20.7)	0.357
			Employed	633 (80.0)	158 (20.0)	
	Social Class	Lower Social Class *	Not Lower Social Class	2372 (80.5)	573 (19.5)	0.023 [a]
			Lower Social Class	1561 (78.0)	441 (22.0)	
Intermediary Determinants	Biological Factor	Age Group	65–69	1215 (78.6)	331 (21.4)	0.343
			70–74	1157 (81.4)	264 (18.6)	
			75+	2005 (78.8)	541 (21.2)	
	Material Circumstance	Household Balanced Meals *	Could Afford	3684 (80.6)	886 (19.4)	<0.001 [a]
			Could Not Afford	574 (72.7)	216 (27.3)	
	Psychosocial	Marital Status *	Not Married	1926 (77.2)	568 (22.8)	0.020 [a]
			Married	2447 (81.2)	568 (18.8)	
	Behaviors	Smoking Status	Does Not Smoke	1807 (79.3)	472 (20.7)	0.428
			Smokes	401 (78.8)	108 (21.2)	
	Behaviors	Alcohol Consumption Category *	Heavy	51 (86.4)	8 (13.6)	0.004 [a]
			Light	1644 (80.5)	399 (19.5)	
			Moderate	196 (84.1)	37 (15.9)	
			Never	1209 (77.3)	355 (22.7)	

Table 2. *Cont.*

				Medication Adherence		
				Adherent	Not Adherent	
				N = 4377	N = 1136	
Determinant Type	**Determinant**	**Study Variable**	**Level**	**N (%)**	**N (%)**	***p*-Value**
Intermediary Determinants	Medication Access— Provider Availability	Usual Place for Healthcare *	Does Not Have Usual Place	82 (57.7)	60 (42.3)	<0.001 [a]
			Has Usual Place	4295 (80.0)	1076 (20.0)	
	Medication Access—Disability Status	Disability Status *	No Disability	3140 (81.3)	722 (18.7)	0.014 [a]
			Has Disability	1234 (74.9)	414 (25.1)	
	Medication Access—Provider Availability	Usual Place for Healthcare Type *	Clinic/Health Center	865 (78.6)	236 (21.4)	0.091
			Doctor Office	3190 (81.0)	750 (19.0)	
			Hospital ER	73 (69.5)	32 (30.5)	
			Hospital OP	116 (74.8)	39 (25.2)	
			Other	47 (73.4)	17 (26.6)	
	Medication Access—Insurance	Insurance *	Medicaid	511 (76.4)	158 (23.6)	0.010 [a]
			Medicare	3285 (79.5)	849 (20.5)	
			None	122 (78.2)	34 (21.8)	
			Other	450 (82.9)	93 (17.1)	
	Medication Access—Language	Interview Language	English	3922 (79.4)	1019 (20.6)	0.962
			Spanish	455 (79.5)	117 (20.5)	

Abbreviations: HS—high school; Grad—graduate; ER—emergency room; OP—outpatient. [a] Predictors were significant at the alpha = 0.05 level. * Predictors with *p*-values less than 0.20 were considered in the multivariable analysis.

Lower social class, household balanced meals, ethnicity, and education predictors were excluded from the multivariable analysis due to multicollinearity, while gender and marital status were combined due to significant interactions. This analysis (Table 3) revealed that overall significant differences in medication adherence existed based on two intermediary determinants: alcohol consumption and usual place for healthcare. Alcohol consumption was significantly associated with overall medication adherence ($p = 0.034$), with an increasing trend in odds of medication adherence as consumption increases. The odds of being adherent to prescribed medications were approximately 330% higher for those individuals who usually went to a doctor's office or health maintenance organization (HMO) for healthcare when compared to those who do not have a usual place to go for healthcare ($p < 0.001$) and almost 280% higher for those individuals who usually went to a clinic/health center for healthcare when compared to those who did not have a usual place to go ($p \leq 0.001$).

Table 3. Multivariable analysis of overall high blood pressure, high cholesterol, and/or diabetes medication adherence (N = 3887).

Variables (N = 3887)	Odds Ratio (95% CI)	*p*-Value
Alcohol Consumption Category		**0.034** [b]
Alcohol Consumption Category (Light vs. Never)	1.164 (0.881, 1.538)	0.281
Alcohol Consumption Category (Moderate vs. Never)	1.657 (1.085, 2.531)	**0.020** [b]
Alcohol Consumption Category (Heavy vs. Never)	2.866 (1.122, 7.318)	**0.028** [b]
Disability Status (Disability vs. No Disability)	0.884 (0.659, 1.185)	0.404
Insurance		0.080
Insurance (Medicaid vs. None)	0.885 (0.423, 1.853)	0.744
Insurance (Medicare vs. None)	0.926 (0.502, 1.709)	0.804
Insurance (Other vs. None)	1.597 (0.791, 3.224)	0.189
Gender/Marital Status [a]		0.097
Gender, Marital Status (Female Married vs. Female Not Married)	1.257 (0.855, 1.847)	0.241
Gender, Marital Status (Male Married vs. Female Not Married)	1.337 (0.993, 1.801)	0.055
Gender, Marital Status (Male Not Married vs. Female Not Married)	1.492 (1.050, 2.118)	**0.026** [b]
Race		0.566
Race (Black vs. White)	0.902 (0.727, 1.121)	0.349
Race (Other vs. White)	0.908 (0.694, 1.187)	0.475
Usual Place for Healthcare [c]		**0.001** [b]
Usual Place for Healthcare (Clinic/Health Center vs. None)	3.796 (1.904, 7.569)	**<0.001** [b]
Usual Place for Healthcare (Doctor Office or HMO vs. None)	4.297 (2.274, 8.118)	**<0.001** [b]
Usual Place for Healthcare (Emergency Room vs. None)	2.341 (0.937, 5.850)	0.068
Usual Place for Healthcare (Hospital Outpatient vs. None)	4.068 (1.674, 9.888)	**0.002** [b]
Usual Place for Healthcare (Other vs. None)	1.964 (0.593, 6.510)	0.265

Abbreviations: HMO—health maintenance organization; CI—confidence interval. [a] Predictors with multicollinearity were combined into a single predictor variable. [b] Predictors were significant at the alpha = 0.05 level. [c] Whether the respondent had any usual place for healthcare and the specific type of usual place for healthcare were combined into one predictor variable as all responses for a usual place for healthcare type had a response of "Yes" for a usual place for healthcare. The combined variable includes original responses for the usual healthcare place type variable plus the "Does Not Have Usual Place" level from the usual healthcare binary variable.

4. Discussion

This study examined the association between different domains of SDoH and medication adherence among older adults with concomitant diagnoses of high blood pressure, high cholesterol, and/or diabetes in the US using an integrated SDoH framework [23]. It was hypothesized that structural and intermediate determinants of health would be associated with medication adherence. Study inferences summarize the influence of these upstream factors on older adults' medication adherence, with valuable implications for public health, policy, pharmacy practice, and future research.

The study revealed that ethnicity and several indicators of lower socioeconomic status, including insurance, social class, and ability to afford balanced meals, were significantly associated with medication adherence. Previous studies have also established that medication adherence is lower among racial/ethnic minorities, individuals with no insurance,

and people in lower socioeconomic classes [29,30]. These factors were mostly attributed to cost-related medication nonadherence, which is highly pronounced in older adults and racial/ethnic minority groups. Almost 1 in 5 older adults reported cost-related medication non-adherence in 2022, which can subsequently result in increased healthcare utilization and poor clinical outcomes [31,32]. Economic downturns can constrain the ability to meet basic human needs such as food, housing, clothing, and transportation, and patients may resort to foregoing medication acquisition to meet their needs [33–36]. Hence, pharmacists and other health professionals are encouraged to screen for the SDoH factors associated with medication adherence during clinical assessment using validated SDoH screening instruments while adopting safety net referral programs to achieve longstanding medication adherence outcomes [33].

Multivariable analysis partially supported the hypothesis, as only intermediary determinants of health remained significantly associated with medication adherence. A plausible rationale is that each variable was calculated as if the remaining predictors were held constant and reported independently from associations with other determinants [18]. Alcohol consumption had a significant positive association with medication adherence in this study, which is contrary to most evidence that alcohol consumption has a negative association with adherence [37–40]. A plausible reason for such a positive correlation may be due to self-report bias from NHANES respondents during data collection. There may be several instances of overreporting or underreporting of drinking status culminating in a skewed output. However, recent qualitative studies revealed that study participants consume considerable amounts of alcohol while taking long-term medications [41,42]. This discordant evidence opens a gap for researchers to leverage a mixed-method approach to determine the interaction between self-reported alcohol usage and medication adherence. This is to determine the drinking behavior of patients with comorbidities who are taking many medications. Pharmacists should inquire about the alcohol-drinking behavior of patients during assessment and consciously educate patients on its interactions with several medications after disclosure. A typical screening tool used in clinical practice is the US Alcohol Use Disorders Identification Test—Consumption (USAUDIT-C), which identifies patients who are heavy drinkers [43]. If addiction is present, then patients should be advised to seek behavioral therapy.

The likelihood of positive medication adherence was higher among study participants who visited clinics, HMOs, or doctors' offices to access care. Such patients frequently contact pharmacists and other healthcare professionals who design therapeutic plans aimed at preventing medication nonadherence. This can be a substantial SDoH factor to consider when designing and evaluating interventions for populations living in medically underserved areas, which are characterized by few primary care providers [44]. It has been shown that patients living in such areas have a higher rate of abandoning quality-measured prescriptions compared to those living in areas not considered medically underserved, which is indicative of prescription access disparity [45]. It is pertinent to implement strategies that promote pharmacists' patient care processes, such as medication therapy management, appointment-based models, and pharmacist collaborative practice agreements, to sustain visit regularization and improve medication adherence in these areas [46]. Also, the bipartisan Pharmacy and Medically Underserved Areas Enhancement Act should be adopted to allow pharmacists to be reimbursed for certain healthcare services under Medicare Part B in medically underserved areas with positive implications for healthcare access [47]. The act would specifically grant pharmacists provider status for Medicare patients, which will ensure that they are optimally reimbursed for their services. Via this act, licensed and practicing pharmacists would be reimbursed at 85% of the rate reimbursed to physicians under Medicare Part B in their state if they render their services in a medically underserved

area. The implication is that beneficiaries will have greater access to pharmaceutical care when physicians are in short supply [48]. The adoption of such a bill will help promote sustainable medication adherence programs among health disparity populations and extend the reach of pharmacists in actively providing comprehensive pharmaceutical care.

This study is not without limitations. Due to limited resources, this initial study is limited to the SDoH factors specified in the conceptual framework and captured in the NHANES database; however, a typical variable such as medication cost is not included as a barrier to medication access during analyses because it is not available in the NHANES database. The adherence measure used in the analysis was self-reported, which was not in alignment with standardized metrics used in pharmacy practice. Given that the datasets utilized in this study were collected prior to the COVID-19 pandemic, it is possible that healthcare access and medication adherence were relatively stable compared to the pandemic era. Consequently, interpretation of the findings may be constrained, as the pandemic disrupted access to health and social services. Furthermore, the pandemic triggered economic downturns that had direct or indirect impacts on several social determinants of health (SDoH), thereby limiting the generalizability of the results obtained from this study. Future research should utilize other databases that include these data, such as the Medical Expenditure Panel Survey (MEPS). These study findings are relevant to older adults with any combination of hypertension, cholesterol, and diabetes. There could be differences in SDoH associated with medication adherence by specific disease states and age groups, warranting more research.

5. Conclusions

Study findings highlight public health, policy, pharmacy practice implications, and opportunities for interventions on the prioritized SDoH most likely to impact medication adherence among older US adults. Bivariate analyses provide strong evidence that structural and intermediate determinants of health are associated with medication adherence. Multivariable analysis partially supports the hypothesis. The odds of older adults being adherent to prescribed medications for hypertension, high cholesterol, and/or diabetes are higher among individuals who have a usual place for healthcare. Legislative measures, such as the Pharmacy and Medically Underserved Areas Enhancement Act, could improve healthcare access and medication adherence in medically underserved areas. Additionally, recent pharmacy SDOH intervention measures include integrating community health workers or cross-training pharmacy technicians as community health workers who serve as trusted liaisons between health and social resources while having a close understanding of the communities they serve. Future research should further investigate the reasoning for the observed increasing medication adherence trend with increased alcohol consumption and build on the current study by examining potential nuances in SDoH associations with medication adherence by disease state and age group.

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pharmacy

MDPI

Review

Therapeutic Evaluation and Utilization Analysis of Mental Health Prescription Digital Therapeutics Within the Current Regulatory Landscape

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Abstract: Prescription digital therapeutics (PDTs) are emerging as a pivotal component of digital healthcare, providing software-based therapies for various diseases. This review aims to analyze the regulatory landscape in the U.S., safety, efficacy, and current challenges of PDTs, focusing on mental health conditions. Relevant articles were searched on PubMed, Google Scholar, ClinicalTrials.gov, and FDA Guidance Documents databases, supplemented by manual searches of reference lists from included studies. Inclusion criteria covered English-language studies on the development and application, therapeutic efficacy, and regulatory guidelines of PDTs in mental health. Data extraction and synthesis were conducted to summarize key findings and trends in the literature. FDA regulatory frameworks for PDTs are evolving through pathways of de novo and 510(k) applications, with patient-centric guidance. Clinical trials and real-world data support PDTs' safety and efficacy, while highlighting regulatory needs. Challenges include payer coverage, patient accessibility, and data privacy concerns. Mixed patient feedback reveals areas for improvement. Limited healthcare provider engagement and payer coverage contributed to financial challenges for PDT manufacturers. Future trends suggest that PDTs will expand beyond mental health. The evolving landscape underscores the need for continued research, regulatory refinement, and collaborative efforts across stakeholders to ensure the successful integration of PDTs into healthcare.

Keywords: prescription digital therapeutics (PDTs); digital health; mental health; FDA regulations; safety; efficacy

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1. Introduction

1.1. PDT Definition

PDTs represent a rapidly developing domain within the digital healthcare landscape. PDTs are software-based prescription therapies delivered on software platforms that are designed to directly address and manage a broad spectrum of significant diseases and disorders as a subcategory within the domain of digital therapeutics (Figure 1). The devices are accessible via computers, smartphones, mobile applications, wearable devices, or web portals (Figure 1). Their effectiveness has been validated both as stand-alone and combination therapies. PDTs are "cleared" as Class II medical devices based on clinically relevant safety and efficacy data obtained from clinical trials. Typically, FDA-cleared medical devices are not required to undergo clinical trials, unlike FDA-approved products, which must undergo these trials to demonstrate their safety and effectiveness. However,

PDTs are an exception according to the FDA regulations that despite being FDA-cleared, they are required to undergo clinical trials.

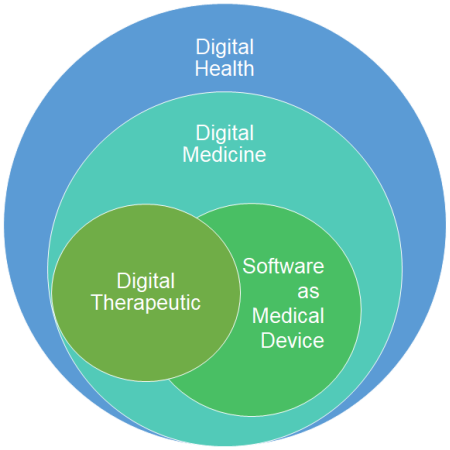

Figure 1. Navigating the PDT landscape.

In contrast to traditional healthcare practices, digital healthcare operates via a patient–machine–HCP interface, providing tailored care and precision medicine through an unconventional workflow [1]. The HCP functions as a consultant, guide, or collaborator, engaging patients actively in the decision-making processes. The health data are disseminated among multiple shareholders, including institutions, hospitals, and patients, facilitated by dynamic point-of-care delivery as long as the patient is present [1].

The objective of this review is to thoroughly examine the therapeutic effectiveness and utilization trends of mental health PDTs in the clinical setting. Additionally, it seeks to explore the impact of PDTs on patient outcomes, the challenges and opportunities in their adoption, and the roles of different stakeholders in facilitating their integration into healthcare systems.

1.2. PDTs in Mental Health

The development and access of PDT products is heavily focused on mental health, driven by the convergence of factors including the high burden of mental health disorders, the technological capabilities of personalized medicine, and regulatory support from the FDA through clear pathways. PDTs have emerged as a transformative force in the prevention, management, and treatment of mental health disorders. They provide innovative solutions to address various types of diseases, including MDD, ADHD, PTSD, etc. [2] Mental health PDTs may function as a stand-alone therapy or part of a combination therapy. Stand-alone PDTs in mental health are individual therapies that operate independently of other interventions, providing patients with tailored tools for self-directed mental health management that cater to their individual needs and preferences. Conversely, most mental health PDTs operate as combination therapy concomitant with existing pharmacological interventions as part of comprehensive treatment plans. The integration of PDTs with traditional treatments expands current clinical practices. They offer evidence-based care to reduce patient stigma, improve access to care, mitigate provider shortages, and streamline complex healthcare systems. Additionally, PDTs may lower the risk of adverse events serving as non-pharmacologic interventions.

2. Regulatory Pathways

In the U.S., the FDA and other regulatory bodies are currently in the process of developing guidelines for digital therapeutics. Nonetheless, some established guidelines exist to evaluate software in clinical settings, particularly in terms of clinical assessment.

The primary oversight of this protocol falls under the IMDRF, a voluntary association comprising international medical regulators [3]. The FDA plays a pivotal role within the IMDRF and holds responsibility for regulating the utilization of PDTs in the U.S. [3].

The FDA regulates PDTs by approving or clearing them as Class II devices [4]. Although PDTs manifest different technology from traditional medical devices, they are reviewed by the CDRH, which may not always align with the iterative and dynamic nature of the software treatments [3].

Following the evaluation of a digital treatment in one or more clinical studies, including randomized controlled trials, the data and formal requests for authorization are subsequently submitted through one of two FDA pathways. Each pathway is characterized by distinct regulatory and evidence-based requirements as outlined below.

2.1. De Novo Pathway

The FDA uses the de novo request pathway to classify novel medical devices that demonstrate reasonable assurance of safety and effectiveness but lack a legally marketed predecessor [5]. Devices classified through a de novo request can serve as references for subsequent premarket notification submissions. There are two options for submitting a de novo request for classification into Class I or II [5]. The first option is to submit after receiving a high-level determination of not SE in response to a 510(k) submission [5]. Alternatively, the second option entails submission without preceding 510(k) submission and determining the absence of a legally marketed device for SE determination [5].

2.2. 510(K) Pathway

A 510(k) is a submission sent to the FDA prior to the commercialization of a device. Its purpose is to demonstrate the device is safe and effective, establishing it is SE to a legally marketed device [6]. Submitters are required to compare their device to one or more similar legally marketed devices, known as "predicates", and support their claims of SE [6]. A device is considered SE to a previously approved predicate device if it has the same intended use and technological characteristics [6]. Until the FDA declares a device is SE to a predicate, it cannot be legally marketed in the U.S. Typically, this determination is made within 90 days based on the information provided by the submitter [6]. Upon receiving confirmation of SE, the device can proceed to be marketed in the U.S. [6]. However, if there are changes to an existing device that could significantly affect its safety or effectiveness, or if it is proposed for a new intended use, a new 510(k) submission is required [6].

2.3. Graphic Comparison of Regulatory Pathway Timelines (De Novo vs. NDA)

2.3.1. IDE to De Novo Timeline

The process of bringing a medical device to market involves several phases with varying timelines. An IDE is a regulatory submission that allows an investigational device to be used in a clinical study to gather data on its safety and effectiveness. Initiating an IDE submission typically requires one to three months, followed by a 30-day FDA review [7]. Subsequently, the IDE clinical trial phase spans several months to years, allowing for comprehensive evaluation. In cases necessitating a de novo submission, the preparation phase also requires one to three months, followed by a five-month FDA review period [7]. After Phase 2, sponsors can seek guidance on designing large Phase 3 studies, which is crucial before submitting an NDA. The submission of an NDA formally requests FDA consideration for marketing approval, with the FDA having 60 days to decide whether to file it for review. If filed, an FDA review team evaluates the drug's safety and effectiveness based on the sponsor's research. The culmination of these phases leads to the FDA's decision, marking the completion of the regulatory journey for the medical device. The comparison between the approval timeline of IDE and de novo is outlined in Figure 2.

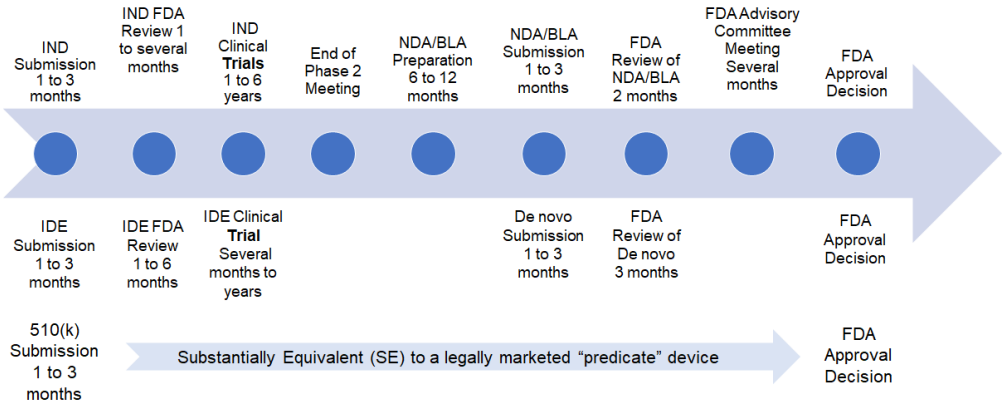

Figure 2. Comparison of drug and device FDA approval timeline.

2.3.2. Comparison of NDA and De Novo Timeline

The processes for bringing medical devices and pharmaceuticals to market involve distinct yet complex stages. Submitting an IDE submission for a medical device typically takes one to three months, followed by a subsequent 30-day FDA review [7]. The IDE clinical trial phase spans several months to years. For devices requiring a de novo submission, the preparation phase also takes one to three months, followed by a three-month FDA review [7]. The FDA decision marks the culmination of the regulatory journey. In contrast, drug development entails an IND submission, which takes one to three months for FDA approval [7]. The FDA review process lasts one to several months, and clinical trials span one to six years [7]. Upon completion of Phase II, an End of Phase II Meeting is conducted, followed by a six to twelve-month NDA or BLA preparation, a one to three-month submission phase, and a five-month FDA review [7]. An Advisory Committee Meeting may be held, and the FDA's final approval decision takes several months [7]. Overall, both processes are intricate and time-intensive, each comprising its unique set of stages and durations (Figure 2).

3. FDA Special Considerations for PDTs

User-centered design and human factors are pivotal for PDTs' success, relying heavily on user engagement. FDA guidelines underscore the importance of incorporating human factor principles into design, including user interfaces, usability testing, and ensuring user-friendliness [8]. Emphasized elements include the provision of clear instructions, effective feedback mechanisms, and flexibility for diverse user needs [8]. As the regulatory landscape evolves, manufacturers are urged to stay abreast of guidelines for successful market entry of innovative digital therapeutics.

Furthermore, PDTs stand apart from conventional pharmaceuticals due to their post-regulatory adaptability, especially when driven by AI or ML technologies [1]. How can a product be approved if it evolves over time and may potentially "hallucinate" responses to input? To address this, the FDA is progressively advancing its comprehensive regulatory framework for digital therapeutics, including PDTs.

Lastly, evolving regulations aim to guide industry players in the nuanced data submissions crucial for establishing safety and efficacy [9]. Instead of evaluating outcomes for clinical and statistical significance, the FDA prioritizes the benefits of PDTs over baseline outcomes in clinical trials, given the assumed lower risk of PDTs.

The FDA's Digital Health Center of Excellence plays a crucial role in aiding manufacturers through the dynamic regulatory landscape. It serves as a comprehensive resource hub, offering insights into innovation, health equity, cybersecurity, and AI/ML applications in wireless devices. The center has issued 23 guidance documents (in draft and final stages) to assist manufacturers in preparing data for regulatory approval [10].

4. PDT Examples with Clinical Trial Data

To gain a comprehensive understanding of PDTs in mental health, we conducted a comprehensive keyword search using databases like PubMed, Google Scholar, ClinicalTrials.gov, and FDA Guidance Documents. The keywords used in our database searches included software as medical device (SaMD), prescription digital therapeutics (PDTs); digital health; mental health. Our research focused on FDA-approved PDTs, covering both de novo and 510(k) pathways, and included all approved mental health and sleep disorder therapies. Key devices examined included reSET®, EndeavorRx®, NightWare®, Sunrise Sleep Disorder Diagnostic Aid®, reSET-O®, Freespira®, Somryst®, Rejoyn™, and PRISM® for PTSD. This review provided valuable insights into how these PDTs are innovating patient care and treatment outcomes.

Data extraction and synthesis were conducted to summarize key findings and identify trends over a five-month period starting 15 December 2023 for studies conducted in the U.S. PDTs that received clearance during this timeframe were included. The analysis compared 510(k) and de novo summaries, providing insights into clinical trial data, device functionalities, and the safety and efficacy of these therapies. Patient reviews were also incorporated to assess the effectiveness of the PDTs. ClinicalTrials.gov was a key source for understanding the clinical landscape, and the inclusion criteria centered on the development, application, efficacy, and regulatory guidelines of mental health PDTs.

4.1. The First Digital Therapeutic

Abilify MyCite® is an aripiprazole tablet equipped with an ingestible event marker sensor [11]. It is indicated for schizophrenia, bipolar I disorder (monotherapy or with lithium/valproate), and MDD when used alongside other antidepressant medications [11]. Abilify MyCite® tracks medication adherence through a combination of an ingestible sensor, a wearable patch, and a smartphone application. The aripiprazole tablet contains a built-in ingestible sensor made of minerals found in most diets [11]. Upon ingestion, the sensor is activated and emits an electrical signal as it contacts stomach fluid. The signal is then detected by a wearable patch worn by the patient, recording the time of medication intake [11]. The data captured by the patch are subsequently transmitted to a smartphone application via Bluetooth, where medication ingestion data are displayed on a dashboard portal. Authorized HCPs can access the data to monitor adherence.

In 2017, Abilify MyCite® was the first FDA-approved digital medicine system designed to enhance adherence in mental health patients through the Class III (higher risk due to ingestion of the device) premarket approval process [12]. In the trial involving 30 patients with schizophrenia, participants were administered the Abilify MyCite® treatment once daily for eight weeks [13]. The safety sample comprised all 30 patients who used the Abilify MyCite system during the trial. Results indicated that most patients (64.9%) had exposure to the system for 50 to 56 days [13]. Adverse events were observed, with 35.1% experiencing device-associated TEAEs and 32.4% experiencing medication-associated TEAEs [13]. Two serious TEAEs were reported but were deemed unrelated to the treatment [13]. Ten patients discontinued the trial, citing reasons such as adverse events, withdrawal of consent, and protocol deviation [13]. These statistics provide insights into the safety and tolerability of the Abilify MyCite® system in patients with schizophrenia during the trial period [13]. The trial concluded that there were not any safety concerns significant enough to change the labeling of the medication [13].

It raised a controversy despite its approval. The debate around Abilify MyCite® centers on its ability to track medication adherence in patients with mental health conditions. The manufacturer Otsuka claims that such technology can offer valuable insights into adherence patterns, facilitating collaborative efforts between patients and HCPs to address

non-adherence issues and improve health outcomes [14]. Notably, Otsuka lacked evidence demonstrating enhanced adherence or improved health outcomes for patients using Abilify MyCite® [14].

Additionally, Abilify MyCite® has raised ethical and privacy concerns regarding the secure handling of sensitive health data. According to Otsuka, the Abilify MyCite® system not only records the timing of medication intake but also tracks the patient's activity level (number of steps) and resting time automatically [12]. Furthermore, a 2019 study criticized the regulatory approval process, citing insufficient evidence and a lack of improved medication adherence with the digital form of aripiprazole compared to the conventional version [15]. Given the ongoing debate, subsequent mental health software devices utilize various clinically meaningful endpoints to optimize clinical outcomes and diminish healthcare expenditures.

4.2. De Novo Devices

Examples of mental health PDTs that have received de novo approval include reSET®, EndeavorRx®, NightWare®, and Sunrise Sleep Disorder Diagnostic Aid®. See Table 1 for the summarized clinical trial information.

reSET® (Version 2.0.1): A software application that utilizes a 12-week outpatient augmentation treatment; patients had to currently be enrolled in outpatient treatment for SUD under the supervision of a clinician. It integrated CBT with daily reminders and contingency management (Table 1) [16,17].

EndeavorRx® (Version 2.5.0): A video game that employs sensory stimuli and motor challenges to engage key attention-related brain regions, encouraging multitasking and distraction management through navigation, target collection, and obstacle avoidance tasks for children (Table 1) [18,19].

NightWare® (2024 Version): A software application on the Apple Watch and iPhone platform provided by NightWare, Inc. It detects nightmares in real time using biometric sensors, like the Apple Watch heart monitor. It interrupts nightmares without fully waking the patient using gentle vibrations, improving sleep within two weeks (Table 1) [20].

Sunrise Sleep Disorder Diagnostic Aid®: A combination of a sensor placed on the mandible with cloud-based software and a mobile app to analyze sleep data. By tracking mandibular movements, it detects respiratory disturbances, identifies sleep states, and assesses the severity of obstructive sleep apnea, while also providing insights into sleep structure and head position (Table 1) [21]. Healthcare providers can interpret integrated data to diagnose sleep disorders effectively.

The clinical trials for these PDTs have demonstrated both potential benefits and challenges. The benefits include demonstrated effectiveness in targeted populations, enhanced accessibility to treatment, and the potential for personalized interventions. The possible benefits are often lower compared to those of pharmacotherapies. Additionally, several limitations must be addressed, such as the quality and generalizability of the studies, small sample sizes, and the need for further evaluation of long-term safety and efficacy. For example, the clinical trial that led to the FDA approval of reSET® was properly powered and detected significant differences in abstinence rates between the treatment and control groups. In contrast, other products, such as NightWare®, faced limitations due to smaller sample sizes. The clinical trial for NightWare® included only 79 patients and was underpowered to detect statistically significant differences in endpoints, primarily because the study was terminated early [20]. Given these challenges, future research should aim for larger, more diverse study populations and extended follow-up periods to gain a more comprehensive understanding of the long-term implications of PDT use.

Table 1. DeNovo devices summarized information.

PDT DeNovo Device	Intended Population	Study Methods	Safety	Benefits	Patient Perspective
reSET® [16,17]	Patients 18 years of age and older with substance use, opioid use disorder.	reSET was tested in a multi-site, un-blinded, randomized clinical trial to characterize its probable benefits and risks. Study participants received 12 weeks of either treatment as usual (TAU) as standard treatment, or reduced TAU supplemented with a desktop version of reSET (rTAU + reSET).	13% (n = 66) patients experienced adverse events: TAU: 11.5% (n = 29) reSET + TAU: 14.5% (n = 37) No significant difference noted (p = 0.3563).	Device exhibited statistically significant improvements in abstinence and retention. Retention rate: 92 out of 252 (36.5%). Dropouts in TAU compared to 71 out of 255 (27.8%) in rTAU with significant difference (p = 0.0316).	Satisfaction surveys were conducted on 1–10 scale (1 = very easy, 10 = very difficult). Responses collected from 233 out of 255 participants (91.4%). System and education useful: 8.64/10. Satisfied with the use of computerized system: 8.86/10. Easy to understand: 3.14/10.
EndeavorRx® [18,19]	Children aged eight to seventeen with primarily inattentive or combined-type ADHD and demonstrated attention issues.	EndeavorRx has undergone five clinical studies involving 600+ children with ADHD. In the randomized controlled trial, it enhanced objective attention in eight-to-twelve-year-olds. With sessions lasting ~25 min daily, five days a week for four weeks, recent trials have shown further benefits with an additional month of treatment.	In a clinical trial, 18% of participants experienced mild to moderate device-related adverse events, with the most common being decreased frustration tolerance. No serious device-related events occurred. Three participants discontinued treatment due to decreased frustration tolerance.	Effectiveness results showed significant improvement in ADHD-specific impairment and symptoms for both On Stimulants and No Stimulants groups after one month of treatment. The improvements persisted after a one-month treatment pause and further improved with an additional month of treatment. All improvements had p-values less than 0.001 compared to baseline.	In market research, 90% of caregivers, physicians, and health insurers showed interest in a non-drug digital treatment like EndeavorRx due to its low side-effect profile and attention efficacy. They cited its perceived effectiveness (75%), potential cognitive enhancement (>82%), improved focus (>83%), and ease of use (80%). Additionally, more than 80% believed it could aid in ADHD management. In the ASD pilot study, EndeavorRx significantly improved attention for children, with 73% reporting improvement compared to 50% in the Control group. Parents also noted enhanced real-life attention in 64% of cases. Additionally, 63.6% of parents found EndeavorRx worthwhile, with 90.9% wanting their child to continue using it, compared to lower percentages in the Control group.
NightWare® [20]	Adults 22 years or older who suffered from nightmare disorder or had nightmares from PTSD.	The 30-day, double-blind sham-controlled randomized clinical trial (70 participants enrolled) was performed to study the safety and efficacy of the device. The "sham system" refers to the device consisting of the same components as the active system, but the application only monitored the subjects' sleep and did not provide any intervention or feedback to the subject.	Patients in both the active and sham arms of the study reported a 1.2-point decrease (less sleepiness) in the Epworth sleepiness scale (ESS) (not statistically significant). Patients in the active arm reported a 0.2-point decrease in the CSSRS, and patients in the sham arm reported no change in the C-SSRS (not statistically significant).	Patients in the active arm had a mean Pittsburgh Sleep Quality Index (PSQI) improvement of 3.2 points, and patients in the sham arm had a mean improvement of 2.2 points (not statistically significant). The secondary outcome of PQSI-A (including sleep disturbance due to anxiety, nervousness, bad dreams, terrors or screaming during sleep) had a mean improvement of 3.3 points in the active arm and 1.4 points in the sham arm (not statistically significant).	Patient perspectives considered for the NightWare Kit (Apple iPhone, Apple Watch, Apple iPhone Charging Cable, Apple Watch Charging Cable) during the review included: Three patients were interviewed on their experiences using the device for 5 weeks. All three patients reported benefit from the device use, noting that the device provided a non-pharmaceutical treatment alternative. The patients noted that the pharmaceutical treatment could leave them feeling "in a fog," while the NightWare device did not.

Table 1. *Cont.*

PDT DeNovo Device	Intended Population	Study Methods	Safety	Benefits	Patient Perspective
Sunrise Sleep Disorder Diagnostic Aid® [21]	Patients 18 years and older with suspicions of sleep breathing disorders.	The sponsor submitted three clinical study protocols and reports to validate the Sunrise SDDA device's safety and efficacy, focusing on assessing agreement with polysomnography (PSG). Notably, no adverse events, adverse device effects, or deficiencies were reported in these studies, which included diverse patient populations covering different ages, sleep-disordered breathing conditions, body mass indices, and neck circumferences, mirroring the intended U.S. patient demographic. The information utilized in the clinical trial was treated as confidential.	Classified information	Primary effectiveness measured by change in daily sleepiness (time frame: 3 months post-diagnosis), time to diagnosis (time frame: up to 12 months), time to treatment (time frame: up to 15 months), change in daily sleepiness (time frame: 3 months post inclusion). Secondary outcomes were measured by change in quality of life, change in work productivity, cost (€)/QALY, net profit for the French social security system, comparison of CPAP compliance data, comparison of sunrise versus PSG diagnosis, and difference in the obstructive respiratory disturbance index	The FDA document lacks specific information regarding patient perspectives on this device.

4.3. 510(K) Devices

Examples of mental health PDTs that have been granted 510(k) approval include reSET-O®, Freespira®, Somryst®, Rejoyn™, and PRISM®. See Table 2 for the summarized clinical trial information.

reSET-O®: A PDT designed for a 12-week (84-day) course, reSET-O® is a software application used alongside outpatient treatment with transmucosal buprenorphine and contingency management to enhance retention in patients with OUD (Table 2) [22].

Freespira®: An at-home therapy that teaches patients diagnosed with panic disorder how to regulate and normalize their breathing patterns (Table 2) [23].

Table 2. 510(K) devices summarized information.

PDT 510k Device	Treatment	Clinical Trial
ReSET-O® [22]	Treatment for OUD	During a 12-week intervention, the reSET-O + Treatment-as Usual (TAU) group showed a higher retention rate of 82.4% compared to 68.4% in the TAU group alone, a significant difference with a p-value of 0.0224. Demographic analysis revealed no significant differences between groups, with most participants being male (54.1%) and white (95.3%), with an average age of 32.9 years. The prevalence of meeting DSM-IV criteria for cocaine dependency was 21.5% in the TAU group and 15.4% in the TAU plus digital therapeutic group, with no statistically significant difference.
Freespira® [23]	Treatment for panic disorder and/or PTSD symptoms. Freespira measures and displays end-tidal carbon dioxide and respiratory rate in real time within a structured breathing protocol	In the single-arm clinical trial (NCT03039231) sponsored by Palo Alto Health Sciences, Inc (n = 55; 18 years and older), participants were treated with device for four weeks twice daily via 17 min sessions at home using a sensor and tablet with pre-loaded software. PTSD and symptoms were assessed at the end of the treatment, two months, and six months post-treatment. Primary efficacy outcome: 50% of participants showing ≥six-point decrease in Clinician Administered PTSD Scale (CAPS-5) score at two-month follow-up. Tolerability, safety, usability, adherence, and patient satisfaction were assessed.
Somryst® [24]	For Chronic Insomnia with CBT-1	In a randomized study, participants were divided into two groups: one receiving their standard care along with SHUTi (now called Somryst), and the other receiving only their regular care. The group receiving standard care plus SHUTi showed improvement, as measured by the Insomnia Severity Index (ISI). The average reduction in ISI score was significantly ($p < 0.0001$) greater at week nine and six-month follow-up for the UC+SHUTi arm (mean −7.83 and −8.52 respectively) than the UC+Control arm (means −2.94 and −5.36, respectively). Notably, no adverse effects were reported during the study.
PRISM® [25]	Utilizes EEG signal input for treating patients with PTSD	Gray Matters Health conducted a study to evaluate PRISM as an adjunct therapy for PTSD. It involved 15 EEG neurofeedback sessions over eight weeks in subjects aged 22 to 65 with chronic PTSD, assessing symptom reduction. The study took place internationally, with baseline assessments and pre-training sessions provided. The response rate, i.e., the percentage of subjects (50%) with at least a six-point improvement in Clinician Administered PTSD Scale (CAPS-5) from baseline to the three month follow-up visit (primary effectiveness endpoint) as well as at 8 weeks (exploratory endpoint) was deemed to have been successfully met. While 50.6% (40/79) of the subjects experienced adverse events (AEs), the majority were mild AEs (headache, fatigue) and they recovered right after the training sessions with no further intervention. The pre-specified safety goals of this study were met, and the safety profile was found to be acceptable.

Table 2. *Cont.*

PDT 510k Device	Treatment	Clinical Trial
Rejoyn™ [26]	Treatment of MDD symptoms as an adjunct to clinician-managed outpatient care for adult patients with MDD aged 22 years and older who were on antidepressant medication	In a 6-week, multicenter, randomized controlled trial (NCT04770285), 386 participants (aged 22–64) diagnosed with MDD who were on antidepressants were divided into two arms: one receiving Rejoyn, and the other a sham control app. The control app included a cognitive training exercise of shapes memory task. The results indicated that the Rejoyn arm met the primary endpoint by demonstrating a significant mean change on the Montgomery-Åsberg Depression Rating Scale from baseline to Week 6 compared to the sham group (−8.78 vs. −6.66, respectively; with a treatment difference of −2.12 [95% CI, −3.93, −0.32]; $p = 0.0211$). Symptom improvement was also noted through assessment by both patients (Patient Health Questionnaire-9) and clinicians (Clinical Global Impressions-Severity scale). No TEAEs were reported during the trial.

Somryst®: A digital therapeutic that functions like a personal sleep coach. Using CBT-I, the app guides users through six lessons over a period of up to nine weeks, helping them fall asleep faster and stay asleep longer (Table 2) [24].

PRISM®: An FDA-cleared, neuroscience-based prescription therapy for treating PTSD. PRISM® uses a computer simulation and EEG headset to create a non-trauma-based environment where patients can learn to manage their PTSD symptoms effectively (Table 2) [25].

Rejoyn™: A digital therapeutic for treating depression symptoms through brain-training exercises and short, skills-based therapy lessons. Unlike medication, Rejoyn™ leverages the brain's natural ability to adapt, known as neuroplasticity (Table 2) [26].

4.4. Pharmacovigilance

Safety concerns regarding the use of PDTs in real-world scenarios have arisen due to the likelihood of indirect adverse incidents not being immediately recognized during treatment. The negative aspects of technology use are often studied independently from clinical trials that focus on technology outcomes [27]. However, app–app interactions are unpredictable, given the increasing use of portable technology in the largely unregulated digital environment [27]. Therefore, adverse events and unexpected interactions, systemic reports, and meta-analyses should be considered early during the design and development phase of PDTs [27]. In the U.S., the MAUDE database compiles adverse event reports concerning medical devices from manufacturers [28]. It encompasses the latest decade of medical device report data, detailing malfunctions or incidents resulting in death or serious injury. The releasable MAUDE data are accessible to clinicians and the public for voluntary adverse event reporting [28]. However, while the FDA mandates manufacturers to report events leading to death or serious injury, it lacks clear guidance regarding less severe adverse events, and clinicians are requested to use MedWatch form 3500 for voluntary reporting.

In contrast, the Medicines and Healthcare Products Regulatory Agency in the United Kingdom has issued guidance on reportable adverse incidents for digital therapeutics, outlining key considerations for HCPs when evaluating the safety of PDTs [29]. These include performance issues, diagnostic accuracy issues, decision support software resulting in harm, issues with connected hardware or software, human–device interface problems, user error resulting in harm, inadequate labeling or instructions for use, and computer system security problems [29].

4.4.1. Adverse Events

Somryst®

On 22 May 2022, a MAUDE event was reported involving a patient's experience of muscular rigidity, anxiety, neck pain, sleep dysfunction, and convulsion/seizure. The nature of the event was classified as an injury [30].

EndeavorRx®

The reported MAUDE event pertained to a patient presenting no clinical signs, symptoms, or conditions. Categorized as a malfunction, the event description indicated a lack of efficacy [31].

NightWare®

Two adverse events were reported during the study. Neither was determined to have a probable correlation with the use of the device under investigation. One participant was hospitalized due to a suicidal attempt after study enrollment but prior to the use of the investigational device [20]. Another participant who was enrolled and using the device was diagnosed with sleep apnea, but the contributing factors were determined to be likely present before the device usage (Table 1) [20].

In the context of post-marketing surveillance, a MAUDE event was documented involving a patient experiencing high blood pressure or hypertension [32]. Classified as an injury, the event description specified a medical finding of an elevation in blood pressure, with a noted association with the use of NightWare® [32].

4.5. Cost Comparison

In comparison to pharmacotherapy, software medical devices typically recruit fewer study participants in clinical trials, reflecting the unique characteristics of device trials [33]. The availability of alternative treatments may also pose challenges in recruiting voluntary participants. Additionally, conducting medical device clinical trials can be expensive, making smaller sample sizes more feasible from a cost perspective. Consequently, regulatory authorities allow smaller sample sizes for device trials compared to drugs.

Post-regulatory approval, PDT devices generally entail higher upfront costs than drugs for patients. This is attributed to their common adoption of a one-time payment model that covers the length of time that the device was studied, establishing a distinct financial structure [34]. In contrast, pharmaceutical treatments for mental health conditions typically involve continuous duration. Therefore, it is challenging to compare the cost of therapy between devices and pharmaceuticals. These discrepancies must be taken into account when evaluating the cost differences of mental health treatments within the pharmaceutical and software medical device domains.

Currently, there are no cost-effectiveness studies available for PDTs. However, a direct comparison of costs between PDTs and pharmaceutical interventions can be found in Table 3. The average wholesale price of these PDT devices is mostly higher than the first-line pharmaceutical treatments for relevant mental health conditions. Please be aware that Rejoyn™ is not featured in the table as it obtained FDA approval in only March 2024 and is not currently accessible to patients. However, few insurance companies provide coverage for these devices, as such manufacturers may also offer coupons to mitigate costs. For example, Pear Therapeutics, the manufacturer of Somryst®, attempted to lower the costs by extending savings cards to eligible patients [35].

Table 3. Cost comparison of PDTs vs. conventional first-line treatment with drugs.

Treatment	Average Wholesale Price (AWP) [36]	Applicable Clinical Trial and Participant Numbers
Substance Use Disorder (3-month treatment)		
reSET	USD 2231.91	255
Buprenorphine-Naloxone 8 mg-2 mg Sublingual tablet BID	USD 1963.44	ISTART trial (NCT05362357) and 759
Methadone 10 mg	USD 62.74	OPTIMA trial (NCT03033732) and 272
Naltrexone 50 mg	USD 380.22	NCT02537574 and 380
Panic Disorder (1-month treatment)		
Freespira	USD 850–1000	55
Paroxetine 20 mg	USD 76.76	NCT00000368 and 379
ADHD (1-month treatment)		
EndeavorRx	USD 621.69	165; 223
Amphetamine-Dextroamphetamine 20 mg	USD 62.41	NCT00507065 and 329
Methylphenidate 20 mg	USD 50.35	NCT01259492 and 725
PTSD (Continuous treatment)		
Nightware	USD 7000 (Apple Watch® included)	63
Prazosin 1 mg	USD 46.28 for 30 capsules	NCT00532493 and 304
Obstructive Sleep Apnea (diagnosis and continuous monitoring)		
Sunrise Sleep Disorder Diagnostic Aid [37]	USD 399	848 enrolled; still in active state
Positive airway Pressure (PAP) Therapy [38]	CPAP machine rental cost USD 649–USD 989	NCT00051363 and 1105
Chronic Insomnia (9-week treatment)		
Somryst	USD 2071.34	N/A
Ramelteon 8 mg	USD 939.26	NCT00237497 and 275
Daridorexant 50 mg	USD 1404.18	NCT03545191 and 930

5. Patient Access to PDTs

The process for a patient to access a PDT involves multiple stages. Initially, a patient consults an HCP to evaluate their mental health condition and determine their suitability for the PDT [39]. The patient will receive a comprehensive education from the HCP regarding the proper use, benefits, and potential risks associated with the PDT [39]. If deemed appropriate, the HCP will then issue a prescription specifying the PDT's details, typically directly on the product website [39]. Afterwards, the health insurance provider may initiate a prior authorization claim for the prescription [39]. The patient will then acquire the device and/or software with an activation code from a pharmacy, medical supplier, or directly from the manufacturer [39]. Upon obtaining/downloading the PDT, the patient proceeds to set up and activate it according to the instructions [39]. Throughout the treatment, the software application collects data at intervals and generates insights for HCPs to review remotely [39]. Follow-up appointments may be scheduled based on the data collected to assess the treatment's effectiveness [39]. Adjustments or prescription renewals may be made based on the patient's response [39]. The overarching goal of the process is to seamlessly integrate PDT into the patient's healthcare plan, fostering a strong connection between HCP and patient while improving health outcomes [39].

6. Real-World Situation

6.1. Patient Perceptions

To understand the patient feedback on the mobile application-based PDTs' usage, we went through the user reviews in the Apple App Store.

reSET®: Rated 3.3/5.0 (28 users), with only five users giving the feedback [40]. All the reviews stated that the update made to the application has made the usage worse and unsatisfactory [40]. These reviews mentioned that while the previous version of the application had been instrumental in helping their sobriety and stability, they found themselves unable to utilize the updated version in the same effective manner [40].

reSET-O®: Rated 3.2/5.0 (77 users) [41]. The usage showed a slight improvement in user engagement compared to reSET® [41]. However, it still received lower ratings overall [41]. There were mixed reviews about the application interface, its level of engagement, and the effectiveness of its reward-based system [41]. A recurring theme in feedback was dissatisfaction with the rewards program and interface functionality due to the software updates [41].

EndeavorRx®: Rated 3.9/5.0 (790 users) [42]. Even though the app received more 5.0 ratings, the common reasons for user dissatisfaction included disinterest in repetitive tasks, frustration with device movement requirements, and disengaging content [42]. Although a few positive reviews highlighted the intriguing software functions and their efficacy in improving conditions, it is notable that the number of positive reviews was quite limited [42]. However, the company has developed a separate mobile application called EndeavorRx Insight® (Companion app) for parents/guardians, where they can monitor their children through the platform, which reflects positive ratings and reviews (rated 4.4/5.0, 136 users) [43].

Somryst®: A few articles discussed and compared the existing chronic insomnia treatment with Somryst®, highlighting the reduced costs, coverage options, and product availability, but did not provide the patient feedback and prescription fill rate [44,45].

NightWare®: One user shared his initial impressions and concerns regarding NightWare®, highlighting issues such as the 30 min delay in intervention, lack of documentation, and challenges with the Apple Watch's performance and technical support [46]. Despite ongoing struggles with nightmares and medication adjustments, he encouraged others to try NightWare® while expressing optimism for potential product improvements [46].

6.2. HCP Involvement

The engagement of HCPs plays a vital role to drive the adoption of PDT and potentially improve health outcomes. Initially, HCPs can contribute by streamlining education, support, engagement, and empowerment processes. Through ongoing virtual interactions with patients, HCPs can evaluate the clinical efficacy of PDTs [47]. Secondly, HCPs can offer insights to software developers to better integrate PDT use into their usual workflow within the EHR systems [47]. The integration will achieve security, reliability, and interoperability across entities for the benefit of the patient. Thirdly, HCPs are instrumental in upholding stringent regulatory compliance concerning personal health information data, preserving data privacy and security [47]. Lastly, aligning PDTs with value-based care requires the collaboration of HCPs, who can incorporate these novel technologies into a value-based care framework, thereby optimizing patient care.

7. Discussion

Current challenges in the use of PDT include payer dilemmas, limited accessibility to PDT technology, and concerns over patient data privacy. Additionally, despite the comprehensive nature of the review, several limitations should be acknowledged.

7.1. Payer Dilemma

In the U.S., the CMS has issued a new code under the HCPCS regarding the use of PDTs for various public and private insurers [48]. In 2022, the American Medical Association

Relative Value Scale Update Committee proposed that CMS assign a contractor-priced status (a reimbursement rate negotiated with the contractor/payer) for a new HCPCS code describing digital therapeutics-related care under the Medicare Physician Fee Schedule [49]. As of 2023, only the Massachusetts Medicaid Agency, MassHealth, and Florida's Agency for Healthcare Administration provide coverage under Medicaid for PDTs [50]. However, the bankruptcy of Pear Therapeutics in 2023 has led the Oklahoma State Medicaid program to take a cautious approach to digital therapeutics due to concerns about their stability and reliability [51].

Contrarily, there is a growing trend of private insurers extending coverage for PDTs via pathways of value-based payment models, flat fee reimbursement, subscription fees, bundled payments, or direct contracts among the plan, employers, and prescribers [52]. However, a dilemma still exists especially among private insurers. While PDTs promise to improve patient outcomes and mitigate healthcare costs in the long run, they often entail significant initial expenses. Payers may be hesitant to cover these devices due to concerns about the upfront financial investment, uncertainty about the devices' real-world effectiveness, and the absence of well-defined reimbursement mechanisms.

PDTs usually serve as extensions of direct patient care, with a focus on minimizing in-person interactions between HCPs and patients, generating the collection of off-site data for monitoring mental health conditions, and offering real-time data to HCPs. Ultimately, PDTs will enhance behavioral health outcomes for patients [50]. However, payers may face the challenge of determining the value proposition of PDTs. Unlike conventional medications, these devices may not align seamlessly with existing reimbursement models, posing difficulties for payers in assessing their cost-effectiveness and allocating resources appropriately.

Moreover, robust evidence demonstrating the real-world impact and cost-effectiveness of PDTs may be needed, which requires dedicated timeframes and continuous surveillance. The available clinical trials failed to perform "dose"-finding studies to identify optimal usage, recruit diverse participants, reflect significant improvement upon the current standard of care, or explore long-term adverse events [53]. Consequently, payers may be cautious about covering these devices until there is a breakthrough PDTs in which there are sufficient data to support clinical effectiveness.

Therefore, the dilemma for payers revolves around balancing the potential advantages of PDTs in improving patient outcomes and reducing long-term healthcare costs with the immediate financial considerations and the need for robust evidence to justify coverage. Manufacturers are implementing marketing strategies to drive sales of PDTs due to the lack of insurance coverage. For example, Akili, Inc., the manufacturer of EndeavorRx® has introduced EndeavorOTC®, a non-prescription alternative for adults with ADHD, utilizing the same technology [18,54]. EndeavorOTC contains mostly identical elements to EndeavorRx® but at a lower cost of USD 24.99 monthly or USD 124.99 annually [55]. While EndeavorRx® prescription targets attention function improvement in children aged 8 to 17 with ADHD, EndeavorOTC® is designed for adults aged 18 years and older. Findings from the STARS-ADHD-Adults trial support EndeavorRx®'s effectiveness in adults with primarily inattentive or combined-type ADHD [56]. Freespira® is also switching from prescription to OTC status [57]. The switch offers manufacturers an alternative way of continuous profit, particularly following patent expiration. Also, it can happen only if the manufacturers satisfy the regulatory expectations, such as that the device should be safe and effective for self-use based on clear labeling [58]. Switching a prescription device to OTC might require a new premarket submission to the FDA because directions for safe use by patients differ from those of HCPs. This switch from prescription to OTC might benefit the manufacturer in one way but on the other end. Considering the payers' perspective,

their willingness to pay for it might not be increased. This is mainly due to PDTs becoming one of the alternative options rather than the primary choice of treatment. Until PDT access is expanded and it demonstrates significant benefits for the disease state, payers' willingness to purchase PDTs is unlikely to change substantially.

7.2. Enhancing Accessibility and Integration for PDTs:

The adoption of PDTs by patients and clinicians encounters challenges related to technology accessibility. Older and lower-income adults may lack access to devices compatible with a PDT operating system [59]. Moreover, patients may experience confusion with the rapid implementation of software updates and content enhancements desired by manufacturers [59]. Alternatively, providers confront challenges associated with complex e-prescribing logistics and unfamiliar patient scenarios due to limited training in real-world situations [59].

7.3. Addressing Patient Concerns and Privacy

Patient privacy concerns are addressed by HIPAA, ensuring strict protection of EHR. However, specific provisions regarding PDTs are not explicitly outlined [60]. HIPPA Protects the health information of individuals who receive substance use disorder treatment in federally funded programs subjected to additional privacy protections under 42 USC § 290dd-2 and 42 CFR § 2.11 (Part 2) [61]. It provides extra protection related to psychotherapy records compared to normal medical records, most of the notes cannot include any information related to medication prescribed, treatment plan, results, summary of diagnosis, etc. (45 CFR 164.501), and privacy protection requires a covered entity to obtain a patients authorization prior to the disclosure of these notes for any purpose, including any other HCP other than the originator (45 CFR 164.508 (a)(2)) [61]. Some of the policies in place to protect EHR information are inclusion of access control, encrypting the data, and audit trails [62].

Concerns arise regarding patient data protection in situations where manufacturers of PDTs face financial challenges, such as bankruptcy [63]. One such recent example is Pear Therapeutics, which recently sold its product lineup for USD 6.05 million due to financial difficulties, highlighting uncertainties regarding ongoing patient coverage [64].

Ongoing challenges hinder the broad adoption and coverage of PDTs. There is a lack of comprehensive open-source information regarding approved PDT usage, patient perspectives, feedback, and prescription fill rate. Access to such information could benefit stakeholders in better understanding PDT products and addressing existing gaps in knowledge. The evolving regulatory landscape is coupled with rapid advancements in PDT manufacturing, requiring stakeholders, including patients, HCPs, payers, and regulatory bodies, to adapt and integrate these devices effectively into healthcare practices.

7.4. Study Limitations

This review has several key limitations. First, there is limited open-source information about PDT usage, patient feedback, and prescription rates, which hinders comprehensive understanding of these products. Second, available clinical trials have methodological constraints, including small sample sizes, lack of diverse participants, insufficient long-term data, and limited studies on optimal usage patterns. Third, the rapidly evolving regulatory landscape and technological advances make it challenging to draw definitive conclusions about long-term outcomes. Finally, financial instability of PDT companies, as evidenced by recent bankruptcies, raises concerns about long-term data accessibility and continued patient support.

8. Future Directions

Currently, 9 out of 20 approved PDTs address chronic mental, behavioral, and cognitive disorders, including opioid use disorder, MDD, insomnia, ADHD, etc. [65]. Future PDTs aim to monitor vital signs and address a broader range of therapeutic areas such as blood disorders, circulatory issues, respiratory disorders, and nervous system disorders [66]. The expanding landscape indicates a growing scope for digital therapeutics in diverse healthcare applications. Clinical trial data are typically included in the 510k and de novo summaries as well as other sources, but often remain un-updated on the clinicaltrials.gov website. Investment in PDTs remains limited, which could hold back progress. Without a groundbreaking device that grabs widespread investor interest and sets a clear path for PDT companies, the future might not seem as promising. Some companies are contemplating a shift to OTC products because they believe these can bring in more profits. This transition reflects a strategic move to take advantage of market opportunities and potentially expand revenue sources. However, it also highlights the challenges faced by PDT companies in attracting sufficient investment and establishing a sustainable business model.

The FDA seeks to improve medical device evaluation by collecting post-market, real-world data through the National Evaluation System for Health Technology system, supporting new technology applications, and incorporating real-world evidence in regulatory decision-making guidelines [67].

9. Conclusions

PDTs represent a significant advancement in the realm of digital healthcare, offering innovative solutions for the management and treatment of various mental health disorders. Regulatory adaptation and continuous research are essential to ensure safety and efficacy. Despite challenges such as upfront costs, PDTs offer an advanced future and hold promise for a broader healthcare transformation. Continued efforts are needed to harness their full potential and improve patient outcomes across various conditions. Limited investment in PDTs may slow the progress, prompting some companies to consider shifting to OTC status to increase profit opportunities, despite challenges in attracting investors and establishing sustainability. However, collaborative efforts among stakeholders, including HCPs, payers, manufacturers, patients, and regulatory agencies, are essential for achieving meaningful integration of PDTs into treatment plans, demonstrating their effectiveness in real-world settings. In summary, PDTs have the potential to revolutionize the treatment landscape and improve patient outcomes across diverse therapeutic areas. However, further research is needed to address the challenges and embrace the emerging trend in digital therapeutics.

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List of Abbreviations

Abbreviation	Definition
PDT	Prescription Digital Therapeutics
HCP	Healthcare Provider
SaMD	Software as a Medical Device
MDD	Major Depressive Disorder
ADHD	Attention-Deficit/Hyperactivity Disorder

PTSD	Post-Traumatic Stress Disorder
IMDRF	International Medical Device Regulators Forum
FDA	Food and Drug Administration
CDRH	Center for Devices and Radiological Health
SE	Substantial Equivalence
IDE	Investigational Device Exemption
NDA	New Drug Application
AI	Artificial Intelligence
ML	Machine Learning
TEAE	Treatment-Emergent Adverse Event
CBT	Cognitive Behavioral Therapy
U.S.	United States
MAUDE	Manufacturer and User Facility Device Experience
AWP	Average Wholesale Price
CMS	Centers for Medicare and Medicaid
HCPCS	Healthcare Common Procedural Coding System
OTC	Over-the-Counter
EHR	Electronic Health Record
HIPAA	Health Insurance Portability and Accountability Act
OUD	Opioid Use Disorder
CBT-I	Cognitive Behavioral Therapy for Insomnia
BLA	Biologics License Application

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Review

Intravenously Administered Nonsteroidal Anti-Inflammatory Drugs in Clinical Practice: A Narrative Review

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Abstract: Intravenously administered nonsteroidal anti-inflammatory drugs (NSAIDs) constitute a crucial component of multimodal analgesia strategies in surgical settings. This narrative review aims to provide an up-to-date evaluation of the efficacy, safety, and clinical use of intravenous (IV) NSAIDs for perioperative pain management in adults and children. The NSAIDs and selective COX-2 inhibitors (coxibs) approved in Europe for the short-term symptomatic treatment of acute, moderate perioperative pain via IV infusion in adults and/or children have been influenced by US and global guidelines and practice: the drugs primarily reviewed here are ibuprofen, ketorolac, ketoprofen, naproxen, paracetamol, and acetylsalicylic acid. Furthermore, intravenous ibuprofen is authorized for the short-term symptomatic treatment of fever. In contrast to intravenous ketoprofen, intravenous ibuprofen is authorized for administration to children over 6 years of age or weighing more than 20 kg. Overall, IV ibuprofen had a more favorable profile with regard to peri- and postoperative opioid sparing and pain relief. Oral ibuprofen and IV ibuprofen have similar levels of efficacy, although IV ibuprofen has a shorter onset of action and is required in patients who are unable to take oral medications. The frequency of significant adverse events appears to be similar for ibuprofen and paracetamol. Systematic reviews and meta-analyses report that intravenous NSAIDs reduce postoperative opioid consumption by approximately 20–60%, improving pain management with fewer opioid-related side effects. In indications in infants, the choice of medication is limited, and the oral route is not always feasible; IV formulations of ibuprofen are preferred in this setting. Topics for further research should include head-to-head trials of IV NSAIDs.

Keywords: NSAID; diclofenac; ibuprofen; ketoprofen; paracetamol; acetaminophen; coxib; pain; surgery

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1. Introduction

Ensuring the sufficient relief of pain (whether acute or chronic) remains a major clinical issue [1]. Specifically, the inadequate relief of acute pain after surgery not only degrades the patient's quality of life but may also slow wound healing, increase the risk of adverse events, accentuate the development of chronic pain, and worsen treatment observance [2,3].

Opioids are commonly utilized for acute pain relief in perioperative pain management [4] but their high level of effectiveness is accompanied by significant concerns—including the notable issues of misuse and addiction observed, particularly in the USA [5]. In pharmacological terms, centrally-acting opioids do not counter local, pain-inducing inflammation, do not have antipyretic activity, and may trigger severe adverse drug reactions, such as confusion, nausea, constipation, pruritus, urinary retention, ileus, over-sedation, and respiratory depression [6,7].

In order to prevent or reduce these drawbacks, opioids may be supplemented or replaced with other analgesic medications and therapies. In 1986, the World Health Organization introduced a framework to help non-specialist physicians manage cancer pain; this "analgesic ladder" emphasized the use of nonsteroidal anti-inflammatory drugs (NSAIDs) for mild pain, with the option to escalate to "weak" opioids for moderate pain and "strong" opioids for severe pain [8–10]. The concept of a bidirectional strategy (emphasizing that the intensity of pain management can also be decreased, when appropriate) was subsequently introduced [10–12]. However, this intensity-based WHO analgesic ladder has several shortcomings: it is overly simplistic, it does not take good account of neuropathic pain or the acute vs. chronic nature of pain, and it tends to suggest that a given step on the ladder requires a single treatment strategy. Furthermore, the concepts of "adjuvant" analgesics and "weak" vs. "strong" opioids have become outdated. Hence, the model has since evolved to reflect progress in understanding and managing pain. In 2010, Lussier and Beaulieu published a taxonomy of analgesics based on the physiological mechanism of action: antinociceptives (including paracetamol, NSAIDS, opioids and cannabinoids), antihyperalgesic drugs (including NMDA antagonists, anti-epileptics, and nefopam), compounds that modulate the descending pain pathway (including tricyclic antidepressants, and serotonin and noradrenalin reuptake inhibitors), compounds that modulate peripheral transmission and sensitization (including local anesthetics, carbamazepines, topiramate, and capsaicin), and mixed compounds [13]. Lussier and Beaulieu's taxonomy encourages the physician to diagnose the source of pain precisely, and fits well with the multimodal analgesia concept that arose progressively in the late 1980s and early 1990s; i.e., the use of several treatment modalities that target different receptors along the pain pathway [14].

Nonsteroidal anti-inflammatory drugs (NSAIDs) have a significant role in perioperative analgesia as antinociceptive analgesics with anti-inflammatory properties. Indeed, NSAIDs have become the cornerstone of a multimodal strategy designed to decrease postoperative opioid usage, pain, and inflammation, while also reducing the risk of opioid-related adverse effects [15]. Conventional NSAIDs act by competitively inhibiting the central and/or peripheral cyclooxygenases (COXs) responsible for converting arachidonic acid into pro- and/or anti-inflammatory prostaglandins, prostacyclin, and thromboxanes; this action is thought to be responsible for the efficacy of NSAIDs (mainly when the inflammation-induced COX-2 isoform is inhibited) but also adverse drug reactions (mainly when the constitutively expressed COX-1 isoform is inhibited) [16]. Oral NSAID use has been linked to gastrointestinal track complications (such as nausea, vomiting, pain, flatulence, diarrhea, and constipation) in a duration- and dose-dependent manner, although the risk varies markedly from one drug to another and one patient population to another [17–19]. A multicenter case-control study in children showed that even short courses of oral treatment with an NSAID or acetylsalicylic acid were associated with an elevated adjusted odds ratio [95%CI] (vs. controls) of these complications: 3.7 [2.3–5.9] for ibuprofen, 2.6 [1.2–5.6] for ketoprofen, and 2.5 [0.9–7] for acetylsalicylic acid [20]. In a network analysis of studies of NSAID-treated patients with arthritis, naproxen was associated with a higher incidence of renal events and edema, whereas ibuprofen was associated with a higher incidence of cardiovascular events and hypertension [21]. Ketoprofen and ibuprofen inhibit COX-1 more than COX-2 but are usually considered to be

non-selective COX inhibitors [22]. However, Henry et al.'s systematic review linked ketoprofen's higher selectivity for COX-1 to greater gastrointestinal toxicity, whereas ibuprofen had the lowest risk among the studied NSAIDs [23].

The beneficial effects of COX-2 inhibition prompted the development of selective COX-2 inhibitors (coxibs) with a lower potential for serious gastrointestinal adverse effects than conventional NSAIDs [24–26]. However, it has been reported that even selective COX-2 inhibitors have enough COX-1-inhibiting activity to affect the gastric synthesis of prostaglandin E2 associated with adverse events [27]. Furthermore, the observation of cardiovascular adverse effects during long-term use led to the market withdrawal of rofecoxib and valdecoxib [28].

The core principle of multimodal postoperative analgesia including paracetamol and/or NSAIDs (in the absence of contraindications, such as patients undergoing coronary artery bypass graft surgery) has been endorsed as a strong recommendation, with high-quality evidence by the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council [29]. The guideline suggested that IV and oral administrations were similar for pain relief, but the onset of action might be faster with IV administration [29]. According to the guidelines published by the European Society for Paediatric Anaesthesiology (EPSA), the consistent intra- and postoperative use of non-opioid drugs (including NSAIDs) has an opioid-sparing effect and is a cornerstone of intraoperative pain management [30,31]. The EPSA recommends (if available) an intravenous paracetamol/NSAID after the induction of anesthesia and throughout the postoperative period for several types of surgery, including limb fracture repair, Nissen fundoplication (open and laparoscopic), thoracoscopy/thoracotomy, appendicectomy, hypospadias repair, and the correction of congenital hip dislocation [30,31]. The EPSA's dose-level suggestions are 0.5 to 1 mg per kg (up to 30 mg) for a single intraoperative dose, and 0.15 to 0.2 mg per kg (up to 10 mg) every 6 h (for no more than 48 h) for ketorolac, 1 mg per kg every 8 h for ketoprofen, and 10 mg per kg every 8 h for ibuprofen [31].

In terms of pharmacokinetics (PK; see below for more details), NSAIDs are rapidly absorbed and bind strongly to plasma proteins (mainly albumin) [32–35]. Oral, rectal, and IV doses of ibuprofen tend to give similar area under the curve (AUC) values. Unsurprisingly, the peak plasma concentration (C_{max}) value is higher for IV administration than for oral administration. For ibuprofen, the physiologically inactive R isomer binds even more strongly than the active S isomer. Following IV and oral administration, the respective elimination half-lives are similar. Ibuprofen is mostly oxidized by cytochromes P450 2C9 and 2C8 in the liver, with subsequent renal excretion of the metabolites [36].

The primary objective of the present narrative review is to provide an updated evaluation of the efficacy, safety, and clinical use of intravenous NSAIDs for perioperative pain management in adults and children, in order to highlight certain aspects of IV NSAID use. The secondary objective is to identify potential future trends in the use of IV NSAIDs.

We searched the MEDLINE database (via the PubMed web portal) for publications by using logical combinations of the following keywords in English: intravenous, IV, infus*, diclofenac, ibuprofen, ketoprofen, paracetamol, acetaminophen, aspirin, NSAID, nonsteroidal anti-inflammatory drug, pain, relief, surgery, non-opioid, analg*, preoperative, pain, inflamm*, perioperative, pre-emptive, postoperative, fever, combination, fixed-dose, multimodal, children, child, infant, adult, coxib, COX-1, COX-2, and cyclo-oxygenase. We focused on publications in the 10 years prior to 1 May 2024. The titles and abstracts listed in the search report were screened by one of the investigators (A M.-S.). Relevant publications in the investigators' personal collections (including French-language publications) were also considered. Case reports, conference abstracts, oral abstracts, studies describing

the results of solely in vitro studies, and publications for which a full-text version was unavailable, were excluded. The full-text versions of publications of interest were assessed by all the investigators.

2. Indications

2.1. Indications and Formulations for IV NSAIDs in Adults

The list of NSAIDs and coxibs approved in Europe for the short-term symptomatic treatment of moderate, acute pain via intravenous infusion in adults and/or children has been influenced by US and global guidelines and practice. For example, the European summaries of the product characteristics (SmPCs) for IV NSAIDs echo the American Heart Association's 2007 scientific statement and recommend the lowest effective dose for the shortest duration needed to control symptoms [37]. The French National Agency for the Safety of Medicines and Health Products (ANSM—Agence Nationale de Sécurité du Médicament et des produits de santé) has approved ibuprofen, ketoprofen, and parecoxib solutions for infusion for the short-term treatment of postoperative pain. The French SmPCs state that intravenous administration is only justified when other routes of administration are not possible. The IV ibuprofen product for use in adults is typically supplied as a 100 mL solution containing 400 mg ibuprofen (i.e., 4 mg/mL), with infusion every 6 to 8 h as required and no more than three administrations over a given 24-h period. The recommendation infusion time is 30 min. Combination with other NSAIDs or aspirin should be avoided, and combination with the platelet aggregation inhibitor ticlopidine is prohibited. In contrast to the prescribing guidelines in some countries, treatment with lithium is not an absolute contraindication for IV NSAIDs; however, close monitoring of the blood lithium concentration is recommended. In some countries (e.g., France), the same IV ibuprofen product is also authorized in indications of fever [38–40].

Ketoprofen for IV use in individuals aged 15 or over is supplied as a powder (100 mg for reconstitution in 100 to 150 mL isotonic glucose solution or saline) or as a bag containing 100 mL of a 1 mg/mL solution. The recommended infusion time is 20 min, and the 24-h limit is 100 to 300 mg (i.e., one to three doses). Again, combination with coxibs or other NSAIDs should be avoided, and close monitoring of patients treated with lithium is recommended.

Parecoxib for IV use in adults is supplied as a powder (containing 40 mg of active substance) for reconstitution in 2 mL of 0.9% sodium chloride (solution). The initial dose of 40 mg can be followed every 6 to 12 h by a dose of 20 mg or 40 mg. The 24-h limit is 80 mg. Opioid analgesics can be used concurrently with parecoxib.

2.2. Indications and Formulations for IV NSAIDs in Children

Children often have variable renal function, protein binding, and metabolic pathways, which can alter NSAID pharmacokinetics. Current labeling restricts IV formulations of some NSAIDs to older children, leaving limited approved options for infants and toddlers. Clinicians must therefore apply weight-based dosing and monitor closely for adverse events. Ongoing research is needed to refine age-specific guidelines and extend licensing to broader pediatric populations.

In contrast to the USA (where the indications for IV ibuprofen were extended to pediatric patients as young as 6 months in 2015), the lower limit for the administration of IV ibuprofen in France is 6 years of age or a bodyweight of 20 kg. In that case, the drug is supplied as a 50 mL solution containing 200 mg of ibuprofen (i.e., 4 mg/mL, the concentration used in adults). The recommended dose is 20 to 30 mg/kg of body weight administered in three to four doses (5–10 mg/kg), with a 24-h maximum cumulative amount of 600, 800, or 1200 mg, depending on bodyweight. In contrast to IV ibuprofen,

ketoprofen solution for infusion has not been approved for administration to patients under the age of 15. Nevertheless, a report from the French health authorities in 2022 acknowledged that off-label use of ketoprofen solution for infusion in children between 1 and 15 years of age (i.e., including those below 6 years of age, the current age cut-off) was widespread [39]. This off-label use by practitioners might be encouraged by clinical trial data showing that the pharmacokinetic and short-term safety profiles of IV ibuprofen in very young patients (1–6 months of age) are similar to those in older children [41]. Lastly, diclofenac solutions for infusion (25 mg/mL) are authorized for short-term use in patients aged 16 and over in the following indications: acute rheumatic inflammation, acute back pain, nerve root pain, and renal colic; hence, diclofenac for infusion is not indicated in general surgical settings.

3. Studies of the Efficacy, Safety, and Pharmacokinetics of IV NSAIDs for the Relief of Acute Perioperative Pain

3.1. Studies in Adults

The wide perioperative use of intravenously administered NSAIDs has prompted extensive debate and research on whether one of these drugs is safer and/or more effective than the others [42]. The relative lack of randomized, head-to-head comparative trials of IV NSAIDs makes it hard to answer this question; most trials have been placebo-controlled, rather than active-comparator-controlled (Table 1) [43–68]. In one head-to-head trial, Kostamovaara et al. compared treatment with IV ketorolac, IV diclofenac, or IV ketoprofen for pain relief after total hip replacement surgery in 85 patients; there were no significant differences between these three NSAIDS with regard to pain scores or opioid consumption [69].

Table 1. Clinical studies of perioperative IV infusion of ibuprofen and comparators in surgery patients.

Type of Surgery (in Alphabetical Order)	Reference	Study Design	Patient Age	Number of Patients	Ibuprofen Dosing Regimen	Other Drugs	Control or Comparator	Main Results	Adverse Events
Bunionectomy	Daniels et al. 2019 [45]	DBPC RCT, 3 arms, 2 centers	18 to 65	276	Postop: IV FDC (ibuprofen 300 mg + paracetamol 1000 mg) every 6 h for 48 h	Rescue medication: primary, oral oxycodone 5–10 mg; secondary, IV morphine sulfate 2–4 mg)	Ibuprofen 300 mg or paracetamol 1000 mg, or placebo	The mean (standard error) SPID48 score was higher for the FDC (23.4 (2.5) mm) than for ibuprofen alone (9.5 (2.5) mm) or paracetamol (10.4 (2.5) mm); all $p < 0.001$ vs. placebo (−1.3 (3.1)). The proportion of patients using opioid usage was lower for the FDC (75%, vs. 92% for ibuprofen, 93% for paracetamol, and 96% for placebo).	The safety profile of the FDC was similar to that of IV ibuprofen or paracetamol alone
Cervical cancer surgery	Liu et al. 2018 [56]	Prospective, DBPC RCT, 3 arms, single center	18 to 70	60	IV ibuprofen 400 mg, or ibuprofen 800 mg 30 min before end of surgery then every 6 h for a total of 8 doses in the first 48 h	Morphine PCA, followed by tramadol	Placebo group: saline?	IV ibuprofen 800 mg was associated with a significant reduction in the morphine requirement during the first 24 h (17.6 ± 3.2 mg vs. 19.7 ± 3.0 mg with the placebo; $p = 0.04$)	Safety assessments and adverse effects were similar in the three groups

Table 1. *Cont.*

Type of Surgery (in Alphabetical Order)	Reference	Study Design	Patient Age	Number of Patients	Ibuprofen Dosing Regimen	Other Drugs	Control or Comparator	Main Results	Adverse Events
Cleft palate repair	Peng et al. 2021 [59]	Prospective, DBPC RCT, 2 arms, single center	9 to 24 months	40	Pre-emptive IV administration ibuprofen 10 mg/kg at induction	Rescue with titrating IV fentanyl 0.5 µg/kg	Saline	Significant opioid-sparing effect in early postoperative period in the ibuprofen group (mean ± SD total fentanyl dose = 3.20 ± 4.49 µg, vs. 9.40 ± 4.49 µg in the placebo group; $p < 0.001$)	No obvious adverse events reported
Inguinal and umbilical hernia repairs	Sparber et al. 2017 [63]	Prospective, DBPC RCT, single center, 2 arms	18 and older	48	800 mg of IV ibuprofen or placebo preoperatively (30 min before)	IV hydromorphone, or oral oxycodone/paracetamol, paracetamol only, or ibuprofen, or in combination	Placebo: normal saline	Pre-op IV ibuprofen did not significantly reduce postop pain	No major serious adverse events were reported
Knee arthroscopic surgery	Uribe et al. 2018 [65]	DB pilot RCT, single center, 2 arms,	18 and older	51	Ibuprofen IV, two 800 mg doses (the first 2 h before surgery)	IV hydromorphone 0.5 mg as needed	IV ketorolac: a single 30 mg dose after surgery	The use of pre-emptive IV ibuprofen 800 mg could be considered to reduce postop pain and opioid consumption. The mean ± SD time to first rescue medication was 77.62 ± 33.03 min in the ibuprofen group and 55.78 ± 35.37 in the ketorolac group ($p = 0.0456$).	No significant intergroup differences in patient satisfaction and documented AEs during the first 24 h
Knee or hip arthroplasty	Gupta et al. 2016 [50]	RCT, single center, 2 arms	26 to 70	78	Ibuprofen IV + paracetamol IV up to 5 days (peri- and postoperative)	Morphine and/or hydromorphone	Ibuprofen alone	Patients on ibuprofen + paracetamol had lower VAS scores vs. ibuprofen alone on Day 3, only 6.7 vs. 4.9, respectively ($p < 0.002$), together with lower median (range) opioid requirements (20 (5–25) vs. 25 (10–35), respectively; ($p < 0.001$))	Patients treated with ibuprofen + paracetamol experienced fewer opioid-related adverse events than those treated with ibuprofen ($p < 0.001$)
Laparoscopic cholecystectomy	Mohammadian Erdi et al. 2022 [57]	DBPC RCT, single center, 3 arms	20 to 60	90	800 mg IV ibuprofen or 1 g IV paracetamol 3 times (during the operation and 8 and 16 h after)	Fentanyl (15 µg/mL) as PCA, meperidine	Placebo: normal saline	The mean abdominal pain scores were not significantly different in the ibuprofen (3.02) and paracetamol (2.89) groups ($p = 0.719$), but both were significantly lower than in the control group (5.10; $p < 0.001$)	Shoulder pain, nausea, and vomiting were not significantly different in the ibuprofen and paracetamol groups
Laparoscopic cholecystectomy	Lee et al. 2022 [54]	Retrospective study, single center, 2 arms	18 and over	163	Pre-op IV ibuprofen (400 mg)	Tramadol 50 mg	IV ketorolac (30 mg)	Postop pain score measured in the recovery room was significantly higher in the ibuprofen group than in the ketorolac group (mean value: 5.09 vs. 4.61; $p = 0.027$)	No bleeding event of the operative site or gastrointestinal mucosa in either group

Table 1. *Cont.*

Type of Surgery (in Alphabetical Order)	Reference	Study Design	Patient Age	Number of Patients	Ibuprofen Dosing Regimen	Other Drugs	Control or Comparator	Main Results	Adverse Events
Laparoscopic cholecystectomy	Ekinci et al. 2020 [48]	DBPC RCT, single center, 3 arms	18 to 70	90	Postop: 800 mg of IV ibuprofen, or 1000 mg of IV paracetamol	Rescue opioid	Placebo: saline	Compared with postop paracetamol, IV ibuprofen resulted in a lower mean ± SD pain score (at 24 h: 1.16 ± 0.79 vs. 0.26 ± 0.44, respectively; $p < 0.001$) and reduced opioid use (342.33 ± 65.59 vs. 215.66 ± 97.26, respectively) in the first 24 h	The incidence of nausea was significantly lower ($p < 0.05$) in the ibuprofen group than in the paracetamol group
Laparoscopic cholecystectomy	Ahiskalioglu et al. 2017 [43]	Prospective, DBPC RCT, single center, 2 arms	18 to 65	60	400 mg IV ibuprofen in 100 mL saline 30 min before surgery	Postop: 1000 mg paracetamol/6 h + patient-controlled IV fentanyl	Placebo: 100 mL saline solution	24-h opioid consumption was significantly lower in the ibuprofen group (303.33 ± 132.08 mcq vs. 553.00 ± 257.04 for the placebo; $p < 0.001$). Rescue medication (meperidine) use was lower in the ibuprofen group than in the placebo group (125 mg vs. 350 mg, respectively; $p = 0.012$).	The incidences of nausea and vomiting were lower in the ibuprofen group
Laparoscopic cholecystectomy	Le et al. 2016 [53]	Prospective, DBPC RCT, 3 centers, 2 arms	18 or older	55	IV ibuprofen 800 mg preoperatively	Rescue opioids	Placebo: saline	Pre-op IV ibuprofen was associated with lower mean ± SD levels of cortisol (173.6 ± 29.5 pg/mL vs. 289.5 ± 25.9 for placebo, $p = 0.001$), lower mean ± SD intraoperative norepinephrine levels (0.52 ± 0.09 pg/mL, vs. 1.06 ± 0.12 pg/mL for placebo, $p = 0.004$), and no decline in the QoR40 recovery score	Three cases of postop nausea in the placebo group
Laparoscopic hernia repair	Lee et al. 2021 [55]	Prospective, DB RCT, single center, 3 arms	6 months to 6 years	159	10 mg/kg IV ibuprofen or 10 mg/kg IV ibuprofen + 30 mg/kg IV propacetamol during anesthesia	1.0 µg/kg fentanyl was administered as a rescue analgesic	30 mg/kg IV propacetamol	Ibuprofen + propacetamol immediately following surgery in children was associated with a lower proportion of patients using fentanyl (12.8%, vs. 28.6% for ibuprofen alone and 66.7% for propacetamol alone; $p < 0.001$)	There were no safety differences between the groups and no perioperative adverse events
Orthognathic surgery	Tomic et al. 2022 [64]	Prospective, DB RCT, single center, 2 arms	18 to 61	109	Postoperative IV 600 mg ibuprofen	Metamizole 500 mg. Rescue pain medication: paracetamol 1000 mg and piritramide 7.5 mg.	IV 75 mg diclofenac + 30 mg orphenadrine given twice daily	Ibuprofen administration was associated with less pain on the third postop day for patients who underwent bimaxillary osteotomy (1.23, vs. 2.73 for diclofenac + orphenadrine; $p = 0.015$)	No major postoperative complications or AEs due to pain medication

Table 1. *Cont.*

Type of Surgery (in Alphabetical Order)	Reference	Study Design	Patient Age	Number of Patients	Ibuprofen Dosing Regimen	Other Drugs	Control or Comparator	Main Results	Adverse Events
Orthopedic trauma surgery (fracture of the ribs, face, extremities, and/or pelvis)	Weisz et al. 2020 [67]	Prospective, DBPC RCT, single center, 2 arms	18 to 75	99	800 mg IV ibuprofen or placebo administered every 6 h for a total of 8 doses within 48 h of admission	PRN pain medications	Placebo: saline	IV ibuprofen was associated with significantly less opioid consumption compared with placebo (difference in least-square means [95%CI] = 222.9 [241.4–24.2] mg; $p = 0.017$) and greater pain reduction 8 h after start of infusion (difference in least-square means [95%CI] = 1.1 [0.2–2.0]; $p = 0.013$)	Not reported
Orthopedic surgery (knee or hip replacement, reconstruction or arthroplasty)	Singla et al. 2010 [61]	DBPC RCT, 8 centers, 2 arms	18 to 80	185	800 mg IV ibuprofen or placebo every 6 h, first dose administered preoperatively	IV morphine for rescue	Placebo: saline	Patients receiving IV ibuprofen used 30.9% less morphine (mean ± SD: 41.1 (27.3), vs. 59.5 ± 29.9 in the placebo group; $p < 0.001$) and experienced less pain (43.2 ± 3.6, vs. 51.8 ± 3.7 in the placebo group: $p < 0.001$)	Similar treatment-emergent AEs occurred in both groups
Third molar surgery	Demirbas et al. 2019 [46]	Prospective, DBPC RCT, single center, 3 arms	18 to 50	75	IV ibuprofen 60 min before surgery + IV placebo (saline) after surgery, or IV placebo before + IV ibuprofen after surgery	Rescue paracetamol	Placebo: IV saline before and after surgery	Pre-emptive use of IV ibuprofen resulted in less pain (42.6% lower) and less rescue analgesia (640 mg of paracetamol, vs. 1840 mg for placebo; $p < 0.001$) during the first 24 h	There were no postoperative complications and no adverse events in any of the groups
Third molar surgery	Küpeli and Gülnahar 2019 [52]	DBPC RCT, single center, 3 arms	20 to 35	60	Preoperative ibuprofen 800 mg IV + dexketoprofen 50 mg, or pre-op ibuprofen 800 mg IV alone	Postoperative infusion of dexketoprofen + methylprednisolone 40 mg + sultamicillin tosilate	Placebo: saline	No significant difference in postop pain scores between the two treated groups but both were lower than in the placebo group	Not reported
Third molar surgery	Viswanath et al. 2019 [66]	Single center randomized SB study, 2 arms	Median [interquartile range] = 22 [6] in the ibuprofen group	41	Preoperative IV ibuprofen (800 mg)	Postoperative analgesic (narcotic and over-the-counter)	Pre-op IV paracetamol (1000 mg)	The pain level was significantly lower in the ibuprofen group than in the paracetamol group ($p = 0.004$) at 4 h, 24 h ($p = 0.019$), and 48 h ($p = 0.017$). Ibuprofen was associated with less opioid use (2.68 ± 2.26, vs. 7.32± 6.68 in the placebo group; $p = 0.005$).	No adverse effects were reported in either group
Tonsillectomy	Cui et al. 2022 [44]	DBPC RCT, single center, 2 arms	6 months to 12 years	95	15 min before surgery with IV ibuprofen 10 mg/kg	Postop: IV fentanyl (0.5 µg /kg) when needed	Placebo: saline	Rescue fentanyl was 18% lower in the IV ibuprofen group ($p = 0.043$). There was no significant difference in the amount of fentanyl administered postop ($p = 0.127$).	No significant differences in terms of operative blood loss ($p = 0.978$), vomiting, or postop bleeding ($p = 0.474$)

Table 1. *Cont.*

Type of Surgery (in Alphabetical Order)	Reference	Study Design	Patient Age	Number of Patients	Ibuprofen Dosing Regimen	Other Drugs	Control or Comparator	Main Results	Adverse Events
Tonsillectomy	Gao et al. 2022 [49]	DBPC RCT, single center, 2 arms	3 to 9	89	During operation, dose of 10 mg/kg of IV ibuprofen slowly infused over 15 min	Fentanyl 0.5 µg/kg (max dose of 2 µg/kg) administered postop if necessary	Placebo: saline	Ibuprofen decreased the incidence of emergence agitation at 15 min after extubation (8.9%, vs. 34.1% in the control group; $p = 0.004$) and the median [interquartile range] pain score at 15 and 30 min (e.g., 1.0 (0–3.0) for ibuprofen and 3.0 (1.0–6.0) for placebo at 15 min, respectively; $p = 0.007$)	No postoperative hemorrhagic complications
Tonsillectomy	Moss et al. 2014 [58]	DBPC RCT, multicenter, 2 arms	6 to 17	161	Preoperative IV ibuprofen dose of 10 mg/kg	IV fentanyl (0.5 µg/kg) as needed	Placebo: saline	The proportion of patients requiring fentanyl was significantly lower in the IV ibuprofen group than in the placebo group (42% vs. 62%, respectively; $p = 0.021$). There was no significant difference in the time to first analgesia request.	No significant differences in the incidence of serious AEs, surgical blood loss ($p = 0.662$), or postop bleeding
Total hip replacement	Gürkan et al. 2019 [51]	Prospective, DBPC RCT, single center, 2 arms	18 to 70	40	800 mg ibuprofen IV every 6 h for 24 h, first dose 30 min before the end of surgery	After surgery tramadol 100 mg IV and paracetamol 1 g IV + morphine PCA	Not reported	In the ibuprofen group, the mean ± SD postop 24 h pain VAS was significantly lower (1 ± 1.05, vs. 2 ± 2.25 for placebo; $p = 0.006$), as was morphine consumption (14.90 ± 9.33 vs. 21.93 ± 11.35 for placebo; $p = 0.026$)	Vomiting: 5 patients in the control group and 3 patients in the ibuprofen group
Transsphenoidal surgery	Shepherd et al. 2018 [60]	DBPC RCT, single center, 2 arms	Adults	62	Postop: scheduled IV ibuprofen, scheduled oral paracetamol	Rescue opioids	Placebo: saline	Mean ± SD opioid use was 58% lower in the ibuprofen group (26.3 ± 28.7 mg, vs. 62.5 ± 63.8 mg in the placebo group; $p < 0.0001$). The pain score was 43% lower in the ibuprofen group (1.7 ± 2.2, vs. 3.0 ± 2.8 in the placebo group; $p < 0.0001$).	There were two AEs, probably related to IV ibuprofen: a burning sensation at the infusion site, and postoperative hyperkalemia
Various types of abdominal or orthopedic surgery	Zhou et al. 2023 [68]	DBPC RCT, multicenter, 3 arms	18 to 75	345	IV ibuprofen 400 mg, or IV ibuprofen 800 mg or placebo (30 min before end of surgery then every 6 h)	IV morphine (0.5 mg/mL) as PCA	Placebo: not reported	Total morphine consumption was significantly lower in the ibuprofen 400 mg group (11.14 ± 7.14 mg; $p = 0.0011$) and the ibuprofen 800 mg group (11.29 ± 6.45 mg; $p = 0.0014$) than in the placebo group (14.51 ± 9.19 mg)	No difference in the incidence of AEs between groups

Table 1. *Cont.*

Type of Surgery (in Alphabetical Order)	Reference	Study Design	Patient Age	Number of Patients	Ibuprofen Dosing Regimen	Other Drugs	Control or Comparator	Main Results	Adverse Events
Various types of urogyneco-logical surgery	Dwarica et al. 2020 [47]	Prospective, RCT, single center, 3 arms	Over 18. Mean (SD) = 55.52 (14.30) in the ibuprofen group	224	IV ibuprofen 800 mg IV every 8 h for 3 doses. IV ketorolac 30 mg IV (15 mg if >65 years of age or <50 kg).	Hydromorphone as PCA, oral paracetamol 650 mg every 6 h	IV ketorolac 30 mg IV (15 mg if >65 years of age or <50 kg) or ibuprofen oral (800 mg)	Levels of pain control and satisfaction were similar in the IV ketorolac and IV ibuprofen groups	Not reported

DB: double-blind; DBPC: double-blind, placebo-controlled; RCT: randomized clinical trial; SB: single-blind; FDC: fixed-dose combination; IV: intravenous; SPID48: sum of the pain-intensity difference over the 48-h period; PCA: patient-controlled analgesia; VAS: visual analog scale; AE: adverse event.

A network meta-analysis extensively reviewed the benefits of NSAIDs vs. other non-opioid analgesics, highlighting their ability to significantly reduce opioid use and reduce pain, especially when combined with drugs such as paracetamol or nefopam. The analysis calls for more direct comparisons and improved reporting on serious adverse events to better assess the balance between efficacy and safety [42].

With regard to safety, two meta-analyses published in 2011 and 2012 found that ibuprofen (administered intravenously or orally) had a more favorable profile than diclofenac and ketorolac with regard to upper GI and cardiovascular adverse events [70,71]. Koh et al.'s 2015 review of a small number of randomized clinical trials (RCTs) of NSAIDs for peri- and postoperative pain management found that intravenously administered ibuprofen was associated with significant opioid sparing and was well tolerated.

In 2020, Southworth et al. updated their previous safety analysis by publishing a narrative summary of the results of nine clinical studies of perioperative pain management with IV ibuprofen. The studies covered 1062 adults, 757 of whom received IV ibuprofen and 305 of whom received either a placebo or a comparator drug [62,72]. The researchers concluded that the administration of IV ibuprofen was associated with lower postoperative pain levels, lower opioid use, better recovery, less fatigue, a less intense surgical stress response (i.e., lower levels of catecholamines, cortisol, and cytokines), and less postoperative use of over-the-counter medication [72]. Zhou et al.'s meta-analysis (published in 2023) considered 32 studies (with 3716 participants and 18 types of surgery) of multiple-dose or single-dose IV ibuprofen [40]. The level of evidence was judged to be low-moderate. With regard to postoperative pain, IV ibuprofen gave lower scores than placebo (mean difference: −3.53 at 0 min and −0.96 at 24 h) and IV paracetamol (mean difference, −1.54 at 0 min and −0.36 at 24 h). In terms of antipyretic activity, IV ibuprofen and IV paracetamol showed similar, satisfactory levels of effectiveness. The researchers concluded that their results supported the use of IV ibuprofen for adults with postoperative pain and fever, and those who are unable to take oral medications [40].

These results are in line with the large body of safety data for orally administered ibuprofen and paracetamol in a setting of acute pain. For example, Moore et al.'s PAIN study of 8677 patients with acute pain found that the frequency of significant adverse events was similarly and significantly lower for ibuprofen and paracetamol (13.7% and 14.5%, respectively) than for aspirin (18.7%) [73,74]. Lastly, the market withdrawals of the coxibs rofecoxib and valdecoxib focused attention on the safety of NSAIDS more generally and prompted Thomas et al. to conclude that the "preferred NSAIDs are ibuprofen and naproxen" [75].

3.2. Studies in Children

In a recent Cochrane Collaboration review of diclofenac for the relief of acute postoperative pain in children (covering 32 RCTs and 2250 children, most of whom were over the age of three), Ringsten et al. emphasized their uncertainty about the efficacy of this NSAID over placebo and active comparators, regardless of the administration route [76]. However, the researchers pointed out that this uncertainly was mainly due to the absence of data on clinically important outcomes in some trials and/or poor trial conduct. In a separate Cochrane Collaboration review, the same group of researchers found that this uncertainly also applied to studies of the relief of acute postoperative pain in children by ibuprofen [77]. Nevertheless, on the basis of three studies in 259 children, Pessano et al. concluded that there was moderate-certainty evidence to suggest that ibuprofen reduces child-reported pain intensity less than 2 h post-surgery, relative to placebo (standard median difference [95%CI] = −1.12 [−1.39 to −0.86]) and low-certainty evidence for an effect up to 24 h post-surgery [77]. According to Pessano et al., the low-certainty evidence was largely due to poor reporting on serious adverse events, poor study conduct, or poor reporting.

In the studies reviewed here, the overall safety profile appeared to be similar for ibuprofen, paracetamol, and ketorolac (Table 1). Perioperative adverse events (especially bleeding) were often infrequent or absent [46,54,59,63,64,66]. In Ahiskalioglu et al.'s study, the incidences of nausea and vomiting were lower even in the ibuprofen group than in the saline placebo group [43].

Overall, PK data for IV NSAIDs in infants are scarce. According to Khalil et al.'s multicenter study of 43 pediatric inpatients receiving IV ibuprofen, the area under the curve (AUC) from time zero to 4 h (AUC 0–4) ranged from 22.96 to 162.06 µg.h/mL, and the peak plasma concentration (C_{max}) was usually around 60 µg/mL and ranged from 15.91 to 96.31 µg/mL [78]. The median time to C_{max} (t_{max}) was 10 min, and the mean (range) elimination half-life was 1.55 h (0.79–2.87). As expected, the clearance and distribution volume increased with age. By way of a comparison, the value of tmax for single-dose oral administration achieving the same Cmax is reportedly 1.5 to 2 h [79]. Kokki et al. reported a mean (range) elimination half-life of 1.3 (0.8–1.7) h for a 24-continuous infusion and 1.5 (0.7–3.0) h for a single intravenous injection of ketoprofen 1 mg/kg [80,81]. The steady-state plasma concentration of ketoprofen was 2.0 µg/mL (range: 1.3–2.7) for a 24-continuous infusion, and C_{max} ranged from 10.5 to 22.2 µg/mL for a single injection (tmax was not reported) [80,81]. For single IV doses (0.5 or 1 mg/kg) of IV ketorolac in infants, Lynn et al. reported respective mean ± SD C_{max} values of 1.1 ± 0.6 and 2.0 ± 11 for S-ketorolac and 2.5 ± 1.4 and 4.1 ± 1.8 for R-ketorolac [82].

3.3. Comparisons of NSAIDs with Paracetamol

Intravenous formulations of paracetamol were approved in Europe in 2002 and in the USA in 2009 for the treatment of mild-to-moderate pain and (when combined with opioids), severe pain. The main safety concern with paracetamol is hepatotoxicity if used above the recommended maximum dose of 4 g per day in adults. Although often used as an active comparator in trials of NSAIDs such as ibuprofen and ketorolac, paracetamol has very weak peripheral anti-inflammatory effects and lacks an effect on platelet function [83]. Koh et al.'s 2015 review of studies of peri- and postoperative pain management found that like ibuprofen, IV paracetamol was associated with significant opioid sparing and was well tolerated [84].

Qureshi et al. systematically reviewed the literature (27 trials; 5427 patients) on the use of intravenous paracetamol, intravenous or intramuscular NSAIDs, and intravenous opioids for the relief of moderate-to-severe pain in the emergency department. The researchers found that all three drug classes provided similar levels of pain relief but that opioids

were associated with more adverse events and intravenous paracetamol was associated with a greater need for rescue analgesia. Hence, Qureshi et al. recommended NSAIDs as the first-choice analgesia [85]. With regard to efficacy, Dogan et al.'s recent randomized, double-blind study of 210 trauma-free patients with acute low back pain did not evidence a significant difference in pain relief (0-, 15-, 30- and 60-min post-infusion) between IV paracetamol, IV dexketoprofen, and IV ibuprofen [86].

3.4. Combining an NSAID with Paracetamol

According to Crook, the UK National Institute for Health and Clinical Excellence recommended that ibuprofen and paracetamol should be used separately because there was no evidence of greater effectiveness when combined [38]. Somewhat in contrast, Hamdi et al. considered that the continuous infusion of ketoprofen in a binary mixture with paracetamol, nefopam, or ketamine was safe [87]. Martinez et al. performed a network meta-analysis of 135 randomized trials (13,287 patients) of non-opioid analgesics in adults after major surgery, looking at morphine consumption, pain, and adverse effects. The researchers concluded that with regard to the reduction of opioid consumption, a combination of paracetamol with an NSAID or nefopam was superior to most non-opioid analgesics used alone. NSAIDs and COX-2 inhibitors alone were superior to paracetamol alone [42]. For example, Gupta et al.'s RCT in the USA found that perioperative IV ibuprofen combined with IV paracetamol was associated with significantly greater pain relief (but on POD 3 only), lower opioid use, and fewer opioid-related adverse events when compared with IV ibuprofen alone [50]. In contrast, in the context of total hip arthroplasty and oral administration, Thybo et al. found that the combination of ibuprofen and paracetamol did not result in a clinically significant improvement over ibuprofen alone [88]. Furthermore, the guideline on postoperative pain management after total hip arthroplasty issued by the PROSPECT Working Group and the European Society of Regional Anaesthesia and Pain Therapy states that IV paracetamol has a limited impact when added to a regimen including coxibs or NSAIDs [89].

4. Study Strengths and Limitations

The present narrative review has several strengths. Firstly, we covered a broad, topical issue with immediate clinical relevance. Secondly, we reviewed publications available solely in French, as well as those in English.

Our review also has limitations. Firstly, it was not systematic. However, several systematic reviews of some of the subtopics addressed here are available [40]. Secondly, in view of the investigators' affiliation, the review was centered on practice in France and Europe, and cannot be extended to all healthcare systems and clinical frameworks. Thirdly, five of the studies reviewed here in detail were published after 2020 and were conducted during or following the global pandemic of coronavirus disease 2019 (COVID-19). Early in the pandemic, unsubstantiated media reports suggested that NSAIDs might exacerbate the signs and symptoms of COVID-19. The results of a number of robust clinical studies have now demonstrated that NSAID use is not associated with worse COVID-19 outcomes, and the European Medicines Agency (EMA), and the US Food and Drug Administration (FDA) did not advise against using NSAIDs [90–93]. On the contrary, some studies even found a modest survival benefit for treatment with NSAIDs [91].

A shortage of head-to-head RCTs comparing different IV NSAIDs limits direct comparisons. Most data come from placebo-controlled or observational studies, which can restrict the accuracy of clinical decision-making. Future trials should assess the comparative efficacy, safety, and cost-effectiveness of various IV NSAIDs in diverse populations.

5. Conclusions

Our review of the literature data in various surgical settings indicated that intravenous NSAIDs are well tolerated and usually associated with significant (~20–60%) opioid sparing, postoperative pain relief, and fewer side effects. Intravenous formulations of NSAIDs will probably continue to be of value in the multimodal approach to perioperative analgesia and enhanced recovery after surgery. In pediatrics in particular, the choice of medication is limited to ibuprofen at early ages and the oral route is not always feasible; hence, IV formulations of NSAIDs are the preferred allies in this setting. Topics for further research should include head-to-head trials of IV NSAIDs. In this respect, the American Pain Society's Clinical Practice Guideline on acute postoperative pain recommends (i) both RCTs and observational studies that capture real-world data and rare AEs, (ii) the stratification of groups according to the baseline pain level, (iii) standardized outcome measures for pain, function, safety, harms, and patient satisfaction, and (iv) measurement periods extending over days and weeks, rather than hours [94].

6. Future Directions

6.1. Continuous Infusion vs. Intermittent Infusion

One can hypothesize that continuously infused NSAIDs are superior to intermittent dosing due to the pre-emptive inhibition of inflammation and thus greater pain relief. Continuous infusion also limits the peak concentration of the drug and so might have safety benefits. Indeed, multiple intermittent doses of IV ibuprofen led to a slight accumulation of the drug in some studies [15] but not in others [95]. On the one hand, continuous infusion reduces the number of handling procedures by the nursing staff. On the other, the infused NSAIDs must be compatible with other infused products.

Howard et al. have extensively reviewed studies of continuous NSAID infusion lasting more than 12 h against intermittent dosing in various surgical settings [4]. In the literature on abdominal surgery, ketorolac was the most commonly reported continuously infused NSAID; of the 10 trials of ketorolac, half did not find a difference in reported pain levels at any of the time points, and half found a difference in reported pain levels at some time points [4]. The benefits in terms of reduced morphine consumption were more visible, especially when patient-controlled analgesia was available. Howard et al.'s analysis was limited by heterogeneity in study outcomes, the lack of head-to-head comparisons between continuous infusion and intermittent dosing of the same NSAID, and a relatively short observation period per patient (which limited the detection of medium- and long-term adverse events). The researchers concluded that in orthopedic surgery for adults, there was strong evidence of benefits in pain relief and opioid sparing for continuously infusion NSAIDs vs. placebo, especially at doses approaching the maximum recommended daily level [4]. For example, the results of Ready et al.'s multicenter, double-blind, placebo-controlled study showed that at similar cumulative doses, morphine patient-controlled analgesia (PCA) use was 25% lower in the continuously infused ketorolac group than in the bolus group [96]. Unfortunately, Howard et al.'s analysis of studies in children was restricted by the scarcity of data and the lack of availability of IV ketoprofen in some countries (including the USA, notably) [4].

6.2. Rapid Infusion vs. Standard Infusion

The results of a Phase IV multicenter clinical surveillance study conducted in the USA and described by Bergese et al. and Gan et al. showed that rapid IV administration of ibuprofen (over 5 to 10 min, rather than the standard 30 min stated in the SmPC) was well tolerated in hospitalized patients in general and surgical patients in particular [97,98]. The

most common adverse event (in 34 (11%) of the 300 surgical patients) was infusion site pain, and none of the serious adverse events were judged to be related to ibuprofen.

6.3. Pre-Emptive Analgesia

It has been suggested that in the broad setting of multimodal analgesia, pre-emptive analgesia can reduce pain levels and opioid use in the days following surgery, notably for lower third molar removal, tonsillectomy, total knee or hip arthroplasty, hysterectomy, and lumbar spine surgery [99–102]. Pre-emptive analgesia with IV formulations of NSAIDs has been evaluated in a small number of trials. For example, a series of placebo-controlled studies by Ahiskalioglu et al. found that a pre-emptive single dose of IV ibuprofen before laparoscopic cholecystectomy and other operations was associated with lower postoperative pain levels and 45% less opioid consumption in the first 24 h after surgery [43,103,104]. However, the literature data are contradictory: a recent review of five trials in lower third molar surgery found that there was insufficient evidence in favor of pre-emptive ibuprofen administration for the reduction of postoperative pain in this indication [105]. A similar conclusion was reported in a review of intramuscular or intravenous administration of ketorolac in lower third molar surgery [106]. Lastly, a recent (2022) network meta-analysis highlights NSAIDs (along with paracetamol and epidural anesthesia) as among the most effective treatments in pre-emptive analgesia [107].

6.4. Dosing Adjustments for Specific Patient Profiles

Given that NSAIDs are hydrophilic molecules, we suggest that the ideal body weight or lean body weight (rather than the actual body weight) should be taken into account for obese patients, as with antibiotics [108,109]. This question has also been considered for paracetamol [110].

6.5. Fixed-Dose Combinations

Some experts recommend fixed-dose combinations (FDCs) over the parallel administration of separate drugs for effectiveness and safety reasons [111]. In a randomized, open-label, five-period cross-over pharmacokinetic study, Atkinson et al. compared a single dose of an intravenously administered FDC of 3 mg/mL ibuprofen and 10 mg/mL paracetamol with single doses of the individual components (IV 3 mg/mL ibuprofen alone; IV 10 mg/mL paracetamol alone) and an orally administered combination (ibuprofen 150 mg + paracetamol 500 mg). With regard to the C_{max}, area under curve, and bioavailability, the IV FDC did not alter the pharmacokinetic profile of either drug [112].

6.6. Pharmacogenomic Profiling

Pharmacogenomic questions are increasingly being raised in the field of pain and NSAID use [113]. Given their extremely wide use, NSAIDs are the primary cause of drug hypersensitivity reactions [114]. These reactions may be broad (i.e., cross-reactive) or narrow (i.e., selective) and are related to the expression levels and methylation status of immune-response genes [114]. For example, polymorphisms in the genes coding for COX-1 and COX-2 (*PTGS1* and *PTGS2*, respectively) are linked to cross-reactive NSAID hypersensitivity, and the N-acetyltransferase 2 *5, *6, *7, and *14 genotypes are associated with selective NSAID hypersensitivity [115,116]. It has been known for several decades that the metabolism of NSAIDs (including ibuprofen, celecoxib, piroxicam, and diclofenac) is influenced by cytochrome P450 polymorphisms [117]. The pharmacokinetics of S-ibuprofen and R-ibuprofen are affected by CYP2C9*2 and CYP2C9*3 polymorphisms and sex [118]. These concerns might open up long-term perspectives for the greater safety and effectiveness of IV NSAIDs.

In the era of personalized medicine, further research on inter-individual differences in reactions to and the effectiveness of IV NSAIDs is necessary.

6.7. Environmental Concerns

Regulatory measures are increasingly being taken to reduce the amount of plastic waste (notably microplastics and nanoplastics) and xenobiotics being generated and released into the environment, and the medical device and drug industries are not exempt from such considerations [119–121]. Due to the resources consumed and the large amount of waste produced, operating theaters contribute significantly to a hospital's environmental impact [122]. The production and supply of ready-to-use products (e.g., prefilled syringes of commonly used anesthetic drugs) might reduce production waste, favor the use of lighter and more recyclable inner and outer packaging, and reduce phthalate and bisphenol A contents [123]. It has been reported that IV paracetamol has an environmental impact that is 8 to 16 times greater than that of the orally administered drug [124]. We suggest that ready-to-use IV formulations may be preferred by some users and may be well suited (but not limited) to certain patient profiles (e.g., infants, with a lower likelihood of dosing errors) and clinical settings (e.g., emergency departments, where rapid preparation is an advantage).

It remains to be seen whether these environmental factors are considered by physicians and administrators when choosing between IV and oral NSAID formulations, or between a ready-to-use IV formulation and an IV formulation requiring preparation.

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Designing Effective Protocol-Based Pharmacotherapy Management: Assessment of the Development Processes and Outcomes in Inflammatory Bowel Disease Care Prescription Management

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Abstract: Prolonged working hours among physicians in Japan, alongside rising inflammatory bowel disease (IBD) cases, have heightened the need for additional support in IBD care. Protocol-based pharmacotherapy management (PBPM) has emerged as an effective approach that allows pharmacists to assist in prescription management under predefined protocols, potentially reducing physicians' workload. However, the detailed process of formulating PBPMs remains unclear. This study developed effective PBPM protocols by reviewing past provisional prescriptions. Provisional prescriptions made by pharmacists based on verbal instructions from physicians were reviewed to develop new PBPMs at Tsujinaka Hospital, Kashiwanoha. We retrospectively analyzed the PBPM application rate during three months before and after this initiative based on the proportion of prescriptions processed under standard procedure (SP), pharmacist provisional prescribing (PPP), and PBPM (PBPM-P). A total of 1259 prescriptions were retrospectively analyzed in this study. Before the initiative, there were 586 prescriptions (oral/topical, 128; injection, 458); after the initiative, there were 673 prescriptions (oral/topical, 242; injection, 431). The pre-initiative rates for SP, PPP, and PBPM-P were 68.3%, 30.7%, and 1.0%, respectively. Post-initiative, the rates were 48.3%, 26.6%, and 25.1%, respectively. A significant decrease was observed in the proportion of SP and PPP, while PBPM-P showed a significant increase after the initiative. Specifically, the proportion of PBPM-P increased by 24.1 percentage points, reflecting its broader adoption. In terms of safety, the proportion of pharmacists' prescription questions decreased significantly from 3.1% before to 0.3% after the initiative. Additionally, the proportion of prescription changes resulting from these questions decreased significantly, from 1.2% to 0%. The PBPM development process evaluated here could successfully form effective PBPMs, which have the potential to reduce physicians' workload, indicating that the process detailed in this study could be applied to future protocol development.

Keywords: inflammatory bowel disease; protocol-based pharmacotherapy management; pharmacist-led prescription

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1. Introduction

The problem of prolonged working hours among physicians in Japan has received significant attention recently, with numerous recommendations issued by the government.

According to a report by the Ministry of Health, Labour and Welfare [1], physicians are the professionals most affected by long working hours, necessitating urgent intervention. Additionally, a rapid increase in the number of patients diagnosed with inflammatory bowel disease (IBD) has been observed in Japan [2]. Nationwide data indicate that the prevalence was 24 per 100,000 population in 1991, increasing to 76 per 100,000 during the period of 2003–2005 and reaching 228.5 per 100,000 in 2014 [3,4]. This corresponds to a rise in the estimated number of individuals with IBD from 29,700 in 1991 to 290,400 in 2014. In addition, the prevalence of ulcerative colitis (UC) in Japan has exhibited substantial growth, with reports showing an increase from 5 per 100,000 population in 2010 to 98 per 100,000 in 2019 [5]. Consequently, support from physicians involved in IBD care is anticipated to be critical for patients with IBD, further escalating the workload of these physicians.

Pharmacist-led prescription has been successfully implemented in several countries, including the USA, the UK, and Canada, to manage physicians' tasks effectively. For example, collaborative drug therapy management (CDTM), a common practice in some countries, such as the USA, involves contractual partnerships between physicians and pharmacists to manage specific patient treatments, with pharmacists playing an active role in pharmacotherapy management [6]. This approach has been proven highly effective by numerous studies [7,8]. In Japan, the Japanese Society of Hospital Pharmacists advocates the use of protocol-based pharmacotherapy management (PBPM), which has also been recommended in documents related to the promotion of team-based healthcare by the Ministry of Health, Labour and Welfare [9]. PBPM enables the active involvement of pharmacists in roles that, like in many other countries, legally cannot include prescribing medications or ordering tests in place of physicians. Therefore, instead of directly adopting CDTM, Japan has chosen to implement PBPM, a solution that has demonstrated its effectiveness. PBPM simplifies interactions between physicians and pharmacists by establishing predetermined protocols that pharmacists can follow to process prescriptions. This management occurs within legal boundaries and follows the guidelines of the Ministry of Health, Labour and Welfare. The specifics of PBPM are delegated to individual healthcare facilities.

Naturally, provisional prescriptions drafted by pharmacists are legally recognized only once confirmed and approved by a physician. PBPM is an effective and robust management tool for shifting and sharing tasks from physicians to pharmacists. The Japanese Society of Hospital Pharmacists has published a guide, "Smooth Implementation and Practical Examples of Protocol Based Pharmacotherapy Management (PBPM) Ver. 1.0", which serves as a reference for medical facilities across Japan to formulate their PBPMs [10]. Numerous studies have highlighted the practical applications and benefits of PBPM [11–13].

In the context of IBD care, PBPM plays a crucial role in managing the increasing complexity of treatment regimens. For example, PBPM facilitates the initiation and adjustment of therapies, such as corticosteroids and biologics, ensuring timely and consistent patient management. Pharmacists can use PBPM to address routine tasks, including monitoring therapeutic drug levels, managing medication adherence, and providing prophylactic measures to prevent infections associated with immunosuppressive treatments. By reducing the need for verbal instructions and streamlining workflows, PBPM improves communication efficiency and reduces the burden on physicians while maintaining high standards of patient safety.

Despite its establishment, in the field of IBD, PBPM has been reported to have a low adoption rate [14]. This suggests that even when protocols are in place, they are not always utilized effectively and thus do not contribute to the intended physician task shift/share. Although there are case collections and reports on PBPM initiatives in Japan [15,16], detailed reports on the adoption status or protocol development process are currently lacking.

This study aimed to retrospectively assess the effectiveness of the PBPM development process by evaluating the impact of a newly developed PBPM, which was determined by measuring how pharmacists were involved in the prescribing process.

2. Materials and Methods

2.1. Study Design

This study was a prescription-based retrospective study. The target prescriptions were judged using the electronic medical record's checking system function according to the pre-determined PBPM criteria. These prescriptions were then analyzed for this study.

2.2. Additional Formulation of PBPM

Prior to this study, a total of 37 PBPMs had been established at our hospital. Among these, 10 protocols were designated for use in departments other than the IBD center, while 11 were specific to outpatient care. The remaining 16 protocols were common across all departments and applicable to inpatients at the IBD center. These 16 protocols served as the foundation for the development of additional IBD-specific PBPMs in this study (Table 1).

Table 1. Overview of PBPMs already implemented before the initiative.

Classification	No. of Prepared Protocols	Description
Omission of prescription question	3	This protocol stipulates the omission of some steps in the usual process of prescription verification and inquiry. It includes procedures to simplify or omit inquiries for clear prescriptions or routine cases.
Prescription support	7	This protocol includes a system where pharmacists support the prescription process by adjusting dosages or modifying prescriptions when necessary due to patient background or drug interactions.
Prescription completion	5	This protocol includes procedures to support pharmacists in completing the process for prescriptions that are incomplete or partially missing.
Dispensing support	1	This protocol includes the process wherein pharmacists adjust dispensing instructions given by doctors based on the patient's condition and other factors.

The protocols listed in the table were established before the initiative. Of the 37 PBPMs that had already been established, the table displays 16 that were applicable to the subjects of this study.

We reviewed records of provisional prescriptions made by pharmacists based on verbal instructions from physicians between October and December 2021. In this context, verbal instructions refer to specific directives from physicians regarding the treatment or medication for individual patients. For example, these instructions may include prescribing antibiotics to prevent infections associated with steroid therapy or continuing a patient's current oral medications. Such instructions were communicated directly to pharmacists,

who then created provisional prescriptions in accordance with the physician's guidance. Two pharmacists from the IBD team selected records that contained universal and robust prescription instructions suitable for incorporation into the protocol. Sporadic instructions were excluded based on the expert judgment of two pharmacists from the IBD team. Ad hoc instructions referred to directives tailored to individual cases without general relevance, and patient-specific instructions, such as dose adjustments for unique physiological conditions, were also excluded. The selected records were classified using an open card sorting method, a qualitative technique where pharmacists grouped similar records into thematic categories without predefined criteria. The pharmacists aimed to group the records as broadly as possible while maintaining clinical relevance. Each group was assigned a descriptive label, and actionable protocols were formulated based on these labels. These protocols defined the specific actions for pharmacists in prescription management. The pharmacists and physicians of the IBD team reviewed the articulated protocols multiple times in January 2022 to refine the phrasing to ensure that the protocols accurately reflected the physicians' intentions without any misinterpretation. The consultations also verified the feasibility of the protocol. After reaching a consensus, these protocols were formalized according to hospital regulations, resulting in an additional formulation of PBPM.

2.3. Participants

This study retrospectively investigated the involvement of pharmacists in providing prescriptions that were effective for inpatients treated at the IBD Center of Tsujinaka Hospital Kashiwanoha (hereafter referred to as "our hospital") during the three months before and after the development of the new PBPM (October to December 2021 and February to April 2022). The evaluation examined whether the pharmacists were involved in issuing the prescriptions under review. Additionally, the prescription type, content, and patient demographics (sex, age, and IBD diagnosis) were analyzed. IBD diagnoses included UC, Crohn's disease (CD), and other diseases managed at the IBD Center, including but not limited to Behcet's disease. The number and details of errors related to pharmacist involvement in prescribing were also extracted.

2.4. Outcomes

The primary outcome measure of this study was the change in pharmacist involvement in prescription issuance before and after the implementation of the newly developed PBPM. Pharmacist involvement was categorized into three types: no pharmacist involvement (SP), provisional prescribing upon a physician's directive (PPP), and prescribing based on PBPM protocols (PBPM-P). Detailed definitions of these categories are provided in the following section. This change was further examined according to prescription type. In the exploratory analysis, we performed factor analysis to identify the variables influencing pharmacist involvement in the issuance of provisional prescriptions. Additionally, a comparative analysis was conducted on the number of errors and prescription queries involving pharmacist participation.

2.5. Pharmacist Involvement in Prescription Issuance

In this study, we defined how pharmacists were involved in the prescription processes initiated by physicians. Specifically, pharmacist involvement was categorized into three types: (1) no pharmacist involvement (standard process: SP), where physicians managed all prescription tasks independently; (2) pharmacists creating a provisional prescription upon a physician's explicit request or directive (pharmacist provisional prescribing: PPP); and (3) pharmacists autonomously drafting prescriptions based on established PBPM protocols (PBPM-P). Provisional prescriptions were created using the requesting physician's function in the Fujitsu Electronic Medical Record System (HOPEEGMAIN GX). This was performed

according to the hospital guidelines, confirming prescriptions issued based on physician requests and those based on PBPM.

2.6. Types and Content of Prescriptions

The categories of prescriptions at our hospital follow the typical classification in Japan, divided into two types: those for oral and topical medications (hereafter referred to as "prescriptions") and those for injectable medications (hereafter referred to as "injection prescriptions"). Analyses were conducted for each type, as required.

2.7. Safety of Prescription Practices

Safety in this study was evaluated through two distinct measures. First, we examined the number of prescription questions raised by pharmacists during their audits. These questions were triggered when pharmacists identified potential issues warranting clarification or modification, including concerns about dosage and administration schedules, the appropriateness of the medication's indication, potential allergies or contraindications, risks of side effects or adverse drug reactions, possible drug–drug interactions, and verification grounded in clinical and pharmaceutical knowledge. The total number of questions and subsequent modifications to prescriptions were recorded, and the ratios of these occurrences to the total number of prescriptions were calculated and compared between the periods before and after the initiative. Second, the safety of the prescription process was assessed by tracking all errors that occurred during pharmacist involvement in the provisional prescription processes under PPP and PBPM-P. Errors were identified during the pharmacist's provisional prescription entry, as well as at all stages of these processes. All identified errors were aggregated and analyzed as proportions of the total number of prescriptions within the PPP and PBPM-P categories. These proportions were compared between the pre- and post-initiative periods to evaluate the impact of the initiative on prescription safety.

2.8. Statistical Analyses

Statistical analyses were conducted using chi-square tests and logistic regression. The chi-square test was used to examine any significant changes in the ratio of pharmacist involvement in prescription issuance before and after the intervention. If significant, Pearson's chi-square residuals were calculated, as required, for a more detailed analysis. Additionally, factors affecting pharmacist involvement in prescribing were explored using multiple logistic regression. The analysis involved several steps utilizing a multiple logistic regression model. Initially, pharmacist involvement in prescription issuance was treated as the outcome, with SP and PPP as the reference category, and univariate analyses were conducted for provisional prescriptions based on PBPM-P. Factors showing a p-value of <0.10 in the univariate analyses were forcibly entered as explanatory variables in the multiple logistic regression. The presence of multicollinearity among independent variables was assessed using the variance inflation factor (VIF), with values above 10 indicating multicollinearity and thus excluded from the model. The goodness of fit of the model was post-estimated using the C Index and considered well-fitted if it was greater than 0.70 and poorly fitted if the lower limit of the 95% confidence interval (CI) was below 0.50. The results are presented as crude odds ratios (ORs) or adjusted odds ratios (adj-ORs), with the significance level set at 0.05 for all analyses. Statistical analyses were performed using R (The R Foundation for Statistical Computing, Vienna, Austria, version 4.1.1).

3. Results

3.1. Prescriptions Analyzed

A total of 1259 prescriptions were analyzed in this study. Before the initiative, there were 586 prescriptions (oral/topical, 128; injection, 458); after the initiative, there were 673 prescriptions (oral/topical, 242; injection, 431). The median age of the patients for whom prescriptions were issued was 42 years before the initiative and 36 years after the initiative. The breakdown of IBD conditions was as follows: UC accounted for 271 cases before and 497 cases after the initiative, whereas CD accounted for 286 cases before and 114 cases after the initiative (Table 2).

Table 2. Characteristics of studied prescriptions.

	Overall	**Initiative** [a]	
		Before	**After**
Number of prescriptions	1259	586	673
-Oral and topical medication	370	128	242
-Injectable medication	889	458	431
Sex			
-Male	953	422	531
-Female	306	164	142
Age (IQR)	39 (28–49)	42 (30–52)	36 (21–43)
Disease			
-CD	400	286	114
-UC	768	271	497
-Others [b]	91	29	62

[a] This refers to a series of interventions through which the PBPM was developed. [b] Other diseases managed at the IBD Center besides UC and CD, including but not limited to Behcet's disease. IQR, inter-quartile range; CD, Crohn's disease; UC, ulcerative colitis.

3.2. Implementation of New PBPM Protocols

Following a predetermined method, the records were classified into 12 categories, from which 13 protocols were developed. These protocols were discussed and adjusted in consultation with IBD physicians, resulting in a final addition of 13 new PBPMs (Figure 1). The additional protocols were specific to patients with IBD. For example, for patients receiving more than 30 mg/day of steroids in prednisone equivalents, pharmacists were authorized to initiate the process of provisional prescription of antibiotics and gargle solution for infection prevention after verifying the patient's allergy history and confirming its applicability. This meant that the study compared two conditions: before the initiative, when 16 PBPMs were available, and after the initiative, when 13 additional PBPMs were added, resulting in a total of 29 PBPMs.

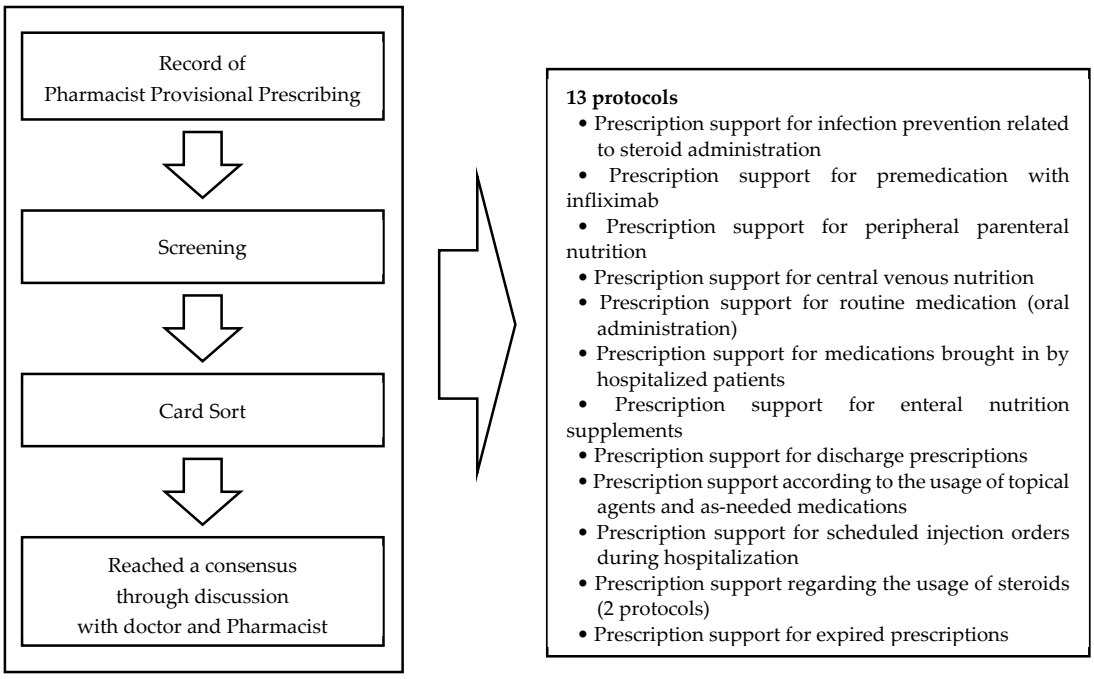

Figure 1. Development and implementation process of additional PBPMs. The protocols were generated using several processes. We developed 13 protocols for these 12 items. Each protocol specifies the actions that pharmacists should take regarding prescriptions.

3.3. PBPM Application Rates

When comparing the periods before and after the initiative, the overall prescription data showed significant changes. Initially, the breakdowns were 400, 180, and 6 for SP, PPP, and PBPM-P, respectively; however, these changed to 325, 179, and 169, respectively, post-initiative. Chi-square tests indicated a significant difference in pharmacist involvement before and after the initiative (X^2 = 154.3, df = 2, $p < 0.001$, Cramer's V = 0.35). Further analysis using adjusted standardized residuals (adj-R) showed values exceeding 1.96 for both SP and PBPM-P, suggesting a significant decrease in SP and a significant increase in PBPM-P after the initiative. When analyzed by prescription type, the oral/topical prescriptions shifted from 36 SP, 86 PPP, and 6 PBPM-P pre-initiative to 52 SP, 130 PPP, and 60 PBPM-P post-initiative, showing a significant difference (X^2 = 23.1, df = 2, $p < 0.001$, Cramer's V = 0.24). Residual analysis indicated a significant increase only for PBPM-P. The pre-initiative figures for injectable prescriptions were 364 SP, 94 PPP, and 0 PBPM-P, which changed to 273 SP, 49 PPP, and 109 PBPM-P post-initiative. This also showed a significant difference (X^2 = 135.4, df = 2, $p < 0.001$, Cramer's V = 0.39), with residual analysis showing significant decreases in SP and PPP, while PBPM-P significantly increased (Table 3).

Table 3. Changes in pharmacist involvement in prescriptions before and after the initiative.

Label		Overall		Medication			
				Oral and Topical		Injectable	
		Initiative		Initiative		Initiative	
		Before	After	Before	After	Before	After
SP	Observed	400	325	36	52	364	273
	Expected	337.5	387.5	30.4	57.6	328.2	308.8
	Std_Residuals	3.41	−3.18	1.01	−0.73	1.98	−2.04
	Adj_Std_Residuals	7.15	−7.15	1.43	−1.43	5.33	−5.33

Table 3. *Cont.*

Label		Overall		Medication			
				Oral and Topical		Injectable	
		Initiative		Initiative		Initiative	
		Before	After	Before	After	Before	After
PPP	Observed	180	179	86	130	94	49
	Expected	167.1	191.9	74.7	141.3	73.7	69.3
	Std_Residuals	1.00	−0.93	1.30	−0.95	2.37	−2.44
	Adj_Std_Residuals	1.61	−1.61	2.50	−2.50	3.71	−3.71
PBPM-P	Observed	6	169	6	60	0	109
	Expected	81.5	93.5	22.8	43.2	56.2	52.8
	Std_Residuals	−8.36	7.80	−3.52	2.56	−7.49	7.72
	Adj_Std_Residuals	−12.32	12.32	−4.81	4.81	−11.49	11.49

SP, standard process; PPP, pharmacists' provisional prescription; PBPM-P, process through which pharmacists create provisional prescriptions based on PBPM.

3.4. Factor Analysis of PBPM Implementation

This analysis utilized logistic regression to examine the factors influencing the adoption of PBPM-P compared with SP and PPP, categorizing SP and PPP as the reference groups and PBPM-P as the target group. The results of the univariate analysis are presented in Table 4. As pre-specified, factors with an OR below 0.10 in the univariate analysis were included in the multivariate analysis to ensure comprehensive consideration of potentially influential variables. The effort variable, reflecting changes before and after the initiative, showed a substantial increase in the likelihood of achieving the desired outcome, maintaining its significance even in multivariate analysis with an OR of 39.47 (95% CI: 16.87–92.33, $p < 0.001$). The other factors examined included sex, age, disease state, and prescription type. Sex was not significantly associated with the outcome, whereas age was inversely associated with positive outcomes, decreasing slightly with each additional year (OR = 0.98, 95% CI: 0.9–70.99, $p < 0.001$). Patients with UC had significantly lower odds of achieving a positive outcome than those with CD (OR = 0.16, 95% CI: 0.05–0.52, $p = 0.002$), while other disease categories did not show significant differences. Injectable versus oral prescription types showed lower odds for injectables (OR = 0.64, 95% CI: 0.46–0.90, $p = 0.01$), although this factor was not significant in the multivariate context (Table 3). The Hosmer–Lemeshow test confirmed the adequacy of the model ($p = 0.138$). It demonstrated good discriminatory ability, with an area under the curve (AUC) of 0.83 (95% CI: 0.80–0.83).

Table 4. Logistic regression analysis of factors influencing PBPM implementation.

Factor	Crude OR (95% CI)	*p*-Value	adj. OR (95% CI)	*p*-Value
Initiative				
-Before (ref)	-	-	-	-
-After	32.41 (14.23–73.81)	<0.001	39.47 (16.87–92.33)	<0.001
Sex				
-Male (ref)	-	-		
-Female	0.72 (0.48–1.07)	0.106		
Age (per 1-year increase)	0.97 (0.95–0.98)	<0.001	0.98 (0.97–0.99)	<0.001

Table 4. *Cont.*

Factor	Crude OR (95% CI)	*p*-Value	adj. OR (95% CI)	*p*-Value
Disease				
-CD (ref)	-	-	-	-
-UC	0.18 (0.06–0.57)	0.004	0.16 (0.05–0.52)	0.002
-Others	1.37 (0.96–1.95)	0.086	0.50 (0.33–0.76)	0.001
Prescription category				
-Oral and topical medication (ref)	-	-	-	-
-Injectable medication	0.64 (0.46–0.90)	0.009	0.82 (0.57–1.18)	0.275

The left side of the table shows the results of the univariate analysis, while the right side shows the results of the multivariate analysis. SP and PPP are used as reference groups, with PBPM as the target group. Other diseases managed at the IBD Center besides UC and CD, including but not limited to Behcet's disease. OR, odds ratio; adj. OR, adjusted odds ratio; CI, confidence interval; ref, reference; CD, Crohn's Disease; UC, ulcerative colitis.

3.5. Safety Outcomes of the Initiative

Before the initiative, there were 18 instances of prescription questions by pharmacists (3.1%, 18/586), which decreased to 2 instances post-initiative (0.3%, 2/673), showing a significant reduction ($p < 0.001$). Additionally, of the pre-initiative prescription questions, seven (1.2%, 7/586) resulted in changes to prescriptions, whereas no changes occurred post-initiative (0%, 0/673), also showing a significant decrease ($p = 0.013$) (Figure 2). Errors in pharmacists' prescription entries, including those involving PBPM-P, did not exist before the initiative (0%, 0/186), and there were two instances (0.6%, 2/348) after the initiative; however, this difference was not statistically significant ($p = 0.770$). These errors included one electronic medical record registration error and one omission in prescription transcription. Both errors were promptly corrected, and no patient was harmed.

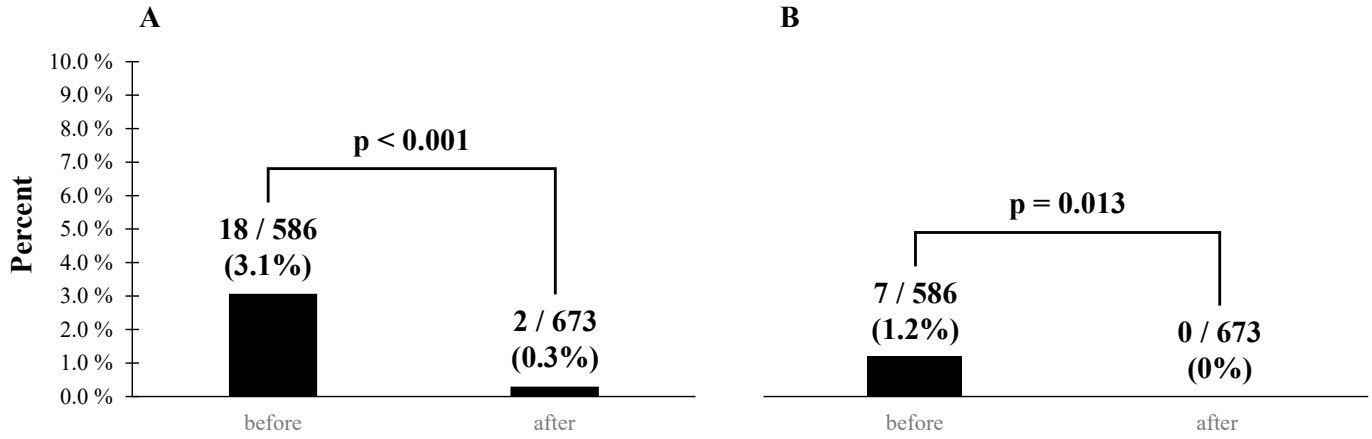

Figure 2. Comparison of pharmacist prescription questions and errors pre- and post-initiative. (**A**) Number of pharmacist prescription questions before and after initiation. (**B**) Number of prescription changes resulting from the pharmacists' questions before and after the initiative.

4. Discussion

This study utilized insights from past pharmacist involvement in prescription processes to successfully develop and expand the application of PBPMs. Although there are numerous reports on the effectiveness of PBPM in Japan, to the best of our knowledge, no study has elaborated on the process of formulating PBPMs. Following the initiative described in the present study, there was a significant and consistent increase in the use of PBPM-P across all prescription categories. Even with adjustments, the current initiative

has proven to be a significant factor in promoting PBPM. These findings suggest that this initiative is beneficial in creating effective PBPMs.

This study has several notable strengths. First, it provides a detailed and systematic approach to the development of PBPM, tailored specifically to IBD care. By analyzing real-world data from past pharmacist-led provisional prescriptions, the study bridges the gap between theoretical protocol design and practical application in clinical settings. Second, the methodology, which involved iterative discussions and collaboration between pharmacists and physicians, highlights an innovative and replicable approach to protocol development. Finally, the findings underscore the potential of PBPM to significantly reduce physician workload and improve the efficiency of multidisciplinary teamwork in healthcare settings.

This study also highlights the value of analyzing past practices. Focusing on a specific medical department simplifies the selection of experts for protocol creation. If the tasks within a department are somewhat standardized, they can be effectively translated into protocols, naturally leading to the development of more applicable protocols. Previous surveys have established that pharmacist involvement in rounds and participation in clinical conferences increase the delegation of provisional prescription upon a physician's request or directive. However, the application rate of PBPM remained low [14]. This could indicate that pharmacists become more proactive in prescription activities when they are allowed to alter or innovate their involvement in routine clinical practice. However, this does not necessarily extend to the applications of PBPM.

Thus, the development of PBPM is crucial for making it more practical and widely utilized. However, pharmacists in Japan cannot independently prescribe medications currently. The distinction between PPP and PBPM-P in this study lies in the source of directive initiation. While PPP involves a physician directing a pharmacist, leading to pharmacist involvement in prescription issuance, PBPM-P enables pharmacists to autonomously engage in prescription issuance based on established protocols. The subsequent process after a pharmacist issues a provisional prescription remains the same in both models. However, if physicians and pharmacists follow appropriate methodologies, pharmacists can be involved in the prescription process. The formation of provisional prescriptions by pharmacists can facilitate physicians' tasks even when physicians are not in the electronic medical record system. Reports suggest that pharmacists' engagement in prescribing activities has been beneficial [17,18], highlighting the potential for pharmacists to significantly assist in managing physician tasks. While the creation of provisional prescriptions by pharmacists was active in this study and prior research, it necessitated verbal directives, implying high communication density due to the frequency of such interactions. In contrast, PBPM-P operates under predefined protocols, thus reducing the need for verbal communication and lowering communication density.

Tahara and colleagues have reported a negative correlation between the amount of communication and teamwork [19], indicating that PBPM could clarify actions and improve teamwork. This also implies that PBPM reduces communication costs between doctors and pharmacists, potentially easing the burden on physicians. Therefore, to assist physicians effectively, pharmacists must do more than merely facilitate provisional prescriptions. To meaningfully reduce physician workload, the application rate of PBPM must be enhanced. By streamlining communication and clarifying prescription procedures through PBPM, the healthcare system can improve efficiency and potentially enhance patient care outcomes by ensuring that pharmacists are better integrated into the care delivery process, without the constant need for direct physician oversight.

Risk assessment in tasks based on PBPM is crucial. Although creating provisional prescriptions by pharmacists may carry risks, as they are not directly legislated, this study

did not observe increased risks associated with this initiative. Intriguingly, the initiative reduced the number of prescription questions and subsequent changes, which often indicate prescription errors. This suggests that the active implementation of PBPM helps suppress prescription errors. Furthermore, reducing errors aligns with broader goals of enhancing patient safety and care quality. Poh et al. reported that when pharmacists prescribe drugs according to protocols, they adhere to the dosing guidelines and significantly reduce prescription errors [20]. Moreover, Lloyd et al. reported that pharmacists who received training in discharge prescription transcription had a lower error rate than doctors during discharge [21]. These reports support the findings of our study. In other words, the implementation of PBPM not only serves to reduce the workload of physicians but also provides a beneficial approach that contributes to patient safety. Because the analyses in this study were exploratory, further research focusing on operational errors within PBPM may be necessary.

This study has some limitations. First, the legal framework governing prescriptions varies significantly across countries and is unique even in Japan. This study was conducted at a single facility, which may limit the generalizability of the findings. However, the results indicate that pharmacists can deepen their involvement in prescription issuance by analyzing past cases, which is likely applicable in settings where legal restrictions on pharmacists are similar to those in Japan. Second, the process of formulating additional PBPMs in this study involved the card sorting method, which is an inherently narrative approach and may lack the systematic rigor that methods like text mining or clustering can provide. Although there is room for improvement in the development of a more theoretical approach, incorporating a narrative method by experts into protocol articulation is considered effective, as supported by the findings of this study. Third, this study focused primarily on applying PBPM and its impact on physician task shifting/sharing without clarifying its effects on patient outcomes. Although the beneficial effects of PBPM on patient outcomes have been extensively reported in Japan, these effects were not verified in the present study. However, the reduction in prescription queries and changes owing to the initiative can indirectly contribute to patient safety. This remains an area for future research. Finally, provisional prescriptions based on PBPM may not sufficiently assist in reducing physician tasks because they require physician approval to become formal prescriptions. In other countries, pharmacist-led models, such as the CDTM, have proven beneficial [22], highlighting the potential advantages of granting more autonomy to pharmacists [23]. This suggests a possible direction for future policy and practice changes in Japan, aiming to enhance the effectiveness of pharmacist involvement in patient care.

Therefore, a system similar to the CDTM that grants prescription autonomy to pharmacists is also desirable in Japan. The implementation of such a system may involve significant challenges, including legislative changes. Thus, further research on PBPM is essential to verify its effectiveness and safety. This could pave the way for the establishment of frameworks enabling pharmacists to play a more active and autonomous role in patient care management.

5. Conclusions

This study underscores the essential contribution of analyzing pharmacists' provisional prescriptions in developing effective PBPM systems. Key variables analyzed in this study included the rates of SP, PPP, and PBPM-P. These variables provided valuable insights into the changes in prescription processes before and after the initiative.

The implementation of new PBPM protocols significantly increased the use of PBPM-P while reducing SP and PPP rates. This demonstrates their effectiveness in optimizing prescription processes, enhancing communication, and improving task distribution between

pharmacists and physicians. Additionally, the observed reduction in prescription questions and changes highlights the initiative's impact on improving safety and efficiency.

Looking ahead, the findings of this study provide a solid foundation for exploring the broader application of PBPM in diverse medical fields. Expanding the use of PBPM has the potential to reduce physician workload, enhance interdisciplinary collaboration, and improve patient safety. Future research should evaluate the applicability of PBPM in various clinical settings, focusing on long-term patient outcomes, cost effectiveness, and interdisciplinary workflow optimization. These efforts will help establish PBPM as a cornerstone for improving healthcare efficiency and outcomes, paving the way for its integration into broader medical practices.

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Informed Consent Statement: Information about the study, including the purpose of the study, was provided or made public, and the study was conducted in an opt-out format that guaranteed the opportunity to refuse whenever possible.

Data Availability Statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Quality-of-Life Assessment and Pharmacokinetic Study in Hemophilia A Patients Undergoing Prophylactic Treatment

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Abstract: This study evaluates the health-related quality of life (HRQoL) among patients with hemophilia A currently undergoing prophylactic treatment at the Hemophilia Center of Northern Greece. Using the Haem-A-QoL questionnaire, we assessed various HRQoL dimensions in a cohort of 29 adult male patients, analyzing the impact of age, disease severity, and treatment regimens. The results revealed that younger patients (18–30 years old) exhibited significantly better overall HRQoL scores (total score of 25.36) compared to older age groups (37.81 for the 31–45 group and 43.71 in the 45+ group), particularly in the physical health (29.16 vs. 48.43 vs. 58.57) and mental well-being domains (25 vs. 37.11 vs. 41.07). Interestingly, moderate hemophilia patients reported lower HRQoL (42.31) than those with severe form (34.85), suggesting unique challenges in managing their condition. The 'Sports/Free Time' domain had the highest scores (65.81), indicating significant limitations in physical activities in the everyday lives of affected individuals. However, better outcomes were observed in the mental dimension (36.09), work/study (34.88), family planning (10.68), and relationships aspects (16.67), where our cohort reported very low scores compared to similar studies, indicating a significantly better quality of life in these domains. These findings highlight the importance of personalized psychosocial support and targeted interventions to address the specific needs of hemophilia patients, particularly in enhancing physical activity opportunities and managing the psychological burden of moderate hemophilia. The study contributes valuable insights into the HRQoL of hemophilia patients and underscores the necessity for tailored approaches to improve patient outcomes across all dimensions of life.

Keywords: hemophilia A; health-related quality of life; pharmacokinetic study; Greece; Haem-A-QoL; prophylactic treatment

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1. Introduction

Hemophilia is a hereditary genetic disorder characterized by frequent bleeding episodes. It is an X-linked recessive condition, predominantly affecting males, and arises due to the deficiency of coagulation factor VIII (hemophilia A) or factor IX (hemophilia B) [1,2]. Hemophilia A is a rare hematological disorder, affecting approximately 1 in 5000 individuals, while hemophilia B affects 1 in 30,000 [1]. The risk of bleeding is correlated with the severity of the condition, which is classified as mild (5–40%), moderate (1–5%), or severe (<1%) based on the factor levels in functional plasma [3]. In severe cases, hemophilia can become a significant clinical challenge; however, nowadays it typically

reduces life expectancy by only a few years compared to the healthy population [4]. Recurrent bleeding episodes in joints and muscles are the most prevalent symptoms of the condition and may have a variety of long-term clinical repercussions, including chronic musculoskeletal disruptions, joint diseases, constant pain, and limited range of motion [5,6]. In addition, the regularity of treatment injections, the absence from school/work due to hospital visits, clinical manifestations, and limited engagement in social activities, such as sports, are typical [7]. Thus, hemophilia and its management have a significant effect on the health-related quality of life (HRQoL) of affected individuals. The World Health Organization's (WHO) definition of HRQoL is 'an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns' [8]. Based on this definition, the term includes a range of patients' mental, emotional, physical, social and behavioral aspects [9]. In short, HRQoL is directly affected by parameters like disease severity and management strategies, the existence of comorbidities, personal socioeconomical status and living environment, and each individual's coping mechanisms of pain, anger, and anxiety [10,11].

Advances in treatment have significantly improved life expectancy for hemophilia patients [4,12–14]. In mild and most moderate cases, the management strategy includes symptomatic treatment, involving the administration of clotting factors only during bleeding episodes or when there is a risk of hemorrhage, such as major surgeries (on demand treatment). In contrast, severe cases require continuous prophylactic treatment, necessitating frequent injections, hospital visits, and regular social absenteeism throughout the patient's life [15,16]. This management strategy significantly impacts an individual's daily life, social activities, and mental health [16–18]. Accurate HRQoL evaluation can inform treatment decisions, optimize therapeutic strategies, and enhance overall supportive care for hemophilia patients [19–21]. Self-assessment by patients is also vital for personalizing treatment, as it can reveal important subtle characteristics, such as anxiety or depression, that may not be readily apparent to healthcare providers [22–24].

Standard half-life factor VIII (SHL FVIII) products have been the cornerstone of hemophilia A treatment, providing a temporary elevation of FVIII levels to prevent or manage bleeding episodes [4]. These products typically require frequent infusions, due to their relatively short half-life, which generally ranges from 8 to 12 h. This frequent dosing schedule can place a substantial strain on patients, impacting their quality of life and adherence to treatment. In response to these challenges, extended half-life (EHL) FVIII products have been developed. EHL FVIII products are engineered to remain in the bloodstream longer, thereby extending the dosing intervals to every 3–7 days, depending on the specific product and individual patient pharmacokinetics. The advent of EHL FVIII products has significantly improved the management of hemophilia A, offering patients greater flexibility, reducing the frequency of infusions, and potentially enhancing adherence and overall quality of life [25].

Pharmacokinetic (PK) studies have emerged as a crucial tool in the personalized management of hemophilia, enabling healthcare providers to tailor prophylactic treatments to each patient's specific needs [26]. Traditional prophylaxis regimens may lead to suboptimal dosing, either increasing the risk of bleeding or unnecessarily frequent infusions [27]. Population pharmacokinetics (PopPK), utilizing Bayesian models, allows for the development of individualized PK profiles that consider factors such as age, weight and factor concentrate type. These profiles can predict how long a patient will maintain therapeutic levels of clotting factors, thereby optimizing treatment schedules and reducing the overall burden of therapy [28].

The implementation of PK-tailored prophylaxis has shown promise in improving clinical outcomes for hemophilia patients by reducing the frequency of bleeds and enhancing

the overall quality of life [26–30]. Tools like the Web-Accessible Population Pharmacokinetic Service—Hemophilia (WAPPS-Hemo ©) (McMaster University, Hamilton. Canada) facilitate the integration of individualized PK data into routine clinical practice, thus allowing clinicians to make informed decisions in alignment with the clinical and social needs of patients [31]. Despite the potential benefits, the widespread adoption of PK-tailored prophylaxis faces challenges, including patient recruitment and the models' adjustments in newer therapies like emicizumab [26,28,32].

The primary objective of this study is to evaluate the HRQoL of hemophilia A patients undergoing prophylactic treatment at the Hemophilia Center of Northern Greece, utilizing the Haem-A-QoL questionnaire. Additionally, this research aims to examine the pharmacokinetic parameters of different FVIII products already included in their treatment regimens.

2. Materials and Methods

2.1. Study Population

The study included 29 consecutive male hemophilia patients registered and monitored at the Hemophilia Center of Northern Greece. Participants were classified based on factor levels: those with levels <1% were considered to have severe hemophilia, while levels 1–5% indicated a moderate form of the condition. The inclusion criteria required participants to be under prophylactic treatment, to be at least 18 years old with severe/moderate hemophilia, and capable of understanding the questions and willing to complete the questionnaire. The questionnaire and the blood sampling were conducted in person at the center between June 2023 and September 2023. Participation was voluntary, while parameters like age, height, weight, disease severity, baseline factor levels, blood type, the factor VIII product being used in prophylaxis, and dose regimen were collected. The study complied with the Declaration of Helsinki and was approved by the Institutional Review Board of Hippokration General Hospital, with informed consent collected from all participants. To ensure patient confidentiality, all collected data were anonymized, analyzed and stored securely, with access restricted to authorized personnel only. The approval code of the study was 585/25.7.2019.

2.2. Measuring Tools

For our study, the Haem-A-QoL© (Haemo-QoL© group, Hamburg, Germany) quality-of-life index questionnaire for adults with hemophilia was employed. This questionnaire was selected for our research because it has been extensively tested in various studies to ensure its reliability and specificity [11]. The questionnaire consists of 46 items distributed across 10 dimensions, including physical health, emotional well-being, self-perception, leisure and sports, work and school, condition management, treatment satisfaction, future outlook, family planning, and partnership-sexuality, as well as a cumulative score scale [33]. Scores are calculated by converting the raw scores for each dimension and the overall score to a scale of 0 to 100, where 0 indicates the best health-related quality of life and 100 reflects the worst [34]. In our study, we employed the Greek version of the Haem-A-QoL© questionnaire, used with permission from the Haemo-QoL© group [35].

FVIII levels were measured from plasma samples (one-stage clotting assay, Pathromtin SL reagent) taken before and 2 h after the administration of the factor concentrate, according to each patient's normal prophylaxis regimen. Pharmacokinetic models were generated using the McMaster PopPK© clinical calculator (Version 1.2 (2022-05-04)© 2024 McMaster University, Hamilton, Canada), powered by WAPPS-HEMO©. The tool was utilized after the expressed permission of the McMaster group.

2.3. Statistical Analysis

Sample size was calculated based on estimated QoL differences between severe and moderate hemophilia. Power was defined at 80% for a 1% level of significance. Total sample size was determined at 25 subjects. The mean and standard deviation were utilized for the descriptive analysis of quantitative variables, while relative frequencies and absolute values (n, %) were applied to qualitative variables. The Shapiro–Wilk normality test was employed for variables with fewer than 50 subjects. To investigate correlations between the scores of the 10 subscales and the overall score of the Haem-A-QoL questionnaire in relation to factor concentrates, disease severity, and age groups, comparisons were conducted among three or more independent groups. When subscale scores followed a normal distribution, a parametric one-way analysis of variance (ANOVA) was applied; otherwise, when the assumption of normality was not met, a non-parametric Kruskal–Wallis test was used. Similarly, to assess correlations between the Haem-A-QoL subscale scores and the overall score with regard to prophylaxis, comparisons were performed between two independent groups. The parametric Independent Samples t-test was applied for normally distributed subscale scores, whereas the non-parametric Mann–Whitney test was utilized when normality was not observed. Non-parametric tests are robust to deviations from normality and do not rely on distributional assumptions; thus, they are suitable for analyzing non-normally distributed data. The χ^2 test was utilized to examine associations between clinical and demographic characteristics. Data analysis was executed by using the statistical software "IBM SPSS Statistics, Version 23.0," with the significance level established at 5%.

3. Results

For this research, a group of 29 adult males with hemophilia A completed the Haem-a-QoL questionnaire and agreed to blood sampling. Participants ranged in age from 19 to 70 years and exhibited severe and moderate hemophilia. The sample population was geographically diverse, including individuals from both rural and urban areas across Thrace, Macedonia, Thessaly, and the North Aegean islands. The detailed demographics of the participants are presented in Table 1.

Table 1. The demographic characteristics of the sample population (*n* = 29).

Patients' Data	Categories	Number of Patients (%)
Age	18–30 years	6 (20.7)
	31–45 years	16 (55.2)
	45+ years	7 (24.1)
Height	<170 cm	8 (27.6)
	171–180 cm	9 (31)
	180+ cm	12 (41.4)
Weight	<70 kg	5 (17.2)
	71–85 kg	17 (58.7)
	85+ kg	7 (24.1)
Disease Severity	Moderate	7 (24.2)
	Severe	22 (75.8)

Table 1. *Cont.*

Patients' Data	Categories	Number of Patients (%)
Blood Type	0+	13 (44.8)
	0−	4 (13.7)
	A+	4 (13.7)
	A−	2 (6.8)
	B+	4 (13.7)
	B−	1 (3.4)
	AB+	1 (3.4)
Factor Concentrates	Rurioctocog alfa pegol	3 (10,3)
	Damoctocog alfa pegol	7 (24.1)
	Efmoroctocog alfa	15 (51.7)
	Octocog alfa	2 (6.8)
	Moroctocog alfa	1 (3.4)
	Inn-octocog alfa	1 (3.4)

A significant distribution was identified between age groups and disease severity. Specifically, a considerable proportion (44.8%) of patients with severe hemophilia were in the 31–45 age group, a percentage markedly higher than that observed in the 18–30 (20.6%) and 45+ (10.3%) age groups. In contrast, among those with moderate hemophilia, the distribution of patients was more consistent across the 18–30 and 45+ age groups, with percentages of 10.3% and 13.7%, respectively. The distribution between age groups and disease severity is available as Supplementary Material in the Word file entitled 'Distributions'.

Table 2 displays the standard deviation, mean score, minimum, and maximum values for the scores from each of the 10 subscales of the questionnaire as well as the overall score, categorized by age group. Data indicate that the 18–30 individuals have a significantly lower mean score (25.36) compared to the other two age groups (37.81 and 43.71, respectively), suggesting a markedly better quality of life. In particular, the domains of family planning and relationships stand out with a notably low score of 4.16, reflecting a positive outcome. Similarly, low scores are observed in these domains for the other age groups (12.89–23.43 and 12.5–15.47), indicating an overall good quality of life in these areas. However, the highest score, and thus the lowest quality of life, is found in the sports/free time domain, which includes questions related to avoiding sports due to hemophilia, limitations on freedom to travel, and the necessity of planning activities in advance. Additionally, the only domain where the 18–30 age group exhibits a higher score, and thus a lower quality of life, is in coping with the disease. This domain includes questions about the patients' efforts to recognize bleeding episodes promptly, understand whether they are bleeding, and manage the control of such episodes.

Table 3 encompasses the statistical parameters (mean value, standard deviation, and minimum and maximum values) across each of the 10 questionnaire subscales, categorized by condition severity, alongside the total score.

Table 2. The statistical parameters of the 10 Haem-A-QoL questionnaire subscales, categorized by age group.

	Age Group					
	18–30		**31–45**		**45+**	
	n	Mean Score ± SD (Min–Max)	*n*	Mean Score ± SD (Min–Max)	*n*	Mean Score ± SD (Min–Max)
Physical Health	6	29.16 ± 11.33 (10–45)	16	48.43 ± 22.48 (15–95)	7	58.57 ± 19.11 (0–100)
Mental Dimension	6	25 ± 14.43 (0–43.75)	16	37.11 ± 18.94 (6.25–68.75)	7	41.07 ± 24.69 (0–100)
Perception	6	25.83 ± (16.93) (0–45)	16	38.75 ± 18.32 (5–65)	7	47.14 ± 20.15 (10–75)
Sports/Free Time	6	45.83 ± 25.06 (0–80)	16	72.5 ± 13.57 (35–90)	7	62.85 ± 29.74 (0–90)
Work/Study	6	23.95 ± 17.08 (0–50)	16	35.54 ± 14.61 (6.25–62.5)	7	38.39 ± 23.72 (0–62.5)
Coping	6	26.38 ± 11.2 (12.5–46.88)	16	17.71 ± 14.98 (0–50)	7	15.47 ± 16.32 (0–41.67)
Treatment	6	31.25 ± 11.12 (12.5–46.88)	16	37.11 ± 17.39 (9.38–75)	7	58.03 ± 18.43 (31.25–87.5)
Future	6	21.66 ± 12.13 (0–35)	16	35.62 ± 15.99 (5–55)	7	48.57 ± 20.43 (10–85)
Family Planning	6	4.16 ± 5.89 (0–12.5)	16	12.89 ± 20.42 (0–62.5)	7	12.5 ± 21.39 (0–62.5)
Relationships	6	4.16 ± 9.31 (0–25)	16	23.43 ± 26.71 (0–83.33)	7	15.47 ± 24.57 (0–58.33)
Total Score Haem-A-QoL	6	25.36 ± 8.96 (9.24–34.24)	16	37.81 ± 13.53 (15.22–64.13)	7	43.71 ± 19.51 (10.33–63.59)

Although the study involved a small sample size, it is particularly noteworthy that both the overall questionnaire score and the scores on 9 of the 10 individual sub-scales were higher in patients with moderate hemophilia. The exception was the treatment domain, which includes questions related to bleeding episodes, where patients with moderate hemophilia exhibited a better quality of life, likely due to the lower annual bleeding rates typically observed in this group. Consistent with earlier findings, the family planning and relationship domains yielded low scores, while the highest scores were again found in the category related to sports and social activities, reflecting significant limitations for affected individuals.

The standard deviation, mean score, minimum, and maximum values for the scores from each of the 10 subscales of the questionnaire as well as the overall score, categorized by the factor concentrate, are available as Supplementary Material in the Word file entitled 'Scores—sFactor Concentrate'. Due to the uneven distribution of patients across FVIII products, definitive conclusions cannot be drawn; however, the family planning and relationship domains consistently scored low, while the sports/free time and physical health domains showed particularly high scores on a case-by-case basis, indicating substantial challenges for patients with hemophilia in these aspects of their daily lives.

Table 3. The statistical parameters of the 10 Haem-A-QoL questionnaire subscales, categorized by condition severity.

	Disease Severity			
	Moderate		**Severe**	
	n	Mean Score ± SD (Min–Max)	*n*	Mean Score ± SD (Min–Max)
Physical Health	7	53.57 ± 27.47 (0–100)	22	44.77 ± 23.32 (10–95)
Mental Dimension	7	43.75 ± 20.06 (0–100)	22	32.95 ± 20.65 (0–75)
Perception	7	45.71 ± 20.94 (10–75)	22	35.68 ± 18.84 (0–65)
Sports/Free Time	7	66.42 ± 21.47 (0–90)	22	64.09 ± 20.31 (0–85)
Work/Study	7	36.60 ± 23.01 (0–62.5)	22	32.95 ± 16.66 (0–62.5)
Coping	7	11.91 ± 10.78 (0–25)	22	21.21 ± 18.24 (0–66.67)
Treatment	7	52.23 ± 19.6 (31.25–87.5)	22	37.36 ± 17.76 (9.38–75)
Future	7	41.42 ± 21.49 (10–75)	22	34.09 ± 21.61 (0–85)
Family Planning	7	18.75 ± 23.14 (0–62.5)	22	8.52 ± 16.7 (0–62.5)
Relationships	7	20.23 ± 22.64 (0–58.33)	22	16.66 ± 25.37 (0–83.33)
Total Score Haem-A-QoL	7	42.31 ± 19.11 (10.33–63.59)	22	34.85 ± 14.08 (9.24–64.13)

Table 4 presents the mean scores for each of the 10 questionnaire subscales for the entire sample of 29 patients. The overall score of 37.02 suggests a relatively good quality of life across the cohort, with notably low scores recorded in the coping (18.04), family planning (10.68), and relationships (16.67) domains.

The analysis of each question individually revealed significant statistical differences based on the patient's treatment regimen in various aspects of the questionnaire. These differences were particularly evident in how hemophilia affects patients' lives ($p = 0.007$), their concern about the condition worsening ($p = 0.021$), fear of potential complications ($p = 0.001$), discomfort associated with both the frequency and the process of injections ($p = 0.012$), ability to attend work or school despite the disease ($p = 0.001$), levels of anger and pain ($p = 0.019$), the time required to prepare for daily activities ($p = 0.014$), and the sense of social exclusion experienced ($p = 0.045$). Significant statistically differences were also observed in responses related to injection procedure ($p = 0.014$) and the impact on daily activities ($p = 0.022$), depending on the severity of the disease. Additionally, significant differences were noted in the responses concerning overall physical health ($p = 0.015$), participation in sports activities ($p = 0.004$), and treatment-related complications ($p = 0.015$), which varied according to the age of the patients (Table 5).

Table 4. Mean scores for each of the 10 domains of the questionnaire of all the 29 patients.

Haem-A-QoL Domains	Score
Physical Health	48.71
Mental Dimension	36.09
Perception	38.39
Sports/Free Time	65.81
Work/Study	34.88
Coping	18.04
Treatment	40.73
Future	36.45
Family Planning	10.68
Relationships	16.67
Total Score Haem-A-QoL	37.02

Table 5. The quality-of-life dimensions that exhibited the most significant statistical variation, along with their corresponding varying factors.

Quality-of-Life Dimensions	Variable (*p*-Value)
Patient's Life Plans	Factor concentrate (0.007)
Concerns about Complications	Factor concentrate (0.001)
Potential for Deterioration	Factor concentrate (0.021)
Pain Levels	Factor concentrate (0.013)
Anger Levels	Factor concentrate (0.019)
Discomfort during Infusions	Factor concentrate/Disease Severity (0.012)
Disruption in Daily Activities	Factor concentrate (0.001)
Social Exclusion Perception	Factor concentrate/Disease Severity (0.04)
Total Physical Health	Age of patients (0.015)
Engagement in Physical Activities	Age of patients (0.04)
Treatment-related Complications	Age of patients (0.04)

Concerning the pharmacokinetic properties of factor FVIII concentrates, rurioctocog alfa pegol demonstrated the longest half-life at 24.5 h, followed by damoctocog alfa pegol at 20.5 h, octocog alfa at 19.3 h, efmoroctocog alfa at 18 h, moroctocog alfa at 16.2 h, and INN-octocog alfa at 12 h. In terms of the average time required to reach 5% of FVIII levels, INN-octocog alfa had the shortest duration at 38.2 h, with moroctocog alfa at 71 h, octocog alfa at 72.7 h, efmoroctocog alfa at 79.3 h, damoctocog alfa pegol at 92.2 h, and rurioctocog alfa pegol at 110.9 h following (Figure 1).

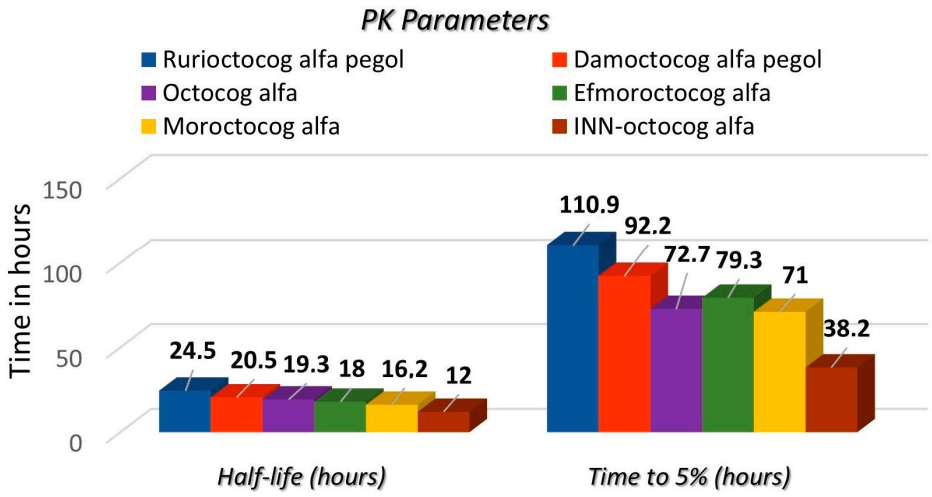

Figure 1. The pharmacokinetic properties of different FVIII concentrates used in the 29 patients' prophylaxis regimens.

4. Discussion

This study from the Hemophilia Center of Northern Greece evaluated the HRQoL of patients with hemophilia A undergoing prophylactic treatment, along with the pharmacokinetic properties of the factor VIII concentrates that are being used. By utilizing the Haem-A-QoL questionnaire, we assessed various dimensions of HRQoL, revealing significant differences based on age and disease severity.

Notably, our study found that patients aged 18–30 exhibited significantly better overall HRQoL scores compared to older age groups (25.36 vs. 37.81 vs. 43.71), particularly in the domains of physical health (29.16 vs. 48.42 vs. 58.57), mental well-being (25 vs. 37.11 vs. 41.07), and perception (25.83 vs. 38.75 vs. 47.14). This finding aligns with the results of our previous study, where the highest HRQoL scores were observed in the same age group, along with patients over 60 years old with mild hemophilia, while the lowest was in individuals aged 46–60 [36]. The early initiation of primary prophylactic therapy in younger patients, especially with extended half-life products, has been shown to mitigate the severity of hemophilic complications, thereby significantly enhancing their HRQoL. This observation aligns with the extant literature, which suggests that early prophylactic intervention in young patients with severe hemophilia is associated with improved HRQoL outcomes [37–40]. The beneficial effects of early prophylaxis were also highlighted in a non-interventional study which examined 94 patients from Asia, North America, Oceania, and Europe. In this study, individuals under prophylaxis treatment showed substantially improved total HRQoL compared with on-demand (26.6 vs. 40.1) [41]. In contrast, older individuals who either received insufficient treatment or were untreated during childhood and adolescence have developed severe difficulties [42]. This progression has markedly impaired their HRQoL, primarily due to mobility constraints, reduced physical activity, and diminished independence. These limitations, in conjunction with chronic pain, often lead to feelings of irritability, anger, and helplessness [43–46].

Another critical finding of our study was the impact of disease severity on HRQoL. While severe hemophilia generally correlates with poorer outcomes, due to the increased frequency of bleeding episodes and greater physical limitations, the moderate group in our study showed unexpectedly lower HRQoL in 9 out of 10 total domains, particularly in those related to mental health and coping with the disease, in disagreement with findings from other studies [47–49]. One hypothesis for this finding is that this cohort of individuals may not receive the same level of medical attention (no initiation of prophylaxis therapy) and psychosocial support as severe cases, potentially leaving them underserved [50,51].

Inconsistent bleeding patterns may also create uncertainty and stress, as these patients may not feel as adequately prepared to manage their condition.

To address these unique challenges, a multifaceted approach may be of utmost importance. For example, the implementation of comprehensive structured therapy, counseling programs, and potential patient education initiatives will offer psychosocial support and equip patients with treatment-related strategies for managing clinical symptoms [24,52–55]. Furthermore, to connect patients with others in similar situations and alleviate feelings such as social exclusion, depression, anxiety, and fear, peer support groups could be encouraged [56]. Lastly, given the fact that in the post-COVID era society has increasingly embraced remote methods for addressing various challenges, a shift towards the implementation of telehealth and digital applications that promote continuous monitoring, and guidance can be particularly valuable. Helpful paradigms are mobile health applications that empower patients by offering tools for symptom tracking, medication reminders, and providing educational content, thus fostering greater self-management and improving overall outcomes [57–61].

In terms of specific domains, we observed specific patterns across various dimensions. Specifically, our study revealed that the 'Sports/Free Time' domain had the highest scores (a total score of 65.81), indicating the poorest quality of life. Participants in the study reported significant limitations not only in engaging in physical activities, a common issue among hemophilia patients due to the increased risk of bleeding and joint damage, but also impairment in traveling, due to need for exhaustive preparation. This result aligns with the findings of studies from India, Korea, Turkey, Brazil and Iran, where participation in physical activities and travel also emerges as one of the most impacted domains [62–68]. Our study also points out that the mental dimension (36.09), perception (38.39), family planning (10.68), and relationships (16.67) of the affected individuals showed better HRQoL outcomes, not only compared to other similar cohorts [69] but also compared with our previous study [36]. The increased HRQoL observed in these domains for our patients can be explained by the fact that our previous study included both on-demand and prophylaxis patients, but also due to the transition of the majority of patients under prophylaxis from SHL to EHL factor concentrates. The overall improvement compared with older studies highlights the advancements in medical management and psychosocial support that have transformed the field of hemophilia over the years [70].

This study provides a comprehensive evaluation of the HRQoL in hemophilia A patients undergoing prophylactic treatment and explores the pharmacokinetic properties of various factor VIII concentrates. Our findings reveal notable variations in HRQoL across age groups and disease severity, with younger patients demonstrating significantly better overall outcomes, particularly in physical health and mental well-being domains. Contrary to expectations, patients with moderate hemophilia reported lower HRQoL compared to those with severe forms, highlighting the possible unique psychosocial and management challenges faced by this subgroup. Our data underscore the substantial impact of hemophilia on patients' everyday lives, particularly in domains like physical activity and social participation, as evidenced by high scores in the 'Sports/Free Time' domain. However, relatively lower scores in domains of family planning and relationships suggest better perceived outcomes in these areas among the study cohort compared to similar studies. From a pharmacokinetic perspective, given the small sample size of our cohort and due to the imbalanced proportion of individuals for different FVIII products, robust and valid conclusions about the role of factor concentrates cannot be drawn. These findings contribute to a growing body of evidence advocating for personalized therapeutic strategies that account for patient-specific factors such as age, severity, and psychosocial needs.

Addressing gaps in physical activity opportunities and providing targeted psychological support could enhance the overall well-being of hemophilia patients.

5. Limitations and Future Work

The primary limitation of our research is the small sample size of patients whose data were analyzed. While these individuals represent the majority of patients receiving prophylactic treatment at our center, the limited sample size reduces the generalizability of our findings to other populations. Additionally, due to the imbalanced proportion of patients across different replacement products, safe and specific conclusions about the role of factor concentrates in HRQoL cannot be drawn. Moreover, the influence of coexisting conditions in affected individuals is not taken account in this study, since possible comorbidities were not established as an exclusion criterion. We also recognize the inherent limitations of self-reported data in HRQoL assessments, which rely heavily on each individual's subjective perception. Furthermore, potential selection bias may exist, as patients who are more engaged in their treatment and motivated to participate in studies may report better HRQoL compared to those who decline participation. Such biases may have affected the accuracy and consistency of the results, particularly in domains like mental health and coping. Future research with larger and more diverse cohorts, longitudinal designs, and complementary assessment tools is essential to enhance the robustness and validity of these findings and address the limitations of this study.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/pharmacy13010016/s1, Table S1: Distributions title; Table S2: Scores-Factor Concentrate.

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