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Editorial

Peer review and publication delay

Fernando FERNANDEZ-LLIMOS, Pharmacy Practice 2018 peer reviewers.

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Abstract:
Selecting peer reviewers is a crucial stage of the editorial process that ensures the quality of scholarly publications. An alternative to selecting peer reviewers from data bases created with expressions of interest of volunteers consists in systematically searching PubMed for similar articles and inviting their authors to act as peer reviewers. Although this process might identify more appropriate peers, it also can increase the time of the editorial process. In 2018, Pharmacy Practice had to invite 4.70 (SE=0.33) potential reviewers per one accepting. The time from the first reviewer invitation to the last reviewer report received was 61 days (SE=2.1). These figures confirm the existence of a peer review crisis which is significantly increasing the publication delay.

Keywords: Peer Review; Peer Review, Research; Open Access Publishing; Periodicals as Topic

Despite the efforts that some publishing platforms are devoting to convince researchers about the convenience of eliminating pre-publication reviews, these pre-publication peer review externally-done process continue to be the gold-standard in scholarly publication. However, we have to recognize that the peer review crisis does exist. Some optimistic editors in the early 2010s refused to accept the facts, reporting that the proportion of reviewers invited per accepting reviewer increased only from 1.38 (SE=0.02) in 2001 to 2.03 (SE=0.05) in 2010.[1] Conversely, other editors started recognizing the increasing difficulty recruiting peer reviewers, with an increase from 1.8 (SE=0.07) attempts to obtain an acceptance in 2008–2011 to 2.3 (SE=0.13) in 2014–2016, and 15% papers requiring more than 8 invitations.[2] Many alternatives to the traditional external peer review have been suggested, but their efficiency could not be demonstrated.[3] But, more importantly, their influence in evidence-synthesis has not been evaluated at all. Should we include an article uploaded to a pre-print repository in a systematic review or a meta-analysis, before a sufficient number of post-publication reviews have been performed?

In 2018, Pharmacy Practice publicly recognized suffering from the peer review crisis.[4] During 2018, Pharmacy Practice invited 879 potential peer reviewers, but only 198 (22.5%) accepted the task. This means that Pharmacy Practice invited 4.70 (SE=0.33) potential reviewers per one accepting. Additionally, 15 reviewers who accepted to review a paper did not deliver the review report. Peer reviewer selection process performance indicators in Pharmacy Practice seem to be quite below the two aforementioned journals. In fact, after the complete automation of the editorial process, selecting peer reviewers became the most time-consuming task in Pharmacy Practice's editorial process.

Pharmacy Practice editorial board started an in-depth analysis of the causes and potential solutions to solve this problem, while ensuring maintenance of high quality standards. Many journals created reviewer databases using the expression of interest received to act as a peer reviewer. Commonly, these databases use candidate-reported keywords as a means to identify areas of expertise to facilitate manuscript assignment. Criticisms regarding the poor quality of peer review reports received are frequent. Every researcher has personal anecdotes about their experience with peer reviewers' reports. One of my systematic reviews was rejected in a journal based on a reviewer's report that criticized our selection of bibliographic databases. The reviewer asked why we have not used Medline or Embase, when we had reported using PubMed and Scopus. In 2013, and to avoid the potential excessive self-esteem of spontaneously offered reviewers, Pharmacy Practice established a systematic peer reviewer selection process based on searching similar articles on PubMed and identifying the authors of those articles as the hypothetical best reviewers for the new manuscript.[5] This selection process involves inviting researchers that have previously volunteered to serve as reviewers for the journal, which may partially explain the lower acceptance rate in Pharmacy Practice.

An immediate consequence of the number of failed review requests is the increased publication process time. During 2018, Pharmacy Practice original research articles obtained the first response after peer review comments in 92 days (SE=5.7). The time from the first reviewer invitation to the last reviewer report submission was 61 days (SE=2.1). As major aim for 2019, Editorial Board have established the reduction in the time to make decisions, which means reducing the about 30 days that currently takes to: a) decide sending the manuscript out for peer review or desk-reject it; and b) analyze peer reviewers' reports received to decide whether manuscript modifications could make the article acceptable. Reducing the remaining 61 days will depend on our ability to convince pharmacy practice researchers that acting as a peer reviewer is probably the most important part of a collaborative publishing scheme.

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Pharmacy Practice 2018 peer reviewers.

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Following the tradition initiated last year, Pharmacy Practice is pleased to recognize the contribution to the journal of those who served as reviewers, and reward their efforts by publishing the first editorial of the year with a collective authorship including all the reviewers that contributed during 2018.

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Review

Expanding the role of Australian pharmacists in community pharmacies in chronic pain management - a narrative review

John MISHRIKY, Ieva STUPANS, Vincent CHAN.
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Abstract

Chronic pain is a condition where patients continuously experience pain symptoms for at least 3 to 6 months. It is one of the leading causes of disabilities across the globe. Failure to adequately manage chronic pain often results in additional health concerns that may directly contribute to the worsening symptoms of pain. Community pharmacists are an important healthcare resource that contributes to patient care, yet their roles in chronic pain management are often not fully utilised. This review aimed to investigate and explore pharmacist-driven chronic pain educational and medication management interventions in community pharmacies on an international level, and thereby identify if there are potential benefits in modelling and incorporating these interventions in the Australian community. We found a number of studies conducted in Europe and the United States investigated the benefits of pharmacist-driven educational and medication management interventions in the context of chronic pain management. Results demonstrated that there were improvements in the pain scores, depression/anxiety scales and physical functionality in patient groups receiving the pharmacist driven-interventions, thereby highlighting the clinical benefit of these interventions in chronic pain. In conclusion, pharmacists are trustworthy and responsible advocates for medication reviews and patient education. There are currently very limited formal nationally recognised pharmacist-driven intervention programs dedicated to chronic pain management in Australian community pharmacies. International studies have shown that pharmacist-driven chronic pain interventions undertaken in community pharmacies are of benefit with regards to alleviating pain symptoms and adverse events. Furthermore, it is also clear that research around the application of pharmacist-led chronic pain interventions in Australia is lacking. Modelling interventions that have been conducted overseas may be worth exploring in Australia. The implementation of similar intervention programs for Australian pharmacists in community pharmacies may provide enhanced clinical outcomes for patients suffering from chronic pain. The recently implemented Chronic Pain MedsCheck Trial may provide some answers.

Keywords

Pain Management; Professional Role; Community Pharmacy Services; Pharmacies; Nonprescription Drugs; Pharmacists; Review Literature as Topic; Australia

Introduction

Pain is a commonly presenting condition that can affect patients of all age groups. The International Association for the Study of Pain (IASP) defines pain as an 'unpleasant sensory and emotional experience associated with actual or potential tissue damage.[1,2] Although there is no clear definition of chronic pain, it is commonly defined as pain that has been present for at least 3 to 6 months. An estimated 20 per cent of Australian adults suffer from chronic pain.[3] Even though physical injuries appear to be the most common cause of chronic pain, one third of individuals have been unable to identify the original cause.[4] Inadequate diagnosis and treatment gives rise to clinical as well as practical health concerns for chronic pain sufferers, resulting in significant costs to the healthcare system and also causing financial strain on sufferers and their families in dealing with pain management.[5] Several studies have also revealed links between chronic pain and other conditions, such as depression, anxiety and sleeplessness/insomnia, which further contribute to the deterioration of the quality of life of chronic pain sufferers.[6-8]

This narrative review will only briefly cover the impacts caused by chronic pain, particularly relating to the health and wellbeing of patients and their families. This review will focus on investigating and exploring the potential pharmacist roles and pharmacist-driven chronic pain education and medication management interventions in community pharmacies on an international level, and thus identify if there are potential benefits in modelling and incorporating these interventions in the Australian community where the current roles in specific chronic pain management are quite limited.

With the aim to provide an evaluation of the current knowledge on the role of pharmacists in chronic pain management, systematic searches of the following electronic databases were carried out; Pubmed, Medline, Science Direct, Proquest and Google Scholar. Results were limited to January 1988 to October 2018. Search items used for each database included: 'chronic pain', 'chronic pain management', 'education', 'medication management' 'pharmacist intervention' and 'community pharmacist.' References from identified journal articles were also screened to identify further relevant articles. Studies were

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included if they assessed the impact of educational or medication management interventions in community pharmacies provided by pharmacists in the context of chronic pain management.

The health burden of chronic pain

As is the case with many other chronic illnesses, chronic pain can potentiate negative health outcomes and introduce additional health concerns.[3,7,9] Research has suggested that chronic pain substantially affects physical functionality. A European large-scale study demonstrated that of the participants who suffered from pain, 23% were no longer able to drive and around 40% were less able to walk and perform household daily chores due to their pain symptoms.[10] Additional studies have indicated that mental health disorders are common amongst chronic pain sufferers, resulting in a greater disease burden and a downwards spiral in the quality of life.[6,7] It is for these reasons that chronic pain sufferers express the desperate need to seek help from numerous healthcare providers, and in particular, pharmacists for pain relief.[10] It is therefore essential to understand the important and significant role of Australian community pharmacists in chronic pain therapy, given the fact that community pharmacists are often considered one of the most trusted health professionals in Australia. Before beginning to implement a much broader adoption of pharmacist-specific therapeutic approaches to managing chronic pain in a community pharmacy, an in-depth analysis of the current roles and responsibilities of Australian pharmacists is necessary.

The role of community pharmacists

Over time, the position of a community pharmacist in the healthcare system has evolved and will continuously evolve. Traditionally, the primary focus of a pharmacist has been to dispense medications as prescribed by a physician and to ensure that the drugs prescribed meet the required legislative standards.[11] Now, pharmacists often play a more proactive and significant role of consulting on pharmacotherapy. In Australia, pharmacies are considered to be important sources of a wide range of healthcare services in the community.[12,13] Australian pharmacists are unique in that they are educated at university level, undergo internship, become registered health professionals by the Australian Health Practitioner Regulation Agency (AHPRA), work in an accessible retail environment handling a multiplicity of medicines and have extensive interactions with other healthcare professionals.[12] The provision of professional health services and pharmacist-driven clinical interventions from the community pharmacy destination can serve the cost-effective, simple and imperative contribution to improved health outcomes.[14] It is therefore unsurprising that people perceive pharmacists as highly reliable and accessible advisers on many health related issues, whilst also being trustworthy purveyors of healthcare products and steadfast partners of the medical profession.[12,14]

For many chronic illnesses, medicines remain the major modality of treatment.[15,16] Chronic pain is no different in this context. It is inevitable that pharmacists should contribute to the management of chronic illnesses through the conduct of medication reviews, with the view to achieving the quality use of medicines.[12,14] A published systematic literature review explored the extensive roles of community pharmacists regarding the supply and management of medicines.[17] It was found that interventions involving pharmacists in medication management were generally effective in improving medicine use, adherence, adverse event detection and harm minimisation producing positive health outcomes.[18] The fact that pharmacists are experts in the supply and use of medicines suggests that they too have a key role in educating patients on the appropriate use of their medications.

Pharmacists can indeed provide education, counselling and advice on medication management to patients, with the goal of equipping patients with self-management skills aiming to have positive effects on adherence, appropriate medicinal use and clinical outcomes.[12,13,19] The important role of pharmacists in the quality use of medicines is further highlighted given the high likelihood that patients who suffer from chronic pain are using multiple analgesic medications. While treating chronic pain with different medications for synergistic effects may assist with the management of pain relief, this therapeutic strategy accentuates potential harm exposure.[20] The pharmacist's role in profiling all pain medications contributing to 'polypharmacy' has been reviewed in a number of studies, and it is unsurprising that pharmacists who are recognised as medication experts, can in fact play an active role in minimising harmful exposure due to medication misuse and abuse.[12,20,21]

The literature also contains numerous studies outlining the beneficial components of community pharmacist interventions in chronic illnesses. For example, pharmacists in community pharmacies have played key roles in minimising primary as well as secondary cardiovascular events in high risk patients to developing cardiovascular disease.[22-24] These community pharmacist-driven interventions in cardiovascular health showed significant improvements in hypertension as well as improved control of hyperlipidaemia.[22,23] Likewise, community pharmacist interventions focusing on patient education and healthy lifestyle promotion in type 2 diabetes have also resulted in significant reductions in HbA1c levels and improved glycaemic control.[25,26] Additional studies investigating community pharmacist interventions in asthma resulted in enhanced asthma control as well as improved medication adherence and inhaler technique.[27-29] Taken together, such research supports that pharmacists are indeed capable of carrying out interventions in community pharmacies which can improve patient health outcomes in a variety of different chronic disease states. As chronic pain is no different in this context, there are potential benefits to be expected from chronic pain interventions carried out by pharmacists in a community pharmacy, as well as lessons that can be learnt. This is particularly true for the Australian context where research around the application of pharmacist-driven chronic pain interventions is lacking.

Pharmacist-driven chronic pain interventions: a look at the roles of pharmacists in education and medication management

A systematic review and meta-analysis published by Bennett *et al*. in 2011 identified studies investigating the effectiveness of educational interventions by pharmacists in community pharmacies to patients with chronic pain.[30] Pharmacists delivering these educational interventions aimed to increase patient knowledge and understanding by relaying information, behavioural instructions or advice in relation to the management of chronic pain, thereby enabling patients to manage their pain more effectively.[30] Studies included in this systematic review consisted of patients suffering from chronic pain associated with knee pain, arthritis pain and cancer pain.[30] The mode of delivery of the pharmacist-driven educational intervention was comprehensive and involved patient follow-up during the study period. In two prospective studies, the pharmacist educational intervention comprised of face-to-face clinical consultations throughout the study period.[31,32] One study, however, also provided group educational sessions run by pharmacists on arthritic pain relief, whereas the second study only included two individualised face-to-face consultations on cancer pain, as well as follow-up daily telephone consultations as part of the educational intervention.[32] The daily telephone calls included advice and recommendations with regards to drug information, dosage adjustments and supportive counselling. Patients receiving these interventions experienced significant benefits in a reduction of pain intensity and in adverse effects.[30-32] Results also indicated that the greatest impact the pharmacist educational interventions had was mainly on patients experiencing chronic low back pain.[30]

There was some degree of overlap amongst the studies included in the systematic reviews on pharmacist-driven medication management interventions and pharmacist-driven educational interventions. Two individual studies included an educational and thorough medication review as part of the pharmacist-driven intervention.[32,33] Additionally, a systematic review and meta-analysis published in 2014 identified studies investigating the effectiveness of pharmacist-led medication review interventions in chronic pain. Studies included in this systematic review consisted of randomized control trials involving more than 1000 patients suffering from persistent pain with differing aetiologies.[34] The mode of delivery of the pharmacist-led medication interventions differed amongst the published studies. One longitudinal randomised exploratory study consisted of a control group receiving standard primary care, and two intervention groups, one of which included an in-depth medication consultation arranged by a pharmacist with prescribing rights.[35,36] The prescribing pharmacist intervention involved pharmacists completing a paper-based medication review of each patient's medical record. Patients were also asked to complete a pain diary for follow up consultations. Similarly, another published study also consisted of two groups, one of which included an intervention group of patients receiving a face-to-face consultation with a pharmacist on osteoarthritic pain, followed by an in-depth medication review.[37] Patients suffering from osteoarthritic pain who were placed in the control group only received an educational leaflet on knee osteoarthritis.[37] Pharmacists included in this particular study offered an educational leaflet on osteoarthritis to the control group, whereas the patients assigned to the intervention group received self-management education, medication reviews and a referral to a physiotherapist-guided exercise program. Outcomes from the pharmacist-patient consultation were then communicated to the patient's primary care physician. Pharmaceutical care plans were prepared by the pharmacists that included any necessary referrals to medical practitioners, recommendations for changes to medication regimens and whether non-pharmaceutical treatments had been considered previously by the patient.[37]

Prospective randomized control trials conducted in England and Northern Germany also investigated the perceived benefits of a pharmacist-led medication management intervention for pain.[38-40] In one of these studies, the mode of delivery of the pharmacist-led intervention was unique, in that patients who were assigned to the intervention group were either screened before and/or after receiving the intervention via telephone.[38,39] An additional published study investigated migraine and headache pain. Patients suffering from these specific types of pain who were assigned to the intervention group were interviewed via telephone before receiving the 'pharmaceutical care' intervention (defined as intensified structured counselling between patient and pharmacist).[39] Patients were then followed up via telephone four months after receiving the intervention. Despite reports of improved mental health and self-assessment of headache and migraine pain, there was no significant change in the number and severity of headache attacks reported by patients.[39] It was also reported that the lack of significance in this case could be due to the limitation in time of this particular study.[39]

The effectiveness of the pharmacist-led medication management interventions in these studies was assessed via different primary endpoints, with pain intensity and physical functioning being the major endpoints.[34] Pain intensity was recorded before and after receiving the pharmacist-led intervention in all of these studies using different scales.[34] One study reported a statistically significant reduction in pain scores at 3-month follow up.[33] However another trial reported a statistically significant reduction in pain score at both the 3 and 6 month follow-up in their prospective study.[37] Results from one clinical trial also demonstrated that there was a statistically significant improvement in the 'Chronic Pain Grade' (CPG) and depression/anxiety scales in groups receiving the pharmacist-intervention.[35,36] Pharmacists and GPs who were involved in this trial were later interviewed and reported that they were pleased with the improvements this intervention had provided in chronic pain management.[35,36] Physical functioning was also measured in all of the studies via the use of different validated questionnaires (such as SF-12, SF-36 and WOMAC).[41-43] Of the pharmacist-led intervention studies, only one reported a statistically significant improvement in physical functioning at both the 3 and 6 month follow up in the intervention group compared to the control group.[37] Results demonstrated that the group receiving the intervention gained an improvement in their physical

functionality and quality of life while also decreasing pain symptoms.[37] There were statistically significant improvements observed in the 'Lower Extremity Function Scale (LEFS), where a higher LEFS score indicates decreased physical disability.[37]

Despite reports from pharmacists on their views of the benefits of a pharmacist-led medication intervention in these studies (excluding Marra's trial), there appears to be some uncertainty around the clinical significance of these benefits due to the limitation of literature in this space.[34,37] However, as recognised internationally, pharmacist-driven interventions have demonstrated that pharmacists can and do play an important, key and necessary role in chronic pain management.

Community pharmacy and pain management in Australia: implications for future research

As previously indicated, approximately 20% of Australians experience chronic pain.[44] This figure is set to rise as the population ages. Inadequately treated chronic pain has significant impacts on function and quality of life. There are a number of specialised pain clinics throughout Australia that provide care and specialized treatment and incorporate a multidisciplinary approach to chronic pain therapy. However, with the growing number of chronic pain patients, the capacity for these clinics to manage people with chronic pain is already diminished with high waiting lists and the care of such patients will likely shift to other healthcare practitioners. This is where the role of an Australian community pharmacist may further be appreciated and better utilised in chronic pain management.[44,45] Evidently, community pharmacies across Australia are considered one of the most frequently and easily accessed primary healthcare services and are regularly the first point of contact for many Australians.[46]

Additionally, chronic pain patients tend to use over-the-counter (OTC) non-prescription drugs to self-medicate and manage pain.[47,48] The accessibility of these OTCs from pharmacies (and many also outside of pharmacies), often leads to patients purchasing analgesic medicines without the valuable advice provided by pharmacists.[18] Pharmacies are considered important checkpoints whereby the appropriateness of non-prescription medications can be validated, the patient's queries attended to and clinical interventions made if necessary.[18] Research has suggested that failure to receive professional pharmaceutical advice can lead to incorrect use of medicines by the consumer, inadequate chronic pain management as well as increasing the likelihood of experiencing adverse effects from self-management.[49]

As primary healthcare professionals, pharmacists can address this health concern by effectively engaging with the patient at each purchase and supply of analgesic medication and improving patient knowledge regarding the appropriate use of OTC medicines. This can be achieved by developing a good understanding of chronic pain management and becoming aware of the factors that deter patients from seeking and receiving appropriate advice. It is timely and appropriate that the issue of chronic pain management is addressed by the health professions more broadly and at least in the short to medium term, pharmacists delivering more optimal care and service to their patients suffering from chronic pain.

Lastly, it is of interest and indeed opportune to note that there have been recent developments for Australian community pharmacies in the chronic pain management space. In 2018, the Australian Government has announced the implementation of The Chronic Pain MedsCheck Trial. This initiative is funded by the Australian Department of Health as part of the Sixth Community Pharmacy Agreement (6CPA) Pharmacy Trial Program (PTP).[50] The main objective of The Chronic Pain MedsCheck Trial is to examine the effectiveness of a specialised Chronic Pain MedsCheck service in patients with chronic pain, specifically delivered by pharmacists within community pharmacies.[50] The intervention will include components such as specialised consultation, education, self-management, medication review, provision of an action plan, appropriate referrals, and follow up.[50] This is an exciting new initiative and the pending outcomes from this trial program will provide valuable insights and evidence on the expanding role of community pharmacists in the context of delivering primary healthcare services, especially for chronic pain management.

Conclusion

Pharmacists make trustworthy and responsible advocates for medication treatment and management.[14] However, the role of pharmacists in chronic pain management requires further exploration, especially in Australia where research is lacking. International studies investigating the effectiveness of pharmacist-driven interventions have demonstrated that there are benefits of pharmacists going beyond standard primary care practice in the context of chronic pain management. Current evidence suggests that pharmacist-led educational and medication reviews in community pharmacy settings are effective in reducing pain intensity, whilst improving physical functionality of chronic pain patients.

The high prevalence of chronic pain in Australia and its associated burden on the health and wellbeing of patients and their families demands for high quality research in this space to broaden the roles and responsibilities of pharmacists in Australian community pharmacies. Studies demonstrating positive health outcomes in the roles of European pharmacists should be considered and adopted in Australia to further expand the current, and often informal, Australian pharmacists' healthcare provision. This could help positively influence and benefit chronic pain sufferers in the provision of easily accessible support in chronic pain management from a trusted and expertly trained pharmacist professional.

Finally, research needs to be extended to further demonstrate the clinical benefit of pharmacist-led interventions in chronic pain management. With the recent implementation of the Chronic Pain MedsCheck Trial in Australia, this is a start. It would be of interest and importance to further explore the benefits of broadening the roles of community pharmacists in Australia in this space, especially when considering the fact that there is

limited published literature outlining the perceived benefits of pharmacist-led chronic pain interventions in Australian community pharmacies. As such, the implementation of similar community pharmacy intervention programs for Australian pharmacists may provide enhanced clinical outcomes for patients suffering from chronic pain. This may in turn prove to positively impact and benefit how chronic pain sufferers are provided with easy access to beneficial healthcare services for their pain management provided by Australian community pharmacists.

CONFLICT OF INTEREST

Authors have no conflicts of interest to disclose.

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Original Research

Effect of a smoking cessation educational intervention on knowledge and confidence of pharmacy students versus community leaders

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Abstract

Background: Training programs of various intensities and durations have been implemented to assist healthcare providers and students in leading smokers in a quit attempt. While some training programs have been developed to help community leaders provide these services, the focus for community leaders has been to assist with recruitment efforts.

Objective: The objective of this study was to compare knowledge and confidence of students and community members before and after a smoking cessation educational intervention.

Methods: After approval from the institutional review board, pharmacy students and community members were recruited for two-hour educational interventions. Topics covered included smoking health risks, benefits of quitting, behavioral, cognitive, and stress-management techniques, smoking cessation medications, and how to start a formal class. Pre- and post-intervention survey instruments were given to all participants with comparisons made via Student's or Paired T-tests, as appropriate.

Results: Knowledge scores increased significantly ($p<0.05$) after the educational intervention for pharmacy students (n=30) and community members (n=8). Confidence scores increased significantly for pharmacy students ($p<0.05$), but not for community members. Pharmacy students had significantly greater knowledge score changes (53.7%, pre-intervention; 81.8%, post-intervention; $p<0.05$) versus community members (32.1%, pre-intervention; 50.1%, post-intervention; $p<0.05$). When comparing individual confidence questions, only scores evaluating the change in confidence for providing counseling were higher for students versus community members (2.13 vs. 1.8, respectively; $p<0.05$).

Conclusions: Pharmacy students and community leaders exhibited increased knowledge after a smoking cessation educational intervention, and pharmacy students had increased confidence scores. All confidence scores did not change significantly for community members. Developing coalitions between healthcare providers and community leaders, focusing on the roles of each, may be productive in initiating smoking cessation programs.

Keywords

Smoking Cessation; Smokers; Students, Pharmacy; Community Participation; Counseling; Patient Education as Topic; Surveys and Questionnaires; United States

INTRODUCTION

Smoking remains the largest preventable cause of death in the United States, with over 480,000 people dying per year due to related disease states.[1] Rates have been slowly decreasing over the past decade due to population-based interventions and an increased awareness of health consequences among smokers. However, it was determined in 2016 that 15.5% of the adult population still smoke. Cigarette smoking still remains high among certain disadvantaged groups, including those with lower education, below poverty level, uninsured or on Medicaid, disabled persons, and those with serious psychological distress. In response, training programs for healthcare professionals and students to assist with tobacco cessation have increased over the past few years. Pharmacists, nurses, and physicians have undergone training sessions of various lengths and intensities to increase knowledge and confidence.[2-5] Training has ranged from short continuing educational sessions to day-long and multiple-day sessions. Educational topics generally include harms from nicotine use, principles of nicotine addiction, the benefits of cessation, how to assist patients with quitting, pharmacology, and cessation aid counseling.

The need exists for strengthening cessation education in the curricula for professional healthcare programs. For example, one survey of pharmacy faculty shows that tobacco cessation education is covered for a median of 170 minutes throughout the required curricula.[6] In response, formalized Train-the-Trainer three-day educational interventions have been conducted for pharmacy faculty. This has increased the perceived ability of faculty to train students and has led to high curricular acceptance in many schools of pharmacy.[7] In turn, workshops lasting a few hours implemented for pharmacy students has resulted in increased smoking cessation knowledge.[8] Despite increasing emphasis for students as to their role in tobacco cessation, barriers such as a lack of confidence continue to exist.[9]

Recruitment for cessation interventions has also been a barrier. However, partnerships have been developed between community leaders and healthcare professionals.[10-12] For example, community-based participatory research has been implemented as a partnership between community members, organizations, and academic researchers.[11,12] These partnerships have been successful in recruiting smokers for cessation

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programs. Other programs to develop such services have involved training members of social and community service organizations and providing church-based cessation activities.[13-15] For community leaders to provide smoking cessation services, research has not been extensive regarding an analysis of their unique training needs to develop such services.

Training programs of various intensity, duration, and success have been implemented to assist healthcare providers, students, and community members in leading smokers in a quit attempt. Assessing the efficacy of an educational intervention through a direct comparison of healthcare students and community members has not yet been published. The objective of this study was to compare knowledge and confidence of students and community members before and after a brief smoking cessation educational intervention.

METHODS

This study was approved by the Institutional Review Board (IRB). After a recruitment period May through September 2015, the educational interventions were conducted in Fall 2015. Educational interventions were held to train and educate pharmacy students and community leaders on leading smoking cessation classes. Interventions were designed to provide knowledge and to equip trainers to successfully start and lead their own smoking cessation classes for members of the community. A total of three 2-hour sessions were held: two for pharmacy student trainers, and one for community leader trainers. Sessions were located in three rural Mississippi communities: Belzoni, Batesville, and Yazoo City. This study was funded by the University of Southern Mississippi Service Learning Program.

Recruitment

Recruitment for the educational intervention was open for all students in their second through fourth year at the University of Misssissippi School of Pharmacy. Recruitment for the interventions occurred via email through a pharmacy student message board. Recruitment for community leaders occurred via flier, email, and other personal contact with local churches, schools, and free clinics. All respondents who identified themselves as community leaders over the age of 18 years were eligible and included in this intervention. Pharmacists and pharmacy students were excluded from recruitment of community leaders. All participants were given a USD25 gift card upon completion of the educational session.

Description of the educational session

Educational interventions were equal in content for each session. Each discussed facts and statistics regarding smoking, including health risks, community and economic impact, and the benefit of quitting. The instructor, the lead author, is a pharmacy faculty member with extensive education and experience conducting cessation classes. The instructor reviewed behavioral, cognitive, and stress-management techniques. Smoking cessation medications and their proper use were also reviewed. The educational session discussed techniques and procedures for starting a smoking cessation class. At the conclusion of the educational intervention participants were encouraged to implement smoking cessation services within the community.

Table 1. Confidence statements on a Likert scale
Statement 1. I feel confident that I can/could counsel a person who wanted assistance with a smoking cessation attempt.
Statement 2. I feel confident that I can/could recommend a medication that would be most helpful in a person's smoking cessation attempt.
Statement 3. I feel confident that I can/could assist and arrange multiple smoking cessation sessions with a patient, if needed, to help in their smoking cessation attempt.

Description of the survey instrument

A survey was implemented before and after each intervention that measured knowledge and confidence levels of prospective smoking cessation trainers. The baseline questionnaire included 3 confidence items (Table 1) and 14 knowledge items. The follow-up survey contained the 3 confidence items repeated. It also contained 14 identical knowledge items from the pre-intervention questionnaire (post-intervention Part A) with an additional 14 knowledge comprehension items (post-intervention Part B). These additional knowledge items were inserted to decrease recall bias and to measure understanding of the overall concepts learned from the educational intervention. Each item in Part A was matched a conceptually similar item in Part B. A question regarding the role of pharmacists in providing smoking cessation services was included in both pre- and post-educational intervention surveys.

Smoking cessation services

Each participant was encouraged to start a smoking cessation service for community members seeking aid regarding smoking cessation. Trainers were offered USD50.00 for each smoking cessation class member whom they recruited and successfully quit smoking by the end of the class. Trainers who conducted a class were provided with materials and funds to conduct the class appropriately, including a urine cotinine test, as applicable. Smokers who set a cessation date received a week's supply of a nicotine replacement of their choice at each subsequent session, with a maximum of 4 weeks supplied.

Statistical analysis

Student's or paired t-tests were utilized to analyze collected data, as appropriate. Subsequent services are described using descriptive statistics. Knowledge scores were compared each for students and community leaders before and after the educational intervention. The questionnaire given after the intervention consisted of two parts: Part A that included the exact same questions as given prior to the intervention, and Part B than included 'matched' questions with the same concepts but different questions. A comparison of each was made versus the pre-interventional questionnaire. Confidence scores were compared pre- and post- educational intervention for both students and community leaders. A p-value of less than 0.05 was considered statistically significant.

Table 2. Demographics		
	Students (n=30)	**Community leaders (n=8)**
Race		
Caucasian	28	5
African American	1	3
Asian	1	0
Sex		
Male	9	5
Female	21	3
Age	23.59 (1.90)	36.88 (16.88)
Smoking History	7	1
Previous cessation training	23	2

Table 3. Smoking Cessation Class Demographics and Data	
	Class Members (n=8)
Ethnicity	
African American	8
Gender	
Male	3
Female	5
Age	53.13 (9.14)
Smoking Years	28.14 (17.18)
Previous Quit Attempts	0.88 (0.99)
Classes Attended	4.13 (1.13)
Cessation Aids Chosen By Participants	
Patches	6
Gum	2
Cessation attempt by last session	8
Cigarettes per Day	
Baseline	13.13 (7.04)
9 month follow-up	8.42 (7.42)
Cessation attempt ongoing at 9 month follow-up (n=6)	1
Length of cessation attempt (months)	3.55 (4.33)

RESULTS

In total, 30 pharmacy student and 8 community leader trainers for smoking cessation services attended a two-hour education intervention (Table 2). The mean age of the student participants and community leaders was 23.59 (SD 1.90) and 36.88 (SD 16.88), respectively, with community leaders being significantly older. A higher percentage of the students in attendance had a smoking history (23.3% vs. 12.5%). Students were also more likely to be female and Caucasian in comparison to community leaders. Unlike the community leaders, the majority of student participants had previous smoking cessation training (76.7% vs. 25%). Students reported an average of 3.00 (SD 3.78) hours of smoking cessation training from both the Doctor of Pharmacy curriculum (66.7%) as well as a smoking cessation elective (16.7%).

Knowledge Scores

At baseline, the pharmacy students had a significantly higher knowledge score than the community leaders ($p<0.05$; Figure 1). Scores for the identical pre- and post-intervention (Part A) knowledge items increased significantly ($p<0.05$) after the educational intervention for both pharmacy students and community members. Overall, however, pharmacy students had a significantly higher post-intervention knowledge score than community members ($p<0.05$). Pharmacy students also had a significantly greater knowledge score change (53.7%, pre-intervention; 81.8%, post-intervention Part A; $p<0.05$) versus community members (32.1%, pre-intervention; 50.1%, post-intervention Part A; $p<0.05$).

Both pharmacy students' and community leaders' scores increased significantly between pre-intervention knowledge items and conceptually similar post-intervention Part B items. When comparing post-intervention Part A scores (knowledge) versus Part B scores (comprehension), pharmacy students had significantly higher post-intervention Part A knowledge scores ($p<0.05$).

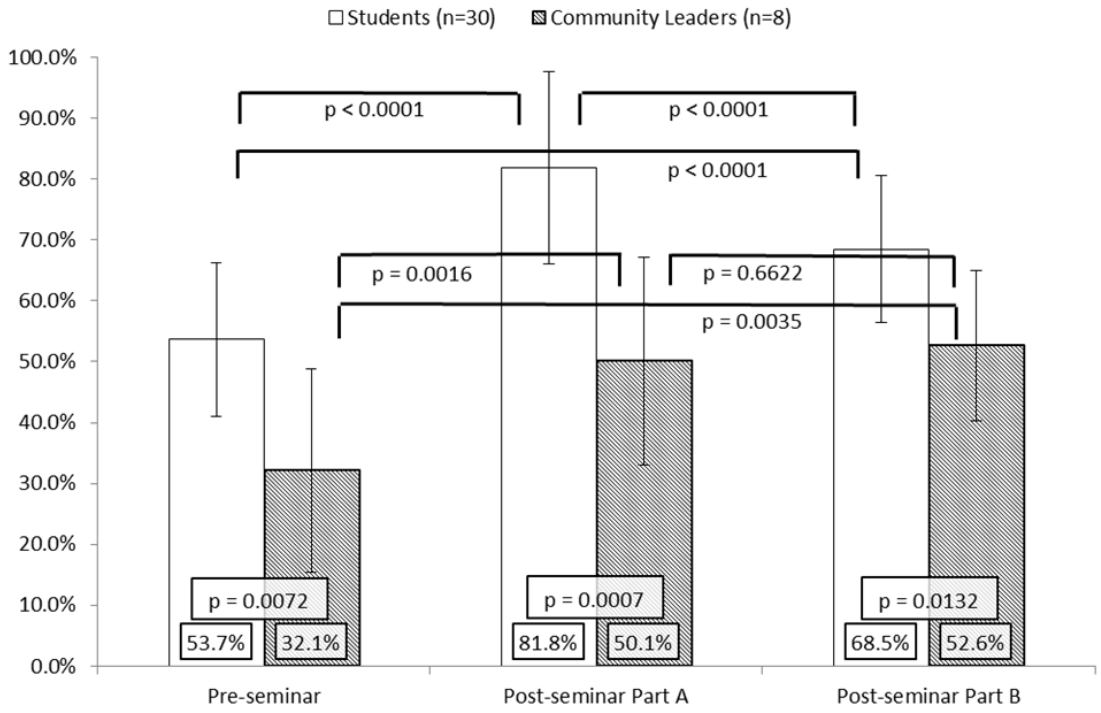

Figure 1. Mean knowledge scores – Students vs. Community leaders

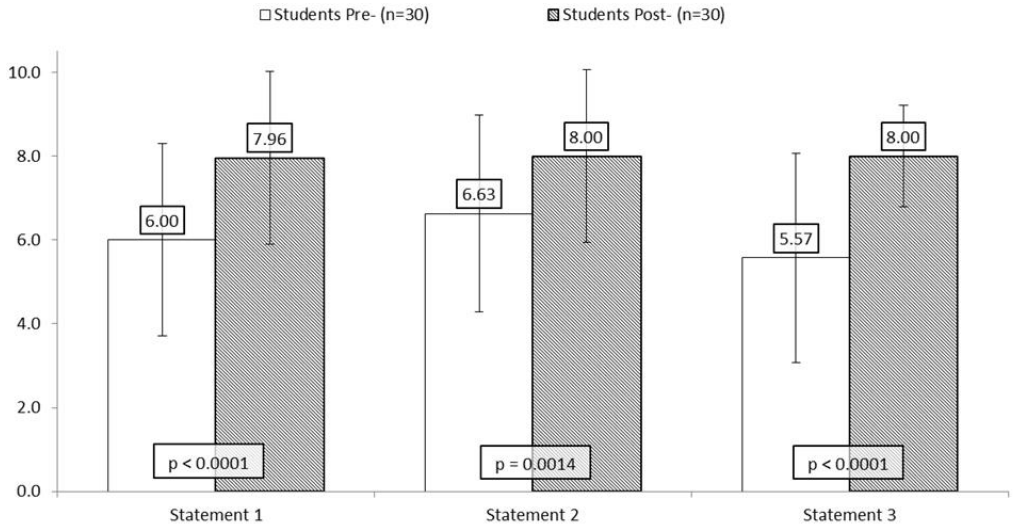

Figure 2. Student mean confidence scores – Pre-seminar vs. Post-seminar.

Community leaders did not have a significant difference between Part A knowledge and Part B comprehension scores.

Confidence scores

At baseline, student confidence scores versus community leader scores were not significantly higher with the exception of confidence in recommending a medication for a cessation attempt (6.63; SD=2.34 vs. 4.13; SD=2.75, for students versus community leaders, respectively; p=0.04). After the educational intervention, confidence scores for each statement increased significantly for pharmacy students (p<0.05; Figure 2). Community leader confidence scores significantly increased for only Statement 1 regarding confidence in counseling (p<0.05; Figure 3). However, there was not a significant difference between post-intervention confidence scores for students versus community leaders. There was also no significant difference in the change of confidence scores between students and community leaders, except for a more significant change in students' counseling confidence scores (p<0.05; Figure 4). Both pharmacy students' and community leaders' scores significantly increased regarding their perception of the pharmacist's role in smoking cessation versus baseline (6.83; SD=2.46 vs. 8.13; SD=1.87, p=0.0008; 6.25; SD=3.24 vs. 7.63; SD=2.97, p=0.0038; for students and community leaders, respectively).

Smoking cessation services

One smoking cessation class was held as a result of the educational intervention attended by pharmacy students, while the intervention attended by community leaders did not result in any formalized cessation program. The subsequent class was held once weekly for six weeks by four pharmacy students in Yazoo City, Mississippi. A total of eight class members, recruited from a local clinic, attended at least two sessions (Table 3). The mean age of these community members was 53.13 (SD 9.14). At baseline, the members smoked an average of 13.13 (SD 7.04) cigarettes daily with an average of 28.14 (SD 17.18) smoking years between them. Four of the members had at least two past quit attempts, but the remaining four participants had never attempted to quit smoking. Each class member set a quit date and began a cessation attempt prior to the end of

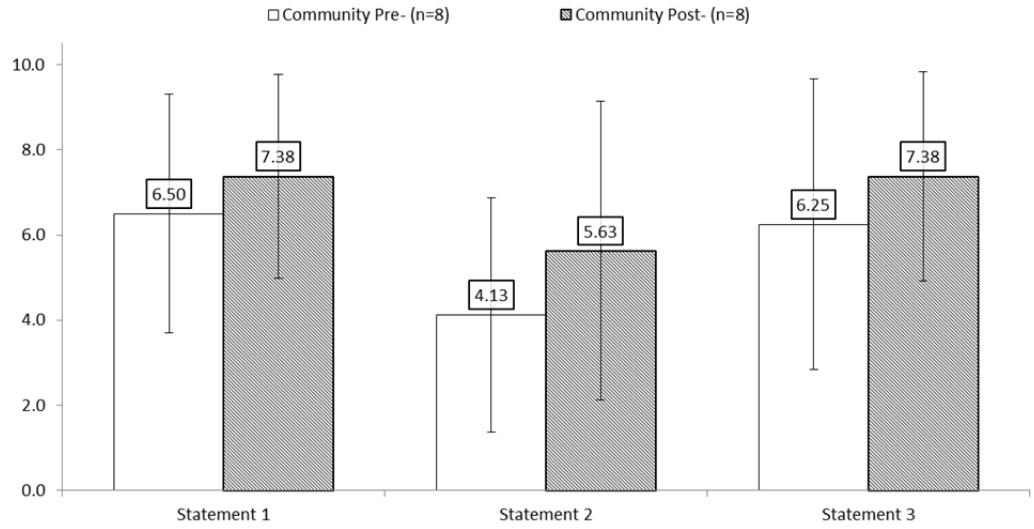

Figure 3. Community leader mean confidence scores - Pre-seminar vs. Post-seminar

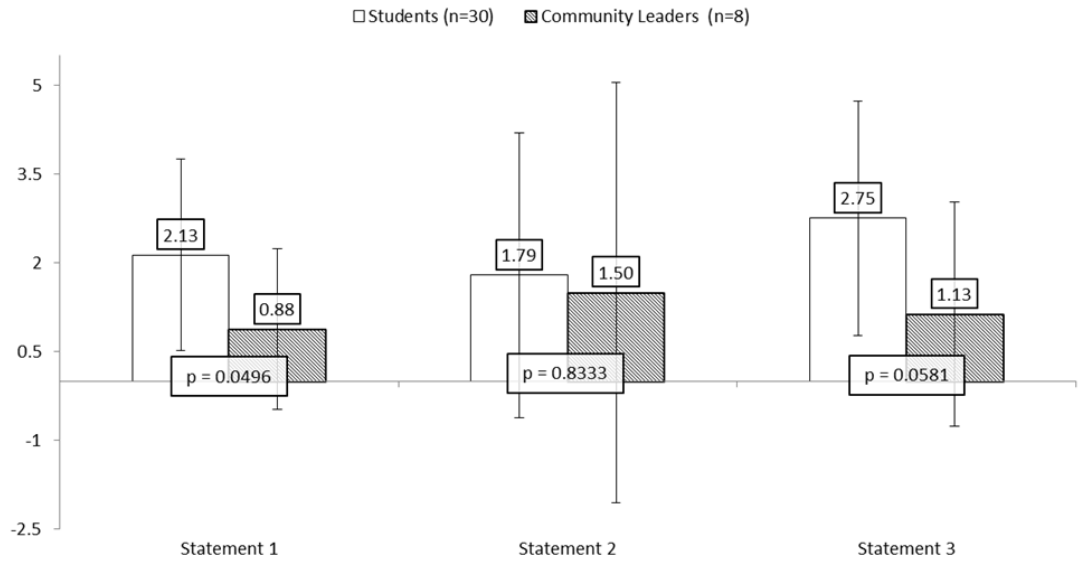

Figure 4. Mean change in confidence scores – Students vs. Community leaders.

the six-week class series. Six of the members used nicotine patches as a cessation aid and the remaining two members used nicotine gum. Two class members were not included in follow-up data (one lost to follow-up, one deceased). At nine-month follow-up, the class members smoked an average of 8.42 (SD 7.42) cigarettes daily. One participant still had a successful cessation attempt after nine months. All eight participants attempted to stop smoking prior to the end of the smoking cessation class series. The participants' average length of successful cessation was 3.55 (SD 4.33) months. Cessation was determined using urine cotinine tests.

DISCUSSION

Pharmacy students and community leaders exhibited increased knowledge after a two-hour smoking cessation educational intervention. Confidence scores also increased for pharmacy students after the educational intervention with regards to counseling smokers, recommending medication for cessation, and assisting with longitudinal cessation attempts. In contrast, only confidence scores for providing counseling to smokers increased for community leaders after the intervention. Acceptance for a role for pharmacists in assisting with smoking cessation efforts increased for both groups after the intervention.

Baseline knowledge scores were higher for pharmacy students, which can be explained by the fact that students were more likely to have had previous cessation training. However, the change in pre- versus post-intervention knowledge scores was also higher for students in comparison to community leaders. For students, a significant increase in knowledge scores (i.e., post-educational intervention Part A) occurred in comparison to comprehension scores (i.e., post-educational intervention Part B). In contrast, there was no such increase in comparison of post-educational intervention Part A and post-educational intervention Part B knowledge scores for the community leaders. While questions in Part A were the same questions that were given in the pre-educational intervention questionnaire, the questions in Part B were similar in content only. Thus, questions in Part B evaluated comprehension of the topic in the question. A reasonable explanation for this finding is that pharmacy students could be more attuned to attending presentations and discerning the most applicable information.

Confidence continues to be a significant barrier for implementing smoking cessation services by both healthcare professionals and community groups.[5,9,10,16,17] Thus, the finding of this study regarding the change in confidence scores between the two groups is encouraging. Pharmacy students had increased confidence for counseling smokers, recommending cessation medication, and assisting with longitudinal cessation attempts. These three items reasonably could be hypothesized to reflect an increasing skill-set needed to provide fully realized smoking cessation services. Thus, the fact that confidence scores increased for community leaders only for providing counseling, and not for the other items, is particularly meaningful.

Furthermore, both groups were encouraged to begin implementing smoking cessation services. Only the pharmacy students were able to successfully assist smokers in a cessation attempt. While the number of smokers impacted was small (i.e., eight smokers participated in a 6-week class run by the students), all the smokers attempted to stop smoking during the class. In the long-term follow-up period of nine months, participants had reduced their average nicotine consumption and one person successfully maintained abstinence.

Taken together, the data shows that a brief, two-hour educational intervention was successful in increasing the knowledge base and confidence level of pharmacy students to the point that actual smoking cessation services could be implemented. The knowledge base and confidence to provide counseling increased for the community leaders through the brief educational intervention. However, the intervention did not increase the confidence of community leaders to provide longitudinal cessation assistance, nor did it lead to provision of actual services.

Successful partnerships in the form of community-based participatory research have been formed between community members, organizations, and academic researchers.[11] The community members have been ideal for recruiting participants for smoking cessation. However, barriers include the time and funding needed to build and solidify partnerships within the political and social complexities of many community settings. Especially in disadvantaged communities, aggressively recruiting and training community leaders would be needed to create successful cessation programs. Such programs would also need to be able to provide nicotine replacement therapy (NRT).[12]

Initiatives in the community include smoking cessation interventions provided through social and community service organizations and through church-based cessation activities. In particular, one project with members of a SCSO in Australia was successful in both providing smoking cessation training, and in the members implementing such counseling services.[13,14] Training for the staff, who did not previously have medical experience, included a half-day of raising awareness, followed by a full day of cessation training. As a result, the attitudes and confidence levels to assist with smoking cessation for their clients increased significantly. Although the SCSO workers were not able to assist smokers in achieving total abstinence, time spent talking about cessation increased significantly. Also, smokers reduced the number of cigarettes smoked per day from 20.5 at baseline to 15 per day at six-month follow up.

Another study conducted community-based activities with individualized counseling through church coalitions in a rural, predominantly African-American county.[15] While interventions led to progress along the stages of behavior change, the smoking cessation rate was not significantly increased in comparison to the comparator county. For the members attending the interventions at the participating church, there was an increased awareness of and contact with smoking cessation programs.

As evidenced by the limited amount of research noted, training community leaders to provide cessation services is difficult. This current study suggests that a brief, two-hour educational intervention increases community leaders' knowledge and confidence to counsel smokers, but it is unable to provide enough confidence to provide longitudinal services. While research with SCSO workers was effective in decreasing the daily number of cigarettes smoked by their clients, training to produce this result was one and a half days.[13,14]

The results of this study should be taken together with previous research regarding possible strategies to provide cessation services. Training synergistically for two different groups who would provide smoking cessation services can be beneficial and cost-effective.[17] However, synergistic training has been provided in previous research for two different groups of healthcare providers. This study was unique in that training was targeted for both pharmacy students and community leaders who are not necessarily in or have been in the healthcare field. The results of this study indicate that, if training time is limited, the best role for community leaders may be to concentrate on developing coalitions with healthcare providers to develop services. Training should be focused on helping community leaders understand the health consequences in their overall community, the role that healthcare providers can play in achieving tobacco abstinence, and the need of their leadership to recruit smokers to participate in cessation services. Especially with regards to recruitment, the assistance community leaders can give is vital.

A few limitations need to be discussed with this study. The groups were dissimilar in number and in several demographic areas. However, each group was a representative sample of pharmacy students and community leaders, respectively, for which a basis of comparison could be made. Pharmacy students may have had various formal training that could not be accounted for prior to participating in this study since included students were at different points of the curriculum (professional years two through four). The educational intervention was the same for both groups, as was the questionnaire. Another limitation is that a widely accepted and validated survey instrument of knowledge and confidence questions for either pharmacy students or community leaders does not currently exist. In the future, such instruments should be targeted to elicit information that would be most useful during the educational intervention. Recruitment of community leaders was difficult, with the recruitment period having to be extended from the initial three month period for another two months in order to reach out to communities through churches, schools, and free clinics in the area. Most of the resulting participants were educators or those who worked in the healthcare industry. Thus, the possibility of recruitment bias must always be factored into the final analysis.

CONCLUSIONS

Pharmacy students and community leaders exhibited increased knowledge after a smoking cessation educational intervention, and pharmacy students had increased confidence scores. All confidence scores did not change significantly for community members. Developing coalitions between healthcare providers and community leaders, focusing on the roles of each, may be productive in initiating smoking cessation programs.

CONFLICT OF INTEREST

Justin J. Sherman has received grants from the University of Southern Mississippi Service Learning Program.

FUNDING

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CPPI Practice Forum

Practice Forum: A new section led by the Center for Pharmacy Practice Innovation at Virginia Commonwealth University School of Pharmacy

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Keywords
Pharmacy Research; Education, Pharmacy; Pharmacy; Pharmacists; Pharmaceutical Services; United States

INTRODUCTION

It is our pleasure to introduce a new section in Pharmacy Practice entitled "CPPI Practice Forum", which will be led by the Virginia Commonwealth University (VCU) School of Pharmacy Center for Pharmacy Practice Innovation (CPPI). This invitation-only section will serve as a platform for individuals to share opinions on key issues affecting pharmacy practice across a wide range of areas. The purpose of this initial commentary is to describe the CPPI, how the collaboration with Pharmacy Practice became a reality, and what you can expect from this section.

THE CENTER FOR PHARMACY PRACTICE INNOVATION

VCU is an urban, public research-intensive university known for its commitment to the community, embrace of diversity, and providing state-of-the-art healthcare to everyone. Established in 1898, the VCU School of Pharmacy has embodied these core principles and long been a leader and innovator in pharmacy practice, education, and research. Faculty at the VCU School of Pharmacy have played a significant role in advancing the pharmacy profession across a wide spectrum of practice areas and served as leaders of major professional organizations. In light of the School's history and commitment to advancing pharmacy practice, the School held a Practice Transformation Conference in 2011 to bring together leaders and innovators to advance pharmacist-led patient care activities. Based on the input from conference attendees and the critical need to devise novel solutions to mitigate our nation's health care crisis, the VCU School of Pharmacy launched a research center in October 2015 to lead its pharmacy practice innovation efforts - the Center for Pharmacy Practice Transformation.[1]

In 2016, the Center was officially established under new leadership and renamed the Center for Pharmacy Practice Innovation (www.cppi.pharmacy.vcu.edu). The Center leadership and core faculty agreed on the shared mission to help pharmacists maximize patient outcomes. The CPPI aims to become a leader in transforming ambulatory and community pharmacy practice to advance pharmacists' roles on patient-centered, collaborative care teams. We approach this work from three core values: 'connected' with the reality of the real-world practice; 'committed' to our mission of working with pharmacists to demonstrate the impact of the care they provide; and 'collaborative' with partners from health-systems, community pharmacies, professional associations, and governmental agencies. The four goals of the CPPI are to:

1. Develop, implement, and evaluate innovative and sustainable care models that incorporate pharmacists to optimize medication-related patient health outcomes.
2. Foster collaboration among clinicians and outcomes researchers to determine pharmacist impact on clinical, humanistic, and economic outcomes.
3. Equip pharmacists with the knowledge, skills and abilities to engage in interprofessional, collaborative care.
4. Partner with clinicians, health systems, policymakers, and payers to advance medication and health policies at the local, state, and national level.

Center for Pharmacy Practice Innovation's Research agenda

Similarly to VCU, several other Schools of Pharmacy have established centers focused on practice-based research to propel pharmacy practice advancement and innovation. One of the first research endeavors that CPPI embarked on was to identify and characterize existing centers at Schools of Pharmacy in the United States whose missions involve advancing pharmacy practice through research (manuscript under review). We identified 20 centers across 20 different states as of March 2017. In general, pharmacy practice research centers are relatively small, few conduct multi-site experimental studies, and funding received since center inception is low. We hope that this work will increase awareness of other pharmacy practice research centers and prompt our academic and clinical practice communities to work collaboratively and leverage resources for the conduct of multi-site studies, which will contribute to generate high-quality evidence, improve competitiveness for large funding opportunities, and advance policy to further the pharmacy profession.

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Articles in the CPPI Practice Forum section are the sole responsibility of the VCU School of Pharmacy Center for Pharmacy Practice Innovation and do not undergo the standard peer review process of Pharmacy Practice.

To help us achieve our mission, we established partnerships with various health systems in Virginia, including: VCU Health, Bon Secours Mercy Health, and University of Virginia (UVA) Health System. At VCU Health, we are currently working with health system leadership to innovate the existing care model by shifting to value-based, team-oriented care with a specific focus on improving the quality of care for patients with diabetes and hypertension. The new care model will integrate more clinical pharmacists into endocrine specialty clinics, as well as primary care, to provide chronic disease management. We are also working with our Bon Secours Mercy Health partners to establish the impact of clinical pharmacist services provided by pharmacists incorporated into 12 of the 63 primary care practices in Virginia. The ultimate goal of this collaboration is to provide evidence of the value of pharmacists to the medical group with regard to population health efforts and individual patient health outcomes that could justify expansion of the pharmacists' scope of practice and increase the number of pharmacists providing care within the primary care setting. Finally, our collaboration with the UVA Health System aims to help disseminate several innovative pharmacy services developed and implemented by the pharmacy department in recent years, including a transitions of care meds-to-beds program. Given many pharmacists are employed by health systems that are seeking to provide high-value care at low cost, there is significant opportunity for pharmacists to play a major role in these efforts.

Funded research is important for any research center's success. Recently, the CPPI has successfully obtained its first two extramural grants. In collaboration with the Virginia Department of Health, the CPPI was awarded USD1.3 million in funding over 5 years from the Centers for Disease Control and Prevention (CDC) to implement evidence-based strategies to increase awareness and capacity for the National Diabetes Prevention Program and to improve the management of high blood pressure.[2] The project will seek to utilize pharmacists to meet both of these goals through collaborations with VCU Health, Virginia Premier, Virginia Pharmacists Association, and local community pharmacies. A second project funded by the Community Pharmacy Foundation will explore the feasibility of implementing 24-hour ambulatory blood pressure monitoring in community pharmacies. These projects have several commonalities that highlight the Center's focus on ambulatory/community pharmacy practice, sustainable services, and collaboration with community partners.

Center for Pharmacy Practice Innovation's Commitment to Education and Professional Development

In tandem with the CPPI's research efforts is its commitment to graduate education. Many of the CPPI core faculty are graduate faculty in the VCU School of Pharmacy which facilitates incorporation of PhD students within the research activities of the Center. Additionally, we continuously host PharmD students for research summer internships and research electives. As a means to promote the visibility of CPPI among students, we organize quarterly student engagement activities with key opinion leaders or pioneers in pharmacy practice innovation. In the future, we plan to establish a fellowship to train PharmDs interested in practice-based research who may wish to enter academia or acquire research skills to measure the impact of their work in clinical practice. The CPPI's education efforts also extend to practicing pharmacists in need of education and training to develop new skills as pharmacy practice continues to evolve.

PHARMACY PRACTICE AND CPPI COLLABORATION

In August of 2018, the CPPI established a partnership with **Pharmacy Practice**, wherein CPPI is responsible for managing a dedicated section within the journal named "CPPI Practice Forum". The goal of this section is to serve as a platform for researchers and clinicians to share innovations in pharmacy practice that are under way at their institutions, whether it be academic or clinical-based, and to publish short articles (up to 2,000 words) expressing viewpoints on pharmacy practice-related topics. This section will not publish original research articles, which should be submitted to the journal following the standard process. Authors interested in providing a contribution to this section should contact CPPI prior to submission (cppi@vcu.edu), as this is an invitation-only section. We hope to see the contribution of national and international leaders in pharmacy, both practicing clinicians and researchers.

Future topics lined up for upcoming issues of **Pharmacy Practice** include: pharmacist expansion to outpatient pediatric immunizations, role of Board certification in advancing pharmacy practice, role of pharmacists promoting the use of biosimilars, conflict management in health care, amongst others.

CONCLUSION

We are excited about this partnership with Pharmacy Practice and invite you to become part of the conversation about pharmacy practice advancement. We look forward to welcoming your contribution to the dissemination of innovations that are taking place in your country.

CONFLICT OF INTEREST

None to declare.

FUNDING

No external funding was received.

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Original Research

Evaluation of renal drug dosing adjustment in chronic kidney disease patients at two university hospitals in Lebanon

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Abstract

Background: Inappropriate medication dosing in patients with chronic kidney disease can cause toxicity or ineffective therapy. Patients are at a high risk of developing related adverse events caused by the altered effect of drugs in conjunction with the use of polypharmacy to treat comorbid conditions. This necessitates adequate renal dosing adjustments.

Objective: The current study aims at assessing whether appropriate dosing adjustments were made in hospitalized patients with chronic kidney disease.

Methods: A retrospective descriptive study was conducted at two university hospitals in Beirut between January and December 2016. All adult CKD patients with creatinine clearance less than 60 ml/min and receiving at least one medication that require renal dosing adjustment were included. Kidney function was estimated from serum creatinine using Cockcroft-Gault equation, and dose appropriateness was determined by comparing practice with specific guidelines. The rates of renal drug dosing adjustment were investigated, in addition to the influence of possible determinants, such as the severity of renal impairment, reason of hospital admission, and other patient characteristics.

Results: 2138 patients admitted in 2016 were screened. 223 adults receiving 578 drug orders that require adjustment were included. Among the 578 orders, 215 (37%) were adjusted adequately, 284 (49%) were adjusted inadequately, and 79 (14%) were not adjusted at all. Beta-blockers were the most inadequately dosed (83.6%) class of medication, whereas lipid-lowering agents had the highest percentage of adequate dosing (65.1%). As per patient, 84.3% of patients appeared to be receiving at least one inappropriate drug dose.

Conclusions: Our study confirms that physicians are not prescribing appropriate dosing adjustments in chronic kidney disease inpatients, which may have deleterious effects. This highlights the need for more nephrology consultation and the implementation of physician education programs.

Keywords

Renal Insufficiency; Kidney Function Tests; Metabolic Clearance Rate; Drug Overdose; Medication Errors; Clinical Competence; Physicians; Retrospective Studies; Lebanon

INTRODUCTION

Chronic kidney disease (CKD) has globally become of substantial health and economic burden. An estimated 5–10 million people die annually from kidney disease.[1] In Lebanon, 10% of the population suffers from kidney disease at various stages, of whom 3500 patients are on dialysis.[1] With decreased renal function, the pharmacokinetics of many drugs are significantly altered so that the effect of usual doses becomes either augmented or diminished.[2-4] Moreover, the patient's response may be changed due to the disease effect on multiple organ systems, making patients more susceptible to the effect of drugs.[2-4] CKD patients are subject to significant accumulation of renally eliminated drugs.[4,5] When a drug accumulates, the risk of side effects increases, and may lead to toxicities. In contrary, under-dosing in dialysis patients may decrease efficacy and result in suboptimal response. In hospitalized patients, toxic or ineffective doses increase the length of hospitalization and cost of treatment, and thus, increase burden on both patient and healthcare systems.[1] Although adverse outcomes can often be delayed or prevented by inexpensive interventions, different studies have showed that during hospital stay, drug doses in patients with CKD are not adjusted properly in 25-77% of cases.[6,7] In order to improve drugs' prescription in CKD patients, it would be necessary to have collaboration between all healthcare providers.[8] The primary objective of the current study was to assess adherence to dosing guideline in hospitalized patients with renal impairment, whereas the secondary objective was to assess appropriateness of drug dosing adjustment in those patients recruited from two university hospitals in Beirut, Lebanon.

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METHODS

Study population

A retrospective cross-sectional study was conducted between January and December 2016 at two university hospitals in Beirut, Lebanon. Databases of the two hospitals were computerized and established since 2008. Records of all patients admitted in 2016 to any hospital floor were screened. Initially, databases were searched using International Statistical Classification of Diseases and Related Health Problems (ICD-10) coding system for code of

N18 (chronic kidney disease). However, since the use of coding system didn't yet become an obligatory practice in these hospitals, some doctors mentioned the N18 label to CKD patients, while others did not. The computerized typed reports were used as further reference.

Patients over 18 years of age, receiving at least one pharmacological agent requiring renal dose adjustment, with initial serum creatinine (SCr) level over 1.2 mg/dl (greater than the upper normal limit) were included in the study.[9] SCr level was used in the initial selection of subjects rather than creatinine clearance (CrCl) because SCr values were available in all patients' medical files while CrCl values were not, and therefore was calculated by study investigators with values <60ml/min considered for analysis. Patients not receiving any pharmacological agent requiring adjustment, female patients who were pregnant and, patients with unreported age, weight or serum creatinine level were excluded from the study.

A sample of 217 patients was targeted to allow for adequate power for bivariable and multivariable analyses to be carried out according to the Epi info sample size calculations with a population size of 400,000 patients with kidney diseases in Lebanon, a 28% expected frequency of appropriately adjusted drug doses according to a previous study in Ethiopia due to the lack of similar studies in Lebanon, and a 95% confidence interval.[10]

Outcomes

The primary outcome was to evaluate the frequency of medication orders with appropriate or inappropriate dose adjustment, or even non-adjustment. The secondary outcome was to assess the presence of at least one inappropriate or no drug dose adjustment per patient.

Dose appropriateness was determined by comparing practice with the guidelines: "Drug Dosing Adjustments in Patients with Chronic Kidney Disease" published by the American Academy of Family Physicians, and "Drug Information Handbook, 25th edition" published by Lexicomp®.[11] The "American College of Physicians' Drug Prescribing in Renal failure" fifth edition, was used in case of hemodialysis.[12]

The evaluation of dose appropriateness was performed by three clinical pharmacists independent from the study and who received thorough training to ensure consistency. For each drug order, when the dose prescribed for the patient was concordant with the dose recommended in the guideline for the patient's creatinine clearance level, it was recorded as adequately adjusted. However, when it was dosed inappropriately, we recorded it as either not adjusted at all, when CKD patients were given doses recommended for patients with normal renal function, or as inadequately adjusted, when doses given matched neither of the above two doses. Each prescribed order, thus, was labeled as one of three practice categories: adequately adjusted, inadequately adjusted, or not adjusted. This enabled to calculate the percent of each category with respect to the total orders and analyze its occurrence with respect to patient factors and drug classes.

Data collection procedures

Individual patient data were obtained from computerized patient records in both hospitals. Each patient was assigned a study ID. Patient characteristic including date of admission, floor, reason of admission, age, gender, weight, serum creatinine, blood urea nitrogen, dialysis status, and comorbidities were collected through Open Data Kit (ODK) collect android application, and directly uploaded to Microsoft excel 2010. However, medication regimens were copied from the hospitals' computerized prescriptions and recorded manually on a data collection sheet that holds the patient-specific study ID, where each medication order was also assigned an ID and written with its corresponding dose and dosing schedule.

From the above data, creatinine clearance of each patient was calculated based on the serum creatinine level, recorded prior to drug prescription, following the Cockcroft Gault (CG), the most frequently clinically used equation (i.e. the one used by physicians at the two hospitals) to estimate glomerular filtration rate (GFR).[13,14] For obese patients, an adjustment factor of 0.4 was used based on a meta-analysis conducted by Wilhelm *et al*.[15] The corresponding GFR category was assigned for each patient based on his current state according to "Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease".[9] Patients included in the analysis belonged to the following GFR categories G3a (45-59 ml/min), G3b (30-44 ml/min), G4 (15-29 ml/min), and G5 (<15 ml/min).

Study drugs were divided into six different classes including: angiotensin-converting enzyme inhibitors (ACEI), beta-blockers, diuretics, antivirals, lipid-lowering agents, and miscellaneous drugs.

Data analysis

Data analysis was conducted using SPSS version 19.0. For study population and drug dosing analysis, descriptive statistics using frequency tables were used to obtain counts and percentages. Dosing appropriateness was compared among different patient/hospital characteristics and analyzed using Chi-square. A multivariable logistic regression was conducted taking the dose adjusted inappropriately as the dependent variable and taking all variables that showed a $p<0.2$ in the bivariate analysis as independent variables. Statistical significance was set at p-value of less than 0.05.

Ethics Approval

A written informed consent from the patients was not needed since this study had no physiologic, psychologic, or social risks on the patients. The Institutional Review Board of each hospital approved the study protocol.

RESULTS

A total of 2138 patients with CKD were identified during the twelve-month study period. Based on the inclusion criteria, a total of 223 patients were considered for evaluation (10.4% of screened subjects). Those patients were prescribed 578 orders of our study medications. The clinical and demographic characteristics of all study patients

Table 1. Clinic and demographic characteristics of study patients	
	Frequency (%)
Gender	
Male	124 (55.6)
Female	99 (44.4)
Age (mean) year	65.78 (range 19-96)
SCr (mean, SD)	4.48 (2.9)
BUN (mean, SD)	61.41 (49)
Estimated CrCl (mean) ml/min	21.42 (range 2.1-59)
Reason for admission	
Renal	27 (12.1)
Non-renal	196 (87.9)
GFR category	
G3a	18 (8.0)
G3b	27 (12.1)
G4	84 (37.7)
G5	94 (42.2)
Admission floor	
IM	104 (46.6)
CCU	57 (25.6)
ICU	37 (16.6)
Other	25 (11.2)
Dialysis	
Yes	95 (42.6)
No	128 (57.4)
Total	223 (100)

(n=223) are summarized in Table 1. The study population consisted of 124 (55.6%) males and 99 (44.4%) females. The mean age was 65.78 years (range 19-96); the mean actual body weight was 76.3 kg; 27 (12.1%) were admitted for a renal reason. Most of the patients 104 (46.6%) were admitted to internal medicine (IM) floor; 84 (37.7%) and 94 (42.2%) patients were in G4 and G5 stages of CKD, respectively. Patients receiving hemodialysis were 95 (42.6%) of study group.

Evaluation of renal dosing adjustment

A total of 578 orders of our study medication list was prescribed. Among these, 215 orders (37%) were adjusted adequately, 284 (49%), corresponding to the majority, were adjusted inadequately, and 79 orders (14%) were not adjusted at all.

Table 2 summarizes the total number of orders of each drug or drug class, with the counts and corresponding percentages of orders that were adjusted adequately, adjusted inadequately, or not adjusted. When type of medication and dose adjustment were evaluated, bisoprolol was the most frequently prescribed drug that required dose adjustment, it was adequately adjusted in 24/196 (12.2 %) and inadequately adjusted in 168/196 (85.8%) of cases; followed by ranitidine which was adequately adjusted in 42/68 (61.7%). Metocolopramide, ramipril, and simvastatin were adequately adjusted in 22/45 (48.8%), 22/35 (62.9 %) and 30/31 (96.8 %) patients respectively. Fenofibrate was associated with highest proportion of not adjusted doses 19/20 (95%), followed by oseltamivir and captopril, which were not adjusted in 5/8 (62.5%) and 3/5 (60%) of cases respectively.

Based on the age, data showed that greater proportion of inadequate dosing adjustment 168/303 (55.4%) was observed in patients aging 65 years and above.

Based on the GFR category, data showed that patients in stages 3a and 3b had a total of 76 and 78 drug orders, of which 25 (33%) and 28 (35.9%) were adjusted adequately. A total of 211/578 (36.5%) and 213/578 (36.8%) drug orders that required dose adjustment was prescribed to patients with stage 4 and 5 respectively.

Table 2. List of renal medications and their adjustment rates.

Medication	Orders	Adjusted adequately		Adjusted inadequately		Not adjusted	
	n	n	%	n	%	n	%
All drugs	578	215	37.2	284	49.1	79	13.7
ACE-I*	42	24	57.1	7	16.7	11	26.2
Captopril	5	1	20	1	20	3	60
Ramipril	35	22	62.9	6	17.1	7	20
Beta blockers	202	28	13.9	169	83.6	5	2.5
Atenolol	6	4	66.6	1	16.7	1	16.7
Bisoprolol	196	24	12.2	168	85.8	4	2
Diuretics	16	3	18.7	12	75	1	6.3
Spironolactone	12	2	16.7	10	83.3	0	0
Thiazide diuretic	4	1	25	2	50	1	25
Antivirals*	9	4	44.4	0	0	5	55.6
Oseltamivir	8	3	37.5	0	0	5	62.5
Lipid-lowering agents*	63	41	65.1	1	1.6	21	33.3
Rosuvastatin	10	9	90	0	0	1	10
Simvastatin	31	30	96.8	0	0	1	3.2
Fenofibrate	20	0	0	1	5	19	95
Other drugs	246	115	46.7	95	38.6	36	14.6
Allopurinol	57	14	24.6	35	61.4	8	14
Gabapentin	5	3	60	2	40	0	0
Metoclopramide	45	22	48.8	16	35.6	7	15.6
Ranitidine	68	42	61.7	18	26.5	8	11.8
Pregabalin	10	6	60	2	20	2	20
Enoxaparin	25	5	20	13	52	7	28
Digoxin	21	12	57.1	8	38.1	1	4.8
Fluconazole	15	11	73.3	1	6.7	3	20

*. Medications that were less frequently prescribed (≤2) were not included in this table.

Table 3. Proportions of dosing adjustments per drug order according to different patient and hospital characteristics.

	Adjusted Adequately		Adjusted inadequately		Not adjusted	
	n	%	n	%	n	%
Age						
Less than 65	118	42.90	116	42.20	41	14.90
65 and above	97	32.00	168	55.40	38	12.50
Gender						
Male	127	39.30	155	48.00	41	12.70
Female	88	34.50	129	50.60	38	14.90
Reason for admission						
Renal	28	43.10	27	41.50	10	15.40
Non-renal	187	36.50	257	50.10	69	13.50
Floor						
IM	104	42.40	105	42.90	36	14.70
CCU	50	29.90	96	57.50	21	12.60
ICU	31	33.30	47	50.50	15	16.10
Other	30	41.10	36	49.30	7	9.60
GFR category						
G3a	25	33.00	40	52.60	11	14.40
G3b	28	35.90	43	55.10	7	9.00
G4	74	35.10	104	49.30	33	15.60
G5	81	38.00	101	47.40	31	14.60
Patient on dialysis						
Yes	94	43.50	88	40.70	34	15.70
No	121	33.40	196	54.10	34	12.40

Of the 211 drug orders, 74 (35.1 %) were adequately adjusted for patients with stage 4. Of the 213 drug orders, 81 (38 %) were adequately adjusted for patients with stage 5 (Table 3).

As per each patient, the average number of drugs received by one patient was calculated to be 2.59. The number of patients receiving at least one inappropriate drug dose was 188 accounting for 84.3% of 223 patients.

Multivariable analysis

The results of a logistic regression, taking the inappropriate vs appropriate drugs doses adjustment as the dependent variable, showed that patients aged 65 years and above had more drugs adjusted inappropriately compared to those aged less than 65 years (OR=0.64). Patients admitted to the CCU floor (aOR=1.384) had more drugs adjusted inappropriately compared to those who did not enter the CCU floor, whereas patients who were not on dialysis had more inappropriate drug adjustment compared to those who were on dialysis (aOR=0.586) (Table 4).

DISCUSSION

Several studies conducted worldwide have focused on the evaluation of medication dosing in patients with renal impairment. Yet, none of the published studies was, to our knowledge, carried in Lebanese hospitals. Our objective was to assess whether proper medication dosing was practiced at two university hospitals in Lebanon. The results of our study demonstrate that among 578 medication orders only 37% of prescription orders were adjusted adequately, and the remaining 63% of inappropriately dosed orders were divided into a majority adjusted inadequately with a rate of 49%, and 19% not adjusted at all. Moreover, among the 223 patients selected in our study, 84.3% received at least one medication without the correct adjustment dose.

Our results were comparable to those obtained by Decloedt *et al*. who reported that 32% of 117 prescription entries were adequately adjusted at a hospital in South Africa, and a slightly lower adequate adjustment rate when compared to 49% found by Getachew *et al*. in Addis Ababa, Ethiopia.[10,16] Several studies had described rates of inappropriately dosed drug orders: Alahdal *et al*., in a study conducted at a university hospital in Saudi Arabia, reported a rate of 53.1%, and another study in Paris by Salmon *et al*., showed a rate of 34%, both rates were lower than the 63% obtained in our study.[17,18] Altunbas *et al*. reported significantly lower rates of 12.6%, but the rate was explained by authors by the fact that the study patients had higher degrees of renal dysfunction, compared to other studies, and thus required nephrology consultation and more careful drug prescription.[19] Another similar study was carried out at a governmental hospital in Palestine, indicated that only 26.42% of medications were found to be appropriately adjusted, compared to 73.58% inappropriately adjusted medication orders.[20]

The rate of inappropriate prescriptions obtained in our study is considered to be high. Several reasons may contribute to inappropriate drug dosing in renal failure.[16,19,21] These include not reviewing renal function tests before prescribing, which was reflected by the high number of exclusions due to missing serum creatinine level in our patients' charts. Moreover, physicians' lack of knowledge concerning all drugs that require dosage adjustment which was revealed here by the high rates of drugs "not adjsusted at all". Furthemore, underestimating the impact of mild renal disease by physicians resulted in higher rates of inadequate adjustment in G3a/3b CKD stages versus more advanced disease stages.

We found a positive association between age greater than 65 years and inadequate dose adjustment; this can be attributed to polypharmacy and incorrect GFR estimation.[10,22] It was noticed that patients admitted to the CCU had higher rates of inadequate adjustment. The latter finding can be explained by the fact that beta-blockers were among the most commonly prescribed class of medication requiring adjustment similar to the results

Table 4. Relationship between independent variables and percentage of at least one inappropriately adjusted drug orders.

	Drugs adjusted inappropriately† Count (%)		P value	Odds Ratio (OR) ‡ 95% CI
	Yes	No		
Age			0.007*	0.65 (0.44, 0.95)
Less than 65	157 (57.09)[a]	118 (42.91)[b]		
65 and above	206 (67.98)[a]	97 (32.02)[b]		
Gender			0.235	0.97 (0.66,1.44)
Male	196 (60.38)[a]	127 (39.62)[a]		
Female	167 (65.49)[a]	88 (34.51)[a]		
Reason for admission			0.298	0.83 (0.45, 1.50)
Renal	37 (56.92)[a]	28 (43.08)[a]		
Non-renal	257 (57.88)[a]	187 (42.11)[a]		
GFR category			0.170	
G3a	51 (67.10)[a]	25 (32.90)[a]		0.75 (0.34, 1.65)
G3b	50 (64.10)[a]	28 (35.90)[a]		0.85 (0.43, 1.67)
G4	137 (64.92)[a]	74 (35.08)[a]		0.85 (0.53, 1.37)
G5	132 (61.97)[a]	81 (38.03)[a]		
Patient on Dialysis			0.015*	0.59 (0.36, 0.95)
Yes	122 (56.48)[a]	94 (43.52)[b]		
No	241 (66.57)[a]	121 (33.43)[b]		
Coronary Care Unit department	117 (70.06)[a]	50 (29.94)[b]	0.004*	1.38 (0.73, 2.61)

†. Drugs adjusted inappropriately are the sum of inadequately adjusted and not adjusted at all.
*. The Chi-square statistic is significant at the 0.05 level.
‡. The reference category is drugs adjusted adequately.
Note: Values in the same row and subtable not sharing the same subscript are significantly different at p< 0.05 in the two-sided test of equality for column proportions. Cells with no subscript are not included in the test. Tests assume equal variances. Nagelkerke R2= 31.7%

obtained by Bailie *et al.*[23] Furthermore, the inadequate adjustment rate of beta-blockers in the present study was 83.6% far more than the 3.78% attained with Altunbas *et al.*[19]

Other finding in our study reported that dialysis patients had lower rates of inadequate adjustment. It seems that physicians were more careful in medication prescription, made appropriate dose adjustments, and more nephrologist consultations among dialysis patients were noted.[21]

This study was subject to some limitations. It was confined to two hospitals, which limits the generalizability of the results. The study was planned as a retrospective, cross sectional study, and thus, data collection may be vulnerable to missing and incomplete data, the method which prescribers used to assess the severity of renal impairment could not always be determined, and we did not evaluate the outcomes. The SCr value of 1.2 mg/dL is considered cut off point for patient inclusion, and this value, alone, cannot confirm the presence of renal impairment as those below 1.2 mg/dL may have severe renal impairment particularly in some special population such as very old or amputated patients. However, because hospital data lack consistent CrCl estimation rates, a cutoff point to start with was necessary. A cutoff point lower than 1.2 would have included huge number of non-CKD patients. Physicians may have referred to guidelines that are different from the ones we used in our study. In addition, the dose of some medications may be adjusted based on different endpoints other than estimated GFR. Moreover, the experience with the use of certain medications in renal dialysis patients is limited and no clear adjustment guidelines.[24] Lastly, GFR may become extremely difficult to estimate and unreliable in critically ill patients who experience rapidly changing renal function.[16]

In consideration of the high prevalence of CKD among medical inpatients, and the significant impact of improper dosing of medications, several methods have been suggested to improve drug dose adjustment recommendations. The collaboration with clinical pharmacists, who are uniquely trained in therapeutics and provide comprehensive drug management to both patients, physicians, and all members of the care team, has been shown to be a vital step towards improving patient care.[17,25] Moreover, improving education, via standardization of prescription sources, updated prescription protocols, and pocket tables with dosing guidelines, as a complete interventional program, have been showed by Martinez-Anton et al. to reduce the rate of prescribing errors from 34.2% to 21.7%.[26] Furthermore, computerized systems are becoming significantly helpful in this area. It has been shown that using computerized physician order entry and clinical decision support system was able to decrease rates of medication dosing errors.[19]

CONCLUSIONS

In conclusion, the frequency of appropriate dosing adjustment as to renal clearance for all non-antimicrobial drugs in patients with CKD at two Lebanese university hospitals was low. Although the rates of inappropriate dosing were relatively low in statins and ACE inhibitors, it was fairly high in bisoprolol and ranitidine dosing. In Lebanon, problems at the organizational and professional levels are contributing to the incidence of medical errors and the associated suboptimal responses.[27] Therefore, increasing nephrology consultation rate and implementation of physician education programs may be helpful to reverse this trend.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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Original Research

Effect of the pharmacist-managed cardiovascular risk reduction services on diabetic retinopathy outcome measures

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Abstract

Background: Diabetic retinopathy (DR) is a progressive, sight-threatening long-term complication of diabetes. Diabetes disease management reduces the risk of developing or progression to a severe form of DR. However, there are no reports of the potential role of pharmacists in DR progression.

Objective: For this study, we performed a retrospective data analysis of patients with diabetes seen at cardiovascular risk reduction services provided by pharmacists with an objective to determine the potential role of pharmacists in the DR progression. These services involve pharmacists working in collaborative drug therapy management (CDTM), using a collaborative practice agreement (CPA) with primary care physicians.

Methods: Patient records and ophthalmological notes were collected for 317 individuals seen by the pharmacists (intervention group) and 320 individuals seen only by a physician (control).

Results: Statistical analysis was performed on 148 individuals in an intervention group and 120 individuals in the control group for which complete records were available. Retinopathy progression remained stable in 89.6 % of individuals in the intervention group compared to 87.9% in the control group. Moreover, the relative risk of retinopathy progressing to a severe form was 1.17 for the control group compared the intervention group.

Conclusions: Our studies provide a proof-of-concept that pharmacists-managed care possesses a potential role in protection from DR, and paves a way for future pharmacists managed care with an emphasis on reducing diabetic complications.

Keywords

Diabetic Retinopathy; Diabetes Mellitus; Pharmacists; Professional Role; Medication Therapy Management; Retrospective Studies; Indiana

INTRODUCTION

The diabetes epidemic is increasing at an alarming rate, with an estimated 30.3 million people, or 9.4% of the US population, having diabetes. With the incidence of diabetes expected to increase to 54.9 million by the year 2030, a precipitous rise in diabetes-associated complications is a major concern.[1] Diabetic retinopathy (DR) is among the most common complications of diabetes and the leading cause of new cases of legal blindness among adults aged 20-74 years in the US. DR is a progressive condition, with nearly all patients with type 1 diabetes (T1D) and > 60% of patients with type 2 diabetes (T2D) develop DR, within 20 years of diabetes.[2] The latest assessment of patients with diabetes suggests a 28.5% estimated prevalence of DR, with a 4.4% prevalence of vision-threatening DR.[3] The vision loss in patients with diabetes occurs through a variety of mechanisms such as retinal detachment, vitreous hemorrhage, macular edema, or capillary non-perfusion. DR is mainly categorized into two stages nonproliferative DR (NPDR) and proliferative DR (PDR). The NPDR is further sub-classified into three stages: mild, moderate and severe NPDR. A meta-analysis study of 27,120 patients reported a pooled incidence of PDR as 11%, and severe vision loss as 7.2% after 4 years.[4,5] Current therapeutic options such as pan-retinal photocoagulation or anti-VEGF work either at the expense of the retina or are only effective in about 35-45% of the population.

The combination of uncontrolled glycemic control and hypertension, failure of timely clinical assessment, and lack of patient awareness are among the greatest risks for vision loss among patients with diabetes.[6-8] Similarly, poor access to care, lack of time, out of pocket expenses, insufficient patient knowledge related to the disease and lack of care/coordination are additional barriers for providing optimal management of DR and its risk factors.[9,10] This leads to an unmet need for developing newer approaches in patients with diabetes to tackle the burgeoning rise in DR.

Primary care physicians (PCP) manage most patients with diabetes, with a recent study suggesting there are 1380 diabetes-related visits to physician offices per 1000 persons aged 65 and over.[11] However, providers of these clinics face significant challenges for providing optimal diabetes care. These include longer time intervals between patient visits,

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limited time during scheduled visits, difficulty scheduling to busy PCP practices, lack of provider awareness of updated diabetes treatment medications, and lack of patient education on diabetes complications.[12,13] The educational, clinical, medication-related, and psychological needs of these patients are complex, and often cannot be addressed during infrequent visits to a PCP.[14,15] Large clinical studies such as the diabetes control and complications trial (DCCT) involving individuals with T1D and UK prospective diabetes study (UKPDS) in patients with T2D revealed tight glycemic, blood pressure, and cholesterol control can substantially reduce risks of microvascular diabetes-related complications. However, the barriers in current healthcare systems make it difficult to achieve the metabolic goals of these patients. There is a requirement of additional resources to overcome deficits in the health care of individuals with diabetes. Many individuals with diabetes fail to receive education about maintaining good glycemic control, medication management, the recommended frequency of tests for better management of diabetes, and information related to the correlation of blood sugar control and prevention of DR.[8,10,16]

Pharmacists are an important pillar of the healthcare system, with evidence supporting joint care with physicians for patients with diabetes. Pharmacist's involvement in medication management, patient education, drug utilization review, and diabetes education have shown significant improvements in HbA1c, LDL-cholesterol, blood pressure, and frequency of adverse drug events.[17-19] Interventions by clinical pharmacists have also led to improvements in medication adherence, patient knowledge, and quality of life. Pharmacist interventions have ultimately lead to dramatic decreases in average medication expenditures per patient and decreased sick days or time away from work.[20-22]

There is a strong association between cardiovascular disease, elevated plasma LDL cholesterol, gross proteinuria, and DR.[23] Long-term maintenance of glycemic control and medication management are some of the greatest challenges faced by individuals with diabetes. However, there are no reports documenting whether the direct intervention by a pharmacist in the management of diabetes and associated micro- and macrovascular outcomes leads to beneficial effects regarding DR progression. To evaluate the potential benefit of pharmacists' interventions on protection from DR progression, a retrospective observational study was completed evaluating retinopathy progression in patients with diabetes managed by pharmacists and physician (intervention group) versus those in routine care (control group). The pharmacists worked in a collaborative drug therapy management (CDTM) service, using a collaborative practice (CPA) agreement with primary care physicians to provide comprehensive cardiovascular risk reduction serviced to patients with diabetes. Pursuant to this agreement, pharmacists in these clinics were able to independently, start, stop, or adjust medications related to diabetes, hypertension and smoking cessation. The pharmacists were also able to provide necessary counseling related to disease-state education, non-pharmacologic management strategies, and additional referrals. Referrals were made by pharmacists to key collaborating providers for patients with diabetes, including ophthalmology, nephrology, neurology, cardiology, podiatry, dentistry and more.

METHODS

Study Design

The study was approved for a database access (#1506049479) of patients with diabetes seen within any clinic of a safety-net healthcare system in downtown Indianapolis, IN, USA. Data were collected from a group of individuals seen by the pharmacist (intervention group; n=317) along with PCP, and individuals only seen by the PCP (control group; n=320). Information from the following categories was collected and entered into Research Electronic Data Capture database (REDCap; https://projectredcap.org/): (a) age, race, and gender, (b) metabolic parameters such as A1C, LDL, HDL, blood pressure, and triglycerides, (c) current medications, and (d) diabetic retinopathy-related information (including ophthalmology appointment dates and retinopathy ratings, as per ophthalmologist's notes). An attending ophthalmologist categorized retinopathy; these notes were used for study purposes. Retinopathy status was graded on the scale of zero to three: no retinopathy (0), mild NPDR (0.5), moderate NPDR (1), severe NPDR (2), and PDR (3). The date of the appointment, the level of retinopathy indicated, and ophthalmologist's name were all recorded under the ophthalmology appointment dates and retinopathy-rating category. (e) The last category was exclusive to the intervention group and included the date(s) of an appointment(s) with the pharmacist.

Statistics

Data analysis was performed on individuals having a record of at least two eye examinations and a complete set of demographic information. The demographic variables such as age, race, and gender were included in the analysis in order to offset any potential sampling bias in the study. A total of 148 individuals in the intervention group and 120 individuals in the control group met this criterion. In both control and intervention groups age was discretized into four categories (<50, 50-69, 70-79, >80) and participants that were included in the study fell into three self-reported race categories (African American, White, and Multiracial). A Chi-squared test and Fisher exact test were conducted to test the Null hypothesis of an equal distribution between the intervention and control groups for the demographic variables of interest. Laboratory assessments of A1c, LDL, and HDL were presented using median and interquartile range and categorized based on the use of insulin therapy. The Mann Whitney U test was performed to test the Null Hypothesis. A p-value of less than 0.05 suggests a significant difference in medians.

Due to the subjectivity of documentation, severity of assessment by different physicians and diversity of physician visits by a respective patient, three different metrics were used to document the progression of DR. For a given patient, the retinopathy progression status was obtained by first taking the difference in retinopathy score on the first and last visit on record and then coded in the following manner: (a) a positive change was coded as 1

(improved), a change of 0 as (0, stable) and a negative change as -1 (worsen). (b) Both positive and zero change were coded as 1 (stable/ improved) and a negative change was coded as – 1 (worsen). (c) Only zero change (coded as 1) and negative change (coded as 0). For metrics (a, b and c), a Chi-squared test was used in order to study whether the proportion of patients whose retinopathy scores remained stable or improved were significantly different in the control and intervention groups. A chi-squared test was also used to assess whether the risk of worsening DR was significantly higher in one of the two groups. In addition to the binary metrics (b) and (c) a logistic regression analysis was conducted to model the odds of retinopathy worsening in the control group versus and intervention groups. The response variable in the logistic regression model was the binary condition of the patient retinopathy (improve/worsen) and the factor of interest was the indicator variable representing whether the patient belongs to the intervention or control group. Comparison between the control and intervention groups were performed using a likelihood ratio test. The demographic variables gender, race, and age were also added to the model as a covariate to adjust for their effect. We performed a power analysis for comparing the odds of retinopathy worsening in the control and intervention groups for the logistic regression model assuming a moderate effect size. The true but unknown effect size (odds ratio) was assumed to range between 1.2 and 1.5. This would suggest that the intervention group 1.2 to 1.5 times less likely will experience retinopathy than the control group. The power analysis was computed using Shieh-O'Brien large sample approximation.[24,25] Based on this power analysis the required sample size ranges from 899 to 2202 patients in each group depending on the unknown true effect size (odds ratio) and unknown true probability of retinopathy worsening in the two groups. The sample size was estimated at a power of 0.8 and 0.05 level of significance.

In order to further examine the effect of pharmacist's intervention on the progression of DR, patients in the intervention groups were divided into three categories based on the total number of pharmacist visits on record. These categories are 0-5 visits 6-20 visits and >20 visits. The percentage of cases for which retinopathy worsen in each of these three categories was then compared. All analyses were implemented using Statistical Analysis Software (version 9.4, SAS Institute Inc., Cary, 115 NC)

RESULTS

There was no significant difference in distribution in the demographic variables (gender, race, and age) between the control and intervention group (Table 1). This suggests that the control and intervention group used were comparable for further analysis. The intervention group had marginally higher HbA1c, LDL and lower HDL cholesterol with a statistically insignificant difference. Patients in the intervention group were followed on average for 1.77 years with a median duration of a follow-up time of 1.25 years while patients in the control group were followed on average 1.55 years with a median duration of follow up of 1.19 years (Table 1). Patients in the intervention group had marginally more ophthalmology visits than patients in the control group with an average number of visits of 3.32 and 2.27 respectively over the time duration patients were followed (Table 1).

In the intervention group using metrics (c), retinopathy remained stable as compared to a control group. In

Table 1. Baseline characteristics of Pharmacist intervention group and control group

	Intervention (n=148)		Control (n=120)				
Demographic variables	**n**	**%**	**n**	**%**	**Chi-sq (df)**	**p-value**	**Fisher Exact test p-value**
Gender					1.80 (1)	0.179	0.210
Male	65	43.92	43	35.83			
Female	83	56.08	77	64.17			
Race					2.93 (2)	0.230	0.245
Black/African American	99	66.89	75	62.50			
White	43	29.05	34	28.33			
Multiracial	6	4.05	11	9.17			
Age					5.15 (3)	0.160	0.161
< 50	20	13.51	19	15.83			
50-59	48	32.43	27	22.50			
60-69	54	36.49	42	35.00			
>70	26	17.57	32	26.67			
Lab results	**Median**	**IQR**	**Median**	**IQR**	**p-value****		
A1c							
Insulin	8.4	2.6	8.1	2.3	0.241		
Non_insulin	7.1	2.8	7.1	1.9	0.932		
HDL							
Insulin	42	18	45	17	0.098		
Non_insulin	46	20	46	18	0.918		
LDL							
Insulin	96	50	88	56	0.191		
Non_insulin	95	66	98.5	40	0.904		
	Mean (median)	**Min (max)**	**Mean (median)**	**Min (max)**			
Duration of Time (years) patients were followed	1.77 (1.25)	3 days (6.55)	1.55 (1.19)	12 days (5.25)			
Number of Ophthalmology visits	3.32 (3)	2 (20)	2.27 (2)	2 (5)			

Table 2. Effect of Pharmacist intervention on Diabetics Retinopathy

	Intervention		Control				
Demographic variables	**n**	**%**	**n**	**%**	**Chi-sq (df)****	**p-value**	**Fisher Exact test p-value**
a-Retinopathy Progress status					0.350 (2)	0.839	0.837
worsen	13	8.78	12	10.00			
stable	112	75.68	87	72.50			
Improved	23	15.54	21	17.50			
b-Retinopathy Progress Binary					0.115(1)	0.733	0.833
worsen	13	8.78	12	10.00			
stable/Improved	135	91.21	108	90.00			
c-Retinopathy Progress Binary					0.165 (1)	0.684	0.831
worsen	13	10.4	12	12.12			
stable	112	89.6	87	87.87			

Number of pharmacist visits for the Intervention Group	**[0-5]**		**[6-20]**		**[21-60]**	
	n	**%**	**n**	**%**	**n**	**%**
Stable/ Improved	25	92.59	60	85.71	38	79.17
Worsen	2	7.41	10	14.29	10	20.83

addition, there was a decrease in the percentage of patients who progressed to a severe form of DR in the intervention group as compared to control. For metrics (a) and (b) no significant difference was found between the control and intervention groups (Table 2). This corresponds to a relative risk of retinopathy worsening in the control group as 1.17 when compared to the intervention group. After adjusting for the effect of the demographic variables, the odds ratio of retinopathy progressing to a severe form in the control group was 1.31 (95%CI, 0.5 to 3.05) (Table 3).

In order to further examine the effect of pharmacist's intervention on the progression of DR, a comparison was made with DR progression and the number of visits with pharmacists. A higher percentage of patients were classified as having stable DR if they had visited a pharmacist between 0-5 times (95.59%) versus those that visited pharmacists between 6-20 times (85.71%). Also, a lower percentage of patients were classified as stable DR if they visited pharmacists more than 20 times (79.17%) than between 6-20 times (Table 2).

DISCUSSION

Diabetes management programs play an integral role in the management of patients with diabetes.[26] It has been shown that multidisciplinary team care by a PCP, advanced practice nurse and clinical pharmacist leads to significant improvements in glycemic control.[27] Our study further demonstrates that in individuals, which received pharmacists-managed care, remained either stable or improved on retinopathy scale, also the absolute risk of worsening the retinopathy grading reduced in an intervention group. This would roughly lead to 100,000 more cases of stable or improved DR considering 1.2% ARR in our study and taking into account 28.5% prevalence of DR in 30.3 million diabetics in the United States.

A disease management program involving a pharmacist has reported a 0.8% decrease in A1c in 12 months.[28] In our study, the glycated hemoglobin levels between two patient groups differed insignificantly at the baseline. The HbA1c reports were not available at study termination; therefore, we cannot concur that glycemic control indeed helped in protection from DR. However, the unpublished data from our practice site has shown sustained A1c reductions of 1-2% by pharmacist-managed patients for at least 4 years suggest that there may be a similar A1c reduction in our study participants.

This study is among the first of its kind showing a potential role of pharmacists-involvement in diabetes care leading to a reduction in DR progression. While the effect is modest, the concept is quite compelling due to the continued expansion of privileges for pharmacists on a state and national level. This proof of concept of pharmacists role in slowing the progression of DR comes in addition to all previously documented benefits pharmacists can have on glycemic control, medication adherence, healthcare costs, and others. Similarly, community pharmacists are uniquely placed among healthcare individuals and often serve as the first-line of entry into the healthcare system for many patients. With many of these pharmacists expanding roles to include disease education and medication therapy management, there is an increased opportunity for pharmacists to have a significant effect on this important diabetes outcome.

Our results support the hypothesis that inclusion of a pharmacist with an ability to provide direct patient care as part of an interdisciplinary team managing diabetes can lead to less progression of DR. While the specific reason for the lack of DR progression was not determined in our study, there is a direct correlation between improvements in glycemic control and worsening of DR. Exposure to direct care by pharmacists did lead to significant improvements in glycemic control compared to the control group. While the number of ophthalmology referrals was not tracked, the

Table 3. Logistic Regression Results for Comparing the Odds of worsening diabetic retinopathy in Control and Pharmacist Intervention Groups

n_o / total n_o (%)	**Worsening of diabetic retinopathy**	**Adjusted Odds Ratio[ǂ] (95%CI)**	**p-value[ɬ]**
Control	12/ 99 (12.12)	1.31 (0.56-- 3.05)	0.534
Intervention	13/125 (10.40)		

ǂ Adjusted Odds Ratio was obtained using a logistic regression modeling of the odds of retinopathy worsening in patients in the control and interventions groups. The logistic regression was adjusted for the effect of the demographic variables age, gender and race.
ɬ Maximum likelihood test was utilized to generate the p values for comparing the odds of retinopathy worsening in the control and intervention groups.

pharmacist providing direct care to the patients could provide this service and are in a position to help support this important aspect of diabetes care (i.e. serving as another healthcare provider to ensure patients with diabetes received appropriate ophthalmology care).

While this study did not involve community pharmacists, pharmacists working in those settings can assume many roles that mirror what the pharmacist in this study was able to do. Data support the role of community pharmacists in improving glycemic control and they could also serve as an additional healthcare provider monitoring for, and reminding patients about, appropriate ophthalmologic care for their diabetes.[19] Pharmacist in the community also remove, or mitigate, a risk cited for patients with DR. This includes the necessity of having a prior appointment, and potential long wait times just to discuss patient concerns. Pharmacists can also be uniquely positioned to provide education about eye complications related to diabetes and provide screening for ophthalmology appointments of their patients. This supports previous studies suggesting early referral to an ophthalmologist can lead to as much as a 50% reduction in the risk of severe visual loss and vitrectomy.[6,29,30]

With highlighting benefits of pharmacist's intervention on retinopathy progression, the following limitations were perceived; (i) While the baseline demographics of patients included in this study did not differ significantly, retrospective data collection only provided baseline glycemic control of these patients, (Table 1). It would be interesting in future studies to correlate the progression of DR with a degree of glycemic control over time. (ii) Another difficulty of this retrospective analysis was getting accurate retinopathy ratings. (iii) This study involved individuals that received pharmacist's intervention related to a cardiovascular risk reduction, the patients were not educated on eye complications, vision problems.

CONCLUSIONS

Our study provided a proof-of-concept that involving a pharmacist in the progressive care of patients with diabetes can help in both reducing severity of DR and achieving satiety for DR progression. Future studies aimed specifically at educating patients about eye complications and timely reminders at prescription refill may help in reducing the risk of DR in individuals with diabetes.

CONFLICT OF INTEREST

None of the authors have affiliations with or involvement in any organization or entity with a financial interest in the subject matter or material discussed in this manuscript.

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Original Research

Clinical pharmacist implementation of a medication assessment tool for long-term management of atrial fibrillation in older persons

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Abstract

Background: Optimisation of drug therapy is important in the older population and may be facilitated by medication assessment tools (MATs).

Objective: The purpose of the study was to evaluate whether appropriateness of drug therapy and clinical pharmacist intervention documentation improved following implementation of a previously developed MAT for the long-term management of atrial fibrillation (MAT-AF).

Methods: Adherence to MAT-AF review criteria and clinical pharmacist intervention documentation was assessed by the researcher pre-MAT implementation in 150 patients aged ≥60 years admitted to a rehabilitation hospital with a diagnosis of atrial fibrillation. MAT-AF was introduced as a clinical tool in the hospital for identification of pharmaceutical care issues in atrial fibrillation patients. Adherence to MAT-AF and pharmacist intervention documentation were assessed by the researcher post-MAT implementation for a further 150 patients with the same inclusion criteria. Logistic regression analysis and measurement of odds ratio was used to identify differences in adherence to MAT-AF pre- and post-MAT implementation. The differences between two population proportions z-test was used to compare pharmacist intervention documentation pre- and post-MAT implementation.

Results: Adherence to MAT-AF criteria increased from 70.9% pre-implementation to 89.6% post-implementation. MAT-AF implementation resulted in a significant improvement in prescription of anticoagulant therapy (OR 4.07, p<0.001) and monitoring of laboratory parameters for digoxin (OR 10.40, p<0.001). Clinical pharmacist intervention documentation improved significantly post-implementation of MAT-AF (z-score 20.249, p<0.001).

Conclusions: Implementation of MAT-AF within an interdisciplinary health care team significantly improved the appropriateness of drug therapy and pharmacist intervention documentation in older patients with atrial fibrillation.

Keywords

Atrial Fibrillation; Disease Management; Drug Utilization Review; Medication Therapy Management; Inappropriate Prescribing; Pharmaceutical Services; Pharmacists; Aged; Clinical Audit; Malta

INTRODUCTION

Extensive literature has confirmed the value of clinical pharmacist intervention in improving the appropriateness of drug treatment in older patients.[1-5] As the proportion of older persons continues to increase, the role of the clinical pharmacist as a member of a multi-professional team is becoming more crucial for optimisation of drug therapy in this patient population.[4] Documentation of pharmacist interventions provides a record which is important for continuity of care, accountability of pharmacist services and quality assurance.[6,7]

Several medication review tools have been designed to enhance appropriate prescribing in older patients.[8] The medication assessment tool MAT-AF is an innovative and validated tool, previously developed by this research group, for the long-term management of atrial fibrillation (AF) in older persons.[9] MAT-AF incorporates criteria for assessing appropriateness of drug therapy whilst applying the clinical considerations required in managing drug therapy for AF (refer to supplementary material). Review criteria in MAT-AF are composed of a qualifying statement and a standard, sectioned into antithrombotic, rate control and rhythm control therapy. Content validity was tested by an expert group using a Delphi technique and consensus obtained for all final criteria. Inter- and intra-observer reliability and feasibility was demonstrated. An application guide for consistent interpretation and application of the MAT was compiled.[9]

MAT-AF was developed on the basis that AF is associated with substantial morbidity and mortality and requires consideration of management recommendations focusing on thromboembolic risk reduction, rate control and rhythm control.[10-13] MAT-AF considers guidelines on the use of antithrombotic agents endorsed for the prevention of thromboembolism namely warfarin and direct oral anticoagulants (DOACs).[10-13] Recent guidelines recommend that a DOAC be used preferentially to warfarin on the basis of strong evidence of a lower risk of intracranial haemorrhage, although cost effectiveness remains a debatable issue considering the high cost of DOACs.[12-14] Rate control is a key component in the management of AF

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patients. Beta-blockers, nondihydropyridine calcium channel blockers or digoxin are recommended as suitable first-line options.[13] When monotherapy is insufficient to achieve rate control, digoxin is recommended in combination with a beta-blocker or with a nondihydropyridine calcium channel blocker.[10-13] Amiodarone should be considered when other agents are unsuccessful or contraindicated.[10,12,13] Monitoring of serum digoxin levels, renal function, thyroid function and electrolytes is recommended for safe use of digoxin.[15] Liver, thyroid, ophthalmic and pulmonary monitoring is recommended with amiodarone treatment.[16] Restoring and maintaining sinus rhythm is another aspect of AF management.[10-13] Clinical evidence has demonstrated that both rhythm and rate control strategies have resulted in similar outcomes.[17,18] Long-term antiarrhythmic agents should be commenced judiciously after consideration of the extent of symptoms and potential for adverse drug reactions. A rate control strategy is often preferred in older persons.[10,13]

The purpose of the study was to evaluate whether implementation of MAT-AF in clinical practice contributes to improving the appropriateness of drug therapy and clinical pharmacist intervention documentation. Adherence to MAT-AF review criteria was used to measure appropriateness of drug therapy and to determine whether a pharmacist intervention was generated.

METHODS

The study setting was Karin Grech Hospital in Malta, a 280-bed hospital specialising in rehabilitation of older patients. Clinical pharmacists complete a paper-based pharmacy patient profile for each patient at the hospital. Pharmaceutical care issues, interventions and outcomes are documented by the pharmacist on the profile in daily clinical practice.

Adherence to MAT-AF criteria was assessed by the researcher prior to MAT implementation by application of the tool to 150 patients admitted for rehabilitation.[9] Inclusion criteria were a diagnosis of AF and age ≥60 years while transfer of the patient to acute care and death were considered as exclusion criteria. The MAT was applied by the researcher to patients consecutively at discharge from March to September 2016. The pharmacy patient profile of each patient was reviewed to determine whether care issues generated by MAT application resulted in a documented intervention by the clinical pharmacist. The pharmaceutical care issues were classified in terms of a set of care issue types defined in the hospital standard operating procedure for patient profiling.[19]

The use of MAT-AF as a clinical tool was introduced by the researcher to the nine clinical pharmacists at the hospital. Following a training period of two weeks, the pharmacists used the tool in practice by applying the MAT criteria to patients admitted with AF for identification of pharmaceutical care issues which were to be followed by intervention and documentation.

Adherence to MAT-AF and clinical pharmacist intervention documentation were assessed post-MAT implementation for a further 150 patients admitted to the hospital with the same inclusion criteria. MAT-AF was applied by the researcher to audit patients consecutively at discharge from November 2016 to May 2017.

The study protocol was approved by the Karin Grech Hospital Research Committee and the University of Malta Research Ethics Committee.

Statistical analysis

Data analysis was conducted using IBM SPSS® Statistics version 24. Descriptive statistics were generated for the study population in the pre- and post-implementation

Table 1. Patient characteristics for the study population pre- and post-implementation of MAT-AF

(n=150)	Pre-implementation		Post-implementation	
Gender (n)				
male	54	(36.0%)	44	(29.3%)
female	96	(64.0%)	106	(70.7%)
Age (years)				
mean (SD)	81.7	(7.6)	82.7	(6.4)
min, max	60	97	63	97
≥75 years (n)	127	(84.7%)	134	(89.3%)
Atrial fibrillation (n)				
paroxysmal	54	(36.0%)	67	(44.7%)
persistent	12	(8.0%)	11	(7.3%)
permanent	84	(56.0%)	72	(48.0%)
Comorbidities (n)				
heart failure	93	(62.0%)	92	(61.3%)
hypertension	108	(72.0%)	112	(74.7%)
diabetes	48	(32.0%)	59	(39.3%)
stroke/TIA/thromboembolism	51	(34.0%)	50	(33.3%)
vascular disease*	52	(34.7%)	53	(35.3%)
anaemia	68	(45.3%)	82	(54.7%)
chronic kidney disease**	103	(68.7%)	116	(77.3%)
CHA_2DS_2VASc score ≥1 (n)***	149	(99.3%)	150	(100.0%)
HAS-BLED score (0-9)				
mean (SD)	2.0	(0.8)	2.1	(0.8)
min, max	1	4	0	4

*acute coronary syndrome or peripheral arterial disease (including revascularisation), **creatinine clearance <60ml/min, ***excluding gender, TIA – transient ischaemic attack
Data for pre-implementation phase reported by Gauci *et al*.[9]

Table 2. Adherence to applicable criteria of MAT-AF pre- and post-implementation

Criterion focus		Pre-implementation		Post-implementation		Odds Ratio [95% CI]	p-value
		Applicable cases	Adherence	Applicable cases	Adherence		
		n (%)	n (%)	n (%)	n (%)		
Antithrombotic therapy							
1	No antithrombotic therapy if CHA_2DS_2VASc score 0*	1 (0.7)	1 (100)	0 (0)	0 (0)	-	-
2	Prescription of oral anticoagulant if CHA_2DS_2VASc score ≥1*	149 (99.3)	105 (70.5)	150 (100)	136 (90.7)	4.07 [2.12 – 7.82]	**<0.001**
3	Prescription of direct oral anticoagulant at recommended dose if creatinine clearance ≥50mL/min	5 (3.3)	4 (80.0)	7 (4.7)	6 (85.7)	1.50 [0.07 – 31.58]	0.794
4	Prescription of direct oral anticoagulant at lower dose or warfarin if creatinine clearance between 15-49ml/min	47 (31.3)	47 (100)	58 (38.7)	55 (94.8)	-	-
5	Prescription of warfarin if creatinine clearance <15ml/min	1 (0.7)	1 (100)	1 (0.7)	1 (100)	-	-
Rate control therapy							
6	Prescription of beta-blocker, non-dihydropyridine calcium channel blocker and/or digoxin	97 (64.7)	82 (84.5)	95 (63.3)	92 (96.8)	3.92 [1.06 – 14.54]	**0.041**
7	Cardiology referral/follow up if non-dihydropyridine calcium channel blocker and contraindicated/not tolerated	1 (0.7)	0 (0)	0 (0)	0 (0)	-	-
8	Prescription of beta-blocker and/or digoxin if heart failure with left ventricular ejection fraction <40%	12 (8.0)	12 (100)	7 (4.7)	7 (100)	-	-
9	Monitoring of renal and thyroid function, serum electrolytes with digoxin and within range	53 (35.3)	27 (50.9)	59 (39.3)	54 (91.5)	10.40 [3.59 – 30.10]	**<0.001**
10	Monitoring of serum digoxin level if at risk of high serum concentration and within range	23 (15.3)	17 (73.9)	23 (15.3)	20 (87.0)	2.35 [0.51 – 10.86]	0.273
11	Prescription of amiodarone for additional rate control or contraindication/intolerance to other agents	1 (0.7)	0 (0)	0 (0)	0 (0)	-	-
12a	Monitoring of liver and thyroid function with amiodarone and within range	21 (14.0)	17 (81.0)	16 (10.7)	15 (93.8)	3.53 [0.35 – 35.16]	0.282
12b	Monitoring of ophthalmic and pulmonary function with amiodarone	21 (14.0)	0 (0)	16 (10.7)	4 (25.1)	-	-
Rhythm control therapy							
13	Continuation at prescribed dose if maintained in sinus rhythm with antiarrhythmic agent and well tolerated	10 (6.7)	7 (70.0)	10 (6.7)	9 (90.0)	3.86 [0.33 – 45.57]	0.284
14	Cardiology referral/follow-up if maintained in sinus rhythm with antiarrhythmic agent and contraindicated/not well tolerated	3 (2.0)	0 (0.0)	2 (1.3)	0 (0)	-	-
15	Cardiology referral/follow-up if prescribed antiarrhythmic agent and not maintained in sinus rhythm	13 (8.7)	5 (38.5)	10 (6.7)	8 (80.0)	8.00 [1.13 – 56.79]	**0.038**
Total criteria		**458 (19.1)**	**325 (70.9)**	**454 (18.9)**	**407 (89.6)**		

*CHA_2DS_2VASc score excluding gender; Adherence to MAT criteria was calculated by the sum of the 'adherence' and 'justified non-adherence' responses expressed as a percentage of the applicable criteria; Odds ratio not reported for percentage adherence 0 and 100.
Data for pre-implementation phase reported by Gauci *et al*.[9]

phases. Characteristics of the patient populations were compared by the independent samples t-test for quantitative variables and the differences between two population proportions z-test for qualitative variables. Adherence to MAT criteria was computed by the sum of the 'adherence' and 'justified non-adherence' responses expressed as a percentage of the applicable criteria. Criterion responses which were not applicable or which had insufficient data for the qualifying statement were excluded.[9] Logistic regression analysis and measurement of odds ratio was used to identify differences in adherence to MAT-AF pre- and post-MAT implementation. The differences between two population proportions z-test was used to compare pharmacist intervention documentation pre- and post-MAT implementation. The Pearson chi-square test was used to assess the relationship between prescription of anticoagulation with patient age and CHA_2DS_2VASc score.[20]

RESULTS

Patient population characteristics in the pre- and post-implementation phases of MAT-AF application are

Table 3. Documented pharmacist interventions for care issues generated by MAT-AF application pre- and post-implementation

Criterion focus		Care issue type	Pre-implementation		Post-implementation		p-value
			Care issue generated	Intervention documented	Care issue generated	Intervention documented	
			n	n (%)	n	n (%)	
Antithrombotic therapy							
1	No antithrombotic therapy if CHA_2DS_2VASc score 0*	Unnecessary drug	0	0 (0)	0	0 (0)	-
2	Prescription of oral anticoagulant if CHA_2DS_2VASc score ≥1*	Need for additional drug	60	12 (20.0)	51	48 (94.1)	<0.001
3	Prescription of direct oral anticoagulant at recommended dose if creatinine clearance ≥50ml/min	Monitoring need/Dose too low	5	1 (20.0)	2	1 (50.0)	0.430
4	Prescription of direct oral anticoagulant at lower dose or warfarin if creatinine clearance between 15-49ml/min	Monitoring need/Dose too high	1	1 (100)	7	4 (57.1)	0.407
5	Prescription of warfarin if creatinine clearance <15ml/min	Monitoring need/Improper drug selection	0	0 (0)	0	0 (0)	-
Rate control therapy							
6a	Monitoring of pulse	Monitoring need	150	0 (0)	150	143 (95.3)	<0.001
6b	Prescription of beta-blocker, non-dihydropyridine calcium channel blocker and/or digoxin	Improper drug selection	13	1 (7.7)	7	3 (42.9)	0.060
7	Cardiology referral/follow up if non-dihydropyridine calcium channel blocker and contraindicated/not tolerated	Risk for adverse drug reaction	1	0 (0)	0	0 (0)	-
8	Prescription of beta-blocker and/or digoxin if heart failure with left ventricular ejection fraction <40%	Improper drug selection	5	0 (0)	3	1 (33.3)	0.503
9	Monitoring of renal function, thyroid function, serum electrolytes with digoxin and within range	Monitoring need	53	0 (0)	59	50 (84.7)	<0.001
10	Monitoring of serum digoxin level if at risk of high serum concentration and within range	Monitoring need	23	11 (47.8)	23	19 (82.6)	0.013
11	Prescription of amiodarone for additional rate control or contraindication/intolerance to other agents	Improper drug selection	1	0 (0)	0	0 (0)	-
12a	Monitoring of liver and thyroid function with amiodarone and within range	Monitoring need	21	10 (47.6)	16	13 (81.3)	0.037
12b	Monitoring of liver and thyroid function with amiodarone after discharge	Seamless care need	21	1 (4.8)	16	5 (31.3)	0.030
12c	Monitoring of ophthalmic and pulmonary function with amiodarone	Monitoring need/Counselling need	21	0 (0)	16	8 (50.0)	<0.001
Rhythm control therapy							
13	Continuation at prescribed dose if maintained in sinus rhythm with antiarrhythmic agent and well tolerated	Need for additional drug/Dose too low	0	0 (0)	1	0 (0)	-
14	Cardiology referral/follow-up if maintained in sinus rhythm with antiarrhythmic agent and contraindicated/not well tolerated	Risk for adverse drug reaction	0	0 (0)	2	0 (0)	-
15	Cardiology referral/follow-up if prescribed antiarrhythmic agent and not maintained in sinus rhythm	Improper drug selection	11	0 (0)	8	6 (75.0)	<0.001
Total care issues			**386**	**37 (9.6)**	**361**	**301 (83.4)**	**<0.001**

*CHA_2DS_2VASc score excluding gender

presented in Table 1. No significant variation between the two study populations was evident (p>0.05).

Adherence to the 458 applicable criteria was 70.9% before MAT-AF implementation.[9] In the post-implementation phase, adherence to the 454 applicable criteria was 89.6%. Application of MAT-AF post-implementation resulted in a significant increase in adherence from 70.9% to 89.6%. Adherence to MAT-AF criteria for antithrombotic, rate control and rhythm control therapy before and after implementation is presented in Table 2.

MAT-AF implementation resulted in a significant improvement in prescription of anticoagulants (OR 4.07, p<0.001). The CHA_2DS_2VASc score did not have a significant effect on the prescription of anticoagulation both before and after MAT-AF implementation. The prescription of anticoagulation according to age range indicated a significant decrease in anticoagulation with increasing age (chi-square(3)=11.57, p=0.009) pre-MAT implementation. Patient age did not have a significant effect on the prescription of anticoagulation (chi-square(3)=4.119, p=0.249) post-MAT implementation. Recurrent falls or a high risk for falls was the most frequent reason for omission of anticoagulant therapy in the study population.

Adherence to appropriate rate control therapy was 84.5% before implementation and 96.8% after MAT-implementation (OR 3.92, p=0.041) (Table 2). Monitoring of renal function, thyroid function and serum electrolytes in patients receiving digoxin was performed and within limits in 50.9% of patients pre-implementation and in 91.5% post-implementation (OR 10.40, p<0.001). The most common deficiency for this criterion was in the request for monitoring of serum magnesium. Monitoring of serum digoxin levels was indicated due to poor renal function, dose of more than 0.0625mg daily or signs and symptoms of toxicity. Monitoring was conducted and was within limits in 73.9% of patients in whom it was indicated pre-implementation and in 87.0% post-implementation (OR 2.35, p=0.273).

Rhythm control with antiarrhythmic agents was achieved in 8.3% of patients. Adherence to MAT-AF for cardiology referral in patients on antiarrhythmic agents but not maintained in sinus rhythm increased from 38.5% pre-implementation to 80.0% post-implementation (OR 8.00, p=0.038) (Table 2). Liver and thyroid function tests in patients receiving amiodarone therapy were performed and within limits in 81.0% of patients pre-implementation and in 93.8% post-implementation (OR 3.53, p=0.282).

Documented pharmacist interventions for care issues generated by MAT-AF application are shown in Table 3. MAT-AF application before implementation identified 386 care issues, 9.6% of which were documented. After MAT-AF implementation, 361 care issues were identified and 83.4% were documented. The increase in documented pharmacist interventions following MAT-AF implementation as a clinical tool was significant (z-score 20.249, p<0.001).

DISCUSSION

Application of MAT-AF pre-implementation revealed suboptimal adherence to clinical practice guidelines incorporated in the tool. MAT-AF application after implementation denoted a significant increase in adherence from 70.9% to 89.6% principally in prescription of anticoagulation and monitoring of laboratory parameters for digoxin. Documentation of clinical pharmacist intervention improved significantly post-implementation of MAT-AF from 9.6% to 83.4%.

Prior to MAT-AF implementation, adherence to anticoagulation was 70.5% despite a high risk of stroke in the study population. Analysis of the results indicates that there was no correlation between prescription of anticoagulation and CHA_2DS_2VASc score, possibly indicating that stroke risk was not being given due consideration. In contrast, in a study by Lefebre *et al*. among octogenarians, anticoagulation was positively associated with stroke risk score. The HAS-BLED score was applied for assessment of bleeding risk to establish justifications for non-adherence.[21,22] The study population prior to MAT-AF implementation had a mean HAS-BLED score of 2. The principal contributor to the score was the presence of anaemia, which was most commonly mild and would merit monitoring rather than exclusion of anticoagulation.[23] Age is a strong predictor for ischaemic stroke in AF patients and robust evidence exists to support the use of anticoagulation in older persons.[20,24-26] In a systematic review of studies assessing attitudes of physicians regarding anticoagulation for AF, Pugh *et al*. concluded that physicians were reluctant to recommend warfarin for older persons in AF.[27] Implementation of MAT-AF resulted in oral anticoagulants being prescribed irrespective of age.

Recurrent falls or a high risk of falls were common reasons for omission of anticoagulation in the study population, as has been stated in other studies.[28-30] Although the use of anticoagulation in patients at risk of falls requires caution, AF guidelines stipulate that anticoagulants should only be excluded in patients with severe uncontrolled falls, such as epilepsy or advanced multi-system atrophy with backward falls.[13] Conversely, evidence indicates that stroke risk tends to exceed bleeding risk of anticoagulation, even in older persons, in patients with cognitive impairment, or in patients with frequent falls or frailty.[31,32] Documentation of clinical pharmacist interventions regarding the appropriate prescription of anticoagulation therapy was shown to significantly increase following MAT-AF implementation.

MAT-AF implementation significantly increased monitoring of laboratory parameters contributing to the safe use of digoxin therapy. A significant increase in clinical pharmacist documentation for the recommended monitoring to be performed was observed following MAT implementation.

Rhythm control therapy was only prescribed in a minor proportion of patients, which is coherent with evidence which has demonstrated that rhythm and rate control strategies have resulted in similar outcomes.[17,18] MAT-AF implementation significantly increased monitoring for ophthalmic and pulmonary adverse reactions with amiodarone therapy. Although adherence was suboptimal, even after MAT-AF implementation, there was increased awareness among the clinical pharmacists shown by an increase in documentation of the monitoring requirement. MAT-AF implementation significantly increased cardiology referral recommendable to avoid the use of antiarrhythmic agents when not indicated. A significant increase in the respective documentation of clinical pharmacist intervention was observed following MAT implementation.

The value of MAT-AF implementation was demonstrated in the highly significant improvement in documentation of interventions by clinical pharmacists in the rehabilitation hospital. Documentation is of particular importance in the care of the older patient. Multiple morbidities and medication are likely to result in numerous care issues which require prioritisation and resolution in a timely manner. Documentation is more likely to ascertain that all

issues are ultimately communicated with the healthcare team. MAT-AF provides a structured system with the purpose of guiding pharmacists and facilitating the documentation process.

MAT-AF can be implemented in other care settings for older persons including acute, ambulatory and long-term care after validation for adaptation to the setting and patient population. For a more comprehensive approach in the optimisation of drug therapy, it is recommended that MATs for other disease states prevalent in older patients are developed and implemented.

A limitation of the study is that MAT-AF criteria which incorporate aspects of treatment that are relevant to only a few patients resulted in a low applicability when considering the entire patient cohort.[9] Another limitation is that more emphasis may have been given to applying the MAT during the study period since the pharmacists were aware of the audit being conducted by the researcher (Hawthorne effect).

CONCLUSIONS

Implementation of MAT-AF had a significant impact on underprescribing of anticoagulation recommended for the prevention of thromboembolism in patients with AF and on parameter monitoring to ensure safe use of digoxin. Documentation of the care provided by clinical pharmacists at the rehabilitation hospital improved as a result of MAT-AF implementation.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest to disclose.

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Original Research

The impact of turmeric or its curcumin extract on nonalcoholic fatty liver disease: a systematic review of clinical trials

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Abstract

Background: Turmeric and its curcumin extract have been evaluated in patients with nonalcoholic fatty liver disease (NAFLD), a common ailment that can lead to irreparable liver damage.

Objective: To identify the evidence supporting the use of turmeric or curcumin therapy in NAFLD.

Methods: We searched PubMed, EMBASE, and Cochrane Central from the earliest possible date to 12/17/18 including terms for turmeric, curcumin, and NAFLD. We assessed the impact of turmeric or its curcumin extract on alanine transaminase (ALT), aspartate transaminase (AST), and NAFLD severity via ultrasound.

Results: Five trials assessed the comparative efficacy of curcumin/turmeric in NAFLD. One trial was single armed with comparisons only versus baseline and another trial was only available in abstract form. All of the trials had small sample sizes, 4 of 5 trials had limited durations of follow-up, and all trials had methodological limitations that negatively impacted the strength and applicability of evidence. Clinical and methodological heterogeneity precluded statistical pooling. Three of the 4 trials with evaluable data for turmeric or curcumin versus their own baseline demonstrated significant reductions in ALT, AST, and NAFLD severity grade. Two of the 4 placebo controlled trials had significant mean difference reductions in ALT and AST for turmeric or curcumin versus placebo while 2 of 3 of these trials found significant reductions in NAFLD severity grade. Among these trials, only one used turmeric instead of a curcumin extract and this turmeric trial did not demonstrate any differences in ALT, AST, or NAFLD severity between the turmeric and placebo groups.

Conclusions: Curcumin extract is a promising, but not proven, treatment for NAFLD while the role for turmeric is less clear. The general findings are that ALT, AST and NAFLD severity are reduced with the use of curcumin.

Keywords

Curcumin; Transaminases; Non-alcoholic Fatty Liver Disease; Systematic Reviews as Topic

INTRODUCTION

The pharmacist is the most commonly approached health professional for advice on natural products.[1] However, an American College of Clinical Pharmacists White Paper in 2017 reported that pharmacists' self-perceived preparedness for discussing natural products remained low, despite regular questions from patients.[2] Simply discounting the value of natural products can negatively impact the patient-pharmacist relationship, especially when patient self-belief in natural products is strong.[2] Systematic reviews of natural products may be a valuable source of information for practicing pharmacists because they efficiently describe the nature of the data available in a field and can reconcile conflicting information for readers.[3,4]

Non-alcoholic fatty liver disease (NAFLD) ranges from the simple deposition of fats to steatosis-induced hepatitis, fibrosis, cirrhosis, and in some cases hepatocellular carcinoma.[5] It is estimated that 20%-30% of adults in Western countries and 5%-18% in Asia have NAFLD.[5] NAFLD is very common in overweight and obese individuals as well as people with metabolic syndrome or type-2 diabetes mellitus.[5] NAFLD is the second most common reason for liver transplantation and patients with NAFLD have a high risk of developing cardiovascular disease.[5]

Weight loss due to reduced caloric intake or exercise are recommended therapies in patients with NAFLD regardless of severity.[6] In the 2018 guidelines from the American Association for the Study of Liver Diseases, pharmacologic therapy is reserved for patients with a more severe form of NAFLD called nonalcoholic steatohepatitis (NASH; >5% liver fat content and inflammation with hepatocyte injury).[6] While pioglitazone is an option for patients with biopsy proven NASH, the other options including metformin, ursodeoxycholic acid, and omega-3 fatty acid are not recommended.[6] The glucagon-like peptide-1 agonists do not have enough data to recommend them in NASH.[6] Vitamin E may be considered but the risks should be discussed with each patient before starting therapy.[6,7] Vitamin E has evidence of reduced steatosis and decreases in liver function test values but it has no effect on hepatic fibrosis and there are concerns over vitamin E's impact on overall mortality and prostate cancer risk.[6,7] This suggests that an alternative natural product with similar benefits to vitamin E but without the potential risks could be important in the treatment of this common and dangerous condition.

Turmeric (Curcuma Longa) has active constituents in its rhizome called curcuminoids with the most prominent curcuminoid called curcumin.[8] In in vitro and animal

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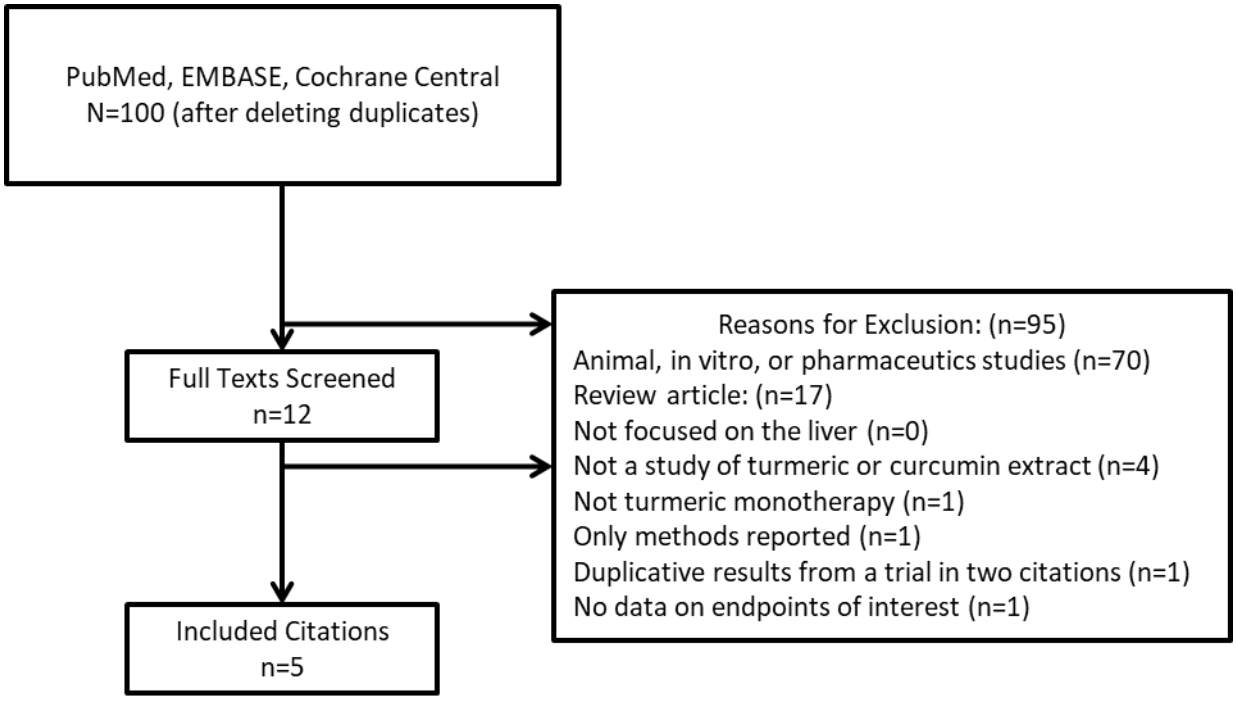

Figure 1. Included and excluded citations.

studies, turmeric has demonstrated potent antioxidant, anti-inflammatory, and antifibrotic properties as well as insulin sensitizing effects.[8] As such, it might hold promise in the treatment of patients with NAFLD.

In this systematic review, we assess the impact of turmeric or its curcumin extract in patients with NAFLD on indices of liver damage or NAFLD severity.

METHODS

Search Strategy

We performed search strategies within PubMed, EMBASE, and Cochrane Central using the MeSH or free text terms "((turmeric OR Curcumin OR Curcuma OR Curcuminoids) AND (NAFLD OR Fatty Liver OR Non-alcoholic steatohepatitis))" from the earliest possible time to 12/17/18. In addition, we conducted backwards citation tracking (a manual literature search of the reference lists of included articles for missing trials).

After de-duplication of citations from the three datasets, two independent investigators applied inclusion criteria to each citation with disagreements resolved via consensus.

Inclusion Criteria

The inclusion criteria were framed in the Population, Intervention, Control, Outcome, Study Design (PICOS) format. Population: Patients with NAFLD. Intervention: Use of turmeric or any curcumin extract (not to be combined with other potentially effective substances except those used to enhance bioavailability).[3] Control: Control groups were not required if baseline comparisons were available and acceptable control groups could contain active therapy, placebo, or no therapy. Outcomes: Evaluable data for alanine transaminase (ALT), aspartate transaminase (AST), NAFLD severity via ultrasound, or liver biopsy results. Study Design: Controlled or uncontrolled trials were permissible but observational studies, case reports, and case series were excluded.

Data Extraction

Two reviewers' independently extracted data from the literature in this review with disagreements resolved via consensus. The extracted data included the following: author, year, geographic location, intervention, comparator, dose, duration, blinding, sample size, gender (M/F), age, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) concentration, NAFLD ultrasound grade, and liver biopsy findings.

RESULTS

The number of citations, trials ultimately included, and the reasons for exclusion for the other citations are provided in Figure 1.[9-14] Authors of the originally included studies were

Table 1. Overview of Included Trials.[9-14]

Name/Year	Chirapongsathorn, 2012	Panahi, 2018	Panahi, 2017	Rahmani, 2016	Navekar, 2017
Design, Sample Size	DB, PC; n=20	SA, OL; n=36	DB, PC; n=87	DB, PC; n=80	DB, PC; n=46
Intervention	Curcumin (Dose NR)	Curcumin 1500mg/day	Curcumin 1000mg/day	Curcumin 500mg/day	Turmeric 3000mg/day
Duration	6 months	8 weeks	8 weeks	8 weeks	12 weeks
Age	53-57 years	49 years	45-47 years	46-49 years	40-42 years
Gender	55% Male	NR	59% Male	48% Male	43% Male
Country	Thailand	Iran	Iran	Iran	Iran

DB = double blinded, OL = open label, NR = not reported, PC = placebo controlled, SA = single arm (no control group)

Table 2. Impact of turmeric or curcumin extracts on outcomes.[11-14]

	Turmeric/Curcumin		Placebo		Active vs. placebo change from baseline
Panahi 2018 (n=36)					
ALT	Baseline: 40.7 (SD 15.0)		--		--
	Final: 22.0 (SD 7.2)^		--		--
AST	Baseline: 35.4 (SD 11.9)		--		--
	Final: 22.6 (SD 7.2)^		--		--
NAFLD	Before	After^	--	--	--
	Grade 0: 0.0%	11.1%			
	Grade 1: 50.0%	36.1%	--	--	
	Grade 2: 38.9%	52.8%	--	--	
	Grade 3: 9.1%	0.0%	--	--	
Panahi 2017 (n=87)					
ALT	Baseline: 35.46 (SD 22.97)		Baseline: 36.81 (SD 24.32)		-10.61 (SD 15.49) vs. +4.51 (SD 7.40)#
	Final: 24.85 (SD 12.84)^		Final: 41.33 (SD 23.97)*		
AST	Baseline: 27.63 (SD 11.35)		Baseline: 27.44 (SD 10.01)		-6.95 (SD 7.47) vs. +3.79 (SD 6.43)#
	Final: 20.68 (SD 6.65)^		Final: 31.23 (SD 12.80)*		
NAFLD Severity	Before	After^	Before	After *	NAFLD severity improved in 75% vs. 4.7%# NAFLD severity worsened in 4.5% vs. 25.6%#
	Grade 0: 0.0%	34.1%	Grade 0: 0.0%	2.3%	
	Grade 1: 38.6%	47.7%	Grade 1: 39.5%	23.3%	
	Grade 2: 52.3%	13.6%	Grade 2: 44.2%	48.8%	
	Grade 3: 9.1%	4.5%	Grade 3: 16.3%	25.6%	
Rahmani 2016 (n=77)					
ALT	Baseline: 39.07 (SD 19.79)		Baseline: 30.35 (SD 13.97)		-2.99 (SD 47.38) vs. -1.62 (SD 12.30)#
	Final: 36.08 (SD 46.58)^		Final: 28.72 (SD 10.93)		
AST	Baseline: 28.88 (SD 10.60)		Baseline: 32.05 (SD 17.64)		-5.04 (SD 6.49) vs. +2.02 (SD 11.79)#
	Final: 23.84 (SD 7.83)^		Final: 34.07 (SD 18.73)		
NAFLD Severity	Before	After^	Before	After	NAFLD severity improved in 78.9% vs. 27.5%# NAFLD severity worsened in 0.0% vs. 17.5%#
	Grade 0: 0.0%	15.8%	Grade 0: 0.0%	0.0%	
	Grade 1: 25.6%	71.1%	Grade 1: 32.5%	35.0%	
	Grade 2: 48.7%	13.2%	Grade 2: 55.0%	60.0%	
	Grade 3: 25.6%	0.0%	Grade 3: 12.5%	5.0%	
Navekar 2017 (n=42)					
ALT	Baseline: 23.07 (Range 9-112)		Baseline: 23.67 (Range: 10-125)		Mean difference = -2.25 (95% CI: -8.96 to 4.45)
	Final: 19.87 (Range 10-51)		Final: 22.85 (Range 10-60)		
AST	Baseline: 24.00 (SD 11.59)		Baseline: 24.33 (SD 13.69)		Mean difference = +0.49 (95% CI: -2.98 to 3.97)
	Final: 24.14 (SD 8.90)		Final: 24.04 (SD 5.40)		
NAFLD Severity	Before	After	Before	After	No differences noted between groups
	Grade 0: 0.0%	0.0%	Grade 0: 0.0%	0.0%	
	Grade 1: 57.1%	66.7%	Grade 1: 47.6%	66.7%	
	Grade 2: 42.9%	33.3%	Grade 2: 52.4%	33.3%	
	Grade 3: 0.0%	0.0%	Grade 3: 0.0%	0.0%	

^ Denotes significant intragroup DECREASES from baseline. * Denotes significant intragroup INCREASES from baseline. # denotes significant intergroup differences between groups. -- = No Control Group/Not Applicable, NG = Not Given.

contacted for missing data via email, where possible. Studies were assessed using the Cochrane risk of bias tool with all identified potential biases described in the narrative text below.

Five trials met our inclusion criteria with methodologic and demographic information provided in Table 1.[9-14] Panahi 2018 was a single arm and open label trial.[11] All of the other included trials specified that they were randomized, double-blinded, and placebo-controlled.[9,10,12-14] However, the Panahi 2017 trial allocated therapy on an alternating basis (Bottle A, then B, then A, then B, etc) instead of performing true randomization.[12] Specifics of the other trials' randomization strategies were not provided.[9-14] The evidence of incomplete data is indeterminate in all trials and there was no evidence of selective reporting except in the trial by Chirapongsathorn 2012 where 53 patients were reportedly enrolled but only 20 had outcome data reported.[9-14] Chirapongsathorn 2012 is only available in abstract form and the length of time without a resulting publication suggests the possibility of methodological issues.[9,10]

Given the heterogeneous forms and doses of curcumin and turmeric, different durations of therapy, and differences in baseline NAFLD severity scores and concentrations of ALT and AST, we did not believe that statistically pooling results was prudent.[9-14] None of the trials had data on liver fibrosis.[9-14]

The trial by Chirapongsathorn 2012 was difficult to interpret because it was only available in abstract form and it had typographical issues.[9] They enrolled 53 patients in Thailand but only reported data on 20 patients. These patients were randomized to receive curcumin (at an unspecified dose or formulation) or placebo. The mean differences for ALT [-9.11 (95%CI, -21.49 to 3.27)] and AST [-9.8 (95%CI, -20.42 to 0.82)] were nonsignificantly lower when curcumin was compared to placebo.[9,10]

Outcome data for all the other trials are provided in Table 2.[11-14] The first trial by Panahi 2018 allocated all 36 Iranian

patients with NAFLD to curcumin (500mg three times daily) or placebo for 8 weeks.[11] The curcumin extract was a phytosomal formulation that contained a complex of curcumin and soy phosphatidylcholine (Meriva®, Indena Corp, Milan, Italy). This means the pure curcuminoid content was 20% of the total or 300mg a day. All of the patients were analyzed. The use of curcumin therapy reduced ALT, AST, and NAFLD severity versus baseline (p<0.001 for each comparison).[11]

Panahi 2017 alternately allocated 102 Iranian patients with NAFLD to receive the same curcumin product as Panahi 2018 (Meriva®, Indena Corp, Milan, Italy) but at a lower dose (500mg capsules twice daily) or placebo for 8 weeks.[12] The pure curcuminoid content in this trial was 200mg a day. Six patients in the curcumin group and 9 in the placebo group discontinued therapy for self-perception of lack of benefit so only 87 patients were analyzed. The use of curcumin therapy reduced ALT, AST, and NAFLD severity versus baseline but worsened with placebo therapy over time. This led to marked differences between the curcumin and the placebo groups for these variables (P<0.001 for each comparison).[12]

Rahmani 1996 randomized 80 patients with NAFLD in Iran to receive curcumin (500mg capsules twice daily) or placebo or 8 weeks.[13] The capsules were described as an amorphous dispersion preparation comprising 70mg of pure curcuminoids but the manufacturer or the process was not further described. As such, the pure curcuminoid dose was 140mg daily. Three patients withdrew from the curcumin group due to stomach pain/nausea versus no patients in the placebo group. There was no intention to treat analysis with data analysis limited to the 77 subjects completing the trial.[13] Like the Panahi 2017 trial, patients in Rahmani 2016 had significant reductions in ALT, AST, and NAFLD severity grade when treated with curcumin versus baseline and had significantly better effects than with placebo (p=0.001, p=0.002, p<0.001, respectively).[12,13] However, in the placebo group the ALT, AST, and NAFLD severity grade did not continue to worsen versus baseline like with Panahi 2017 (p=0.409, p=0.284, p=0.622, respectively).[13]

Navekar 2017 randomized 46 Iranian patients with NAFLD to receive turmeric (3000mg daily given as six 500mg capsules) or placebo for 12 weeks.[14] In this trial, locally purchased turmeric rhizome was washed, dried, and cut into small pieces. The pure curcuminoid dose is unknown. Two patients in each group did not complete the study for "personal reasons" and no intention to treat analysis was performed, leaving 21 patients per group to be analyzed. In this trial, turmeric did not reduce AST or NAFLD severity grade versus baseline and did not significantly reduce ALT versus baseline. No differences occurred between the turmeric and placebo groups for any of these three outcomes.[14]

DISCUSSION

In contrast to Panahi 2017 and Rahmani 2016, Navekar 2017 did not significantly reduce ALT, AST, or NAFLD severity grade versus placebo.[9-14] The active group in Navekar 2017 also did not reduce ALT, AST, or NAFLD severity grade versus baseline, unlike Panahi 2018, Panahi 2017, or Rahmani 2016. The first potential explanation for these findings is related to differences in the severity of disease. ALT and AST are validated measures of ongoing liver damage with normal ranges of 1 to 27u/L in most commercial laboratories.[5] Unlike the other trials, in Navekar 2017 the ALT and AST concentrations at baseline were only elevated toward the upper end of the normal range, not exceeding that range.[9-14] NAFLD severity grade is determined by ultrasound with hepatic steatosis graded from 0 (lack of liver fat accumulation) up to 3 (severe increase in echogenicity with markedly impaired visualization of the diaphragm, intrahepatic vessel borders, and posterior portion of the right hepatic lobe).[5] In Panahi 2018, Panahi 2017, and Rahmani 2016, some patients had NAFLD severity grade 3 but in Navekar 2017, people only had grade 1 or 2 disease.[11-14] A second potential explanation is related to the form and dosage of the active product being used in different trials.[9-14] Panahi 2017 and Rahmani 2016 used 500 mg of curcumin extracts dosed twice daily (1000mg daily) and Panahi 2018 used 500mg three times daily (1500mg daily) while Navekar 2017 used locally purchased raw turmeric rhizomes which were washed, dried, and cut into small pieces and dosed at 3000 mg once daily.[11-14] It is known that the bioavailability of curcumin from raw turmeric is very low.[8]

In November 2018, a meta-analysis of trials was conducted assessing the impact of curcumin on ALT and AST in patients with NAFLD.[10] The meta-analysis only discovered the trials by Chirapongsathorn 2012 and Rahmani 2016 and found no significant mean difference between the curcumin and placebo group for ALT [-6.02 (95%CI: -15.61 to 3.57)] but did find significant differences for AST [-7.43 (95%CI: -11.31 to -3.54)]. In light of the many instances of clinical and methodologic heterogeneity with the trials, we disagree with their decision to meta-analyze this data. Their conclusion is that curcumin is effective in lowering AST levels in NAFLD and that there was high evidence supporting the use for curcumin lowering ALT and AST concentrations in NAFLD patients.[10] We disagree that with only two trials, one of which providing no information into the dose of curcumin used and with a very large withdrawal rate, that this is a correct determination.

Given the available data, curcumin is a promising but not proven therapy for NAFLD at this time and the role of turmeric is unclear. None of the trials assessed for the impact of turmeric or curcumin on liver fibrosis.[9-14] This is a critical omission since other therapies that are not recommended for use in NAFLD such as metformin also reduce ALT and AST but were unable to impact liver fibrosis.[6] In addition, none of the trials had patients mean ALT or AST concentrations greater than 3 times the upper limit of normal so whether the reductions in the liver function tests would be consistent or accentuated in patients with more severe NAFLD is unknown. It is also unknown how the magnitude of these reductions in liver function tests would diminish the risk in patients with more severe manifestations of NAFLD such as NASH.[5,6,9-14] There are other methodological limitations such as small sample sizes, relatively short durations of follow-up, and lack of intention to treat analyses in these trials.[9-14] There are also variations in the curcuminoid content of the products,

different dosing schedules, and insufficient probing of safety endpoints in these trials.[9-14] While these trials were said to be randomized, double-blinded, and placebo-controlled, the specifics were not provided to verify whether the trials actually conformed to these factors.[9,12-14] Panahi 2017 was the only trial that gave enough information to assess for randomization and this trial did not meet the definition of true randomization.[12]

There is an ongoing clinical trial by Jazayeri-Tehrani and colleagues that is assessing the impact of curcumin on insulin resistance, lipids, and inflammatory mediators but those results, while desirable, will not fill the evidence gap needed to determine curcumin's place in therapy.[15] A larger controlled trial with longer duration of follow-up assessing a standardized commercially available product that assesses ALT, AST, NAFLD severity, liver fibrosis, and safety endpoints is needed.

CONCLUSIONS

Curcumin extract is a promising, but not proven, treatment for NAFLD while the role for turmeric is less clear. The general findings are that liver damage, characterized by ALT and AST, as well as NAFLD severity are reduced with the use of curcumin.

CONFLICT OF INTEREST

None declared.

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Original Research

A qualitative assessment of the pediatric content in pharmacy curricula adopted by pharmacy schools in Jordan

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Abstract

Objective: The present study aimed to explore faculty (i.e., professors of various ranks) opinions and views regarding the pediatric content in courses taught to pharmacy students in Jordan.

Methods: Purposeful sampling was used to identify faculty from ten pharmacy schools. Participants were identified through their institutions' websites. After obtaining required approvals, twelve in-depth interviews were conducted, recorded, transcribed and analyzed using NVivo 11 Software. Interviews followed a previously prepared and validated interview guide. The interview guide covered various aspects of pediatric undergraduate education and training.

Results: Twelve professors (eight assistants and four associate professors) agreed to take part in the study. Qualitative analysis revealed four themes each with regard to respondents' knowledge of the pediatric content and their students' competency in dealing with pediatric patients. The emerging themes were: the lack of pediatric content in their current curriculum, the need for exposing students to more courses teaching pediatrics, and future aspirations to deal with this, and implications on practice.

Conclusions: This study highlights the deficiency of pediatric courses in pharmacy curriculum in Jordan. Respondent believed that this will have negative implications on pediatric pharmaceutical care and treatment efficacy and safety. It was thought that adding more pediatrics topics to undergraduate curricula, offering pediatric specialized postgraduate education, and implementing pre-registration training could alleviate the current situation.

Keywords

Child; Education, Pharmacy; Students, Pharmacy; Schools, Pharmacy; Faculty; Curriculum; Pharmaceutical Services; Qualitative Research; Jordan

INTRODUCTION

Pharmacists are trained to provide patient care to all age groups. Pediatric patients (i.e., up to the age of 18 years) can make up to 25% of the patients served by pharmacists.[1,2] This ratio is even higher in developing and low socioeconomic status countries.[3] Pharmacists who work in hospital and community settings have an integral role in pediatric care.[4,5] In these practice settings, pharmacists are required to have sufficient knowledge and training to provide patient care to pediatric patients and ensure medication appropriateness to this age group (e.g., dosage and administration).

Unlike adult patients, pediatrics do not commonly suffer from complicated and chronic diseases. Therefore, children usually require less medicines when compared to adults, leading to a relatively small pediatric market share.[6] Moreover, a few medications have been approved to be used in the pediatric patients due to several ethical issues and parental barriers regarding pediatric clinical trials.[7] This is known as the as unlicensed and 'off-label' medicine use in children.[8,9] Consequently, pharmacists and other healthcare providers usually face difficulties in selecting the appropriate medication, dosage, and route of administration for pediatric patients.[10] Therefore, it is essential to incorporate sufficient pediatric care training and education within the pharmacy curriculum in order to graduate more competent pharmacists to provide care for this age group. Ultimately, this will result in less medication errors and drug related problems for pediatric patients. Evidence from the literature showed that pharmacists had a significant improvement in both confidence and competence in pediatric pharmacotherapy following a pediatric pharmacy education program.[11]

In Jordan, there are 18 pharmacy schools (5 public and 13 private). All pharmacy schools in Jordan offer a bachelor of pharmacy program, while two public schools offer a PharmD program (Table 1).[12] The majority of students in these schools (77.6%) are enrolled in the bachelor of pharmacy program, and the remaining 22.4% are PharmD students.[12] The PharmD program in Jordan has additional therapeutic modules and hospital-based clinical rotations. The curriculums of these programs are routinely reviewed by the Higher Education Accreditation Commission (HEAC). However, the HEAC is not a pharmacy specific accreditation body; it is responsible for reviewing all programs offered by all higher education institutions in Jordan. The HEAC mandates all pharmacy curriculums to have at least 8 credit hours of pharmacotherapy courses with no recommendations to the specific contents for these courses. A previous study conducted in Jordan highlighted

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Table 1. This study interview guide

Number	Discussion Points
1	How many therapeutic courses does your pharmacy curriculum have and how many credit hours does those courses constitute of?
2	Do you teach any specialized therapeutic topics? Do those courses have any content that concentrates on pediatrics?
3	Do you have any elective pediatric courses in your curriculum?
4	Do you offer any pediatric oriented community or clinical training?
5	Do you think that courses supplied in your curriculum lack basic pediatric knowledge?
6	Would this effect the ability of your graduates to deal with pediatric patients?
7	How we overcome this problem (lack of pediatric courses)?

that current pharmacy graduates in Jordan lack basic competencies in pediatric pharmaceutical care.[13]

Thus, the present study aims to explore faculty (i.e., professors of various ranks) opinions and views regarding the pediatric content courses taught to pharmacy students in Jordan, and about ways to increase pharmacy students' experiences and knowledge regarding pharmaceutical care in pediatric patients.

METHODS

Qualitative one-on-one interview sessions were conducted. Purposive sampling was employed whereby websites of all pharmacy schools was searched for faculty involved in teaching patient-care related modules. In this study, we only included ten out of 18 pharmacy schools as the remaining eight schools started accepting students since 2013; therefore, they were excluded from the study as students in those schools were still in the first three years of their pharmacy programs and did not complete therapeutics or patient care courses. Identified faculty were contacted by phone or email and asked to take part in the study. Interviewees were informed that their responses would be anonymized and audio-recorded. To achieve maximum comfort, respondents were offered to do the interview in a place of their choice. Respondents were interviewed either in their work place, a public place of their choice, or over the phone. Written consent to record the interview was obtained and respondents were allowed to see the interview guide before the study begun.

The interview guide was developed based on the study objectives, as well as a review of the literature. Face and content validation were done by experts in qualitative research, and academics involved in undergraduate pharmacy teaching and training, who were not involved in the study. The interview guide covered various aspects of pediatric undergraduate education, including the number of hours dedicated to pediatric content, the number of students involved, the topics addressed, the methods of instruction, and the assignments involved. The guide also covered future plans and programs that could be implemented to increase the pediatric content in undergraduate programs and pediatric experiential education for both PharmD and BSc students. A detailed interview guide is displayed in Table 1.

Interviews took place between November 2016 and May 2017 and were conducted by two authors at a time convenient to the study participants, and were conducted in private to ensure confidentiality. Each session lasted between 30 minutes to one hour, and during the interview, field notes were also taken to capture key points. Participants were also requested to provide some demographic details via email or fill a form designed for this purpose.

Recorded interviews were transcribed verbatim, and de-identified prior to analysis. Results were then imported into QSR International's NVivo 11 Software. All audio recordings and interviewer field notes were also imported into NVivo for comparison and analysis. Thematic analysis was performed on the transcripts by two authors. Discrepancies were resolved by consensus. Quotations by respondents were edited on a limited basis to remove content that did not convey meaning (repeated words, stutters, etc), and to correct for grammar. An ellipsis mark was used to note removal of such extraneous content. Square brackets are used in quotations to supply words omitted by the speaker or to replace sensitive information where names were mentioned. The research protocol was reviewed and approved by the Institutional Review Board at the King Abdulla University Hospital and the Deanship of Research at the Jordan University of Science and Technology (119-2016/ 20160191).

RESULTS

The characteristics of pharmacy schools that took part in the study are shown in Table 2. All ten schools offered Pharmacy BSc programs; two of them offer PharmD programs. A total of twelve professors (eight assistant and four associate professors) took part in the study. One faculty refused to take part in the study and was replaced by another from the same university after consulting with the dean of the school. Of the respondents seven were male and five were between 35 and 40 years of age. Ten respondents taught therapeutics courses, while two taught clinical pharmacokinetics. Of the respondents 3 were responsible for the clinical training of PharmD students to deliver clinical pharmacy service in the hospital. Those were only working at the Jordan University of Science and Technology (n=2) and the University of Jordan (n=1). Other demographic characteristics of respondents are presented in Table 3. Qualitative analysis revealed four themes each with regard to respondents' knowledge of the pediatric content and their students' competency in dealing with pediatric patients. The emerging themes are: the lack of pediatric content in their current curriculum, the need for exposing students to more courses teaching pediatrics, and future aspirations to deal with this, and implications on practice. Emerging themes are summarized and in Table 4.

The first theme was the lack of pediatric content in the undergraduate pharmacy and PharmD curricula. Respondents reported not including any content related to pediatrics in the undergraduate curricula taught to Pharmacy BSc students. Regarding PharmD students, they

Table 2. Information regarding pharmacy schools in Jordan

University Name	Year of Establishment	Program(s) Offered	Governorate	University Type
Jordan University of Science and Technology	1979	PharmD and BSc	Irbid	Public
University of Jordan	1980	PharmD and BSc	Amman	Public
Al-Ahliyya Amman University	1990	BSc	Amman	Private
Applied Science Private University	1991	BSc	Amman	Private
Isra University	1991	BSc	Amman	Private
Philadelphia University	1991	BSc	Balqa	Private
Petra University	1991	BSc	Amman	Private
Al-Zaytoonah University of Jordan	1993	BSc	Amman	Private
American University of Madaba	2011	BSc	Madaba	Private
Zarqa University	2011	BSc	Zarqa	Private
Yarmouk University*	2013	BSc	Irbid	Public
The Hashemite University*	2013	BSc	Zarqa	Public
Mutah University*	2013	BSc	Karak	Public
Middle East University*	2013		Amman	Private
Jadara University*	2015		Irbid	Private
Jerash University*	2015	BSc	Jerash	Private
Aqaba University of Technology*	2015	BSc	Aqaba	Private
Amman Arab University*	2016	BSc	Amman	Private

* Pharmacy schools from these universities were not eligible to take part in this study.

were only given a two credit hour pediatric therapeutics course at the Jordan University of Science and Technology as the undergraduate curriculum for PharmD students included specialized therapeutics courses, however the undergraduate curricula for PharmD students at the University of Jordan did include any concentration on pediatric related topics as the PharmD curricula consisted of four general therapeutics courses only. Respondent went on to indicate that the curricula at all universities do not even offer a pediatric elective course for both Pharmacy and PharmD students. Furthermore, respondents reported that this situation is common in other courses taught at their schools and that all the courses do not cover pediatric related topics.

A sub-theme was the reasons for not covering pediatric related topics. Respondent thought that number of credit hours in both Pharmacy BSc and PharmD curricula adopted by their universities was overwhelming for students and it seemed impossible to add any further hours or courses to the program. Another reason reported by respondents was that the Pharmacy BSc and PharmD programs were general programs and if students were interested in any sub specialty this could be done on a postgraduate education or training basis. Some respondents thought that there were many subspecialties of pharmacy, not only pediatrics, and it is impossible to cover all those specialties in the undergraduate curricula while other respondents thought that pharmacy students should be taught and trained to deal with pediatrics, as more than one third of the population in Jordan are younger than 18 years of age. Those respondents said that medicine students get different training for the major specialties before graduation and the situation should be similar for pharmacy students.

Another sub-theme was concerns regarding the lack of pediatric knowledge. Respondents raised serious concerns and doubted the ability of pharmacy graduates to deal with pediatric patients. Except for PharmD students who get pediatric training during their hospital training, other BSc students could graduate and start working without being exposed to the minimum requirement to deal with pediatric patients. Respondents' concerns were supported by the fact that the community pharmacy training for BSc students does not cover pediatrics specifically, and is considered general community pharmacy training. It was made clear by respondents that fresh graduate do not have enough competencies and are not equipped with the required knowledge nor skill to deal with pediatric patients. Respondents indicated that treating pediatric patients needs extra care, especially that dosing is based on body weight and some formulations are not suitable for this age group as well.

The second theme was the need for exposing students to more pediatrics training and courses. Sub-themes were didactic education and experiential education. Respondents agreed that the study plans adopted at their universities to obtain a pharmacy or PharmD degree did

Table 3. Demographic Characteristics of Respondents (n=12)

Participant ID	Age	Gender	Specialty	Taught Modules	Rank
FS 1	34	Male	Clinical Pharmacy	Pharmacotherapy	Associate Professor
FS 2	34	Female	Clinical Pharmacy	Pharmacotherapy	Associate Professor
FS 3	37	Female	Clinical Pharmacy	Pharmacotherapy	Assistant Professor
FS 4	36	Male	Pharmacology	Pharmacology	Associate Professor
FS 5	41	Male	Clinical Pharmacy	Pharmacotherapy	Assistant Professor
FS 6	35	Female	Pharmacology	Pharmacotherapy	Assistant Professor
FS 7	30	Female	Pharmacology	Pharmacotherapy	Assistant Professor
FS 8	35	Male	Pharmacology	Pharmacotherapy	Assistant Professor
FS 9	42	Female	Clinical Pharmacy	Pharmacotherapy	Assistant Professor
FS 10	40	Male	Pharmacology	Pharmacotherapy	Associate Professor
FS 11	33	Male	Pharmacology	Pharmacology	Assistant Professor
FS 12	33	Male	Clinical Pharmacy	Pharmacotherapy	Assistant Professor

Table 4. Emerging themes and selected quotes

Main themes	Sub-themes	Selected quotes
Lack of pediatric content	Reasons for not covering pediatric related topics	• "The current curriculum is full of basic pharmaceutical sciences. There is no space for specialized material" FS 2 • "We are governed by the local accreditation regulations; this gives us little flexibility to add modules to the curriculum" FS 12 • "Even in therapeutic courses we don't have pediatric coverage, there is no enough time to cover specialized material" FS 9
	Concerns regarding the lack of pediatric knowledge	• "It seems dangerous to let pharmacists practice while they did not come across any pediatric related material, would you allow them to treat your child?" FS 3
The need for exposing students to more pediatrics training and courses	Didactic education	• "The curriculum outcomes should serve the patient population in Jordan. Almost one-third of the country are children" FS 8 • "More pediatric topics should be covered in therapeutic and pharmacokinetic courses. This topic should be included in all relevant material" FS 5
	Experiential education	• "Students should be exposed to more specialized pediatric training during their community pharmacy and hospital training" FS 1 • "I would suggest adding more specialized training hours to the curriculum" FS 4
Future aspirations to deal with this	Amending current curricula to cover more pediatric content	• "The current curricula need review, you can remove a lot of topics and add more pediatric related topics" FS 3 • "We could benefit of having a pediatric elective course, I'm sure many students will be happy with that" FS 5
	Requiring specialized postgraduate education in pediatrics	• "Students interested in pediatrics can pursue a postgraduate degree in that topic" FS 7 • "I would encourage establishing postgraduate degrees in Pediatrics, this should be focused and condensed and allow pharmacist to deliver better pediatric care" FS 1
	Adding a pre-registration period	• "One good solution would be adding a pre-registration year before allowing pharmacists to practice, this will allow them to practice under the supervision of senior colleague and deal with all types of patients" FS 9
The implication of lack of pharmacy pediatric education of practice	Effect on patient safety	• "This will have a negative influence on the rate of drug related problem in the pediatric population" FS 2
	Effect on treatment efficacy	• "…Don't tell me that pharmacists who just graduated are able to calculate effective doses, this is why we end up with instructions like: 5mls twice daily with no regard to patient weight..." FS
	Loss of patient trust in pharmacists	• "How would parents trust pharmacists if they knew this information?" FS 10 • "Will parents allow us to treat their children if they knew this?" FS 12

not have any focus on pediatrics or pediatric related topics. Respondents indicated that plans should be put to develop current teaching plans to include more focus on pediatric related topics. Respondents thought that didactic education is not enough to obtain skills in pediatric pharmacy and care, both community and hospital pharmacy training should have some focus on pediatric related topics. Respondents also thought that adding pediatrics topics should be in a variety of courses per curriculum; for instance, therapeutics, kinetics, and pharmaceutics.

Respondents indicated that a pediatric pharmacy elective course should be offered to students who develop special interest in this specialty. They thought that such students should be given further opportunity to develop their skills and knowledge regarding pediatrics. Furthermore, respondents indicated that current training programs adopted for BSc students have no pediatric or other specialized concentration which leads students to lack pediatric specialized experience. Respondents highlighted the importance of adding pediatric training to pharmacy students training program.

The third theme was future aspirations to deal with this. This theme had three sub-themes: amending current curricula to cover more pediatric content, requiring specialized postgraduate education in pediatrics, and adding a pre-registration period that has specialized training before pharmacists were able to practice.

In their suggestions to amend current curricula to cover more pediatric content, respondents highlighted the importance of finding prompt solutions to address the lack of pediatric content in pharmacy curricula. Suggestions covered adding pediatrics elective courses, covering pediatric dosing and recommendations in pharmacology and therapeutic courses, specialized intra curricular pediatric training, specialized pediatric pharmacokinetics courses, and covering more pediatrics topics in pharmaceutical care and pharmacy practice courses.

Respondents highlighted the importance of offering postgraduate pharmacy education that specialize in pediatrics. For instance, one respondent mentioned that the MSc in Clinical Pharmacy offered a pediatric rotation where students are exposed to many pediatric cases in the hospital. This would influence the students practice regarding pediatrics positively. Other respondents suggested offering short postgraduate courses and certificates specialized in pediatrics. The idea behind offering short courses was that it is overwhelming like obtaining a new degree. Respondents indicated that such courses could be offered during work as part of continuous professional development for pharmacists. Respondent suggested that such courses could be supported by employers.

Respondent highlighted that not having a pre-registration period in Jordan has its negative effects on early practice. This practice deficiency would be mostly noticed on topics not covered during pharmacy undergraduate education.

According to respondents, the implementation of a pre-registration period would expose pharmacy recent graduate to topics that were not covered during their education. Respondents indicated that adopting a supervised practice model would help pharmacists gain experience in pediatrics and other topics where they lack knowledge and experience.

The fourth and final theme was the implication of lack of pharmacy pediatric education of practice. Sub-themes were effect on patient safety, effect on treatment efficacy, loss of patient trust in pharmacists. Respondent thought that if pharmacists were allowed to deal with pediatric patients without having a robust base of knowledge covering this topic, this could jeopardize patient safety and put pediatric patients at risk. Respondents reported that pharmacists should give evidence based recommendations to parents when dealing with their children's illness and that this problem could be more serious among pediatrics as pediatric doses are not standardized like doses for adults. Similar thoughts were brought up regarding jeopardizing treatment efficacy in pediatrics. Respondents' thought that if the pharmacist was not able to give correct recommendations, this could not only affect the safety but the efficacy of the treatment. Respondent went further to the fact that if recommended treatments and administration recommendations were not effective and has negative effects this will have negative effects on parental views on the competency of pharmacists treating their children.

DISCUSSION

This study sheds the light on a serious problem that affects pharmacy practice in Jordan. Respondents admitted that except for one PharmD program in Jordan, other PharmD and BSc in pharmacy programs do not cover any topic related to pediatrics. With the lack of pre-registration training programs and continuous professional education programs in Jordan, a pharmacist could start his/her profession having no idea about pediatric treatment options, dosing, and counselling: a situation that needs direct and prompt attention.

This problem is even more serious as 38.6% of the population in Jordan are of pediatrics age.[14] Many Jordanians seek pharmacists as a first port of call for medical and healthcare advice and many pharmacists in Jordan dispense non-prescribed medications directly to patients based on the pharmacist's recommendation or the patients' request.[15] Allowing pharmacists with no or minimal knowledge of pediatrics to work directly after graduation and deal with parents and pediatric patients could put them at risk.

Pharmacists are expected to have at least base-line knowledge in pediatrics. More efforts should be employed to guarantee that pediatrics are prescribed safe and effective medications. This is crucial, specifically when dealing with pediatric medicines that are prescribed in an unlicensed and off-label manner, as it has been reported that such medicines pose three times the risk of harming children compared to labeled medicines used in adults.[8] Studies assessing the role of clinical pharmacists in neonatal intensive care units and pediatric wards showed a significant decrease in drug related problems and prescription errors.[16] It has been further reported that compared to other healthcare team members, pharmacists can deal with pediatric dosing and administration effectively.[17,18] This highlights the need to develop the current adopted curricula to cover more pediatric topics. In the pharmacy curriculum covers a wide range of pediatric related topics and students are trained well regarding this age group before they are allowed to practice.[19] The Accreditation Council for Pharmacy Education state that pharmacy programs should provide a curriculum appropriate to produce general practitioners of pharmacy.[20] To fulfill this, professional pharmacy curricula must include adequate content dedicated to pharmaceutical care of the pediatric patient.

Respondents highlighted the importance of adding pediatric related topics to the current curricula as a first step towards having pharmacists with good pediatric knowledge. This is important, however didactic education regarding pediatric treatments and dosing is not enough. This should be combined with a blend of experiential education programs including simulation pharmacy, community pharmacy training, and hospital pharmacy training. Members of the American College of Clinical Pharmacy Pediatrics Practice and Research Network and the Pediatric Pharmacy Advocacy Group recommendation for faculty who teach pediatric pharmacy to adopt a didactic and experiential teaching.[21] Further liaison between all pharmacy schools in Jordan and the Jordan Pharmacists Association is needed to develop extra-curricular specialized training programs.

Other recommendations included adopting a pre-registration training program where pharmacists are able to train in a work environment before they are fully registered and allowed to deal with patients solely. It is well documented in the literature that adopting pre-registration training programs significantly affects the practice of healthcare professionals positively which enhances patient safety and treatment efficacy.[22] Though respondents highlighted the importance of offering postgraduate pediatric programs, it is still unknown how programs with an academic nature could influence pediatric pharmaceutical care. Respondents also highlighted the importance of adopting continuous professional education programs in Jordan would have positive effects on pharmaceutical care, not only in pediatrics but in all other specialties. Reports indicate that pharmacists attending CPD programs are up to date and have more specialized and cumulative knowledge and experience.[23]

Respondents had true concerns regarding the ability of their graduates to deal with pediatric treatments. Pediatric education should not only be taught as a separate or elective course; it is important to cover pediatric topics in many courses taught to pharmacy students. Pharmacy students should be trained to deal with pediatrics and their parents in pharmacy practice and patient communication courses. Previous studies indicate that health care professionals, in general, fail to communicate with pediatric patients and fail to convey treatment information to their parents.[24-26] Furthermore, dose calculations and

adjustment should be highlighted and covered extensively in pharmacokinetics' courses to make sure that the pharmacists of the future are able to dispense medicines in accurate doses and to minimize dosing errors in children. Pharmacy students should be able to monitor side effects in pediatrics. Previous studies indicate that pharmacists often fail to spot and report adverse drug reactions.[27,28] Further education regarding monitoring side effects and pharmacovigilance in pediatric patients specifically is needed nowadays to optimize the role of future pharmacists regarding pediatric pharmaceutical care.

CONCLUSIONS

This study highlights the deficiency of pediatric specialized courses in pharmacy curriculum adopted by faculty of pharmacy in Jordanian Universities. Respondent thought that this deficiency would have negative implications on pediatric pharmaceutical care and would jeopardize treatment efficacy and safety. It was thought that adding more pediatrics topics to undergraduate curricula, offering pediatric specialized postgraduate education, and implementing pre-registration training could alleviate the current situation. Further research, both qualitative and quantitative should address this issue in the future, which may lead to evidence based solutions for this problem.

CONFLICT OF INTEREST

None to declare.

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Original Research

Efficacy and safety of the pharmacotherapy used in the management of hyperkalemia: a systematic review

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Abstract

Background: Although the management of hyperkalemia follows expert guidelines, treatment approaches are based on traditionally accepted practice standards. New drugs have been assessed such as sodium zirconium cyclosilicate and patiromer; however, their safety and efficacy or effectiveness have not yet been compared to traditional pharmacotherapy.

Objective: The present systematic review had the purpose to evaluate the efficacy, effectiveness, and safety of hyperkalemia pharmacotherapies.

Methods: PubMed, LILACS, Cochrane Library, and ClinicalTrials were searched through November 2018. Clinical trial, cohort and case-control were searched. The risk of bias (RoB v2.0 and ROBINS-I) and quality of evidence (GRADE) at the level of outcomes were assessed.

Results: Sixteen clinical trials and one retrospective cohort were identified regarding efficacy and safety of 24 different alternatives. The management of hyperkalemia remains empirical and off-label, since sodium zirconium cyclosilicate and patiromer are not available in several countries and further studies are required to assess efficacy, effectiveness and safety. Sodium or calcium polystyrene sulfonate (moderate confidence), sodium zirconium cyclosilicate (moderate confidence), and insulin plus dextrose (moderate confidence) showed superior efficacy to, respectively, placebo, no treatment, placebo, and dextrose. Other therapies (low confidence) showed similar efficacy compared to active or inactive alternatives. Most of the adverse events reported were nonspecific, so it was not possible to assign the cause and to classify as defined or probable.

Conclusions: Comparative cohort and case-control studies are need to evaluate the safety and effectiveness of new and traditional pharmacotherapies to support the development of guidelines about acute and chronic hyperkalemia, with high-quality evidence.

Keywords

Hyperkalemia; Potassium; Renal Insufficiency; Treatment Outcome; Silicates; Polymers; Systematic Reviews as Topic

INTRODUCTION

Hyperkalemia (high blood potassium concentration) is one of the most serious electrolyte abnormalities because of its association with the induction or aggravation of cardiac arrhythmias and an increase in mortality rates.[1]

The increase in serum potassium concentration is multifactorial, and the main risk factors are chronic kidney disease (CKD), acute kidney disease, cardiovascular diseases, diabetes mellitus, and the use of medications such as potassium-sparing diuretics, angiotensin-converting enzyme inhibitors (iRRAS), heparins, mineralocorticoid receptor antagonists, and nonsteroidal anti-inflammatory drugs.[2-4] In such cases of drug-induced hyperkalemia, premature withdrawal5 is recommended, but this can expose patients to a higher cardiovascular risk.[4]

The management of potassium homeostasis disorders has not shown any significant advances since the introduction of ion exchange resins in 1958.[6] Sodium polystyrene sulfonate (SPS) is a cation-exchanging resin that has been widely used for several decades as the first-line therapy of mild chronic hyperkalemia.[7] Concerns about the safety profile of SPS have been described, mainly due to severe disorders in the digestive system.[8] Despite this, the Institute of Healthcare Management considers that the drug should be used as a trigger tool to detect drug-induced hyperkalemia.[9]

New potassium binders were developed, such as sodium zirconium cyclosilicate (ZS-9) and patiromer. Their safety and efficacy have been compared among them and/or with polysulfonate resins, but none of them were assessed with temporizing agents or other traditional therapies applied in order to decrease serum potassium levels.[10-12] While Sterns *et al*. described the treatment options for hyperkalemia, including both new and old approaches; they did not evaluate the quality of evidence that supports efficacy and safety of each pharmacotherapy included in the review.[6]

Despite decades of knowledge regarding the potential risks of hyperkalemia, there are no guidelines to advise who should be treated.[13] Treatment approaches are based on small-scale studies, anecdotal experiences, and traditionally accepted practice standards.[14]

Faced with several therapeutic options available to manage the potassium imbalances; which are applied inconsistently, monitoring safety and efficacy of treatment with SPS, as proposed by IHI, might underestimated cases of adverse drug events.[14]

In this setting, our review aimed to describe the new and traditional therapies applied to manage hyperkalemia;

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evaluate the efficacy and safety of the treatments; and assess the quality of evidence.

METHODS

This systematic review was performed and reported in accordance with the relevant consensuses; the PROSPERO registration number is CRD4201705071018.[15-17]

Eligibility and search

The assessed population included patients with hyperkalemia (without restrictions for age, sex, or current or previous past medical history) receiving hyperkalemia treatment: sodium bicarbonate, polarizing solution (insulin + glucose), fenoterol, salbutamol (albuterol), furosemide, bumetanide, calcium (CPS) or sodium polystyrene sulfonate (SPS), patiromer, ZS-9, fludrocortisone, hydrocortisone, or aminophylline compared with placebo, no treatment, or another comparator. These medications were included as search terms based on previously published reviews.[18,19]

Clinical trials, comparative cohorts, and case-control studies comparing mean serum potassium reduction, serum potassium differences at different time points, frequency of adverse events and serious adverse events, and discontinuation due to adverse events were eligible for inclusion in this review.

We excluded studies that recruited patients with normokalaemia, whose serum levels of potassium rise after treatments; and researches aimed at sustained normokalemic levels after prescriptions of treatment of hyperkalemia. Congress, abstracts, dose comparisons, and studies that did not accurately report the treatment were also excluded. There was no language restriction.

A search was conducted in MEDLINE (via PubMed) (from 1940 to present), LILACS (via BIREME) (from 1982 to present), and Cochrane Library (from 1994 to present) in October 2016. It was updated in November 2018. Manual searches in the references of review articles about hyperkalemia, clinical trials, and PROSPERO were also performed. We did not contact with study authors (Appendix A). We did not performed contact with study authors.

Study selection, data extraction, and synthesis of data

Two reviewers selected and extracted a sample of eligible studies and achieve good agreement (at least 80%, considering kappa coefficient). Then, one investigator performed the selection and data extraction, and a second investigator revised the verdicts, as recommended by AMSTAR 2 checklist. In the absence of consensus at all stages, the points of disagreement were solved via a third investigator.

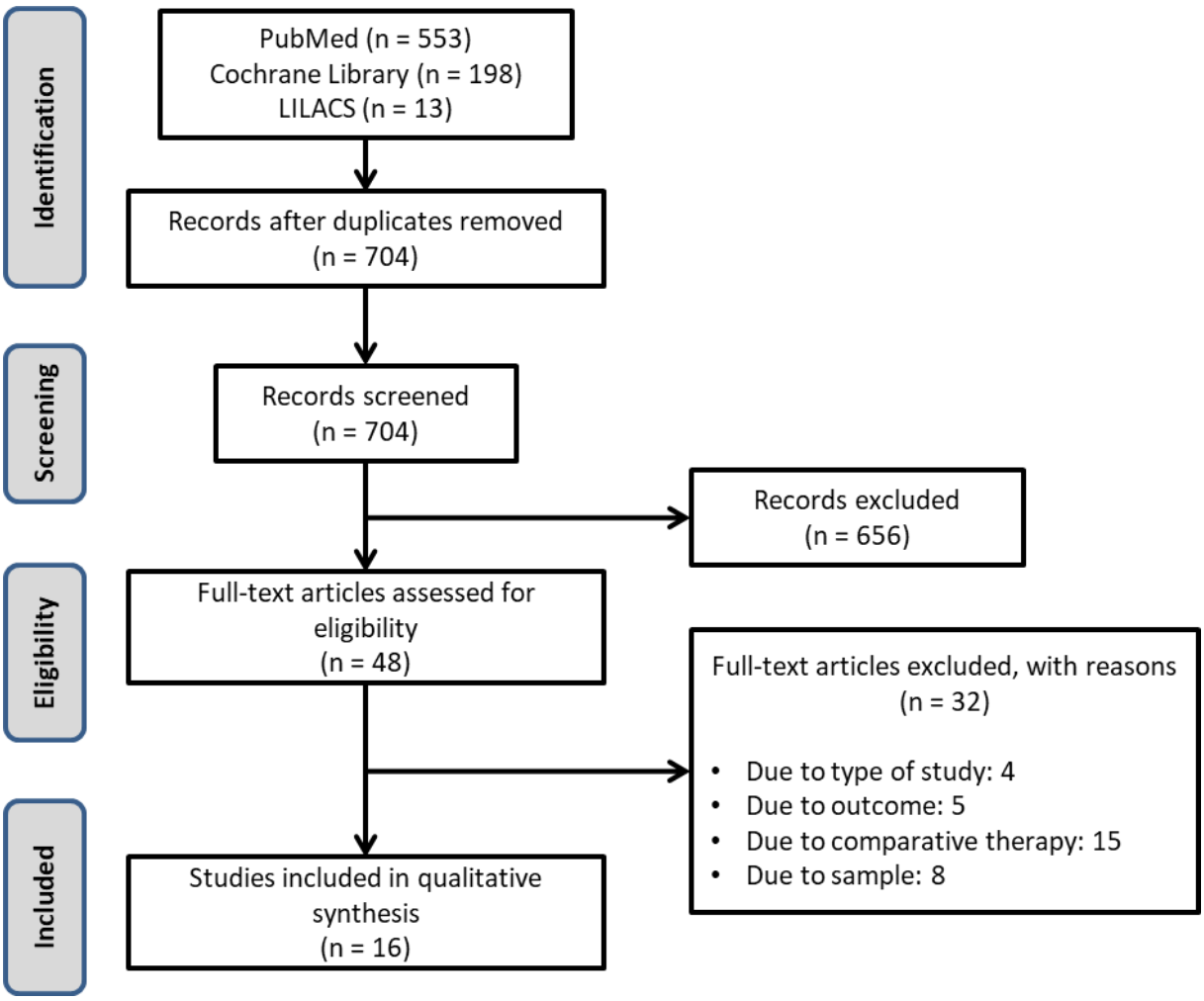

Figure 1. Flowchart of studies selection (PRISMA).

Data were extracted in a worksheet of Microsoft Excel® and included: the type of study, number of participants, age group, disease, comorbidities, compared alternatives and dosages applied to manage hyperkalemia; concomitant drugs, main outcomes (mean, difference or number of serum potassium level), follow-up, adverse drug events reported.

Risk of bias in individual studies and quality of evidence

Assessment of the risk of bias was done at the outcome level (discontinuation due to adverse events, difference in mean serum potassium, baseline mean serum potassium concentration, and final time point) by two independent reviewers. The Cochrane Collaboration ROB version 2.0 tool was used to assess the risk of bias in the clinical trials.[20] The ROBINS tool evaluated the risk of bias in the cohort studies.[21]

The critical evaluation of the bias risk of the included studies was conducted by two independent reviewers using GRADE Working Group guidelines.[22] In the absence of consensus, points of disagreement were resolved by the opinion of a third researcher.

RESULTS

This systematic review identified 704 studies. After considering the strategy search and duplicity elimination, 656 studies were excluded by reading titles and abstracts (Figure 1). No additional studies were identified by manual search. After a full assessment of 48 studies, 32 were excluded (justifications are given in Appendix B).

Included studies

Sixteen studies (n=1,582 participants) were enrolled including clinical trials (n=15) and a retrospective cohort (n=1).[23-38] The studies were published between 1989 and 2018 and described different therapies, mainly for patients diagnosed with chronic kidney disease (n=11). The commonest comorbidities reported were hypertension and diabetes (n=9)

There was no consensus about definition of hyperkalemia. Some authors considered hyperkalemia at baseline when serum potassium level was >4.5 mEq/L. Others when it was >7.0 mEq/L (Table 1). The mean baseline serum potassium ranged from 5.0 to 7.1 mEq/L (Table 2).

We observed follow-up times ranging from 1 to 72 hours (n=10) and reaching 7 days or 12 months for studies in patients with CKD (n=6). There were no studies included that assessed outcomes with patiromer, fenoterol, furosemide, bumetanide, hydrocortisone, or aminophylline. Most subjects were adults and elderly (n=13); 3 studies included neonatal patients (Table 1).

Efficacy

Efficacy outcomes were reported in 14 clinical trials; the only cohort study identified did not report the effectiveness of the therapies, just the safety problems (Table 2). We observed that all treatments assessed were able to reduce serum potassium levels, but most of them did not show any statistical difference among the therapies compared (Table 2).

We noticed statistical significance in six comparisons: I) insulin + glucose vs. glucose alone, II) SPS vs. placebo, III) 2.5 g ZS-9 vs. placebo; IV) 5 g ZS-9 vs. placebo, V) 10 g ZS-9 vs. placebo, and VI) 3-5 g CPS three times/day vs. no treatment (Table 2).[28,32,33,38] All these treatments were prescribed for CKD patients.

Adverse events

There were 24 different adverse events reported in the studies.[23,28,31-34,36-38] Only three showed statistical analysis regarding the occurrence of ADE among therapies compared.[31,32,38] A higher frequency of nausea and anorexia was observed for SPS in relation to CPS ($p < 0.05$).[31] No significance was observed in the occurrence of ADE between placebo and the polystyrene resins (Table 3).[32,38]

Only three studies reported the discontinuation of treatments due to adverse drug reactions.[28,32,37] Lepage *et al*. reported one interruption (6%) in the SPS group and none in the placebo group; Chothia *et al*. reported one interruption (17%) in the insulin + glucose group and none in the glucose group due to serious hypoglycemia.[28,32] Nakayama et al. reported five interruptions [edema (n=3), diarrhea (n=1) and headache (n=1)] in the CPS group and none in the SPS group.[37]

Risk of bias

The predominance of efficacy outcomes suggested a high risk of bias, whereas safety outcomes were at a low risk of bias. Regarding clinical trials, the high risk of bias was mostly due to problems in the randomization process and some concerns over multiple domains. Most studies had a low risk in the outcome measurement domain. Regarding evaluation at the study level, Wang *et al*. 2018, Lepage *et al*. 2015 and Chothia *et al*. 2014 presented a low risk of bias independent of the outcome evaluated (Appendix C).[28,31,32] The only cohort study included presents a serious risk of bias regardless of the outcome evaluated, since it presented serious risk of bias for classification of interventions, deviations from intended interventions and selections of the reported result (Appendix D).

Quality of evidence

Considering recommendations of system GRADE, the assessment of quality of evidence should consider the evidence with higher quality. Therefore, we focused in clinical trials, since only one comparative cohort study was included with serious risk of bias regardless of the outcome evaluated.

There was scant evidence for each individual comparison. There was little viability for the development of direct or indirect meta-analysis. Thus, we did not consider the presence of inconsistency or potential publication bias, and there is a change in the evidence confidence upon the completion of new clinical trials. The difference was evaluated with statistical significance being equivalent to the clinical significance following the tendency proposed by the original authors, as well as with an absence of consensus for this evaluation. This evaluated the presence of precision in efficacy outcomes (serum potassium differences at the final time and differences between means).

Table 1. Characterization of the studies included in the systematic review										
Author, year	**Country**	**Type of study**	**N (# women)**	**Age group**	**Disease**	**Comorbidity**	**Concomitant drugs**	**Compared alternatives**	**Primary endpoint**	**Follow-up**
ACUTE HYPERKALEMIA										
Lens, 1989[25]	Spain	Clinical trial	44 (20)	Adult; Elderly	AKI and CKD with hyperkalemia hyperkalemia ($[K^+]$ ≥6.0 mEq/L])	NR	NR	salbutamol 0.5 mg IV in 15min; glucose 40 g IV +10 unit's insulin IV in 15 min; salbutamol 0.5 mg IV + glucose 40g IV + insulin 10 units IV over 15 min period	Serum potassium level	6h
Ngugi, 1997[32]	Nairobi	Prospective, single-blind clinical trial	70 (NR)	Pediatric; Adult; Elderly	AKI and CKD with hyperkalemia ($[K^+]$ > 5.0 mmol/L])	NR	NR	50 mL of 50% dextrose and 10 units of soluble insulin IV in 15 min **(a)**; 50 mL of 8.4% sodium bicarbonate IV over 15 min **(b)**; Infusion of 0.5mg of salbutamol in 50 mL of 5% dextrose given over 15min **(c);** Treatment combination of **a+b;** Treatment combination of **a+c;** Treatment combination of **c+b;** Treatment combination of **a+b+c**	Serum potassium level	8h
Singh, 2002[33]	USA	Randomized, single-blind clinical trial	19 (8)	Neonate	Neonates <2000g receiving mechanical ventilation with central serum potassium ≥ 6.0 mmol/L	NR	polysterene sulfonate; glucose-insulin; furosemide; insulin infusion; calcium gluconate	400 µg of albuterol in 2 mL of saline solution; Placebo (2 mL of saline solution, only)	Central serum potassium level	12h
Mushtaq, 2006[34]	Pakistan	Interventional study	15 (2)	Adult; Elderly	AKI and CKD with hyperkalemia ($[K^+]$ > 6.0 mmol/L])	NR	NR	0.5 mg salbutamol diluted in 100 ml 5% water; glucose 25 g diluted in 100 ml of water + 10 units of regular insulin; salbutamol 0.5 mg diluted in 100 ml of water with 25 grams of glucose + 10 units of regular insulin	Serum potassium level	6h

Table 1. Characterization of the studies included in the systematic review										
Author, year	**Country**	**Type of study**	**N (# women)**	**Age group**	**Disease**	**Comorbidity**	**Concomitant drugs**	**Compared alternatives**	**Primary endpoint**	**Follow-up**
Oschman, 2011[23]	USA	Retrospective cohort study	39 (NR)	Neonate	Premature neonates, with low weigh and with hyperkalemia hyperkalemia ([K^+] ≥6.5 mEq/L])	NR	bumetanide; furosemide; chlorothiazide; hydrocortisone	50 mL of original k-cocktail (Dextrose 30% + sodium lactate 10mEq + calcium gluconate 1.4 mEq + regular insulin 3 units + heparin 2.5 units); 50 mL of modified k-cocktail Dextrose 20% + sodium lactate 15 mEq + calcium gluconate 1.4 mEq + regular insulin 3 units + heparin 2.5 units;	[blood glucose] ≥150 mg/dL (moderate) or ≥ 200 mg/dL (severe hyperglycemia)	24h
Chothia 2014[35]	South Africa	Randomized, crossover, double-blind study	10 (5)	Adult	CKD in HD	Hypertension	Beta-blockers	10 units of insulin with 100 ml of 50% glucose; 50 ml of 50% glucose only.	Serum potassium level	1h
Ramos-Peñafiel 2015[36]	Mexico	Randomized clinical trial	50 (27)	Adult; Elderly	CKD with hyperkalemia ([K^+] > 7.0 mmol/L])	Diabetes; Hypertension	HD	50 mL of 50% dextrose + 10 unit of regular insulin; hiperK-cocktail (1,000 mL of 10% dextrose + sodium bicarbonate [44.6 mEq] + 20 units of regular insulin)	Serum potassium level	4h
Saw, 2018[37]	China	Prospectively double-blind, randomized clinical	40 (NR)	Neonate	Premature infants with non-oliguric hyperkalemia ([K^+] ≥6.0 mEq/L])	NR	NR	10-15 mg of glucose and 1 unit of regular insulin bolus (RI), maintained at a rate of 6 mg/kg/min Salbutamol (400 mg in 2 ml saline solution)	Central serum potassium, blood glucose, heart rate, and blood pressure	72h
Nasir, 2014[38]	Pakistan	Single blind randomized control trial	97 (61)	Adult; Elderly	CKD patients on conservative management and with serum potassium level of >5.2 mg/dl	Diabetes; Hypertension	Loop diuretics; Thiazide diuretics	5 grams CPS three times per day PO for three days; 5 grams SPS three times per day PO for three days	Weight gain, worsening of blood pressure and effect on electrolytes (Potassium, Calcium, Phosphorus, and Sodium)	12 mo

Table 1. Characterization of the studies included in the systematic review										
Author, year	**Country**	**Type of study**	**N (# women)**	**Age group**	**Disease**	**Comorbidity**	**Concomitant drugs**	**Compared alternatives**	**Primary endpoint**	**Follow-up**
Lepage 2015[39]	USA	Double-blind randomized clinical trial	33 (10)	Adult; Elderly	CKD outpatients with hyperkalemia ($[k^+]$ =5.0- 5.9 mEq/L)	Dyslipidemia; Diabetes; Hypertension; Coronary artery disease; History of stroke; Arrhythmia; Congestive heart failure	Insulin; Beta-blockers; Loop diuretics; ACEIS or ARBs; Thiazide diuretics; Potassium sparing diuretics; NSAIDs	SPS of 30 g orally one time per day; placebo	Serum potassium level	7d
Packham 2015[26]	Australia USA South Africa	Multicenter, two-stage, double-blind, phase 3 trial,	753 (305)	Adult; Elderly	Patients with serum potassium level of 5.0 to 6.5 mmol/L	CKD; Heart failure; Diabetes	Diuretic agents, iRAAS, and antidiabetic therapies.	ZS-9, 1.2 g 3 times daily with meals; ZS-9, 2.5 g 3 times daily with meals; ZS-9, 5 g 3 times daily with meals; ZS-9, 10 g 3 times daily with meals; placebo	Serum potassium level	48h
Ash 2015[27]	USA	Phase 2 randomized, double-blind, placebo-controlled dose-escalation study	90 (38)	Adult; Elderly	CKD with hyperkalemia ($[k^+]$ = 5.0 to 6.0 mEq/l)	Diabetes; Hypertension; Cardiac insuficiency	iRAAS; spironolactone	12–0.3 g of ZS-9 three times daily with regular meals; 24–3 g of ZS-9 three times daily with regular meals; 24 to 10 g of ZS-9 three times daily with regular meals; placebo	Serum potassium level	48h
Kaisar, 2006[28]	Australia	Prospective, open-label, randomized clinical trial	37 (13)	Adult; Elderly	Pre-dialysis CKD hyperkalemia ($[K^+]$ >4.5 mmol/L]) and <7.0mmol/L	Diabetes; Hypertension	ACEI, ARB, beta-blockers, diuretics, cyclosporine	Fludrocortisone acetate 0.1mg per day; No treatment	Serum potassium level	3mo
Kim, 2007[29]	South Korea	Prospective clinical trial	21 (11)	Adult; Elderly	CKD in HD with hyperkalemia ([k+]> 5.0 mEq/l	Diabetes; Hypertension	ACEI, ARB, β-blockers, NSAIDs	fludrocortisone acetate 0.1 mg/day PO; No treatment	Serum potassium level	10mo

Table 1. Characterization of the studies included in the systematic review										
Author, year	**Country**	**Type of study**	**N (# women)**	**Age group**	**Disease**	**Comorbidity**	**Concomitant drugs**	**Compared alternatives**	**Primary endpoint**	**Follow-up**
Nakayama, 2017[30]	Japan	Prospective, open-labeled, randomized, and crossover study	20 (11)	Adult; Elderly	Pre-dialysis CKD 4–5 outpatients with hyperkalemia ([K^+] >5 mmol/L])	Diabetes; Hypertension	iRAAS; Calcium channel blockers; Beta-blockers; magnesium oxide; Sodium bicarbonate	Orally CPS (ARGAMATE 89.29% GRANULE 5.6 g; powder 5 g) after each meal; Orally SPS (KAYEXALATE DRY SYRUP 76% 6.54 g; powder 5 g) after each meal	Serum of potassium, calcium, phosphat, magnesium, intact parathyroid hormone (iPTH)	4we
Wang, 2018[31]	Japan	Prospective, randomized, crossover controlled clinical trial	58 (26)	Adult, Elderly	Hemodialysis patient with hyperkalemia ([K+] ≥ 5.5 mol/	NR	ACEIs; ARBs	CPS 3 × 5 g/day between dialysis sessions for 3 weeks; no treatment	Serum potassium level	3we

AKI: acute kidney disease, CKD: Chronic Kidney Disease; CPS: calcium polystyrene sulfonate NR: not reported; SPS: sodium polystyrene sulfonate; RASi: Renin-angiotensin system inhibitors; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; NSAID, nonsteroidal anti–inflammatory drug; mL: milliliter, min: minutes; mg: milligrams; L: liters; IV: intravenous; HD: hemodialysis; PO: oral route; ZS-9: Sodium Zirconium Cyclosilicate; h: hours; mo: months; we: weeks; d: days.

Table 2. Efficacy of comparative alternatives for hyperkalemia, according to baseline, final serum potassium and mean difference on serum potassium.

Authors, year	Compared alternatives, treatment duration	Serum potassium (SD) mEq/L			
		Mean baseline	Mean endpoint	Mean difference	p-value*
ACUTE HYPERKALEMIA					
Lens 1989[25]	salbutamol 0.5 mg IV in 15min; 6 h	7.00 (0.98) [c]	6.2 (0.98) [c]	-0.80 (0.98) [c]	> 0.05
	glucose 40 g IV +10 unit's insulin IV in 15 min; 6 h	6.70 (0.63) [c]	6.4 (0.95) [c]	-0.30 (0.32) [c]	
	salbutamol 0.5 mg IV + glucose 40g IV + insulin 10 units IV over 15 min period; 6 h	7.10 (0.63) [c]	6.2 (0.95) [c]	-0.90 (0.63) [c]	
Ngugi 1997[32]	50 mL of 50% dextrose and 10 units of soluble insulin IV in 15 min; 0.5h (a)	NR	NR	-0.85 (0.47)	> 0.05
	50 mL of 8.4% sodium bicarbonate IV over 15 min; 0.5h (b)	NR	NR	-0.47 (0.31)	
	Infusion of 0.5mg of salbutamol in 50 mL of 5% dextrose given over 15min; 1 h (c)	NR	NR	-0.90 (0.56)	
	Treatment combination of a+c; 0.5 h	NR	NR	-1.09 (0.58)	
	Treatment combination of a+b; 0.5 h	NR	NR	-1.19 (0.50)	
	Treatment combination of c+b; 0.5 h	NR	NR	-0.71 (0.43)	
Singh 2002[33]	400 µg of albuterol in 2 mL of saline solution; 8 h	7.06 (0.23)	4.06 (0.55)	-1.13 (0.25)	< 0.05
	Placebo (2 mL of saline solution, only); 8 h	6.88 (0.18)	4.89 (0.22)	-0.54 (0.15)	
Mushtaq 2006[34]	0.5 mg salbutamol diluted in 100 ml 5% water; 6 h	6.40 (0.55) [c]	5.90 (0.32) [c]	-0.50 (0.95) [c]	NR
	glucose 25 g diluted in 100 ml of water + 10 units of regular insulin; 6 h	6.50 (0.67) [c]	6.00 (0.45) [c]	-0.50 (0.45) [c]	
	salbutamol 0.5 mg diluted in 100 ml of water with 25 grams of glucose + 10 units of regular insulin; 6 h	6.50 (0.45) [c]	5.80 (0.67) [c]	-0.70 (0.45) [c]	
Chothia 2014[35]	10 units of insulin with 100 ml of 50% glucose; 60 min	6.01 (0.87)	5.18 (0.76)	-0.83 (0.53)	< 0.05
	50 ml of 50% glucose only; 60min	6.23 (1.20)	5.73 (1.12)	-0.50 (0.31)	
Ramos-Peñafiel 2015[36]	50 mL of 50% dextrose + 10 unit of regular insulin; 4 h	6.61 (6.00; 8.00) [a]	6.07 (2.90; 7.80) [a]	NR	> 0.05
	hiperK-cocktail (1,000 mL of 10% dextrose + sodium bicarbonate [44.6 mEq] + 20 units of regular insulin); 4h	6.87 (6.00; 8.20) [a]	5.64 (4.00; 7.80) [a]	NR	
Saw, 2018[37]	10-15 mg of glucose and 1 unit of regular insulin bolus (RI), maintained at a rate of 6 mg/kg/min; 72h	6.50 (6.25; 7.05) [c]	4.30 (3.90; 5.15) [c]	NR	p > 0.05
	Salbutamol (400mg in 2 ml saline solution); 72h	6.35 (6.10; 6.55) [c]	4.05 (3.55; 4.40) [c]	NR	
ACUTE AND CHRONIC HYPERKALEMIA					
Nasir 2014[35]	5 grams CPS three times per day PO for three days;12 mo	5.80 (0.60) [b]	4.80 (0.50) [b]	NR	> 0.05
	5 grams SPS three times per day PO for three days; 12 mo	5.80 (0.60) [b]	4.30 (0.53) [b]	NR	
Lepage 2015[39]	SPS of 30 g orally one time per day; 7 days	5.26 (0.22)	3.99 (0.56)	-1.25 (0.56)	< 0.001
	Placebo, 7 d	5.23 (0.22)	5.03 (0.34)	-0.21 (0.29)	
Packham 2015[26]	ZS-9 1.2 g, 3 times daily with meals; 48 h	5.30 (NR)	5.10 (NR)	NR	> 0.05
	ZS-9 2.5 g, 3 times daily with meals; 48 h	5.30 (NR)	4.90 (NR)	-0.46 (0.53; 0.39) [a]	< 0.001
	ZS-9 5 g, 3 times daily with meals; 48 h	5.30 (NR)	4.80 (NR)	-0.54 (0.62; 0.47) [a]	< 0.001
	ZS-9 10 g, 3 times daily with meals; 48 h	5.30 (NR)	4.60 (NR)	-0.73 (0.82; 0.65) [a]	< 0.001
	Placebo, 48 h	5.30 (NR)	5.10 (NR)	-0.25 (0.32; 0.19) [a]	-
Ash 2015[27]	ZS-9 0.3 g, three times daily with regular meals; 48h	5.20 (0.30)	NR	-0.32 (0.37)	< 0.05
	ZS-9 3.0 g, three times daily with regular meals; 48h	5.00 (0.30)	NR	-0.36 (0.36)	< 0.05
	ZS-9 10 g, three times daily with regular meals; 48 h	5.10 (0.40)	NR	-0.32 (0.48)	< 0.05
	Placebo, 48 h	5.10 (0.40)	NR	-0.17 (0.43)	< 0.05
CHRONIC HYPERKALEMIA					
Kaisar 2006[28]	fludrocortisone acetate 0.1mg per day; 3 mo	5.10 (0.50)	4.80 (0.50)	NR	> 0.05
	No treatment; 3 mo	5.30 (0.70)	5.20 (0.70)	NR	
Kim 2007[29]	fludrocortisone acetate 0.1 mg/day PO; 10 mo	6.10 (5.30; 6.80) [a]	5.20 (4.40; 6.00) [a]	NR	> 0.05
	No treatment;10 mo	6.00 (5.40; 6.50) [a]	5.80 (4.80; 6.30) [a]	NR	
Nakayama, 2017[30]	Orally CPS (ARGAMATE 89.29% GRANULE 5.6 g; powder 5 g) after each meal; 4 weeks	5.39 (0.49)	4.14 (0.91)	-1.25 (-1.90, -0.60)	0.51
	SPS (KAYEXALATE DRY SYRUP 76% 6.54 g; powder 5 g) after each meal; 4 weeks	5.60 (0.54)	4.12 (0.64)	-1.48 (-1.88, -1.08)	
Wang, 2018[31]	CPS 3 × 5 g/day between dialysis sessions; 3 weeks	5.93 (0.39)	5.61 (0.65)	-0.48 (-0.75, -.016)	< 0.01
	No treatment; 3 weeks	5.97 (0.51)	5.29 (0.51)	−0.1 (−0.49,0.32)	

* Statistical analysis performed for comparison of serum potassium at the endpoint or for difference between means; [a] Median (interquartile range); [b] Reported as mg/dl and converted to mEq/L; [c] Standard error of mean converted to standard deviation; min: minute; h: hour(s); d: day; mo: months; SD: standard deviation. NR: not reported; [1] Original k-cocktail: Dextrose 30% + sodium lactate 10mEq + calcium gluconate 1.4 mEq + regular insulin 3 units + heparin 2.5 units; [2] Modified k-cocktail: Dextrose 20% + sodium lactate 15 mEq + calcium gluconate 1.4 mEq + regular insulin 3 units + heparin 2.5 units ; IV: intravenous, IN: inhalation, ZS-9: sodium zirconium cyclosilicate; CPS: calcium polystyrene sulfonate, SPS: sodium polystyrene sulfonate.

Table 3. Frequency of adverse events considering clinical trials and retrospective cohort.

Authors, year	Adverse events	Outcome
Ash, 2015 [27]	Anemia	ZS-9 0.3 g: 0 in 12 ZS-9 3 g: 0 in 24 ZS-9 10 g: 1 in 24 (4%) Placebo: 0 in 30
Nasir, 2014 [38]	Anorexia	CPS: 7 in 50 (14%) SPS: 16 in 47 (34%), p = 0.01
Ash, 2015 [27]	Heartburn	ZS-9 0.3 g: 0 in 12 ZS-9 3 g: 0 in 24 ZS-9 10 g: 1 in 24 (4%) Placebo: 0 in 30
Lepage, 2015 [39]	Constipation	SPS: 6 in 16 (38%) Placebo: 4 in 16 (25%), p = 0.70
Nasir, 2014 [38]	Constipation	CPS: 6 in 50 (12%) SPS: 8 in 47 (17%), p = 0.40
Ash, 2015 [27]	Constipation	ZS-9 0.3 g: 0 in 12 ZS-9 3 g: 1 in 24 (4%) ZS-9 10 g: 0 in 24 Placebo: 0 in 30
Wang, 2018 [31]	Constipation	No treatment: 4 in 22 (19.2) CPS: 9 in 28 (32.1), p> 0.05
Packham, 2015 [26]	Cardiac disorders	ZS-9 1.25 g: 1 in 154 (1%) ZS-9 2.5 g: 0 in 141 ZS-9 5 g: 3 in 157 (2%) ZS-9 10 g: 2 in 143 (1%) Placebo: 0 in 158
Packham, 2015 [26]	Gastrointestinal disorders	ZS-9 1.25 g: 7 in 154 (5%) ZS-9 2.5 g: 3 in 141 (2%) ZS-9 5 g: 6 in 157 (4%) ZS-9 10 g: 5 in 143 (4%) Placebo: 8 in 158 (5%)
Lepage, 2015 [39]	Diarrhea	SPS: 4 in 16 (25%) Placebo: 8 in 16 (50%), p = 0.27
Nasir, 2014 [38]	Diarrhea	CPS: 1 in 50 (2%) SPS: 0 in 47, p = 0.34
Ash, 2015 [27]	Diarrhea	ZS-9 0.3 g: 1 in 12 (8%) ZS-9 3 g: 0 in 24 ZS-9 10 g: 1 in 24 (4%) Placebo: 0 in 30
Nasir, 2014 [38]	Abdominal distention	CPS: 1 in 50 (2%) SPS: 6 in 47 (13%), p = 0.092
Nasir, 2014 [38]	Abdominal pain	CPS: 1 in 50 (2%) SPS: 3 in 47 (6%), p = 0.06
Ash, 2015 [27]	Abdominal pain	ZS-9 0.3 g: 1 in 12 (8%) ZS-9 3 g: 1 in 24 (4%) ZS-9 10 g: 0 in 24 Placebo: 0 in 30
Ash, 2015 [27]	Headache	ZS-9 0.3 g: 0 in 12 ZS-9 3 g: 0 in 24 ZS-9 10 g: 0 in 24 Placebo: 1 in 30 (3%)
Wang, 2018 [31]	Headache	No treatment: 5 in 22 (22.7) CPS: 6 in 28 (21.4), p > 0.05
Nasir, 2014 [38]	Edema	CPS: 3 in 50 (6%) SPS: 4 in 47 (9%), p = 0.573
Chothia, 2014 [35]	Pulmonary edema	Insulin + glucose: 1 in 6 (17%) Glucose: 0 in 5
Nasir, 2014 [38]	Sputum	CPS: 0 in 50 SPS: 0 in 47, p = 1
Lepage, 2015 [39]	Hypernatremia	SPS: 0 in 16 Placebo: 0 in 16
Kim, 2007 [29]	Hypertension	Fludrocortisone: 0 in 13 No treatment: 0 in 8
Ash, 2015 [27]	Hypertension	ZS-9 0.3 g: 0 in 12 ZS-9 3 g: 0 in 24 ZS-9 10 g: 1 in 24 (4%) Placebo: 0 in 30
Lepage, 2015 [39]	Hypokalemia	SPS: 3 in 16 (19%) Placebo: 0 in 16, p = 0.23
Wang, 2018 [31]	Kypokalemia	No treatment: 3 in 22 (13.6) CPS: 5 in 28 (17.9)
Chothia, 2014 [35]	Hypoglycemia	Insulin + glucose: 2 in 6 (33%) Glucose: 0 in 5
Oschman, 2011 [23]	Hypoglycemia	Dextrose 30% + sodium lactate + calcium gluconate + insulin + heparin: 0 in 13 Dextrose 20% + sodium lactate + calcium gluconate + insulin + heparin: 1 in 26 (4%)
Lepage, 2015 [39]	Hypomagnesemia	SPS: 5 in 16 (31%) Placebo: 1 in 16 (6%), p = 0.17
Kim, 2007 [29]	Hypovolemia	Fludrocortisone: 0 in 13 No treatment: 0 in 8
Packham, 2015 [26]	Urinary tract infection	ZS-9 1.25 g: 3 in 154 (2%) ZS-9 2.5 g: 0 in 141 ZS-9 5 g: 1 in 157 (1%) ZS-9 10 g: 0 in 143 Placebo: 0 in 158
Ash, 2015 [27]	Urinary tract infection	ZS-9 0.3 g: 0 in 12 ZS-9 3 g: 1 in 24 (4%) ZS-9 10 g: 2 in 24 (8%) Placebo: 0 in 30
Lepage, 2015 [39]	Nausea	SPS: 4 in 16 (25%) Placebo: 2 in 16 (13%), p = 0.65
Ash, 2015 [27]	Nausea	ZS-9 0.3 g: 0 in 12 ZS-9 3 g: 1 in 24 (4%) ZS-9 10 g: 2 in 24 (8%) Placebo: 1 in 30 (3%)
Nasir, 2014 [38]	Nausea	CPS: 9 in 50 (18%) SPS: 20 in 47 (43%), p = 0.01
Wang, 2018 [31]	Nausea	No treatment: 3 in 22 (13.6) CPS: 4 in 28 (14.3), p > 0.05
Nasir, 2014 [38]	Cough	CPS: 1 in 50 (2%) SPS: 0 in 47, p = 0.348
Lepage, 2015 [39]	Vomiting	SPS: 2 in 16 (13%) Placebo: 1 in 16 (6%), p > 0.99
Nasir, 2014 [38]	Vomiting	CPS: 0 in 50 SPS: 2 in 47 (4%), p = 0.53
Ash, 2015 [27]	Vomiting	ZS-9 0.3 g: 0 in 12 ZS-9 3 g: 1 in 24 (4%) ZS-9 10 g: 3 in 24 (13%) Placebo: 1 in 30 (3%)
Wang, 2018 [31]	Headache	No treatment: 5 in 22 (22.7) CPS: 6 in 28 (21.4), p > 0.05
Wang, 2018 [31]	Hypercalcemia	No treatment: 6 in 22 (27.3) CPS: 4 in 28 (14.3), p > 0.05

Table 3. Frequency of adverse events considering clinical trials and retrospective cohort.

Authors, year	Adverse events	Outcome

IV: intravenous, ZS-9: sodium zirconium cyclosilicate; CPS: calcium polystyrene sulfonate, SPS: sodium polystyrene sulfonate, the bolded results represent those who presented differences with statistical significance.

There was moderate confidence in the evidence supporting the statistical difference of insulin + glucose vs. glucose, SPS vs. placebo, 2.5 g, 5 g, and 10 g ZS-9 versus placebo and CPS vs no treatment. The confidence in the estimate of the effect might change as new studies are reported, and these studies may even modify the effect estimation. Other comparisons showed low confidence in the evidence due to the presence of high risk of bias, as well as imprecision suggesting that future studies will likely have a significant impact on our confidence in the effect estimation (Appendix E).

DISCUSSION

Our findings showed that most studies compared at least two different interventions to manage hyperkalemia in patients diagnosed with CKD, diabetes and hypertension. Despite the potential risks, incidence and prevalence of hyperkalemia in patients with certain comorbidities and medication exposures, and the availability of effective potassium-lowering therapies, there are no guidelines to advise who should, or should not, be treated.[13]

Among individuals with CKD, current guideline recommendations advocate the use of iRAAS as a first-line antihypertensive therapy, which may increase serum potassium levels. Depending on the seriousness of hyperkalemia, their discontinuation is recommended, potentially depriving patients of renoprotective effects.[39,40]

Management of hyperkalemia has traditionally involved a combination of acute treatment and avoidance of potentially contributing factors.[40] Acute therapeutic interventions included those that involve shifting potassium to the intracellular space. We observed that temporizing agents are able to reduce serum potassium levels, but there was no statistical difference between them. Except for insulin plus dextrose, which showed a significant decrease when compared with glucose (moderate confidence) in patients with CKD.

Insulin plus dextrose is a commonly applied method for the displacement of potassium into the intracellular space, which is associated with many complications. This reduces abnormal myocardial conduction from increased potassium, and is a temporary 'fix' at best.[41] However, there is uncertainty whether transcellular shifting causes insufficient potassium removal during hemodialysis, resulting in a subsequent need for further medical therapy or multiple sessions of hemodialysis.[42]

Longer-term management of hyperkalemia has remained a challenge. Currently available therapeutic interventions to control chronic hyperkalemia include dietary potassium restriction, vigorous use of diuretic therapy, correction of acidosis, and administration of sodium polystyrene sulfonate, but these are often problematic and unsuccessful.[43]

Potassium binders such as SPS used to be the only currently available exchange resin in everyday clinical practice.[8] However, its use is controversial, due to its limited profile of safety, the lack of evidence of efficacy and safety in chronic hyperkalemia and also due to the occurrence of life-threatening events, such as bowel necrosis.[7,44,45] In spite of this, the use of SPS (typically with sorbitol added at a concentration of 33%) for acute treatment of hyperkalemia remains common.[4] Owing to concerns related to the safety profile of polystyrene binders, new potassium-exchanging resins are being assessed.

Our data show that when potassium binders (SPS, CPS and ZS-9) were compared with the effects of a placebo they significant decrease serum potassium levels. ZS-9 had a better safety profile. Recent publications suggest that both ZS-9 and patiromer are safer than SPS, however, they are not based on direct or indirect comparison methods.[11,46]

There are several reasons why SPS is an inappropriate therapeutic option for patients with chronic hyperkalaemia or as comparators for ZS-9 in clinical trials, such as serious gastrointestinal side effects, organoleptic characteristics (making it impossible to serve as a marked treatment), and lack of efficacy for acute or chronic hyperkalaemia.[47]

However, a robust and clinically meaningful indirect treatment comparison of ZS-9 to SPS/CPS is infeasible because of heterogeneity between studies, the very small sample sizes in the SPS/CPS trials, and the use of dosing regimens different from those in the product characteristics for SPS/CPS.[11]

Although studies that assess the safety and efficacy of patiromer were not included in the present review, this drug shows promise as a potassium-lowering agent for patients with chronic hyperkalemia, because it may allow for dose optimization of iRAAS and improves the clinical outcomes in patients with CDK, diabetes, and heart failure.[48] However, pharmacovigilance studies are need to assess drug-drug interactions, to obtain more safety data, and to evaluate the effectiveness in long-term use, considering patients in use of mineralocorticoid receptor antagonist and iRAAS use.[11,49,50] In addition, it is necessary that more trials with active comparators are essential to finalize its indication and use in hyperkalemia.[12]

Considering the assessment of safety profile, early detection of adverse drug events considering CPS/SPS as a trigger may have underestimated the cases, since several approaches could be prescribed to treat hyperkalemia in clinical practice, most of them as off-label use, which increase the occurrence of drug-induced harm. Therefore, we suggest serum potassium level as a trigger to detect drug-induced ADE.

Rozenfeld *et al*. observed that hyperkalemia is a high-performance trigger to detect ADE in neonates.[51] Serum potassium could also be used as a predictor of adverse clinical outcomes in patients with chronic ADE, and identify those likely to benefit from strategies that treat hyperkalemia, and prevent iRAAS discontinuation.[52]

Finally, we can notice that there is no single definition about hyperkalemia, although it is considered as serum potassium concentrations greater than 5.0 to 5.5 mEq/L.[53]

The lack of a standardized definition of hyperkalemia hinders comparisons of incidence and outcomes across epidemiological studies, since they are obscured by inconsistent serum potassium thresholds.[52] It is important establish the serum potassium levels and adverse outcomes arising from hyperkalemia, in order to drive the rational therapy to treat the imbalance.

It is recommended that researchers adopt a core outcome set for the evaluation of outcomes in future studies. Sterns et al. considered serum potassium control as a surrogate marker for clinically important outcomes such as mortality rate, reduction in CKD progression, postponement of dialysis, and improvement in outcomes of heart disease.[6] Rossignol et al. suggested as relevant outcomes the time to achieve normokalemia, the incidence of clinically significant arrhythmias, and the need for rescue therapies.[14] Since it is not established in the literature, the parameter that brings clinical benefits to the patient, in order to evaluate chronic pharmacotherapy, is more important to achieve normokalemia than the reduction of potassium.[14]

Limitations of the studies included in this review include the high heterogeneity of data and high risk of bias in the randomization domain. Limitations were also observed in relation to safety outcomes — the form reporting such adverse events is not standardized, and it may come from both the patients' spontaneous reports and an active searching by the researchers.

The limitations of this review were a lack of contact with the authors of the studies to identify omitted data—these are old publications with a low probability of success in reaching the authors. We also excluded congress and abstracts literature due to a low probability of identifying studies that presented complete and reliable information. We did not obtain four studies for the eligibility phase.

CONCLUSIONS

Our results demonstrate that the treatment of acute hyperkalemia is empirical and off-label, since ZS-9 is an unavailable option in several countries. Among the off-label therapies, insulin plus dextrose had better efficacy than glucose (moderate confidence). Other therapies had similar efficacy as active or inactive therapies for hyperkalemia (low confidence). Further studies are need to compare ZS-9 and temporizing agents used in acute hyperkalemia (insulin plus dextrose, beta-2 agonists and sodium bicarbonate), in order to assess the safety, efficacy and effectiveness of pharmacotherapies in hyperkalemic patients without kidney impairment or with chronic kidney disease.

Despite the moderate confidence of SPS vs placebo and CPS and no treatment applied to manage chronic hyperkalemia, data should be analyzed with caution, due to the limitations of the design of the studies and seriousness of adverse events in digestive tract. A new potassium binder (patiromer) has been shown to achieve better outcomes of safety and efficacy. However, there were no studies found comparing patiromer with other alternatives for patients with hyperkalemia. Detection of drug-drug interaction with the new drug binder remains under reported.

Our review demonstrated that most adverse events reported by the studies enrolled were non-specific, making it difficult to attribute the cause and classify it as a defined or probable event. Safety assessment of the available pharmacotherapies could be improved via pharmacovigilance studies, such as contemporary cohorts and case-control designs. Such studies should be delineated with a low risk of bias, large sample size, and good duration of follow-up to recognize the risks associated with treatments and to support the development of guidelines with better evidences.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Original Research

Evaluation of discharge prescriptions for secondary prevention in patients with acute coronary syndromes in Iraq

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Abstract

Background: Optimal prescribing of secondary prevention medications after acute coronary syndrome (ACS) events has been shown to reduce morbidity and mortality. However, it is unknown whether these medications are optimally prescribed at discharge from acute care in Iraq.

Objective: To evaluate whether patients with ACS received optimal secondary prevention medications: antiplatelets, statins, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACEI/ARBs), and beta-blockers at discharge from a cardiology unit, and to assess whether statins, ACEI/ARBs and beta-blockers were prescribed at target doses based on the American Heart Association/American College of Cardiology (AHA/ACC) guidelines.

Methods: Observational retrospective cross-sectional study of patients with ACS admitted to a hospital in Baghdad and survived to discharge between May 2016 and January 2017. Patient-level data and secondary prevention medications at discharge were extracted from routine medical records. Optimal dosing was defined as ≥75%, moderate dosing as 50–74%, and low dosing as <50% of the target dose.

Results: 45.6% (200/439) of eligible patients were included in the study who were aged 25 to 90 years (mean 57.8 years) with 78.0% (156/200) being male. Of those included, 84.5% had a myocardial infarction and 15.5% unstable angina, and the length of hospital stay ranged from 1 to 29 days (median 4 days). In total, 53.5% of patients were prescribed all five secondary prevention medications at discharge, and after accounting for contraindications, 60.0% were treated according to AHA/ACC guidelines. The prescription rate of dual antiplatelet therapy, statins, ACEI/ARBs and beta-blockers was 92.5%, 94.5%, 69.5% and 87.0% respectively. Hypertension, diabetes mellitus and the prescription of oral nitrates were associated with the prescription of optimal secondary prevention therapy. Although 80.9% of patients were prescribed target doses of antiplatelets and statins, only 12.2% and 9.2% were prescribed target doses of ACEI/ARBs, and beta-blockers respectively.

Conclusions: Approximately one in two patients received the recommended secondary prevention therapy. However, only a minority of patients were prescribed optimal doses of ACEI/ARBs and beta-blockers, in line with guidance. Quality improvement strategies should be implemented, which may include greater involvement of pharmacists within the cardiology multidisciplinary team.

Keywords

Acute Coronary Syndrome; Professional Practice; Guideline Adherence; Drug Utilization; Angiotensin-Converting Enzyme Inhibitors; Angiotensin Receptor Antagonists; Clinical Audit; Iraq

INTRODUCTION

Cardiovascular disease is the leading cause of morbidity and mortality globally.[1] In Iraq, cardiovascular disease is the primary cause of hospitalisations and accounts for 33% of total deaths.[2,3] Acute coronary syndrome (ACS) is an umbrella term referring to any group of clinical signs and symptoms consistent with acute myocardial ischemia.[4] ACS includes unstable angina, non–ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI), all of which are life-threatening events and major causes of hospitalisations, rising healthcare costs, morbidity, and mortality.[5,6]

In the acute phase of ACS, aggressive management is required to improve prognosis.[7] Patients surviving ACS are at a high-risk of subsequent cardiovascular events and death:[7-9] one in four men and one in five women will die within 12 months of an ACS event.[7] Fortunately, a better understanding of the pathophysiological mechanisms involved in ACS has allowed the development of invasive interventions such as percutaneous coronary intervention and coronary artery bypass grafting and non-invasive secondary prevention medications, including dual antiplatelet therapy, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACE/ARBs), beta-blockers, and statins.[5,9,10]

Regular use and optimal dosing with secondary prevention medications improve quality of life and survival; reducing cardiovascular events and mortality by up to 80%.[11,12] Therefore, the American Heart Association/American College of Cardiology (AHA/ACC) guidelines, which are used as national guidance in Iraq, recommend prescribing secondary prevention medications before discharge to all patients without contraindications.[13,14]

Unfortunately, the literature indicates that secondary prevention medications are inconsistently prescribed, commonly at suboptimal doses, and poorly adhered to by

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patients.[4,10,11,15,16] Statins can be initiated at optimal doses, while ACE/ARBs and beta-blockers need to be titrated to the optimal dose.[11] Although optimising doses before discharge is recommended, some patients may have contraindications or be unable to tolerate dose titration due to common factors such as hypotension, bradycardia, or worsening renal function.[11,13,17] However, by ensuring patients are prescribed optimal secondary prevention medications at discharge, physicians can increase the likelihood of adherence to these medicines post-discharge and optimise long-term outcomes.[9,11]

Studies evaluating current practices in Iraq against AHA/ACC guidelines are sparse. Therefore, this study's objectives were (1) to evaluate whether ACS patients receive optimal secondary prevention medications, consisting of dual antiplatelet therapy, statins, ACE/ARBs and beta-blockers at discharge from a cardiology unit at a government teaching hospital in Baghdad, as per AHA/ACC guidelines and (2) to assess whether statins, ACEI/ARBs and beta-blockers were prescribed at optimal doses to these patients.[13,14]

METHODS

Ethics approval

This study received ethical approval from the College of Pharmacy at the University of Mustansiriyah. In addition, the hospital gave approval for patient-level data to be collected from medical records. All patient-level data were anonymised prior to analysis to ensure patient confidentiality.

Study design and setting

This study used an observational retrospective cross-sectional design, applied to routinely collected patient-level data. The study was conducted within a major teaching hospital in Baghdad, Iraq's largest city, which provides free state-funded health care and delivers ACS care to approximately 700 patients per year.

Participant identification and data collection

Patients were eligible for this study if they were admitted to the study site and survived an ACS event from May 2016 to January 2017. For the purposes of the study an ACS event was defined as incident STEMI, NSTEMI, or unstable angina recorded in the medical notes of an admitted patient, plus clinical signs/symptoms of chest pain associated with electrocardiography changes and/or troponin level elevation. Patients were excluded from the study if they left against medical advice, died or were transferred to another hospital. If patients were admitted twice during the study, only their first admission was included. Given the descriptive nature of the study, resource constrains and the incidence rate of ACS within the site, a sample size of 200 patients was deemed appropriate. These patients were identified via convenience sampling by hospital administrative staff who screened medical records for incident ACS until 200 patients were included. The sampling methodology was not random and did not include consecutive patients.

Following identification, retrospective patient-level data were collected from written medical records, from October 2016 to February 2017, by one experienced clinical

Table 1. Demographic and clinical characteristics of the study population

Characteristics	All patients n=200 (%)	Five medications received n=107 (53%)	Five medications not received n=93 (46%)	Univariate p-value
Mean age, years (range)	57.8 (25-90)	58.1 (25-90)	57.4 (28-85)	0.677
Gender				0.866
Male	156 (78.0)	84 (78.5)	72 (77.4)	
Female	44 (22.0)	23 (21.5)	21 (22.6)	
Type of ACS				0.509
STEM	134 (67.0)	68 (63.5)	66 (70.9)	
NSTEMI	35 (17.5)	20 (18.7)	15 (16.1)	
Unstable angina	31 (15.5)	19 (17.8)	12 (12.9)	
Past medical history				
Hypertension	117 (58.5)	70 (65.4)	47 (50.5)	0.044
Diabetes mellitus	77 (38.5)	32 (29.9)	45 (48.4)	0.009
Ischemic heart disease	63 (31.5)	38 (35.5)	25 (26.9)	0.223
Heart failure or LVSD	12 (6.0)	8 (7.5)	4 (4.3)	0.388
Cerebrovascular accident	10 (5.0)	5 (4.7)	5 (5.4)	1
Peptic ulcer	6 (3.0)	2 (1.9)	4 (4.3)	0.420
Number of Co-morbidities				0.542
0	37 (18.5)	17 (15.9)	20 (21.5)	
1	70 (35.0)	40 (37.4)	30 (32.3)	
≥2	93 (46.5)	50 (46.7)	43 (46.2)	
Other Medications				
Diuretics	40 (20.0)	22 (20.6)	18 (19.4)	0.861
Nitrates	32 (16.0)	24 (22.4)	8 (8.6)	0.011
Calcium channel blockers	11 (5.5)	5 (4.7)	6 (6.5)	0.758
Vitals at Discharge				
Mean SBP, mmHg (range)	123.8 (85-180)	125.8 (92-180)	121.5 (85-180)	0.114
Mean DBP, mmHg (range	73.3 (50-104)	74.9 (50-104)	71.6 (50-90)	0.036
Mean HR, bpm (range)	78.3 (46-120)	78.2 (46-120)	78.4 (46-110)	0.906
Mean length of hospital stay, days (range)	4.3 (1-29)	4.1 (1-19)	4.6 (1-29)	0.380

STEMI: ST-segment elevation myocardial infarction; NSTEMI: non–ST-segment elevation myocardial infarction; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; bpm: beats per minute.

Table 2. Guideline adherence and target dosing for secondary prevention medications

Prescribed medications	Guideline Adherence		Target Dosing Range		
	On Therapy n (%)	Appropriate secondary prevention therapy[a] n (%)	Low n (%[b])	Medium n (%[b])	High n (%[b])
Clopidogrel	196 (98.0)	196 (98.0)	N/A	N/A	196 (100)
Aspirin	187 (93.5)	190 (95.0)	N/A	N/A	187 (100)
Dual antiplatelet therapy	185 (92.5)	188 (94.0)	N/A	N/A	185 (100)
Statin	189 (94.5)	189 (94.5)	N/A	36 (19.1)	153 (80.9)
Beta-blockers	174 (87.0)	182 (91.0)	76 (43.7)	82 (47.1)	16 (9.2)
ACE/ARBs	139 (69.5)	147 (73.5)	98 (70.5)	24 (17.3)	17 (12.2)
All five medications	107 (53.5)	120 (60.0)	NA	N/A	2 (1.9)

[a] On medication or valid contraindication
[b] Of those on medication

pharmacist using a standardised data collection form. Data included: age, gender, primary diagnosis, past medical history, blood pressure at discharge, heart rate at discharge, and prescribed drugs and doses on the day of discharge. The hospital inpatient prescription on the day of discharge was used to confirm the discharge medication, as the formal discharge prescription is not permanently stored in the patient's records, but given to the patient at discharge.

Measurement of outcomes

The primary endpoint was the number of patients prescribed appropriate secondary prevention medications at discharge. For the purpose of the study, appropriate secondary prevention medications were defined as being prescribed dual antiplatelet therapy, statin, ACEI/ARB and beta-blocker at discharge in accordance with AHA/ACC guidance. When patients had a clinical contraindication, in accordance with AHA/ACC guidance, precluding the use of one or more medications this was also counted as appropriate secondary prevention therapy.[13,14]

Secondary endpoints were the number of patients receiving optimal doses of ACEI/ARBs, beta-blockers, and high-intensity statins at discharge.[13,14] The following daily target doses were used: beta-blockers (metoprolol 200 mg; atenolol 100 mg; carvedilol 50 mg; and bisoprolol 10 mg) ACEI/ARBs (captopril 150 mg; enalapril 20 mg; lisinopril 10 mg; ramipril 10 mg; valsartan 320 mg; losartan 150 mg; and candesartan 32 mg) and high-intensity statins (atorvastatin 80 mg or rosuvastatin 20 mg or 40 mg).[15,16,18] A dose intensity ranking was then used to define optimal doses as low (<50% of target dose), medium (50–74%) and high (≥75%).[11] Systolic blood pressure and heart rate were evaluated for patients to determine whether low systolic blood pressure prevented dose optimization in low dose users of ACEI/ARBs and beta-blockers.

Statistical analysis

Descriptive statistics were used to describe patient demographics, the proportion and percentage of patients receiving secondary prevention medications, and target doses at discharge. Pearson's chi-squared test, Fisher's exact test (categorical variables) and the independent t-test (continuous variables) were used as appropriate, depending on the data, to test for associations between demographic characteristics and the use of medications at discharge. Based on the results of the above tests, variables with statistical significance associated with receiving all five medications at discharge were also subjected to binary logistic regression in order to determine independent predictors associated with receiving all five medications at discharge. Data were analysed using SPSS version 26.0 (INM Corp, Chicago, IL) and two-tailed p- values less than 0.05 were used to indicate statistical significance.

RESULTS

Prescription of secondary prevention medications

During the study period, 522 patients were admitted with ACS. Of these, 439 (84.1%) were eligible for the study, and 45.6% (200/439) were included. Of the 83 (15.9 %) ineligible patients, 39 left against medical advice, 31 died, and 13 transferred to another hospital.

Included patients varied in age from 25 to 90 years old (mean 57.8) and 78.0% (n=156) were male, with 84.5% (n=169) having a primary diagnosis of myocardial infarction and 15.5% (n=31) having unstable angina. Baseline cardiac risk factors included; 58.5% (n=117) hypertension; 38.5% (n=77) diabetes and 31.5% (n=63) with a previous history of ischemic heart disease. The median duration of hospital stay was 4 days, (range 1 to 29 days); see Table 1.

In total, 53.5% (n=107) of patients were prescribed all five medications, see Table 2. Thirteen additional patients had contraindications for one or more secondary prevention medications. Therefore, when valid contraindications were accounted for, 60.0% (n=120) of patients were assessed against guidelines to be prescribed appropriate secondary prevention therapy. Most commonly prescribed medications were: clopidogrel 98.0% (n=196), statins 94.5% (n=189) (52.4% atorvastatin, 47.6% rosuvastatin), aspirin 93.5% (n=187), dual antiplatelet therapy 92.5% (n=185) (aspirin and clopidogrel in all cases), beta-blockers 87.0% (n=174) (78.2% metoprolol, 14.4% carvedilol, 5.7% bisoprolol and 1.7% atenolol) and ACEI/ARBs 69.5% (n=139) (82.7% captopril, 5.0% enalapril, 2.2% lisinopril, 0.7% ramipril, 5.8 % candesartan, 2.2% valsartan and 1.4% losartan). No patients were co-prescribed ACEI and ARB. There was statistically significant association between the use of all five medications and mean diastolic blood pressure. In addition, there was a significant association between ACE/ARBs prescribing and hypertension, diabetes mellitus and being discharged on oral nitrate, see Table 3.

Binary logistic regression indicated that comorbidities such as hypertension (odd ratio=2.05, 95%CI 1.11 to 3.79; p=0.022) and diabetes mellitus (odd ratio=0.42, 95%CI 0.23 to 0.78; p=0.006) as well as oral nitrate prescription (odd ratio=2.95 95%CI 1.22 to 7.12; p=0.016) were associated with receiving all five medications at discharge.

Table 3. Univariate statistical significance of receiving secondary prevention therapy by clinical characteristics

Clinical characteristics	Aspirin	Clopidogrel	Statins	Beta-blockers	ACEI/ARBs
Hypertension	0.725	1	0.531	0.736	0.017
Diabetes mellitus	0.554	1	0.341	0.196	0.040
Receiving oral nitrate	0.697	1	0.218	1	0.016

Dosing of secondary prevention medications

Regarding optimal dosing, all patients prescribed antiplatelets received optimal doses: aspirin 100 mg and/or clopidogrel 75 mg daily. Of the 94.5% of patients (n=189) who received a statin, 80.9% (n=153) were prescribed a high-intensity statin. Of the 69.5% of patients (n=139) that received ACEI/ARBs, 12.2% (n=17) were prescribed a dose in the high target range. Of the 87.0% of patients (n=174) that received a beta-blocker, 9.2% (n=16) were prescribed a dose in the high target range. (Table 2). Of the 53.5% of patients (n=107) prescribed all five medication classes, only 1.9% patients (n=2) were prescribed all five medication classes within the high target dose range.

The number of patients who remained on low or moderate dose of beta-blockers (n=158) and were affected by marginal hemodynamics was low; 4.4% (7/158) had a heart rate >60 beats per minutes (bpm) and were therefore not candidates for titration to target dose whereas 83.5% (132/158) had a heart rate of ≥70 bpm. Only 20.9 % (33/158) had a systolic blood pressure reading >110 mmHg, 24.1% (38/158) had blood pressure level between 110-119 mmHg and 55.1% (87/158) had blood pressure ≥120mmHg.

Of the patients who remained on low or moderate doses of ACEI/ARBs (n=122), only 17.2% (21/122) had blood pressure >110 mmHg and were not considered for dose up-titration whereas 18.9% (23/122) had blood pressure reading between 110-119 mmHg with the majority 63.9% (78/122) had blood pressure over 120 mmHg.

DISCUSSION

This observational study is the first study to deliver a detailed assessment of prescribing, including optimal dosing, of secondary prevention medications at hospital discharge in Iraq. Just over half (53.5%) of patients admitted with ACS were prescribed all five secondary prevention medications at discharge, as advised in AHA/ACC guidelines and the guideline adherence rate was 60% after accounting for valid contraindications.[13,14] The highest adherence was for clopidogrel and the lowest for ACEI/ARBs. While an overwhelming majority of patients were prescribed target antiplatelet and high-intensity statin doses, only a minority were prescribed optimal ACEI/ARB and beta-blocker doses (12.2% and 9.2%, respectively).

This study's main finding that 60% of patients were treated according to the ACC/AHA guidelines when accounting for contraindications is comparable with previous studies from Western countries which found 69.1% adherence to guidance.[8] and from within the Middle East, which showed 62.9% adherence.[5] The prescribing of individual medications within this study is also broadly similar to or higher than studies from Western countries.[8,9,19] Hypertension, diabetes mellitus and being on oral nitrates were associated with receiving all five medications at discharge as observed in previous studies.[8,20] Although these findings show that Iraqi care is in line with current international benchmarks, physicians can still improve the prescribing of these cost-effective medications and thereby reduce further avoidable morbidity and mortality.[8,10]

Early initiation of intensive statin therapy following ACS contributes to improved long-term survival.[21] This study showed a high rate of prescribing statins, i.e., 94.5% of patients, with 80.9% of those receiving a high-intensity statin. However, almost half of the patients received rosuvastatin, for which a-priori mortality and morbidity evidence to support its use in secondary prevention is currently inadequate compared to atorvastatin.[13,17,21,22] In addition, only 63.6% of patients prescribed atorvastatin received a dose of 80 mg while 100% of those prescribed rosuvastatin received a dose ≥20 mg. A preference for prescribing rosuvastatin is not in line with Western practice, where almost all patients receive atorvastatin rather than rosuvastatin at discharge.[8,23] The reasons for the high use of rosuvastatin in this study are unclear.

The ACC/AHA Guidelines indicate that all eligible patients should receive ACE/ARBs before discharge unless contraindicated.[13,14] However, as with previous Dutch and Malaysian studies, ACE/ARBs were the least prescribed medications, and more likely to be missed, with only 69.5% of patients receiving them, and only 4.0% of patients having a valid contraindication.[8,24] In certain patient groups, such as those with heart failure, hypertension, or diabetes, these medications have a strong evidence base (class A, level of evidence A) and are vitally important in reducing morbidity and mortality, and are commonly used as a quality performance measure.[13,14] In this study, there were univariate associations between ACEI/ARB prescribing and target dosing and a history of diabetes or hypertension (see Table 3). A past medical history of heart failure could not be tested due to the small numbers involved. The primary reason for favoring captopril during admission is not entirely clear but may include the fact that it is short acting and avoids a longer period of hypotension caused by longer acting ACEI/ARBs. Within the institution, captopril is also favored due to its generic nature, consistent supply from wholesalers and low acquisition cost which eases economic burden on the patient and hospital.

The percentage of patients prescribed ACEI/ARBs (12.2%) and beta-blockers (9.2%) in the high target range was lower than previous studies where 1 in 3 patients received optimal doses.[11] However, our findings are consistent with a French study and better than a Danish study which reported that 33.0% of ACE/ARBs and 8.0% of beta-blocker users respectively received ≥50.0% of the target doses (moderate to high dose range).[15,16] Previous literature demonstrates that optimal ACEI dosing is achievable with upward titration over 3 days for patients admitted with ACS. However, these patients were not receiving beta-blocker titration at the same time, and so this reflects the challenges of routine clinical practice compared to single drug-disease trial models.[25]

Possible explanations for suboptimal dosing are unknown but may include a lack of physician knowledge regarding target dosing, marginal clinical parameters such as hypotension, worsening renal function, and/or that prescribers do not consider dose optimisation a priority during a short hospital stay (median hospital stay in this study was 4 days).[11] However, only 4.4% of low and moderate dose beta-blocker users had a heart rate of less than 60 bpm and only 17.2% (21/122) and 20.9% (33/158) of ACEI/ARB and beta-blocker users respectively had a blood pressure reading of less than 110 mmHg and were therefore not able to titrate to the target dose. This is in line with a US study which reported that only 19.0% of eligible patients were discharged on goal doses of beta-blockers and that 34.0% and 45.0% of those prescribed low and moderate doses of ACEI/ARBs respectively at discharge had a blood pressure ≥120 mmHg.[11] Thus, it is unlikely that marginal hemodynamic results prevented dose optimization during admission. In such cases, given the nature of the Iraqi healthcare system and with the benefit of secondary prevention medications being dose-related, every effort should be made to optimise doses during the inpatient stay or the importance of post-discharge titrations to optimal doses should be explained to the patient.

Strengths

This is the first study to evaluate the in-depth prescribing of secondary prevention medications, including dose, after ACS in Iraq. The cohort represents nearly half of the eligible patients admitted during the study period and hence should be representative of hospital admissions. The data were collected by one experienced clinical pharmacist, thus limiting inter-researcher variation. Utilizing routine medical records overcomes coding issues associated with electronic databases and thus, represents a more accurate method for data collection.[9,20] Moreover, measuring guideline adherence for prescribing optimal doses of secondary prevention medications overcomes the limitation of previous studies.[8,20]

Limitations

As a retrospective study using routinely collected patient-level data, the study was limited by data accuracy due to record-keeping errors, such as undocumented contraindications or medication intolerance. However, the clinical pharmacist who collected the data was aware of such potential issues and took time to identify contraindications and drug allergies during data collection. The sampling methodology was not random and did not include consecutive patients, which may introduce bias; however, the final cohort constituted 45.6% of eligible patients during the study period. The presence of full echocardiogram and angiography results, incorporating post-infarct left ventricular function and the presence and burden of residual coronary heart disease, was also unavailable. These results may have influenced physician decisions around ACE/ARB and beta-blocker prescribing. As this study was conducted in a single hospital, it may not reflect wider Iraqi practice. Finally, given the cross-sectional nature of the study data on post-discharge mortality rates, new hospitalizations and disease recurrence were not available and would require further research.

Policy, practice and research implications

This study concentrated on the short-term prescription of secondary prevention medications during the discharge phase of ACS hospital care. To date, there is no published literature on the post-discharge phase of Iraqi ACS care. Standard Iraqi post-discharge care, usually involves a patient visiting a cardiologist either in a state-funded or in a private primary care facility. In such settings, the prescriber is expected to optimise ACEI/ARB and beta-blocker doses to achieve the target dose based on the patient's tolerance and hemodynamics. The cost of medication and certain aspects of healthcare is however a potential barrier to the long-term persistence with therapy. In addition, the quality of care in the public sector is suboptimal due to the heavy workload experienced by physicians.[26] Thus, every attempt should be made to titrate the doses during hospital admission, whenever possible.[13,17]

The exact individual reasons for 40.0% of patients not being treated according to guidelines are unknown. The regression analysis showed that patients with hypertension or those using oral nitrates were more likely to be treated in accordance with guidelines. Both of these cohorts represent 'higher' risk cohorts and that may have influenced clinician behaviour. It is uncertain why diabetic patients, another high risk cohort, were less likely to be treated in accordance with guidelines.

Quality improvement strategies such as continued education, integrated care, and pre-discharge checklists have been shown to enhance compliance with evidence-based guidelines.[8,27,28] Addressing the issue of suboptimal ACEI/ARB and beta-blocker prescribing, which is also common in Europe, North America, and the Middle East, seems key.[5,11,15,16] In other countries, pharmacists working in primary and secondary care have been shown to be effective in improving the prescribing rates and dosing of secondary prevention cardiac medications.[29,30] In Iraq, clinical pharmacists are not usually involved in the coronary care unit, as their role is limited to dispensing medications.[31] Thus, the incorporation of pharmacists into the multidisciplinary team to improve the prescribing and dosing of secondary prevention medications may improve the quality of care for these patients.[29,30] In addition, pharmacists can educate patients and caregivers as per the guidelines recommendations about drug therapy, discussing indications, possible side effects, drug-drug or food-drug interactions, and monitoring.[13,14,32]

Iraq has a workforce of over 11,000 practicing pharmacists, most of whom work in state-funded primary and secondary care or privately owned community pharmacies, where services centre on traditional dispensing and distribution of medicines.[31] The opportunities for Iraqi pharmacists to assume clinical roles have grown over the last 20 years.[31] Specialisation, involving post-graduate qualifications and board certification, is becoming commonplace.[31] A future opportunity, therefore, exists to develop extended roles in specialities such as cardiology, as seen in the US and the UK.[32,33] Government funding models and legislation changes many ultimately be required to facilitate this.[31]

Future studies in Iraq should assess barriers and variations to optimal prescribing of ACEI/ARBs and beta-blockers in clinical practice using quantitative and qualitative methods. These studies should also consider assessing and evaluating clinical pharmacist interventions in optimising patient care to support future professional and service developments.

CONCLUSIONS

Approximately one in two patients received the recommended secondary prevention medicines. However, only a few patients were prescribed target doses of ACEI/ARBs and/or beta-blockers. Quality improvement strategies and further research should be implemented to optimise prescribing. This may include greater involvement of pharmacists within the cardiology multidisciplinary team.

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CONFLICT OF INTEREST

None.

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Original Research

Evaluation of aldosterone antagonist utilization in heart failure with reduced and preserved ejection fraction at an academic medical center

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Abstract

Background: Aldosterone antagonists (AA) have historically been underutilized despite evidence that they reduce morbidity, mortality, and readmission rates to the hospital when used appropriately.

Objective: We sought to determine if AAs were being prescribed in accordance with the 2013 ACCF/AHA guidelines and if there was any benefit surrounding 30-day readmissions or 30-day mortality for patients taking AAs with heart failure with reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF).

Methods: We performed a retrospective chart review of adult patients who were discharged between October 1, 2015 and February 1, 2016 with any ICD-10 code for heart failure to assess compliance with guideline directed medical therapy. At baseline, patients were stratified by HFpEF and HFrEF. Patients were excluded if they died during the admission, discharged with hospice care, received a heart transplant or ventricular assist device, if they were miscoded or left against medical advice. Descriptive statistics, and Chi Square were used to evaluate the data.

Results: We reviewed 601 patient charts for eligibility in our study, and determined 438 met the criteria for inclusion. Ninety-seven patients (22%) received an AA. Within the HFrEF group, only 37% of patients who were eligible per 2013 ACCF/AHA guidelines, received an AA at time of discharge. Fourteen percent of HFpEF patients were discharged on an AA. We found a trend towards decreased rates of our 30-day outcomes in patients who took AAs in both the HFpEF and HFrEF groups.

Conclusions: AAs were underutilized during the timeframe we evaluated, despite the evidence for their use.

Keywords

Heart Failure; Mineralocorticoid Receptor Antagonists; Drug Utilization; Guideline Adherence; Clinical Audit; United States

INTRODUCTION

Cardiac remodeling and the progression of heart failure driven by the renin-angiotensin-aldosterone system (RAAS) has been an area of interest for over five decades.[1] Each year our knowledge base becomes more nuanced, and the complex roles of each hormone become further elucidated. Even though there is now evidence of local production of aldosterone by failing cardiac tissues, aldosterone production is primarily dependent upon the activation of systemic RAAS.[1,2]

In heart failure, this cascade of actions is more detrimental than supportive as hypoperfusion is primarily related to a decreased cardiac output, secondary to decreased pump function; not hypotension. With the increase in circulating volume, which may promote systemic congestion, aldosterone directly promotes myocyte hypertrophy, fibrosis, atherosclerosis, reduced baroreceptor sensitivity, and decreased nitric oxide availability among other deleterious effects.[1,3-5] Without intervention, a failing heart will become victim of the body's own compensatory mechanisms in an uncontrolled downward spiral of further hormonal activation, fluid retention, tissue remodeling and pump failure.

Today, we have a large base of clinical evidence to support the use of aldosterone antagonists (AAs) in patients with varying degrees of heart failure with reduced ejection fraction (HFrEF). Over the last 20 years multiple landmark trials have reported encouraging findings which have since been used to synthesize the current guidelines for HFrEF treatment. We suspected that these medications may remain as underutilized as they were years ago.[6] Underutilization of AAs suggest a significant misstep in treatment considering the impact this class of drugs has on morbidity, mortality and readmission rates. In 1999 the "Randomized Aldactone Evaluation Study" (RALES) showed that in patients with an ejection fraction of <35% and New York Heart Association (NYHA) III-IV symptoms, spironolactone led to a 30% reduction in all-cause mortality.[7] Four years later the "Eplerenone, a Selective Aldosterone Blocker, in Patients with Left Ventricular Dysfunction after Myocardial Infarction" (EPHESUS) trial demonstrated a 15% mortality reduction with eplerenone.[8] "Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms" (EMPHASIS-HF) demonstrated a reduction in the composite outcome of cardiovascular deaths and HF related hospitalizations in patients with NYHA class II symptoms.[9] Given the broad range of patient characteristics, among these three trials, the current guidelines recommend utilization of AAs in most patients with HFrEF, unless a contraindication is present.

The 2017 ACC/AHA/HFSA focused update addressed the use of AAs in patients with heart failure with preserved ejection fraction (HFpEF). Patients with HFpEF may have different risk factors, and varying etiology of disease, but have from similar symptoms to those with HFrEF.[10] Prior to the TOPCAT trial, the effects of AAs had not been

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extensively studied in a randomized controlled composite outcome trial in patients with HFpEF.[11] The composite primary outcome of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for heart failure in patients receiving spironolactone was not significantly different from those receiving placebo.[11] Despite the composite outcome results, a significant benefit was seen with spironolactone in reduction of heart failure related hospitalizations. Amid controversy regarding the severity of baseline illness in patients between the two regions within the study, a post hoc/subgroup analysis was performed. After further investigation a positive finding for the composite outcome was found for patients in the American region.[12] Thus far, no other study has since provided evidence to show that AAs may reduce mortality in patients with HFpEF.[13] Today, it is suggested that nearly 50% of patients who have a diagnosis of heart failure, retain a preserved ejection fraction. Despite the lack of a statistically significant benefit, the TOPCAT trial at least suggests that AAs may be an appropriate intervention. The phase 4 SPIRRIT study looking at the use of spironolactone in HFpEF should help clarify this issue.[14]

We sought to characterize the use of AAs at our institution in patients with a heart failure diagnosis. We hypothesized that the use of AAs would be less frequent than the guidelines would recommend. We collected data on 30 days outcomes in both HFrEF and HFpEF patients to see if prescribing AAs would be of benefit.

METHODS

We designed a retrospective chart review to determine if our utilization of AAs corresponded with the number of patients that would be considered eligible for therapy per guideline recommendations. As AA use is considered level IA and IB evidence in the 2013 ACCF/AHA guidelines for HFrEF, we wanted to ensure the patients who could benefit from these medications were receiving them.[15] Due to the findings in the subgroup analysis of the TOPCAT trial, we further divided our patients in two groups; those with HFrEF and those with HFpEF. Ultimately, this decision was made to illuminate a possible link between AA use at discharge, and readmission rate or mortality within HFpEF or HFrEF groups at our institution.

Eligible patients included adults 18 years or older who were discharged from the hospital between October 1, 2015 and February 1, 2016 with an ICD-10 code that indicated any diagnosis of heart failure. This included both new and repeated admissions for heart failure. These dates were

Table 1. Baseline Characteristics.

Characteristic	HFrEF (n = 154)	HFpEF (n = 284)	p-value
Age. years (mean)	63	69	<0.0001
Female gender. n (%)	49 (31.8)	148 (52.1)	<0.0001
Height. cm (mean)	172.1	167.5	0.002
Weight. kg (mean)	85.8	86.4	0.824
Race. n (%)			0.184
White	78 (50.6)	165 (58.1)	
Black	71 (46.1)	115 (40.5)	
Other	5 (3.2)	4 (1.4)	
Heart rate. beats/min	79	77	0.229
Blood pressure. mmHg			
Systolic	118	130	<0.0001
Diastolic	70	72	0.308
Left ventricular ejection fraction. %	28	59	<0.0001
Serum K^+ mmol/L	4.2	4.1	0.103
Serum creatinine. mg/dL	1.8	1.7	0.563
Estimated glomerular filtration rate	47	46	0.888
Medications. n (%)			
Loop diuretic	103 (66.9)	168 (59.2)	0.112
ACE inhibitor	85 (55.2)	91 (32)	<0.0001
ARB	22 (14.3)	44 (15.5)	0.736
ARB/neprilysin inhibitor	1 (0.6)	1 (0.4)	0.66
Aspirin	93 (60.4)	175 (61.6)	0.801
P2Y12 inhibitor	20 (13)	47 (16.5)	0.323
Anticoagulant	61 (39.6)	85 (29.9)	0.04
Hydralazine	24 (15.6)	34 (12)	0.287
Nitrate	31 (20.1)	45 (15.8)	0.258
Potassium supplement	34 (22.1)	68 (23.9)	0.659
Digoxin	27 (17.5)	21 (7.4)	0.001
Statin	102 (66.2)	180 (63.4)	0.552
Beta-blocker	132 (85.7)	209 (73.6)	0.004
IV inotrope	10 (6.5)	2 (0.7)	<0.0001
Medical History. n (%)			
Diabetes mellitus	78 (50.6)	131 (46.1)	0.366
Hypertension	124 (80.5)	257 (90.5)	0.002
Ischemic heart disease (Unstable angina/myocardial infarction/coronary artery disease/ history of coronary artery bypass graft)	82 (53.2)	152 (53.5)	0.956
Device (Implantable cardioverter defibrillator/Pacemaker)	57 (37)	60 (21.1)	<0.001
Chronic kidney disease	56 (36.4)	106 (37.3)	0.842
Atrial fibrillation	59 (38.3)	106 (37.3)	0.839

Table 2. Aldosterone antagonist use.			
	HFrEF (n = 154)	**HFpEF (n = 284)**	**p-value**
Prescribed Aldosterone Antagonist (AA) at hospital discharge	57 (37%)	40 (14.1%)	<0.001
Started on AA after hospital discharge in clinic	3 (2%)	1 (0.3%)	
Of patients NOT on Aldosterone Antagonists	**HFrEF, not on AA (n=97)**	**HFpEF, not on AA (n=244)**	**-**
Indicated (HFrEF) and not on AA	54 (56%)	-	-
HFrEF not on AA due to contraindication	43 (44%)	-	-
Not on AA with HFpEF diagnosis	-	175 (72%)	-
Not on AA with HFpEF and other contraindication	-	69 (28%)	-

selected to provide a pool of roughly 600 patients from the time the EPIC electronic medical record was adopted at our institution. Patients were excluded if they were pregnant, had a planned admission (eg, O.R.), died during the admission or were discharged with hospice care, had received a heart transplant or ventricular assist device, if they had no clear evidence of heart failure (miscoded) or if they left against medical advice. We considered those with the most recent measured ejection fraction prior to or during admission of ≤40% as patients with HFrEF. Despite the classification of borderline HFpEF (EF 41-49%), we decided to consider patients with an EF above 40% to have HFpEF. We used the current ACCF/AHA guidelines to determine the appropriateness of AA therapy. If patients had acute kidney injury, hypotension, eGFR<30 mL/minute/1.73 m2 or creatinine>2.5 mg/dL (men) or >2 mg/dL (women), potassium>5 mEq/L or history of hyperkalemia they were deemed ineligible for AAs. Additionally, we determined if a patient was started on an AA in clinic within 14 days from discharge. Occasionally, patients are not quite stable enough at discharge to start new medications, and initiation or re-initiation of an AA may be indicated, but deferred to the primary care physician or HF clinic provider as the patient continues to improve while other goal directed medications are titrated. As noted in the 2017 Pathways for Optimization of Heart Failure Treatment, it is not necessary to achieve target doses or maximally tolerated doses of other drugs before adding an AA.[16] For patients that met our criteria, investigators manually pulled all variables from patient charts via EPIC universe. This information was then pooled into a secure datasheet available only on a secure network. Baseline characteristics were compared between HFpEF and HFrEF using chi-square tests when assessing differences between the groups with categorical variables, and t-tests for data comprised of continuous variables. These analyses were performed using the statistical functions of Microsoft excel and SPSS statistical software. This study was approved by the institutional review board.

RESULTS

A total of 601 patients with a diagnosis of heart failure from the pre-specified time period were preliminarily included. After evaluation and assessment by the research team, 438 patients were determined to meet criteria for the final data extraction to be further analyzed. Baseline demographic data are presented in Table 1. There were several significant differences noted between the HFrEF and HFpEF patients. In addition to differences in ejection fraction, HFpEF patients were older, more often female, had higher systolic blood pressure, and received an ACE inhibitor, beta blocker, digoxin and IV inotrope less frequently.

Table 2 shows the utilization of AAs in our patient population. The utilization of AAs was significantly more frequent in patients who had HFrEF (37%) compared with that of patients with HFpEF (14.1%). Of the patients who had HFrEF and were not already on an AA over half were considered eligible at the time of observation per the 2013 ACCF/AHA guideline recommendations. Additionally, if we consider the same criteria and apply it to patients with HFpEF not receiving an AA, a majority of patients (72%) would be considered 'eligible' for therapy if there were a similar guideline recommendation as that seen with HFrEF. The remaining patients (28%) with HFpEF had a contraindication to an AA.

Table 3 presents the rates of readmission and death at 30 days. Rates of readmission within 30 days of discharge were assessed within each group and between those who received AAs and those who did not. Among all patients readmitted within 30 days, 15 patients had HFrEF, and 17 patients had HFpEF (9.7% and 6%, p=0.149). Within the HFrEF group, 7% of patients who were readmitted were taking an AA, versus 11.3% for those not taking an AA. Within the HFpEF group, no patients were readmitted within 30 days that were taking AAs, while 7% of patients not taking AAs were readmitted. These differences were not statistically significant.

Additionally, rate of death within 30 days of discharge was assessed within each group and between those who received AAs and those who did not. Among all patients, death within 30 days was observed in 8 patients with HFrEF and in 6 patients with HFpEF (5.2% and 2.1%, p=0.08). Within the HFrEF group, 1.8 % of patients died within 30 days who were taking an AA versus 7.2% of patients who were not taking an AA. Within the HFpEF group, no patients who were taking an AA died within 30 days of discharge, while 2.5% of patients who were not taking an AA died. Again, the differences were not statistically significant.

Table 3. Readmission and death within 30 days.			
Readmission/Death between AA and NO AA	**Prescribed AA**	**Not on AA**	**p-value**
Readmissions			
HFrEF readmitted within 30 days	4 (7%)	11 (11.3%)	0.382
HFpEF readmitted within 30 days	0 (0%)	17 (7%)	0.085
Deaths			
HFrEF death within 30 days	1 (1.8%)	7 (7.2%)	0.14
HFpEF death within 30 days	0 (0%)	6 (2.5%)	0.316

Only two patients were receiving eplerenone, while the vast majority (98%) were prescribed spironolactone. The mean dose of spironolactone per day was 27.5 mg (SD 18.7). Finally, only four patients in total were started on an AA in a clinic appointment within 14 days of discharge (three with HFrEF, and one with HFpEF).

DISCUSSION

We evaluated a diverse group of patients with varying degrees of heart failure prior to discharge in the hopes that we would be able to establish how well we may be using a potentially underutilized medication with clear disease modifying benefits. A few interesting observations were noted within our study population. First, the presence of nearly twice as many patients with HFpEF compared with HFpEF is not reflective of the literature.[17] This likely is a direct result of our exclusion criteria eliminating many sick patients and our choice to use an ejection fraction of 40% as the cutoff for HFpEF vs. HFrEF, with no grouping for intermediate heart failure. Secondly, there was a statistically significant increase in the utilization of anticoagulants in patients with HFrEF, but the rates of atrial fibrillation between groups were roughly equal. This discrepancy would suggest that our population of HFrEF patients had a higher rate of venous thrombosis or pulmonary embolism, though these variables were not explicitly recorded in our study. These results correspond with a subset of existing literature that proposes risk of VTE is directly related to left ventricular function.[18]

In similar fashion to the traditional epidemiology of HFpEF, our patients with HFpEF were predominantly older, female, and had higher rates of hypertension when compared with the HFrEF group.[15,19] The utilization of ACE inhibitors, beta-blockers, hydralazine and nitrates was seen with higher frequency in the HFrEF group, though only ACE inhibitors and beta-blockers were significantly different. This mirrors expectations as these medications comprise the core of our current goal directed medical therapies for HFrEF. Though significantly more patients were on chronic IV inotropes in the HFrEF group, it is worth noting that two patients in the HFpEF group were on chronic IV inotropes. It is possible that these two patients previously had acutely decompensated HFrEF and now have ejection fractions that have recovered secondary to inotrope usage or for other reasons. This points out a limitation of our observational study, but suitably describes heart failure as a syndrome with a continuum of symptoms and objective measurements of disease severity that are rarely static.[20] Finally, use of digoxin and cardiac devices was observed with significantly higher incidence in patients with HFrEF compared with HFpEF.

Over half of the patients who met guideline directed criteria for the utilization of an AA at time of observation were not receiving one. Interestingly, the CHAMP-HF registry observed an AA utilization rate of 33%, which is in line without results.[21] In most instances aldosterone antagonists were avoided due to “soft” blood pressures, laboratory abnormalities, kidney dysfunction or due to titration of other goal directed medications. However, with appropriate prescribing and monitoring, the benefits of treatment often outweigh the risks. The current utilization of AAs at our organization would suggest there is significant room for improvement in the rate of compliance per ACCF/AHA guidelines for HFrEF. This pattern carries significant weight considering the known morbidity, mortality and readmission benefits as seen with patients in the RALES, EPHESUS, and EMPHASIS-HF trials.

The TOPCAT trial suggests this class of medications can at least prevent heart failure related admissions, and possibly improves morbidity and mortality in patients diagnosed with HFpEF using natriuretic peptide levels. While our results did not reach a statistically significant difference, this is likely due to inadequate power. The data from our institution may support the known readmission or mortality benefits as seen in larger trials, as there was a trend in a similar direction among patients with both HFrEF and HFpEF.

Understanding that the prescribing of AAs may not be as frequent as the guidelines recommend, methods to improve compliance with guidelines will undoubtedly help our patients. Considering that the majority of the patients we evaluated were discharged from inpatient cardiology services, we would expect that patients who meet guideline criteria have been assessed for initiation of AAs. As these services are run by a constantly rotating cadre of medical residents and interns, regular education on guideline directed medical therapy from the rounding pharmacist staff is likely the most direct and reliable form of correction. Pharmacists at our institution currently round with the cardiology teams and a majority of other inpatient services on a daily basis and have regular opportunities to impact patient care. Pharmacists share responsibility with senior physicians in directly educating our younger medical colleagues, specifically with regard to pharmacology, and therapeutics of these goal directed medications. Simultaneously, the implementation and creation of an algorithm congruent with heart failure guideline directed medical therapy would provide an easily accessible physical reference for each prescriber that spends a month with the cardiology team. These may be two of the most direct and easily implemented solutions, but new ideas are clearly needed.

Limitations

Certainly, many limitations exist when looking at these outcomes in this study and we are cautious in comparing an observational study to randomized prospective trials. In addition to potentially not meeting power (no power calculation was performed due to the intent of the study), the period of 30 days was likely too short to appreciate a true statistical difference in rates of all cause death or readmissions. For example, the three HFrEF landmark trials specifically evaluated morbidity and mortality over many months, but only within the EPHESUS trial was a mortality benefit appreciated 30 days after randomization.[22] Additionally, it is nearly impossible to account for all deaths or readmissions of a cohort without prospective follow up considering the possibility of readmission or death at another hospital. Finally, we were unable to adjust our data for confounding variables (e.g. other goal directed medications) due to the relatively low number of events.

CONCLUSIONS

We demonstrated that there is significant underutilization of AAs in patients admitted with acute decompensated heart failure in our institution which is similar to national data. Consistent education efforts are still necessary to ensure our patients are receiving guideline directed medical therapy with AAs, which confer significant improvement in various patient-oriented outcomes. Increased prescribing may improve heart failure outcomes across the country, not only for patients with HFrEF, but also for patients with HFpEF.

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CONFLICT OF INTEREST

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Original Research

Community pharmacy ethical practice in Jordan: assessing attitude, needs and barriers

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Abstract

Background: Having a local code of ethics, based on moral obligations and virtues, known to all practicing pharmacists is important in order to guide them in relationships with patients, health professionals, and society.

Objective: To investigate pharmacists' attitude and barriers towards applying the ethical principles published by the Jordanian Pharmacists Association in the Jordanian code of ethics.

Methods: The study objectives were addressed in a cross-sectional study completed by a convenience sample of community pharmacists, in both cities; Amman and Irbid A questionnaire was used to achieve the study objective. The questionnaire was developed and validated, investigating pharmacists' socio-demographic and practice characteristics, perceived attitude toward certain practice scenarios, and perceived barriers towards applying the locally published ethical principles while dealing with their patients. The questionnaire was self-completed by pharmacists between January and August 2017. Collected data was analyzed using SPSS version 21. Descriptive statistics and parametric tests were used with $p<0.05$ set a priori as significant.

Results: Seven hundred and four pharmacists (Amman n=486; Irbid n=218) responded to the questionnaire, providing completely answered questionnaires with a response rates of 69.4% in Amman and 99.6% in Irbid. Pharmacists from both cities revealed that they use the Internet as their main resource to obtain ethical information when they need it, to help them deal with their patients (34.0% from Amman and 31.5% from Irbid). More pharmacists in Amman (57.0%) had access to resources regarding ethical information at their practice sites compared to pharmacists in Irbid (24.0%). Significant differences in attitude was found between pharmacists practicing in both cities, as significantly less pharmacists from Amman (37.8%) declared that they would sell a medication for an unreported indication according to national and international guidelines, if recommended by the consultant, compared to pharmacists from Irbid (77.7%, $p<0.001$).

Conclusions: Despite having ethical guidance from the Jordanian Pharmacists Association, the majority of pharmacists in Jordan do not use this resource; instead, most choose to access ethical guidance on-line. Pharmacists from the capital, Amman, reported to adhere more with the guidelines when selling a medication for an unreported indication compared to pharmacists from the smaller city, Irbid. Results of this study call for more actions from the authorities in the country responsible for setting and enforcing the pharmaceutical Code of Ethics.

Keywords

Ethics, Professional; Pharmacists; Professional Practice; Attitude of Health Personnel; Surveys and Questionnaires; Jordan

INTRODUCTION

Pharmacy ethics is a system of moral principles that affects how pharmacists make decisions related to pharmacy practice.[1-3] Also, it is concerned with what is good for individuals and society as a whole, and has been described as a moral philosophy.[1] Pharmacy ethics encompasses a reasonably well-established definition by national and international professional organizations which have largely defined it through codes of ethics.[4-7] A study by Chaar *et al*. found that it is vitally important to have moral reasoning skills to balance personal values with principles of professional ethics to be able to make ethical and reasonable decisions in pharmacy practice.[8]

Many countries have well established ethical guidelines like the United Kingdom, Australia and USA, yet little is known about ethics in pharmacy, and what pharmacists find ethically problematic in their work.[9-11] Having a Pharmacy Code of Ethics in Jordan, is significant in order to guide pharmacists in their relationship with their patients, healthcare professionals and the society.[12-14] It is important that pharmacists follow the bioethical principles of beneficence, non-maleficence, autonomy and justice, which form the fundamental basis of their role and responsibilities in provision of healthcare.[8,13,15] These values provide the basis for an ethical framework, in which awareness of responsibilities can take place.[13,15] Other factors also play a role in decision making, including culture and moral reasoning capabilities.

The American Pharmaceutical Association stated that "Pharmacists are healthcare professionals who assist individuals in making the best use of medications. This Code, prepared and supported by pharmacists, is intended to state publicly the principles that form the fundamental basis of the roles and responsibilities of pharmacists. These principles, based on moral obligations and virtues, are established to guide pharmacists in relationships with patients, healthcare professionals, and society".[5] So, when pharmacists allow business objectives to influence and control their conduct, the commitment to these concepts can be compromised.[16] For instance, pharmacists face this

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kind of conflict in a number of ways including: when deciding whether or not to sell over-the-counter treatments that are not needed; when deciding whether or not to recommend less expensive generic medications; or when deciding whether or not to report a colleague that they feel has acted unethically.[16,17]

With the evolution of the profession, and the increased focus on patient-centered care services, more ethical challenges are expected to arise. In the United Kingdom, Australia and USA for example, pharmacists are encouraged to carry out more services, such as medication management review (MMR), medication therapy management (MTM) or medicine use review.[18-21] Such services are expected to involve more ethical challenges.[18] In Jordan, the introduction of the PharmD degree in 2011 in the country, led to more pharmacists working in the hospital sector and delivering higher level of patient care to the community.[21] Higher level patient care and interaction is expected to involve higher numbers of ethical dilemmas.[21]

A study by Cooper *et al*., conducted in the United Kingdom, noted that there was a wide variation in pharmacists' ability to identify and describe ethical issues.[18] In Croatia, pharmacy ethical practice has developed relatively slowly with research findings demonstrating a need to aid pharmacists in their decision making processes.[11] Another study conducted in Iran evaluated pharmacists' attitude toward the principles of bioethics, emphasizing the need for further research in the area of pharmacy ethics.[22] In Saudi Arabia, Al-Arifi investigated community pharmacists' perceptions and attitudes toward ethical issues and shed light on the need for Saudi health authorities to implement a code of ethics for pharmacy practice.[17] This is similar to what is found in the majority of Middle East countries.[17,23] In Qatar for example, there is no professional pharmacy association or society that controls, represents or supports the practice of pharmacy.[23] This has meant that pharmacists in Qatar have no code of ethics to guide their practice.[24]

In Jordan, the Pharmacy Code of Ethics, published by the Jordanian Pharmacists Association, consists of a set of principles that pharmacists should adhere to in their practice. It ensures that they act with fairness and equity in the allocation of any health resources made available to patients. It guides pharmacists to maintain priorities of the safety, wellbeing and best interests of those who they provide their services for. This would motivate them to act at all times with integrity in their dealings with patients. In addition, it focuses on the collaborative relationship between pharmacists and other healthcare professionals to ensure that patients, and the public at large, get the best possible care.[4] There is a paucity of previous published studies that have explored community pharmacists' attitudes towards pharmacy practice in Jordan.

Therefore, the aim of this study was to investigate pharmacists' attitude, needs and barriers towards applying ethical principles published by the Jordanian Pharmacists Association in the Jordanian Pharmacy Code of Ethics. A secondary aim was to identify any differences in attitudes between pharmacists practicing in the busy capital of Jordan, Amman, and in the second largest, less advanced city in north Jordan, Irbid.

METHODS

A cross-sectional, descriptive survey of community pharmacists was conducted in two of the largest cities in Jordan (Amman and Irbid). The selection of these two cities came with the Jordanian Pharmacists Association report stating that the highest number of community pharmacies in Jordan is located mostly in these two distinct geographical areas.[4] In addition, it has been reported by the department of statistics in Jordan for the year 2017 that the highest population in Jordan is concentrated in these two cities (Amman followed by Irbid).[25] The data were collected between January and August 2017, using a structured self-administered questionnaire. Ethics approval was obtained from the Faculty of Pharmacy, Applied Science Private University Ethics Committee (reference: 2017/2018/1).

A convenience sample of registered community pharmacists located in Amman and Irbid were chosen to participate in the study and respond to the survey. Community pharmacies were visited by a research assistant who explained the purpose of the study and provided the participant information statement. Following the reading of the information statement, verbal consent was sought from the pharmacists before study participation. The information statement contained important information, including the purpose of the study, the fact that participation was voluntary and did not pose any risk to the respondents, that the collected data would be published anonymously, with no indication to respondents' identity, in addition to whom to contact if any questions were raised. Pharmacists who consented to participate were handed the questionnaire. The completed questionnaires were placed in sealed envelopes by the participants. The questionnaire was followed-up for collection by the researcher on a later date that ranged from one to two weeks. The closed envelopes containing the completed surveys were then delivered to the research team. To avoid social bias, the research assistant did not reveal her own profession to be pharmacy. Returned questionnaires were completed anonymously. Non-respondents were visited to collect their uncompleted questionnaire.

Study tools

The questionnaire was designed and developed following a careful review of the literature and previous studies related to ethics in the community pharmacy setting.[11,17,22] Different scenarios were used in previously developed questionnaires regarding ethics in pharmacy, assessing attitude and barriers towards practice. Similar scenarios were used while developing the survey questions in this study. These questions were then pre-tested by pharmacists with experience in ethics research. A draft of the questionnaire was piloted by ten practicing pharmacists to assess readability, understandability, questionnaire design (suitability of the different segments of the questionnaire) and the length of the questionnaire. Based on the result of the pilot study, the questionnaire was

modified and the final version was ready to be sent to the selected pharmacies.

The survey questionnaire consisted of a brief introduction of the study followed by forty-two questions. The questions consisted of closed ended, and multiple-choice questions. The questionnaire was constructed to include three sections: the first section collected demographic data of the study participants, including age, gender, education (highest degree), years of experience, number of working hours per week, average number of adult patients who visit the pharmacy per day, and type of pharmacy (polyclinic pharmacy, next to a supermarket/ shopping mall, independent pharmacy or other (specified).

The second section of the questionnaire consisted of several scenarios obtained from the literature review conducted for this study based on pharmacy practice and ethical dilemmas experienced in different countries.[11,17,22] Such scenarios were used to evaluate pharmacists' attitude and practice aspects toward ethical issues using a 5-point Likert scale with responses ranging from 1=strongly agree to 5= strongly disagree, or 1= very highly interested to 5= not interested at all, to assess pharmacists' agreement with the presented reaction of the pharmacist in each scenario.

The third section was designed to determine the level of ethical practice knowledge of study participants by asking them about whether they had received previous education on ethics in pharmacy practice in Jordan, whether they discussed healthcare issues with their patients, as a part of respect for patient autonomy and promotion of their right to self-determination and recognition of individual self-worth by encouraging them to participate in decisions about their health. Also, this section reported how often, if any, this information was documented in their pharmacy records.

Furthermore, this section investigated barriers that restricted pharmacists from explaining ethical issues to their patients, which ethical information resources were currently available at the pharmacists' practice sites at the time of the study, resources perceived as important and helpful in caring for the patients, and to whom would participants refer to for advice about their ethical dilemmas once identified.

The Jordanian Pharmacy Code of Ethics was obtained by the research team from the Jordanian Pharmacists Association. The scenarios were formulated according to the stated principles. A revision by an expert in Jordanian pharmacy practice was conducted to ensure that these scenarios represented relevant ethical principles in Jordanian practice.

Sample size

The sample size was calculated based on the current number of pharmacists registered in Amman (11,318) and Irbid (2,051), which were provided by the Jordanian Pharmacists Association. The number of registered pharmacists in both cities was approximately 13,369. The sample size was calculated by the online sample size calculator, using 5% margin of error, 95% confidence level and a response distribution of 50%. The minimum sample size calculated was 372 for Amman and 324 for Irbid.

Data analysis

The data from each of the returned questionnaires were coded and entered into the SPSS version 21 (Chicago, IL, USA), which was used for statistical analysis. Descriptive statistics including percentages, means, and frequency distribution were calculated for each of the questions. Descriptive and univariate correlation analyses, with the Pearson correlation coefficient (r), were used to find correlations at the 5% significance level. A p-value of <0.05 represented a significant difference.

RESULTS

Respondents' socio-demographic and practice characteristics

A total of 750 questionnaires were distributed to community pharmacies in both Amman and Irbid. Most participants (n=704, Amman n=486; Irbid n=218) consented to participate in the study and completed the survey questionnaire (all questions were answered by all of the participants) giving a response rate of 93.8%. The mean age of the respondents was 30.7 (SD 8.2), with more than half of the respondents being females (Table 1). Significantly, more pharmacists from Amman had PhD and/or Masters Degrees than from Irbid (p<0.001). Pharmacists from Amman had more patients visiting their pharmacies than pharmacists from Irbid (p=0.009), and they had a higher number of pharmacy technicians working at their pharmacies (p=0.005). More respondents from Amman were managers or supervisors, and more of them had their pharmacies located next to a supermarket, a shopping mall or a clinic (p<0.001 for all). A related point to consider is that pharmaceutical care in Jordan is provided to patients regardless of the pharmacist's position whether the pharmacist in charge was the pharmacy owner, supervisor, or a locum pharmacist.

The majority of respondents from Amman (66.5%) and Irbid (86.0%) reported receiving previous education on ethics concerning pharmacy practice services in Jordan (p<0.001). In Amman, more than half (56.6%) of the pharmacists reported that they had access to ethical information resources at their practice site versus 24.3% from Irbid (p<0.001). There was a significant difference (p<0.001) between both cities with regards to pharmacists receiving previous education or training on the Jordanian Code of Ethics, and the frequency of their documentation of ethical concerns (Table 1).

Attitude towards specific ethical scenarios

The frequency of occurrence of specific ethical problems in both Amman and Irbid revealed interesting differences between the two cities (Table 2). In response to the survey scenarios, results showed that in Amman and Irbid, the majority of pharmacists (Amman= 52.0%, Irbid= 84.2%, p< 0.001) disagree/strongly disagree with dispensing a drug if the patient did not really need the treatment. The majority of pharmacists (Amman=63.3%, Irbid=89.8%, p<0.001) would not sell (disagree/strongly disagree) an over-the-counter medication if they suspected any drug abuse by the patient.

Table 1. Demographic and other characteristics of the study sample (n= 704), comparing participants from Amman and Irbid

	Amman (n= 486)	Irbid (n=218)	*P* value
Age (years); mean (SD)	30.66 (8.22)	30.60 (8.6)	0.926[1]
Gender; n (%)			0.107[2]
Male	233 (46.2)	86 (39.6)	
Female	260 (53.8)	131(60.4)	
Educational level			<0.001[2]
BSc	377 (77.6)	197 (90.8)	
MSc	57(11.7)	7 (3.2)	
PhD	17 (3.5)	0 (0.0)	
Diploma	35 (7.2)	8 (3.7)	
Number of years since pharmacy graduation			0.835[2]
< 5	235 (48.8)	110 (50.9)	
5 – 10	159 (33.0)	62 (28.7)	
11 – 15	26 (5.4)	14 (6.5)	
16 – 20	26 (5.4)	13 (6.0)	
>20	36 (7.5)	17(17.9)	
Experience as a pharmacist			0.698[2]
< 5	236 (54.1)	116 (53.7)	
5 – 10	138 (28.4)	56 (25.9)	
11 – 15	33(6.8)	13 (6.0)	
16 – 20	23(4.7)	13(6.0)	
>20	29(6.0)	18(8.3)	
Number of adult patients who visit the pharmacy per day			0.009[2]
< 50	194(40.2)	62 (28.6)	
51 – 100	206 (42.7)	116 (53.5)	
>100	83(17.2)	38 (17.5)	
Number of hours worked per week; mean (SD)	47.08 (13.58)	45.39(9.16)	0.1011
Number of pharmacists who work in the pharmacy at any one shift			0.112[2]
0	7 (1.4)	1 (0.5)	
1	261 (53.8)	103 (47.7)	
>1	217 (44.7)	111(51.4)	
Number of pharmacy technicians who work in the pharmacy at any one shift			0.005[2]
0	212 (43.9)	86 (39.8)	
1	191(39.5)	110 (50.9)	
>1	80 (16.6)	20 (9.3)	
Position			0.000[2]
Employee pharmacist	323(66.6)	176 (81.9)	
Pharmacy manager/supervisor	86(17.7)	1 (0.5)	
Pharmacy owner	75(15.5)	36 (16.7)	
Pharmacy setting			0.000[2]
Supermarket or shopping mall pharmacy	86 (18.9)	2 (0.9)	
Polyclinic pharmacy	74 (16.3)	2 (0.9)	
Independent pharmacy	291(64.1)	210 (98.1)	
Have you received any kind of education or training about Jordanian ethical practice in the past? Yes	318 (66.5)	185 (86.0)	< 0.001[2]
Have you ever been accessed for ethical information at practice site? Yes	265(56.6)	52 (24.3)	<0.001[2]
How often do you record ethical concerns in your pharmacy?			<0.001[2]
Never	41 (8.7)	15 (7.0)	
Rarely	103 (21.8)	61 (28.4)	
Sometimes	171 (36.2)	104 (48.4)	
Often	105 (22.2)	26 (2.1)	
Very often	52 (11.0)	7 (3.3)	

[1] t-independent test; [2] Chi-square test

Most respondents reported that they would not (disagree /strongly disagree) dispense a controlled drug without a legal prescription, as it is illegal to dispense such drug class without prescription, (Amman=57.4% versus Irbid=91.7%, p<0.001). More pharmacists from Irbid (75.0%, p<0.001) versus Amman (27.4%) would not (disagree /strongly disagree) inform a terminally ill patient if they asked for a diagnosis in case their doctor decided to hide such information. Also, about half (agree /strongly agree) of pharmacists (from both cities) said that they would withhold the truth about medication side effects if that would make the patient more compliant with their medication. As for generic drugs, the majority (agree /strongly agree) from both cities (Amman 85.4% versus Irbid 89.8%) would inform the patient before they dispense a generic drug if the prescription stated a specific brand of medication and it was not found in stock. Most respondents said they would report (agree /strongly agree) to their manager if they perceived their colleague was doing something unethical, after talking to the colleague in question first. (Amman= 70.3%, Irbid= 76.4%).

Most respondents had a negative (disagree /strongly disagree) response towards dispensing a medication to patients if it is against the international guidelines and therapeutics management of a specific condition (Amman=52.2%, Irbid=59.8%). About 78% (agree /strongly agree) of respondents from Irbid would sell a medication

for an unreported indication in the guidelines if recommended by the consultant; conversely; only 37.8% of pharmacists from Amman would do the same, showing a significant difference ($p<0.05$) between the two cities.

Perceived attitudes toward certain practice scenarios

The majority of participants disagreed/strongly disagreed with dispensing natural health products if their efficacy and safety had not been demonstrated by a regulatory authority (Amman 56.4% versus Irbid 93.0%). Community pharmacists in Amman, perceived an ethical dilemma when they were asked about disclosing to a mother, information on contraceptive usage by her daughter. Many pharmacists from Amman (32.2%) agreed/strongly agreed to disclose the information to the mother, while a clear majority from Irbid (69.3%) agreed/strongly agreed to disclose such information. Most of the participants disagreed/strongly disagreed with dispensing sleeping aids (i.e. alprazolam) for sleeping disorders without a prescription (Amman 78.9% versus Irbid 95.8%; Table 2).

In addition, majority of participants (Amman= 87.9%, Irbid= 99.6%) agreed/strongly agreed to help their patients after their official working shifts, and majority (Amman= 83.9%, Irbid= 84.9%) were interested/ highly interested in calling the patient's doctor if they noticed that there was something wrong with the prescription. In Irbid, majority of pharmacists (61.8%) disagreed/strongly disagreed with the statement about proposing brands instead of generic drugs, in contrary to only 20.4% of pharmacists from Amman (p=0.714). In Irbid, about 77.8% of pharmacists were not interested in talking about the lethal dose of certain drugs if they suspected abuse by the patients versus only 39.6% in Amman ($p< 0.05$; Table 2). Pharmacists from both cities stated that they would refer their ethical dilemmas once identified, mostly to their managers, followed by Jordanian Pharmacists Association (Figure 1).

Table 2. Assessing pharmacists' attitude towards specific ethical scenarios from both Amman (n= 486) and Irbid (n=218).

Statement		Strongly agree	Agree	Neutral	Disagree	Strongly disagree	p-value
1. A customer asks for an over-the-counter treatment. After talking to the patient you come to the conclusion that s/he does not really need the treatment, but you give him/her the medication.	Amman	47 (9.7)	92 (19.0)	93 (19.3)	180 (37.3)	71 (14.7)	0.000
	Irbid	4 (1.9)	25 (11.6)	5 (2.3)	169 (78.2)	13 (6.0)	
2. The prescription states a specific brand of drug. You do not have this in stock but you have a generic clinically equivalent brand in stock. Will you inform the patient before you dispense the generic drug?	Amman	207(42.8)	206 (42.6)	50 (10.3)	17(3.5)	4 (0.8)	0.118
	Irbid	60 (27.8)	134 (62.0)	9 (4.2)	13 (6.0)	0 (0.0)	
3. After questioning, a patient makes it known s/he is going to use the medication she/he is asking to buy against guidelines (e.g. hydrocortisone cream for his/her face). Will you dispense the drug?	Amman	28 (5.8)	76 (15.8)	126 (26.1)	179 (37.1)	73 (15.1)	0.012
	Irbid	0(0.0)	66 (30.6)	20 (9.3)	112 (51.9)	17 (7.9)	
4. A customer wants to buy an over-the-counter medicine you suspect s/he might be abusing (may be this appears likely after speaking to him/ her about it) and the customer does not want an alternative. Will you dispense the drug?	Amman	20(4.1)	65 (13.5)	92 (19.0)	163 (33.7)	143 (29.6)	0.000
	Irbid	2(0.9)	14(6.5)	6 (2.8)	107 (49.5)	87 (40.3)	
5. The husband or wife, or another close family member (other than the parent of a child) of a patient asks for confidential information about that patient's treatment. Will you tell them?	Amman	67 (13.9)	114 (23.6)	108 (22.4)	90 (18.6)	104 (21.5)	0.000
	Irbid	3 (1.4)	19 (8.8)	7 (3.2)	53 (24.5)	134 (62.0)	
6. Someone comes into the pharmacy/phones asking you to identify a particular tablet that does not belong to him/her and you are able to identify the tablet. Will you identify that for the patient?	Amman	95 (19.8)	209 (43.5)	115 (24.0)	38 (7.9)	23 (4.8)	0.000
	Irbid	105 (48.6)	83 (38.4)	15 (6.9)	10 (4.6)	2 (0.9)	
7. You believe that withholding the truth from, or deliberately misleading, a patient would mean s/he would be compliant with a treatment you believe is very important to him/her. Are you going to hold the truth?	Amman	60 (12.6)	177 (37.2)	140 (29.4)	72 (15.1)	27 (5.7)	0.287
	Irbid	7 (3.2)	91 (42.1)	32 (14.8)	79 (36.6)	7 (3.2)	
8. You feel something a colleague has done is unethical and you talk to your colleague, but still s/he does not change his/her behavior. Will you report this to your manager?	Amman	131 (27.4)	205 (42.9)	98(20.5)	32 (6.7)	11 (2.3)	0.214
	Irbid	47 (21.8)	118 (54.6)	11 (5.1)	35 (16.2)	5 (2.3)	
9. A parent of a patient asks for confidential information about his/her son/daughter's treatment. Will you inform the parents?	Amman	155 (32.2)	170 (35.3)	91 (18.9)	37 (7.7)	28 (5.8)	0.479
	Irbid	29 (13.6)	122 (57.0)	25 (11.7)	35 (16.4)	3 (1.4)	
10. A doctor is prescribing, on private scripts, medication you suspect s/he is abusing. You've already talked to him/her about it but s/he has clearly ignored you. Will you dispense it?	Amman	37 (7.7)	87 (18.1)	89 (18.5)	155 (32.2)	111 (23.1)	0.000
	Irbid	2 (0.9)	23 (10.6)	17 (7.9)	116 (53.7)	57 (26.4)	
11. You suspect a pharmacist you work with is using prescription medicine from the controlled drugs cabinet without a prescription. You already talked to him/her about it but s/he clearly ignored. Will you report this to your manager?	Amman	144 (29.9)	173 (36.0)	101 (21.0)	41 (8.5)	21 (4.4)	0.000
	Irbid	61 (28.2)	118 (54.6)	6 (2.8)	29 (13.4)	2 (0.9)	

Table 2 (cont.). Assessing pharmacists' attitude towards specific ethical scenarios from both Amman (n= 486) and Irbid (n=218).

Statement		Strongly agree	Agree	Neutral	Disagree	Strongly disagree	p-value
12. A consultant asks you to dispense a drug for an unreported indication and tells you s/he knows it is used for this indication with great effect in USA. Will you dispense the drug?	Amman	31 (6.4)	151 (31.4)	133 (27.7)	123 (25.6)	43 (8.9)	0.000
	Irbid	64 (29.6)	104 (48.1)	26 (12.0)	21 (9.7)	1 (0.5)	
13. A member of the public comes to the pharmacy and asks for some controlled or RX medications or large quantities. Will you dispense it!	Amman	24 (5.0)	81 (16.9)	99 (20.7)	127 (26.5)	148 (30.9)	0.000
	Irbid	0 (0.0)	10 (4.6)	8 (3.7)	43 (19.9)	155 (71.8)	
14. A terminally ill patient asks you for a diagnosis or prognosis, telling you s/he does not feel the doctor is telling the whole truth. You know the full case history. Will you tell the patient the truth?	Amman	78 (16.3)	145 (30.3)	125 (26.1)	77 (16.1)	54 (11.3)	0.000
	Irbid	1 (0.5)	32 (14.8)	21 (9.7)	61 (28.2)	101 (46.8)	
15. Disclosing to a mother information on contraceptive usage by a daughter	Amman	53 (11.2)	99 (21.0)	152 (32.2)	112 (23.7)	56 (11.9)	0.000
	Irbid	20 (9.3)	129 (60.0)	24 (11.2)	40 (18.6)	2 (0.9)	
16. Dispensing natural health products when their efficacy and safety have not been demonstrated by a regulatory authority?	Amman	22 (4.6)	79 (16.6)	106 (22.3)	155 (32.6)	113 (23.8)	0.003
	Irbid	0 (0.0)	6 (2.8)	8 (3.7)	59 (27.6)	140 (65.4)	
17. Dispensing sleeping aids (i.e. Xanax® (Alprazolam)) for sleeping disorder without prescription.	Amman	19 (4.0)	29 (6.1)	53 (11.1)	101 (21.2)	275 (57.7)	0.000
	Irbid	0 (0.0)	7 (3.3)	1 (0.5)	18 (8.5)	186 (87.3)	
18. Proposing brands instead of generic drugs?	Amman	52 (10.9)	152 (31.9)	174 (36.6)	78 (16.4)	19 (4.0)	0.714
	Irbid	0 (0.0)	40 (18.9)	41 (19.3)	98 (46.2)	33 (15.6)	
19. Disclosing side effect of a drug to a patient?	Amman	68 (14.3)	165 (34.7)	130 (27.3)	77 (16.2)	36 (7.6)	0.299
	Irbid	8 (3.7)	94 (43.7)	64 (29.8)	42 (19.5)	7 (3.3)	
20. If a child has prescription for serious drug and has the money for paying it, do you dispense it to him?	Amman	22 (4.6)	104 (21.8)	127 (26.6)	131 (27.5)	93 (19.5)	0.000
	Irbid	4 (1.9)	61 (28.4)	22 (10.2)	54 (25.1)	74 (34.4)	
		Very highly Interested	**Interested**	**Neutral**	**Not interested**	**Not interested at all**	
21. If you just finished your work and on your way to your home, suddenly a patient called you for a help and advice, you will help the patient.	Amman	231 (48.2)	190 (39.7)	38 (7.9)	12 (2.5)	8 (1.7)	0.000
	Irbid	174 (82.1)	37 (17.5)	0 (0.0)	0 (0.0)	1 (0.5)	
22. Call a doctor if you noticed that there is something wrong in the prescription (about the name of drug for his indication or the dose) in front of the patient.	Amman	231 (48.2)	171 (35.7)	55 (11.5)	14 (2.9)	8 (1.7)	0.419
	Irbid	134 (63.2)	46 (21.7)	14 (6.6)	17 (8.0)	1 (0.5)	
23. If a patient asked you for a drug that you don't have now, and he wants it instantly, you refer the patient to another pharmacy that you know that it has this drug.	Amman	166 (34.7)	187 (39.1)	92 (19.2)	22 (4.6)	11 (2.3)	0.000
	Irbid	153 (72.2)	51 (24.0)	5 (2.4)	2 (0.9)	1 (0.5)	
24. If a patient asked you to tell him the lethal dose of certain drug, you will give him all the information he/she asked for.	Amman	112 (23.4)	78 (16.3)	99 (20.7)	84 (17.5)	106 (22.1)	0.000
	Irbid	7 (3.3)	27 (12.7)	13 (6.1)	41 (19.3)	124 (58.5)	

Perceived barriers for discussing ethical issues with patients

Barriers that limited pharmacists from discussing ethical issues with their patients included: lack of time (Amman 43.0%, Irbid 27.0%) and lack of reliable resources (Amman 15.0, Irbid 17.0%). Lack of ethical knowledge (such as lack of knowledge of basic Jordanian ethical standards), lack of skills in making ethical decisions (including the ability to identify the ethical problem), inability to identify the values or legal constraints involved in each scenario and inability to develop options for action were reported as other barriers by the participants preventing them from performing their role in this area (Figure 2).

Pharmacists reported that they mostly use the Internet as a resource to help them in resolving ethical issues concerning their patients (Amman 43.0% vs. Irbid 31.5%). This was followed by discussions with their peers and other health care professionals about the ethical issue (Amman 19.3% vs. Irbid 25.9%). Brochures designed by the Jordanian Pharmacists Association discussing ethical principles were also mentioned (Amman 15.5%, Irbid 15.7%). Few pharmacists referred back to written materials and books (Amman 9.5%, Irbid 5.1%; Figure 3).

DISCUSSION

To our knowledge, this is the first study conducted in Jordan to explore community pharmacists' attitude in relation to ethical pharmacy practice in the country. The study investigated pharmacists' attitudes towards applying the major ethical principles published by the Jordanian Pharmacists Association in the Jordanian Code of Ethics, including: beneficence, maleficence, autonomy and justice. With the influx of the Syrian refugees into Jordan, and the presence of high numbers of people from surrounding countries, a culture of diverse populations exists in Jordan.[17,26] The existence of a healthcare system based on a set of pre-identified and approved ethical principles is needed to address the different ethical issues arising.

Based on the pharmacy literature, five decision-making approaches are identified, including clinical, managerial, ethical, economical, and legal problem-solving approaches.[27,28] In an ethical decision-making approach,

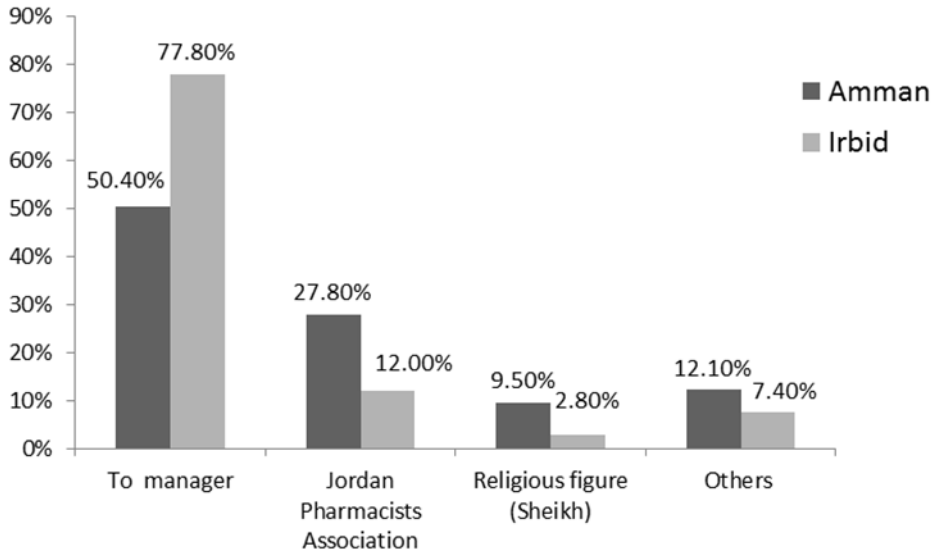

Figure 1. Proportion of pharmacists from Amman (n=486) and Irbid (n=218) choosing different organization/personnel to whom they refer ethical dilemmas

the main focus is achieving a morally defensible solution to the problem.[8,28] Using an economic decision-making approach, the goal is to maximize the cost-effectiveness with a solution that is most profitable or least costly, depending on the situation.[13,28] The legal approach to decision-making is straightforward, and simply involves taking actions that are deemed to be acceptable under the law.[13] Each approach uses a similar general process consisting of: identifying the problem and defining it, suggesting solutions, making a choice, and assessing the results of the choice.[28] The general process of the abovementioned methods differ in two main aspects: first, in how the problem is framed, and second, in the intended outcome of the decision.[27,28] In this study, a bioethical approach was the main ethical foundation used to understand the reasoning and behavior of Jordanian pharmacists; although it is important to acknowledge that in practice, all decision-making approaches may often overlap to determine a final decision.[28-30]

The scenarios used in this study were formulated according to established Code of Ethics. For example, the scenario about "proposing brands instead of generic drugs", represented the principle of respect for a patient's autonomy to select either of the drugs after informing patients of the available alternatives. The study revealed

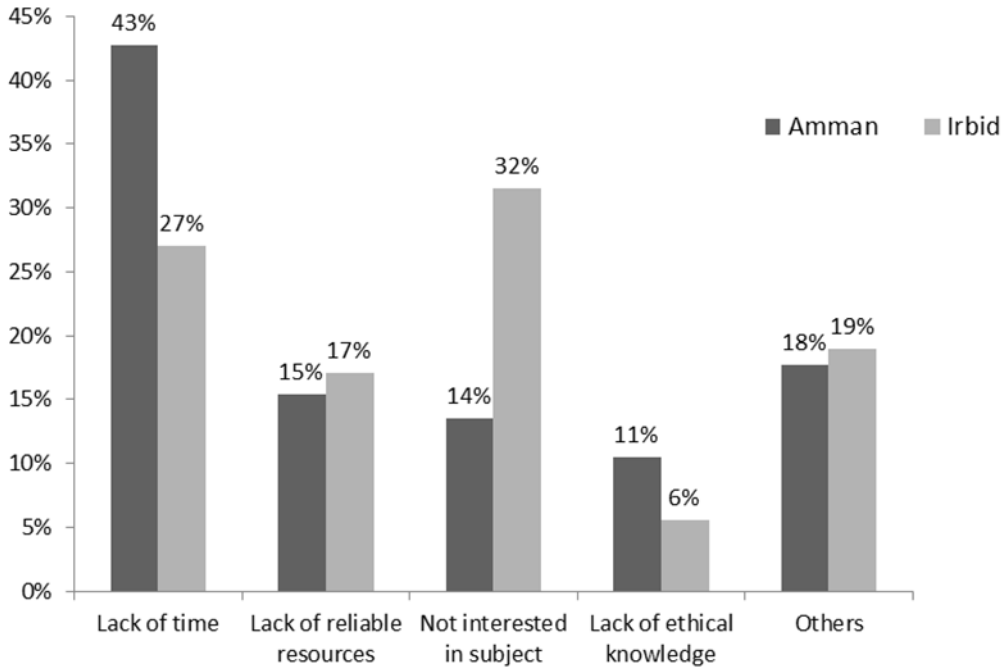

Figure 2. Pharmacists from Amman (n=486) and Irbid (n=218) reported barriers that limited their interaction with their patients regarding ethical dilemmas

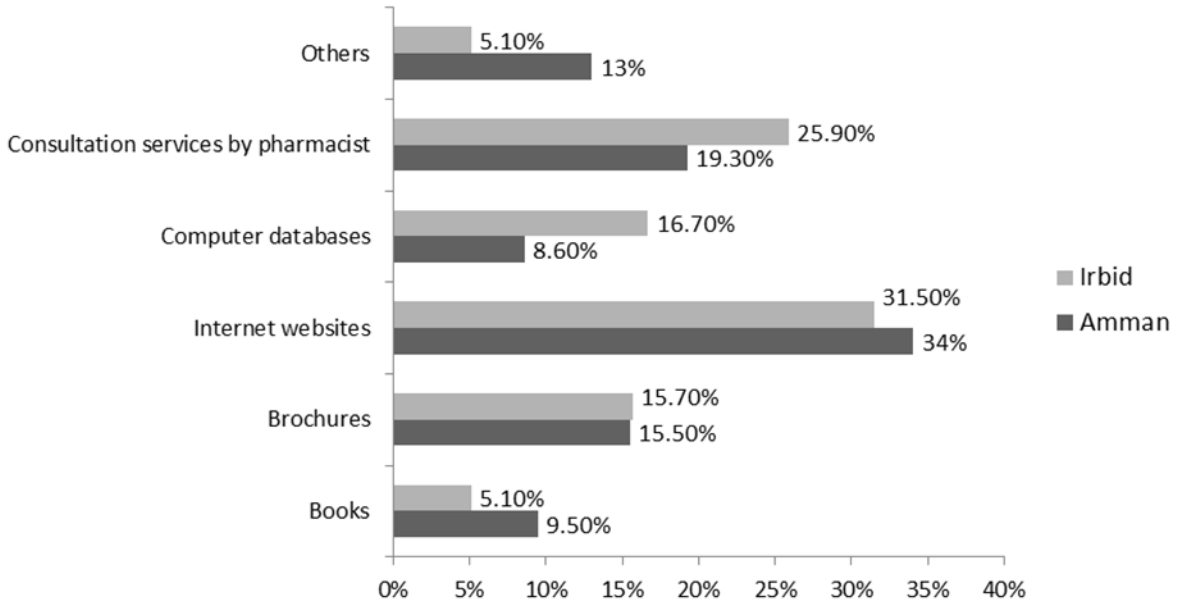

Figure 3. Resources referred to pharmacists from Amman (n=486) and Irbid (n=218) to help them with their interaction with their patients regarding ethical dilemmas

that not all pharmacists know enough about the Jordanian Code of Ethics. This was proven by the finding that only 66% of the study sample in Amman and 86% from Irbid self-reported having received education or training about Jordanian ethical practice in the past. The pharmacists did not follow the Code of Ethics when identifying resolutions for the ethical issues they faced during their work.

Results of this study are interesting and unique as they also compare the two biggest cities in Jordan, Amman- the most populated and busy capital, and Irbid, a representative of another large, less advanced city in the country. Results based on these two most populated cities in the country pave the way for policy makers to take the measures needed for community pharmacists to gain the best possible benefits from the Code of Ethics that exists in the country.

Interestingly for example, more pharmacists from Irbid (77.7%) declared that they would sell a medication for an unreported indication in the guidelines, if recommended by the consultant, compared to Amman (37.8%). Pharmacists from both cities reported a similar 'approving' attitude toward dispensing a generic drug if the prescription stated a specific brand name and it was out of stock. The availability of multinational products on the Jordanian medicine market, including international and national products, play a role here. As a result, this may lead to a number of ethical concerns. A study by Al-Arifi found that 31.0% of pharmacists would dispense a clinically equivalent medication when the pharmacy was out of stock of the brand stated in the prescription; comparable to 29.0% in another local study.[17,26]

Pharmacists' resources for information on ethics are important. More pharmacists from Amman reported having access to ethical information resources at their practice site compared to Irbid. Many pharmacists from both cities used the Internet as their source of ethical information when needed to help in dealing with their patients. The Jordanian Pharmacists Association has the 'Good Pharmacy Practice' booklet on its website, which contains some useful information on the topic. Anecdotal comments indicated that, this was unknown to many of the pharmacists. The Jordanian Ministry of Health has the 'pharmacy laws and regulations' published on its website. Other Internet resources contain international code of ethics. Pharmacists checked these websites looking for laws and regulations in order to decide on how they can deal with ethical dilemmas.

Pharmacists indicated that discussions with their peers and healthcare professionals was a useful resource they referred to, for resolving different ethical dilemmas, indicating positive shared decision making in the pharmacist-patient-doctor confidential therapeutic relationship. The least used resource was books about ethics in pharmacy. In the Al-Arifi study, it was also found that using books about ethics (37.7%) followed by Internet websites (31.1%) and brochures (26.8%), were the major resources used.

It is clear that accessibility of resources on ethics is an issue in Jordan, which is to be expected in a country with a pharmaceutical care system still under development. Providing pharmacists with reliable resources on ethics, and training them on how to use them is vital. Education on pharmacy ethics is not limited to the provision of theory about ethics, but also on training the pharmacists on where to find such information, and how to apply it, to make a suitable decision before making a recommendation and providing information to their patients.[11,17,31]

An updated code of ethics in the country is essential.[17] The current code of ethics in Jordan was established in 2008 by the Jordanian Pharmacists Association, to guide community pharmacists to deal with their patients and other healthcare professionals following good pharmacy practice.[4] These standards were set to achieve the ethical and professional practice needed to positively reflect the

professional image of the role of the pharmacist to patients and society at large.[4] It is important to note that these standards were not published on a large scale to be acknowledged by all pharmacists in the country. The Jordanian Pharmacists Association is the responsible body in the domain of pharmaceutical ethics, and hence should take the lead in this area. Having a well prepared, contemporary pharmacy code of ethics would support and protect healthcare professionals, and enhance the status of the profession and the healthcare system as a whole.[32] The existing code of ethics needs not only to be published broadly, but to be highlighted to the pharmacists through workshops conducted on the national level. Anecdotal comments from the participants indicated that such workshops would be helpful for them to learn about the different and most important ethical issues happening in the country, as lack of familiarity with the topic hinders their ability to easily specify such issues.

Pharmacy schools in the country have a role in this area as well. Courses on ethics with extensive focus on 'ethical dilemmas' identified in the country need to be introduced into the pharmacy curricula at the university undergraduate level.[24,33] Continuous professional development and educational programs would also be valuable.[17,31,34] In addition, a large scale study involving Jordanian pharmacists and the public is needed to assess pharmacist's familiarity and adherence to the Code of Ethics.

Findings from this study were similar to others with regards to the high number of pharmacists dispensing a doctor-prescribed drug in cases where the patient did not really need it. Other studies, including Al-Arifi, and Deans *et al*., reported similar findings.[17,26] In Saudi Arabia, around 43.0% of pharmacists admitted to selling an over-the-counter medication to a patient who does not really need it.[17] In the European countries, a lower proportion was reported; ranging from 13.0% in the UK to 17.7% in Croatia.[11,26] In a developing country, where making a living is not so easy for pharmacists, selling over-the-counter drug in the case where it is not really needed, or dispensing an alternative brand medication to a prescribed drug, is appealing. However, despite the influence of financial gain and economic burden, there should be a desire to respect the autonomy of the patient.[17]

Implementation of the local code of ethics and professional conduct is desired in all healthcare sectors, and in all of the cities in all countries.[35] However, differences in perceptions of pharmacy practice were found between the Jordanian cities in this study. Participants perceived an ethical dilemma when they were asked about disclosing to a mother information on contraceptive usage by a daughter. Such results were not surprising considering previous findings from Saudi Arabia, where the majority of the study respondents (69.2%) agreed to supply and disclose information regarding hormonal contraception when presented with a similar scenario.[17] In the United Kingdom, the situation was different, as only 21.0% of pharmacists agreed to supply/disclose information about hormonal contraception use.[36] Cultural and religion background differences may affect ethical decision making by pharmacists influencing their decision over whether or not to disclose information regarding hormonal contraception. Such differences between the countries are expected, but what was surprising in the findings reported in this study, the differences noted between the cities of the one country. Such outcomes deserve further investigation in future research.

Our findings highlighted a gap between actual professional practice and what pharmacists perceived as their ethical responsibilities. A set of barriers that limited pharmacists from discussing ethical issues with their patients was revealed for the first time. The reported barriers were similar across both cities, Amman and Irbid. Lack of time, lack of reliable resources, and lack of ethical knowledge were the most commonly identified barriers. These findings were consistent with the findings of previous studies.[8,14,28]

Study limitations included pharmacists answering to some of the scenarios presented in the questionnaire in such a way to show that they have high ethical and moral standards. In addition, using closed ended questions in the questionnaire could have implied that ethics in Jordan is about applying principles rather than about shared decision making in the pharmacist-patient-doctor confidential therapeutic relationship. Future studies can benefit from incorporating open-ended questions regarding shared decision making in ethics. This study assessed the attitude/perception toward certain scenarios but did not assess real practice and whether the pharmacists utilized the decision- making process following the principals of professional ethics found in the country. Another limitation is the absence of a direct question regarding the existence of the current Code of Ethics in the country and familiarity of the participants with it. Future studies should focus on assessing pharmacists' familiarity and compliance with the code of ethics set in the country.

CONCLUSIONS

Majority of participating pharmacists in Jordan reported receiving previous education on ethics concerning pharmacy practice. More pharmacists from Amman than Irbid have access to ethical information resources at their practice site. Important differences in attitude between pharmacists in Amman and Irbid were found, as, for example, more pharmacists from Amman agreed with dispensing a drug if the patient did not really need it compared to Irbid. The same finding was reported with selling an over-the-counter medication in the case of suspicion of drug abuse by the patient and with dispensing natural health products when their efficacy and safety have not been demonstrated by a regulatory authority.

Certain barriers that limited pharmacists from discussing ethical issues with their patients were identified. Lack of time and reliable resources were amongst the most important barriers identified. Jordanian Pharmacist Association should take the lead in conducting workshops to educate pharmacists from all cities in Jordan on the existing Code of Ethics and help them overcome the existing barriers. Results of this study are important and call onto the authorities and policy makers in the country to widely distribute the current pharmaceutical code of ethics and support its integration into the pharmacists' day to day practice.

CONFLICT OF INTEREST

No conflict of interest.

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Original Research

Perceptions in the community about the use of antibiotics without a prescription: Exploring ideas behind this practice

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Abstract

Objective: The use of antibiotics without prescription is common in Colombia as well as in other developing countries. The objective of this study is to explore the attitudes and motivations associated with the use of antibiotics without prescription.

Methods: Focus group sessions were held with residents of Bogotá. Different socioeconomic groups were approached to identify possible differences of opinion. A semi-structured interview guide was used to guide the discussion, with thematic analysis used to identify central themes.

Results: In total, 21 people, aged between 25 and 50 years participated in four focus groups. The results suggest that the use of antibiotics without prescription is common practice. The main reasons included barriers to access to prescribed medications due to limited health insurance. Even those with adequate access to health insurance report being willing to use a treatment without a prescription if they have confidence in its effectiveness. The relationship with the physician is important, but pharmacy storekeepers are also highly trusted. While some participants understood that antibiotics can cure infections but cause serious adverse events, several misconceptions about antibiotics therapy were identified. These included a lack of knowledge of resistance transmissibility among communities.

Conclusions: The results have implications for interventions aimed at reducing inappropriate use of antibiotics, highlighting i) how lack of access to timely care creates an incentive to self-prescribe, ii) the key role that pharmacy storekeepers play in the Colombian healthcare system and the need to include them in interventions, and iii) the misconceptions about inappropriate use of medications that need to be addressed by educational programs. These findings provide insights to other countries where antibiotics misuse is also a problem.

Keywords

Anti-Infective Agents; Self Medication; Prescription Drug Misuse; Health Knowledge, Attitudes, Practice; Pharmacists; Pharmacies; Focus Groups; Colombia

INTRODUCTION

The World Health Organization has identified bacterial resistance to antibiotics as a critical public health problem in many parts of the developed and developing world.[1] This health threat is growing quickly, in part because the inappropriate use of antibiotics leads to the loss of efficacy and compromises the ability of health personnel to treat common infectious diseases. Therefore, medical costs increase, hospital stays are prolonged, and mortality increases.[2] There is an urgent need to develop effective programs and interventions aimed at decreasing the inappropriate use of antibiotics.

Non-prescription use of antibiotics is a global problem that particularly affects developing countries, accounting for between 19% to 100% of antibiotic use in Nigeria and Sudan.[3] In many developing countries, access is available without a prescription from pharmacies, and antibiotics are commonly used in communities for nonbacterial diseases. For instance, in Colombia, antibiotics are available without prescription from community pharmacies.[4] Most community pharmacies are not run by professional pharmacists but by 'storekeepers' who have minimal training in pharmaceutical sciences. Although these storekeepers may have many years of experience managing the establishment and serving the community, the result is that antibiotics and other drugs are available in Colombia without oversight of a certified health professional. This is similar to the situation in many countries around the world (including 50% of countries in the Americas and 43% in Europe) where antimicrobials are freely available and regulations are not widely enforced.[5]

Ready access to antibiotics without a prescription is associated with an increase in antibiotic resistance, including outpatient use of antibiotics being correlated with Streptococcal resistance.[3,6] Previous studies have identified a number of factors associated with inappropriate use of antibiotics, including barriers of access to primary care such as cost or a shortage of providers, availability of antibiotics without a prescription, and lack of knowledge about the harms that can arise from the inappropriate use of

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antibiotics.[7-12] These studies highlight the importance of the structure of the healthcare system, norms of use among the population, and knowledge as key determinants in motivating the inappropriate use of antibiotics.

The purpose of this study is to explore the perceptions regarding the use of antibiotics without prescription in Bogotá, Colombia. A previous survey in Colombia identified that over 55% of the population reported using antibiotics without a prescription, citing delays and the time required to seek medical appointments, lack of economic resources, and problems getting leave from work as important factors.[13] This study extends that work by examining the motivations and attitudes toward the use of antibiotics without prescription. Focus groups with residents of Bogotá explored the interpersonal, environmental, and organizational factors influencing decisions about the use of antibiotics.

METHODS

Sampling and recruitment

Participants were from Bogotá, Colombia (population est. of 8 million).[14] Approximately 94% of the residents of Colombia has some access to health insurance.[15] Residents of Bogotá were purposely sampled to obtain diverse experiences and ideas about the use of antibiotics without prescription. Inclusion criteria were being adult (18 years old or older) and literate. To help ensure diversity in socioeconomic status, participants were recruited from different areas of Bogota, including public schools (low to medium socioeconomic levels) and private companies (medium to high socioeconomic levels). Participants' level of education and access to health services were assessed to ensure variability in the sample. Focus groups were held separately for participants from each area.

During the recruitment phase, people were informed about the methodology of the research, that their participation would be voluntary, and that they would receive 20,000 COP (USD 7) in gratitude for their time. There were between four and ten participants per focus group.

Study design

Focus groups sessions were carried out. The aim was to collect information on the factors related to the practice of self-medication to support future interventions.

During the project formulation, researchers spent eight months asking people in Bogotá about the use of antibiotics without prescription, and observing cases when people take antibiotics without prescription. Based on this, four topics of interest were selected:

- Ideas in the community about antibiotics.
- Characteristics of the use of antibiotics without prescription.
- Main motivations for this behavior.
- Potential interventions to avoid the practice.

A semi-structured interview guide was developed using previous literature and knowledge of the Colombian health care setting. Three literature searches targeting Colombian and international studies were conducted. The first searched for studies relating to situational factors influencing the decision to self-medicate with antibiotics (e.g., source of antibiotics, person who advised its use, symptoms of the patient, etc.) in Colombia. The second focused on studies from Colombia that explored the ideas, motivations, or reasons to self-medicate with antibiotics. And the third focused on international studies, including interventions aimed at reducing self-medication. A search strategy for each topic was defined in advance and conducted using Medline, Embase and Lilacs databases. The quality of the papers was assessed using STROBE Statement for Observational Studies and Consolidated Criteria for Reporting Qualitative Research (COREQ).[16,17]

Three relevant papers were found in the first search, two in the second, and a further nine in the third.[4,13,18-27] Some risks of information and selection bias were identified in these studies. The findings of literature review are summarized in Table 1. The semi-structured interview guide was developed and then revised in light of the feedback from an expert in qualitative research. Final version is in Online appendix 1.

The interview guide began by clarifying the concept of antibiotics for all participants; then, the use under prescription was mentioned, along with difficulties in accessing medical services. Next, the use of antibiotics without prescription was discussed and defined as the topic of interest for the conversation. After that, the discussion phase began.

Data collection

Four focus groups were conducted, including two at public schools and two in companies. The focus groups were conducted in Spanish—the participants' native language—by a member of the research team who is a pharmacist and had previous experience in conducting focus groups about the use of antibiotics in the community. Participants in the focus groups were informed that while the sessions would be audiotaped, their comments would be completely confidential and they may leave the session whenever they wished. The estimated duration of each focus group session was one hour. Written informed consent was read and signed by participants before starting.

The focus group sessions were conducted in a private room where the subjects were recruited for the study. Sessions were audiotaped and transcribed verbatim. These transcriptions were subsequently checked against the audios by the interviewer.

A constant comparison approach was used with researchers reviewing and thematically analyzing the transcripts at the end of each session. Data collection ended when the research team concluded that data saturation had been met for each of the different social groups.

Data analysis

Thematic analysis followed the framework method.[28] After becoming familiar with the audios and transcripts, two researchers independently coded data by using the QDA MINER LITE v 1.4.6 program. Transcripts were initially coded line by line, following the topics already identified in

Table 1. Literature review findings about self-medication.

Theme	Code	Findings	Reference
Ideas in the community about antibiotics	Effectiveness	Most people know that antibiotics work for infections.	[4]
	Risks	No study has asked people about this.	
	Resistance	No study has asked people about this.	
Characteristics of the use of antibiotics without prescription	Prevalence	56.1% have already self-medicated with antibiotics.	[13]
	Antibiotic	Amoxicillin, dicloxacillin and cephalexin.	[4,18]
	Symptoms	Respiratory, skin, urinary.	[4,13]
	Sources	Pharmacy, leftovers, shared with partners.	[13]
	Suggested by	Patient, pharmacy worker, relative, friend.	[4,13]
Main motivations for this behavior	Lack of resources	Time, money.	[4,13]
	Ideas	Medical appointment is not necessary: I already know what to take.	
	Health system	Delay in receiving attention.	
	Society	No permission to go to see a doctor. No medical insurance.	
Potential interventions to avoid the practice	Legislation to control antibiotics' sales	Already implemented in Brazil and Mexico.	[19–21]
	Education	Mixed evidence of effectiveness.	[22–24]
	Interventions in pharmacies	Effective.	[25,26]
	Prescriptions by other health professionals	Effective.	[27]

literature reviews (Table 1). The results of the two codifications were combined to obtain a single result. Any disagreement was resolved by consensus. These preliminary findings were analyzed by the research team. During this second discussion, existing codes were analyzed and further codes emerged from the data which could have not been predicted. Ideas mentioned by the participants that were novel in the study of this problem were identified. The final codification is in Table 2. Finally, data were charted into the framework matrix and analyzed by the authors.

Ethics approval

This research was approved by the ethics committee of the school of Sciences of the Universidad Nacional de Colombia on 2 May 2016.

RESULTS

Four focus groups were carried out between June and July 2016. In focus group #1 (FG#1), participants of low to middle socioeconomic level were reached in a public school. Focus group #2 (FG#2) was composed of participants of low socioeconomic level, recruited in another public school. Focus group #3 (FG#3) was intended to interview participants of middle socioeconomic level, workers in a public institution. Finally, focus group #4 (FG#4) included participants of high socioeconomic level who worked in a private company.

In total, 21 people aged between 25 and 50 years participated (four in FG#1, five in FG#2, four in FG#3, and eight in FG#4). Gender, occupation, and educational level of participants are shown in Table 3. All participants contributed to the discussions, and no participant expressed or exhibited discomfort or displeasure with the other participants, the interviewer, or the questions. Participation was rich and fluent throughout sessions. Each session lasted one hour except for FG#2, which lasted 80 minutes. During the recruitment phase, six people refused to participate, claiming time limitations. No participant withdrew during the sessions.

Ideas about antibiotics

A: Antibiotic therapy

Diverse ideas about antibiotic therapy where found among focus groups. Firstly, some participants throughout the conversation confused antibiotics with other medications, even though the concept was explained in advance. For example:

Table 2. Themes and codes for focus groups analysis.

Theme	Code
Ideas about antibiotics	A. Antibiotic therapy
	B. Effectiveness vs. safety
	C. Resistance
Self-medication experiences	A. Awareness and approval
	B. Associated symptoms
	C. Antibiotics known by the community
	D. Source of antibiotics
	E. Agent
Reasons to self-medicate	A. Problems related to health system
	B. Previous experiences
	C. Resources
	D. Society
	E. Factors that discourage self-medication
Possible interventions	A. Suggested by participants
	B. Suggested by interviewer

Table 3. Characteristics of the focus groups participants.

Code	Gender	Education	Occupation	Medical insurance*
FG1-1	Female	Post-graduate	Worker	Regular
FG1-2	Female	Technical	Housewife	Regular
FG1-3	Female	High school	Housewife	Regular
FG1-4	Female	High school	Housewife	Regular
FG2-1	Female	High school	Independent worker	Regular
FG2-2	Female	High school	Independent worker	Regular
FG2-3	Female	High school	Housewife	Regular
FG2-4	Female	High school	Worker	Regular
FG2-5	Female	High school	Independent worker	Regular
FG3-1	Female	Professional	Worker	Special
FG3-2	Female	Professional	Worker	Special
FG3-3	Female	Post-graduate	Worker	Special
FG3-4	Female	Professional	Worker	Regular
FG4-1	Male	Post-graduate	Worker	Special
FG4-2	Male	Post-graduate	Worker	Special
FG4-3	Female	Post-graduate	Worker	Special
FG4-4	Female	Post-graduate	Worker	Special
FG4-5	Female	Post-graduate	Worker	Special
FG4-6	Female	Post-graduate	Worker	Special
FG4-7	Female	Post-graduate	Worker	Special
FG4-8	Male	Post-graduate	Worker	Special

* To facilitate the analysis, participants were classified into two broad categories: Regular health insurance, with normal attention times and basic services; and special health insurance, with expedited access and extra services.

> FG2-1: "(my mom) had medication for the heart, for diabetes, for blood pressure, and my brothers had antibiotics for blood pressure."

> FG3-1: "I think I had used antibiotics, but maybe I'm ignorant. Is acetaminophen an antibiotic?"

However, others had a better idea about which drugs are antibiotics and their use:

> FG2-5: "…to treat infections, like tonsillitis or otitis."

> FG3-4: "Acetaminophen is not an antibiotic. Antibiotics are like amoxicillin."

Participants expressed different positions regarding the duration of the antibiotic therapy. Some people do not understand the need to complete a treatment course and others still have doubts:

> FG3-1: "Once I only gave half the treatment to my son. When I noticed he was fine, I suspended the antibiotic. Because I thought that the less medicine the better. Usually I do not complete the cycles that doctors say, that of eight days."

> FG4-3: "My grandmother used to say that you had to complete the cycle of an antibiotic treatment, otherwise it would not work for you. This is a doubt I'd like to clarify."

B: Effectiveness vs safety

When contrasting the ideas about effectiveness and safety, some participants identified antibiotics as powerful agents with the ability to heal fast:

> FG4-8: "Because I want something that relieves me quickly, I've said to the doctor: give me an antibiotic. Because the belief is that the antibiotic acts faster, it's more effective, much more powerful and then I'll last less time feeling sick."

> FG1-3: "Antibiotics work almost always."

At the same time, acknowledged the risks associated with antibiotics:

> FG1-4: "I have heard that the antibiotics are dangerous, that they affect body defenses and make you feel weak."

> FG4-7: "My family used to say that antibiotics were such a bad thing that they even affect the teeth."

This suggests that participants understood that antibiotics are a strong agents with the capability of healing and hurting at the same time. As one participant expressed it:

> FG2-2: "The antibiotic has a benefit, but at the same time can work against to you. (…) this [the antibiotic] is going to heal you, but also affects other parts of your body. For example, in the case of children, it can affect teeth, eyes, red blood cells…or at least that is what people use to say."

C: Resistance

In all groups, participants expressed some knowledge, even if vague or imprecise, about bacterial resistance. This is obtained through previous experiences, others' experiences, or people's comments.

> FG3-1: "I have not thought about this, but I have heard what people say. Bacteria become resistant—this is to say that suddenly they join together and become stronger and do not accept the antibiotic. Then, if you take the antibiotic, this is not going to work."

> FG4-1: "The doctor said that if we gave the antibiotics four or five times per year, our son would produce defenses against the antibiotics, and he would need a stronger one. If the boy gets used to the antibiotic, he would need a higher level."

When participants were asked about the seriousness of the antibiotic resistance problem, many expressed doubts. In addition, when the interviewer commented that resistance could be transmitted to others, participants showed surprise. Regarding this, participant FG2-5 said: "every day you learn something new".

Self-medication experiences

A: Awareness and approval

In all the focus groups, participants said that in Bogotá self-medication with antibiotics is commonly practiced, either by themselves or by acquaintances. However, in no focus group was it explicitly affirmed that this was a good practice; on the contrary, several comments suggested disapproval. For example:

> FG1-4: "My brothers use to self-medicate, but I do not like it. I rather prefer to go to the emergency room."

> FG4-5: "I want to teach my children to behave correctly. They do not know that I take antibiotics without prescription."

B: Symptoms associated with self-medication

According to participants' comments, self-medication with antibiotics is commonly used to treat respiratory diseases. For example:

> FG3-4: "Once my daughter had a sore throat. I looked for amoxicillin, I already knew that would work. She took three pills, and it was enough."

However, in the hypothetical case that they had urinary symptoms, participants would always prefer to see a doctor, an even wait or pay for a medical appointment. Participant FG3-3 said: "I would see a doctor in that case [urinary symptoms], because those are strange sensations."

C: Antibiotics known by the community

Amoxicillin was frequently mentioned during focus groups. Some participants used this medication to self-medicate:

> FG2-5: "I regularly self-medicate. I already know the symptoms. When I feel earache and fever, I take acetaminophen and amoxicillin for 7 days, 21 capsules."

> FG4-5: "When I have a sore throat, doctors always give me amoxicillin. I already know! Then, when I have the symptoms, I go to buy the same. It always works!"

Other antibiotics mentioned by more than one participant were ampicillin, penicillin, benzyl-penicillin, and trimethoprim. In some cases, these were mentioned when referring to self-medication experiences.

D: Source of antibiotics

Basically, two sources of antibiotics for self-medication were identified. The more common was the pharmacy:

> FG3-2: "If you are not close to a medical center, then, why do you have to go to a clinic? Better, let's go to the closest pharmacy. This is an alternative for you."

> FG4-5: "I have a pharmacy close to my house. They sell them [the antibiotics] to me without any kind of prescription."

The second source is leftovers:

> FG1-4: "I know a lady that was sick and I told her to visit the doctor. She answered that she had leftovers of a previous prescription. That she would take them because in the medical center she would receive the same drug."

> FG2-1: "You can keep some antibiotics for the next time."

In general, participants prefer their own leftovers over others'. The latter option was barely mentioned, and some suggested a disqualification of other's practices of sharing antibiotics with their partners. Online purchase of antibiotics was not mentioned.

E: Agent

The influence of the agent in the decision to take antibiotics was noticed. The agent is known as the person or entity that can make decisions on behalf of another, or that affect another, known as the principal, which in this case would be the patient. The agent-principal relationship that has been most studied in health has been that of the physician and patient, but there may be others, like pharmacy storekeeper-client. The pharmacy storekeeper is the person who serves people at the pharmacy.[29]

Pharmacy storekeepers were frequently mentioned as sources of medical information in the neighborhood. The advantages offered by the pharmacy worker are clear. Definitely, the attention in the drugstores is faster than in medical centers.

> FG1-2: "If I'm caring for a very sick person, but I have to wait many hours [to receive attention] and I notice that he has high fever and notorious symptoms, I get desperate, and leave the medical center. What should I do? Go to the pharmacy storekeeper."

In addition, the pharmacy storekeeper is usually a person known for years in the neighborhood, who is close to their neighbors and they trust him.

> FG1-1: "In my neighborhood, he [the pharmacy storekeeper] was the savior. (…) Anytime you have symptoms, you visit him and get an injection. (…) I think half the neighborhood had contact with antibiotics because of him."

> FG2-2: "I got to know him [the pharmacy storekeeper] because he is broadly known in the neighborhood. (…) If he recognizes that he cannot do anything, he tells patients to go see a doctor. (…) Other pharmacy storekeepers sell the most expensive medicines. The one that I know does not do that."

This person shows professionalism by looking into more about the disease and not prescribing hastily.

> FG2-1: "I like that he asks what I have taken before. No-one else asks me what I have taken before. (…)

> When I show up at the pharmacy, I tell him if I have taken an herbal tea or an acetaminophen. Then he already knows and can identify what I can take now."

Finally, the pharmacy worker has advantages in terms of the quality of the product offered.

> FG2-2: "While you go to the doctor and they give you the acetaminophen, he [the pharmacy storekeeper] changes the acetaminophen for an ibuprofen that works better. That is, while there [in the medical center], one is prescribed acetaminophen but he gives the option of taking something a little bit stronger, not generic."

Even participants with a higher education level or easy access to the medical service trust the pharmacy storekeeper:

> FG4-6: "They [pharmacy storekeepers] learn every day."

However, at this point, there was disagreement, since others argued that the training of professionals such as nurses was better. For example, participant FG3-4 said: "I prefer the nurse [over the pharmacy storekeeper] because he studied more."

Secondly, participants self-medicate with the same antibiotic that already worked to relieve the known symptoms. This is the case of participants FG2-5 and FG4-5, quoted in section 3.2 C, and the experience related by participant FG1-4 in section 3.2 D.

Other agents could be a relative or friend with previous experiences.

> FG2-2: "Your neighbor. Usually you tell her how you feel and she tells you what to take. Could be either your neighbor or your sister."

Finally, people do not trust websites to inform them about the use of antibiotics when they feel sick. Participant FG4-5 said: "According to my experience, searching online was not a good option (…) you are not certain about the sources."

Reasons to self-medicate

A: Problems related to the health system

Regarding reasons to self-medicate with antibiotics, there was a difference between social groups. Problems with access to the health system were referred to as the main cause by workers and housewives from the lower socioeconomic class (FG#1 and FG#2). These are their experiences:

> FG2-1: "They examine you and two hours later they attend to you. Then, they come back to you, examine you again, and ask you to wait again. I tell you this because this has happened to me. I have had to wait almost seven hours to receive attention. That's the reason I do not go to see a doctor."

> FG1-2: "If I go to the emergency room, people are completely gathered (…) and I have to wait hours and hours."

In addition, participants' previous experiences have created distrust in physicians, claiming that they only prescribe analgesics, the criteria between them are contradictory, and sometimes they show little interest in their patients:

> FG2-4: "You stay the whole day there [medical center] and only receive an acetaminophen."

> FG2-5: "[I visit] another doctor, and he says 'why did that other doctor prescribe you this?' And they start to contradict each other, and that has produced distrust in me. This makes me feel unconfident."

> FG2-3: "The drugs I received at the hospital did not work."

It is interesting that groups of people with better access to health services mentioned that if they did not have that possibility, they would self-medicate to avoid having to go to the regular medical service. When asked to suppose they did not have special medical insurance, participants of FG#4 argued:

> FG4-3: "I would go to a pharmacy and do whatever they told me to do."

> FG4-4: "And if dad was not doctor, I would show up at the pharmacy and do whatever they say. I would not stay in a line for 1000 hours."

B: Previous experience

Prior knowledge about the medicine that may work was a reason frequently mentioned by participants with preferential medical service (FG#3 and #4). This is the case of participant FG4-5 in section 3.2 C. Also, a participant of FG#3 said:

> FG3-2: "I considered that the symptoms were the same, and since I had been already prescribed this, and this worked the first time I bought it, in this case I would buy it again, because it was good and worked."

C: Resources

Regarding resources, participants of FG#1 mentioned that self-medication represents some economic savings. However, in FG#2, everybody agreed with participant FG2-1's preference for saving time:

> FG2-1: "If I'm going to spend $10.00 when I visit a doctor, here [in the pharmacy] I spend $20.00, but save time."

D: Society

The only factor related to society was mentioned by participant FG3-3. She answered that one reason to self-medicate with antibiotics would be having to work.

E: Factors that discourage self-medication

On the other hand, three factors that prevent the practice of self-medication with antibiotics were identified. To begin with, a base disease that represents a certain severity can

lead the person to be attentive to any symptom and look for immediate medical attention:

> FG1-2: "I have a heart problem. I cannot take anything without first seeing a doctor. Otherwise, I can aggravate my problem."

It was also found that those mothers who have experienced serious illnesses in their children in some cases become more aware of the risks associated with the misuse of drugs, and they avoid taking them without the prior recommendation of a physician.

Finally, several people in the different focus groups rejected self-medication for the children. Participant FG#2-5 said: "I self-medicate myself and my husband. But I don't do this with my children."

Possible interventions

A: Suggested by participants

When asked about possible interventions to address this situation, education was demanded in all focus groups:

> FG1-2: "There should be advertising to inform about the risks of taking or not taking it, why and what it works for."

> FG4-4: "People can receive education at work, which is the place where people spend most of their time."

Also, in all the focus groups, participants mentioned measures to definitely restrict the sale of antibiotics without prescription. However, some disagreed, arguing that it would be ineffective:

> FG1-2: "I think that it [getting antibiotics] would then become an illegal business. One way or another, people would get them."

Finally, participants of low socioeconomic status suggested improving access to health services. For example:

> FG2-5: "They should improve the medical attention. There is no other solution."

B: Alternative solutions suggested by interviewer

After hearing participants' suggestions, the interviewer suggested a couple of alternative interventions. The first was about having an official call center or website to receive advice on self-care from health professionals. Secondly, a fast service provided by other health professionals, but not doctors, in person and in the medical center was suggested. Neither of these options was well accepted by participants. They demanded a medical service provided by a doctor in person.

DISCUSSION

The objective of this study was to expand the understanding of the motivations, attitudes, and experiences related to antibiotics and their use without prescription in Colombia. The results suggest that access to antibiotics without prescription was widespread throughout pharmacies in Bogotá, in accordance with the findings of previous studies.[30] A primary reason for self-medication was a lack of access to prescribed medications due to difficulties to get health services. Even those with adequate access to health insurance report being willing to use a treatment without a prescription if they have confidence in its effectiveness. In addition, the results suggest that while the patient's relationship with the physicians is highly influential, pharmacy storekeepers have a special position in the community. Some participants reported that these storekeepers are more trusted that other trained health professionals, including medical doctors. Some participants even reported being reluctant to accept prescriptions provided by other professionals. The results also suggest there is a need for reliable information, including the duration of a treatment with antibiotics.

This study builds upon previous quantitative studies of antibiotic use in Colombia. [4,13,18] As in those studies, the results here suggest that the availability of antibiotics without a prescription and barriers to accessing primary care providers (including cost) are contributing factors to inappropriate use of antibiotics. This work extends the analysis by examining the motivations and attitudes toward the use of antibiotics without prescription, including the perceptions about pharmacy storekeepers and misconceptions about antibiotics and bacterial resistance.

The results are broadly consistent with the findings from previous studies. Health care access problems and relationship with doctors have been found in other studies as motivations for the non-prescription use.[8,9,31] In this study, participants of all social groups argued that medical appointments are delayed and that attention in the Emergency Room can take many hours. In addition, service provided by the doctors is insufficient and even negligent. They feel that neither the insurance companies, nor the doctors are really interested in their health.

This is consistent with the results from a study in the U.S. on Latino emigrants, where some new arrivals report dissatisfaction with the services provided by physicians who seem unwilling to help or discuss their diseases and treatment.[9] The emigrants considered that the need to have a medical prescription to buy a drug is just to enrich doctors. Latino adults frequently perceive that doctors want them to go for more than one visit just to earn more money, not for the patients' welfare.[31]

In addition, the important position of the pharmacy storekeeper found in this study is similar to the situation of other countries.[7,8] It has already been described how shopkeepers and drug sellers prescribe drugs, especially in societies with poor health care systems. Their 'recipes' are affordable. Another advantage is that they can also be purchased by a person representing the patient. For the patient, a prescription shows to his peers that he is sick and he is entitled to the privileges and functions reserved for the sick. If the doctor does not prescribe a drug, he will use other means to legitimize his illness.[32]

In the U.S., emigrant community can get antibiotics from small stores in Latino neighborhoods where ethnically consistent and some imported products are sold. The storekeepers are reliable sources of medical information, since they are respected among the community and also

longstanding.[7] They become reputable by the references provided via word-of-mouth, and emigrants have established a close relationship over years. Corner store clerks act also as lay pharmacists or nurses, providing advice about the required drug and required posology. Their advice is highly valuated by community, even more in the absence of a doctor.[8] This situation can take place even in developed countries.

The misperceptions about antibiotics identified in the focus groups is consistent with other studies which found that people expect drugs to be useful in solving their problems regardless of the therapeutic group.[32-35] The fact that some participants did not distinguish antibiotics from other drugs, even after the interviewer's explanation, raises the possibility that antibiotics might have acquired a symbolic role as being an effective treatment for ailments other than the appropriate conditions. That is, people may see antibiotics as a more tangible way to deal with a health issue than other types of treatments.[32-35] The perceived curative value separates antibiotics from other types of treatments that require medical supervision.

The results suggesting that people see antibiotics as effective for treating mild and common condition, like respiratory diseases, is consistent with the results from a study of Latino adults in Charleston, South Carolina. Participants in that study expressed a confidence in knowing how to treat uncomplicated illnesses, with visiting the doctor being reported as being excessive. Previous experiences with antibiotics are taken as reference to use the same antibiotic once again.[31] In this way, they are ignoring that the use of antibiotics in most of the mild and common conditions is unnecessary.[36-38]

The results from this study suggesting that parents would not administer non-prescribed antibiotics to their children are consistent with findings from a previous studies, including cross-sectional study in India that found 85.2% of parents reported not being willing to give leftovers of antibiotics to their children.[31,39] However, a study in Lebanon found that 58.4% of participants thought that administering non-prescribed antibiotics to children was correct.[40] It is unclear whether these differences are due to differing perceptions of the potential impact on children's health or resulting from a lack of access to primary care in some counties.

The understanding of antimicrobial resistance was vague among participants. They had doubts about seriousness of resistance, but at the same time, they could list a number of adverse effects related with the antibiotics. This is consistent with the results of a previous study in New Zealand where concerns about using antibiotics were related with toxicity rather than concerns about drug resistance.[11] Conversely, in Sweden, a country with relatively low rates of inappropriate antibiotic use, participants identified resistance as a health problem with terrible consequences even though it was very unlikely to affect them.[12] Future studies should examine whether an appropriate understanding of the dangers of resistance makes it less likely that people will inappropriately use antibiotics and the stability of those views in the face of barriers to access that exist in other countries.

The results have implications for the development of interventions aimed at reducing inappropriate use of antibiotics. While it has been noted that educational interventions on the use of antibiotics should consider the base knowledge of the audience for its development, the results here suggest these campaigns should also take into consideration the access issues that motivate much of this behavior.[24] These interventions might also include information about the transmissibility of bacterial resistance genes.[41] This concept relates with the individual responsibility of appropriately using antibiotics to avoid affecting members of the community, an issue that is even more complicated when the life is at risk.[12]

Global authorities leading actions to tackle antimicrobial resistance draw attention to interventions to control access to antibiotics in the community.[42] Although, plans have already been developed worldwide on this regard, some difficulties have been identified in these. For example, Mexico implemented programs to restrict the sale of antibiotics in pharmacies. This intervention was boycotted in the mass media by pharmacy owners affected by the measures. Additionally, people found ways to avoid the restrictions and continue to access antibiotics.[43,44] Restrictive access would not completely solve this problem.

The implementation of strong controls to avoid over-the-counter sales of antibiotics was suggested by participants and some people may support this action because the use of antibiotics without prescription is already considered an inappropriate action. However, pharmacy storekeepers and individuals engaged in this practice can find a way to evade any control. This suggests that these actors should be involved as part of the solution, not part of the problem.

Regarding health services, the declared barriers to access to medical attention contrast with the easy and convenient access to antibiotics. It is necessary to favor access to health services to reduce non-prescription antibiotic demand. In the UK and the USA, non-medical prescribing has been authorized to enhance patient access to treatments.[45,46] However, participants expressed disagreement with a measure like this. Appropriate training and the active promotion of capabilities of other health professionals is needed to implement alternative solutions.

On the other hand, former experiences in Mexico identified that education of the community is highly recommended when implementing measures to promote the use of antibiotics solely under prescription.[43] People need to be informed about the difference between viral and bacterial infections. Also, the uselessness of antibiotics needs to be clear. Didactic aids that correlate symptoms with viral disease evolution may prevent people from demanding antibiotics.

Given these findings and the understanding of antibiotic use without prescription, interventions can be designed. Future research can explore the effectiveness of such actions and how the previous knowledge about a public health problem actually supports the development of assertive actions.

The present study has several limitations. First, while the aim was to include participants from a wide range of socioeconomic backgrounds and conditions, the method of

selecting those participants (recruit at various locations) did not assure that there was adequate representation from many groups, including young people, the elderly, and marginalized groups. Thus, these results should be understood as representing the views of the participants in the study but not a thorough exploration of the views of the diverse populations that live in Colombia or even in Bogota. Additional studies are needed to identify how the views of other groups differ from those reported here.

Secondly, because participants were being asked to discuss a behavior – inappropriate use of antibiotics – with a research team, they might have been reluctant to express some views. This could have biased their comments in order to please the interviewer or the other participants. While confidentiality was granted from the beginning, and in all focus groups some participants admitted their bad practices related to antibiotics, future studies should consider other methodologies that might address this issue.

CONCLUSIONS

The study extends the knowledge of ideas in the community about inappropriate use of antibiotics, including the key role of pharmacy storekeepers. The results have implications for interventions aimed at reducing inappropriate use of antibiotics, highlighting i) how lack of access to timely care creates an incentive to self-prescribe, ii) the key role pharmacy storekeepers play in the Colombian healthcare system and the need to include them in interventions, and iii) the misconceptions about inappropriate use of medications that need to be addressed by educational programs.

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CONFLICT OF INTEREST

The authors state that they do not present any conflict of interests in the present investigation.

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Original Research

Communication skills in Brazilian pharmaceutical education: a documentary analysis

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Abstract

Objective: To characterize the inclusion of the teaching of communication skills in the curriculum of Pharmacy Schools of Federal Institutions of Higher Education.

Methods: An exploratory study of documental analysis of curriculum of Pharmacy Schools was carried out. A convenience sample was selected from undergraduate pharmacy courses of Federal Institutions of Higher Education (IFES). The variables collected were related to the identification of the course, its nature (elective or mandatory), workload, semester, and program content.

Results: Among the 49 undergraduate pharmacy courses of IFES, 35 (71.4%) had their curriculum available online. The teaching of communication in health was identified in 26 (74.3%) curriculum. In this study, three courses (7.2%) specifically aimed at teaching communication skills, while 39 (92.9%) had content related to this subject. Most courses (22; 52.4%) belonged to the field of Social, Behavioral, and Administrative Sciences. As for the course period, there was a concentration in the third (19%) and fourth (28.6%) years. The main content present in the curriculum was related to the principles and techniques of health communication (42.8%).

Conclusions: Data obtained enabled the identification of gaps in the curricula of undergraduate courses in pharmacy concerning the inclusion of the teaching of communication skills. These results can be used to reflect the current models adopted in Brazil for the teaching of this skills, especially after the recent publication of the new curricular guidelines for undergraduate pharmacy courses.

Keywords

Health Communication; Social Skills; Education, Pharmacy; Curriculum; Students, Pharmacy; Pharmacists; Brazil

INTRODUCTION

In the last decades, a "silent revolution" has provoked changes in the professional practice of pharmacists through the resignification of their work process, with a focus on patient care.[1-3] In order to guide this transition, the World Health Organization has published a document entitled "Preparing the Pharmacist of the Future: Curriculum Development," suggesting that the pharmacist should develop seven general competencies to carry out his or her activities, including communication.[4] In addition, The International Pharmaceutical Federation (FIP) in Nanjing Statements on Pharmacy and Pharmaceutical Science Education, the American Accreditation Council for Pharmacy Education and the European Union, recommends that Pharmacy students should gain skills in interpersonal communication.[5-7]

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According to Berger, communication can be conceptualized as the process of transmitting verbal (written or oral) or nonverbal information.[8] In many countries, the use of effective communication in the training of pharmacists leads to improvement in clinical outcomes and patient satisfaction, as well as promotion of interprofessional relationships.[9-14] This improvement requires the restructuring of educational processes, going beyond technical knowledge, and contemplating clinical communication, i.e. with the patient, family, and health team.[2,15-16]

In the United States of America (USA), since the 1970s, it has been recommended to include knowledge related to the social and behavioral sciences in the pharmacist training process.[17-20] In 2001, about 75% of the USA universities introduced the teaching of communication skills in their courses.[21] Furthermore, studies highlight investments in research, curricular changes, the use of new teaching techniques, and the creation of laboratories for teaching communication in the USA.[10,22-26] In Europe, however, less curricular emphasis in the social and behavioral sciences may result in deficiencies in pharmacists' clinical training, inhibiting effective communication between pharmacists and patients.[26]

In Brazil, until the beginning of the 2000s, the Pharmacy curriculum was focused on the basic and natural sciences.[27,28] The first guidelines to facilitate training for patient care and the addition of content that included the field of human and social sciences were published at 2002. This curriculum contemplates a minimum workload of 4,000 hours and five years of training. The general training allows the egress to work in the areas of drugs and

medicines, clinical and toxicological analyzes and control, and food production and analysis.[29] Although the Brazilian curricular guidelines emphasize that undergraduate courses in pharmacy should teach content from the human and social sciences, the literature emphasizes that the quality of the communication of Brazilian pharmacists is still ineffective and is often considered "invisible" to patients.[2,29-33]

The teaching of communication skills in Brazil was highlighted by the publication of recent professional legislation with emphasis on patient care, such as Resolutions nº 585 e nº 586 of the Federal Council of Pharmacy, which regulated the clinical attributions of the pharmacist and pharmaceutical prescription. This situation has also triggered the publication of new curricular guidelines, with emphasis on the healthcare, which should correspond to 50% of the hours of training of the pharmacist.[34]

Although Brazilian literature on this subject is scarce, studies recommend changes in the training of pharmacists with the addition of new courses, contents and teaching methodologies related to health communication.[35-39] However, there are no studies published that confirm the implementation of these contents in Brazilian undergraduate curricula in pharmacy. Under this perspective, the objective of this study was to identify and characterize the inclusion of the teaching of communication skills in the curriculum of Pharmacy Schools of Brazilian Federal Institutions of Higher Education.

METHODS

An exploratory study of documental analysis of Brazilian undergraduate pharmacy curriculum was carried out between March and June 2017. There were more than 500 Schools of Pharmacy (publics and privates) in Brazil, however this study included only Schools of Pharmacy from Federal Institutions of Higher Education (FIHE). According to the Brazilian Ministry of Education, FIHE have to available the curriculum on their own electronic page. This curriculum incorporates academic content, workload and years of training of specifics courses.[40]

List of Pharmacy Schools of FIHE were identified in January 2017, through the website http://emec.mec.gov.br/, of the National Institute of Educational Studies and Research Anisio Teixeira (INEP). Schools of Pharmacy of FIHE that provided complete curriculum on the website were included in this study. Data extraction was performed by two researchers independently and data consistency was verified by a third researcher. The collected variables were course denomination, nature (elective or mandatory), workload, semester, and academic content.[21,41-42]

The courses identified in the curriculum were initially classified into two categories: i) specific course for the teaching of communication skills; ii) course with contents related to the teaching of communication skills. Then, the courses were categorized by the researchers in three main areas, according Nunes-da-Cunha *et al.*: a) Social, Behavioral, and Administrative Sciences; b) Clinical Sciences; and c) Basic/Other Sciences.[27]

Finally, the contents related to the teaching of communication skills were analyzed and grouped according to similarity. Before this step, the researchers discussed about the terminology used to ensure consistency. The results obtained from the collection and categorization were represented by descriptive statistics with the presentation in absolute and relative frequency.

RESULTS

Among the 49 courses of the Federal Institutions of Higher Education, 35 (71.4%) had their curricular matrices available online. The teaching of health communication was identified in 26 (74.3%) curricular matrices. Ten (25.7%) curricular matrices did not present content related to this theme. There were 42 courses, among which three (7.2%) were specifically aimed at teaching communication skills and 39 (92.9%) had content related to this subject. The disciplines' profile is described in Table 1.

When grouping the disciplines according to the areas of knowledge, it was observed that most (22; 52.4%) belonged

Table 1. Courses' profile identified in curriculum of Pharmacy courses of Brazilian Federal Institutions of Higher Education, 2017.

	Courses specifically aimed at teaching communication skills	Courses with content to teaching communication skills	Total N (%)
Nature [n(%)]			
Mandatory	-	31 (73.8%)	31 (73.8)
Elective	03 (7.2%)	08 (19.0%)	11 (26.2)
Semester [n(%)]			
1st year	-	04 (9.5%)	04 (9.5%)
2nd year	-	04 (9.5%)	04 (9.5%)
3rd year	-	08 (19.0%)	08 (19.0%)
4th year	-	12 (28.6%)	12 (28.6%)
5th year	-	02 (4.8%)	02 (4.8%)
Undefined	03 (7.2%)	09 (21.4)	12 (28.6%)
Workload [n(%)]			
< 30 hours	-	01 (2.4%)	01 (2.4%)
30-59 hours	01 (2.4%)	24 (57.1%)	25 (59.5%)
≥ 60 hours	02 (4.8%)	13 (31.0%)	15 (35.8%)
Not described	-	01 (2.4%)	01 (2.4%)
Category			
Social, Behavioral and Administrative Sciences Administrativas	03 (7.1%)	19 (45.2%)	22 (52.4%)
Clinical Sciences	-	20 (47.6%)	20 (47.6%)

Table 2. Contents related to the teaching of communication skills identified in the curriculum of Pharmacy courses of Brazilian Federal Institutions of Higher Education, 2017.

Category	Description	N (%)
Principles and techniques of communication	It comprises the teaching of conceptual aspects, principles and communication techniques, as well as syllabus that use generic terms to refer to health communication.	18 (42.8%)
Communication with patients and their families	It comprises specific aspects of communication between pharmacists and patients or their relatives	16 (38.1%)
Interprofessional communication	It comprises specific aspects of communication between Pharmacists and other health professionals	12 (28.6%)
General Principles of Human Relationships	It comprises general aspects of the interpersonal relation and interferences of the psychosocial factors in the human relations	5 (11.9%)

to the field of Social, Behavioral and Administrative Sciences, while 20 (47.6%) belonged to the Clinical Sciences. None of these belonged to the field of Basic Sciences. (Table 1).

From the analysis of the content present in the syllabus, four categories emerged: i) Principles and techniques of communication (18, 42,8%); ii) Communication with patients and their families (16, 38,1%); iii) Interprofessional communication (12, 28,6%); and iv) General Principles of Human Relationships (5, 11,9%) (Table 2).

DISCUSSION

The teaching of communication skills in Brazilian Pharmacy courses is essential to improve the performance of the pharmacist in healthcare, especially after the Brazilian Federal Pharmacy Council regulated their clinical activities.[43] However data obtained enabled the identification of gaps in the curricula of undergraduate courses in pharmacy concerning the inclusion of the teaching of communication skills. In particular 25.7% of the curriculum did not mention communication teaching at any point in the training. Failures in the communication process undermine the quality of pharmaceutical guidance and have generally been associated with the curriculum structure.[44] Such gaps need to be filled, since communication skills do not necessarily improve with professional practice experience, and must be taught during the training process.[45,46]

The communication contents identified in this study were mostly inserted in non-specific and mandatory courses for the teaching of communication. The fact that the subjects are mandatory makes it possible for all students to have access to the teaching of communication, especially since it is an essential skill for all pharmacists' work fields. However, the inclusion of communication could not be characterized as a transversal component, since it was identified as an isolated topic of clinical, behavioral, administrative, and social sciences. The literature has emphasized that the teaching of communication in undergraduate courses in pharmacy in the United States and Canada has occurred both through specific courses for this purpose and by inclusion in other undergraduate courses.[21,41-42] Therefore, it is worth emphasizing that the teaching of communication should not be restricted to specific disciplines, but rather integrated into the learning objectives of other clinical and social sciences courses.

Another point to be highlighted is that communication contents have appeared more frequently since the third and fourth year, when courses related to pharmaceutical care generally begin. A study by Svensberg *et al*., when mapping the teaching of communication skills in pharmacy courses of universities in Nordic countries, also verified that the teaching was not distributed throughout training, but predominantly in the last years.[47] Kimberling found that in the United States, when the teaching of communication skills was restricted to the first two years of the course, there were no training and assessments in the subsequent years to reinforce this ability.[41] On the other hand, when the instructions were given in the third year of the course, teachers felt the need for the training to be carried out earlier to avoid a consolidation of bad communication habits.

Transversality and interdisciplinarity of the teaching of communication skills considers that the contents and learning objectives are included in at different times during the course, allowing the teaching to be carried out in an articulated way, with progression of the complexity of the activities and the competence to be developed by the student.[10,48] Moreover, the sooner the evaluation process is started, the faster the students' weaknesses will be identified, enabling universities to develop strategies to overcome them.[21,42,49] Thus, as well as to synthesize a compound it is necessary in the first years to learn to know the molecular groups, in the training of social skills it is also advantageous to have a progression to consolidate the desired behaviors.

Among the contents identified in the curriculum, it was observed that there was no uniformity among the subjects to be approached in the disciplines. In addition, generic terms were used more often to refer to the content addressed, making it difficult to classify the categories that emerged in this study. Despite the national and international recommendations for inclusion of communication in pharmacy undergraduate curricula, there are no frameworks or consensus aimed at guiding this teaching-learning process through the presentation of contents and teaching strategies and evaluation of communication skills. On the other hand, medical education literature presents several well-defined models.[50-54] In considering this problem, Bachmann *et al*. made an important contribution to the curricula of undergraduate health courses by proposing the Health Professions Core Communication Curriculum, a list of learning objectives for communication skills. In the absence of specific frameworks or guidelines to aid the teaching process of pharmaceutical-patient communication, this list, after adapting the needs of the profession, can be used as a reference in the implementation or restructuring of the

curricular contents of undergraduate courses in pharmacy.[55]

This study had strengths and limitations. In relation to the strengths, this study consists in the first characterization of the inclusion of the teaching of communication skills in Brazil. These results can be used to reflect the current models adopted for the teaching of this set of skills, especially after the recent publication of the new curricular guidelines for undergraduate pharmacy courses in Brazil, which recommend that the "health care" axis should correspond to 50% of the training time of the pharmacist.[34]

The first limitation is the possibility that the curriculum do not represent the content covered in the course, the information for which is described in more detail in the syllabus contents. In addition, teaching methods, and student outcomes have not been studied, so the true teaching potential of skills is unknown.

CONCLUSIONS

This study made possible to identify gaps in pharmacy undergraduate curricula regarding the inclusion of communication skills, which occurred in a specific way in clinical, social, behavioral, and administrative subjects with a concentration in the third and fourth years of the course. Good communication skills are essential to helping patients use medicines properly. The inclusion of communication skills teaching in Pharmacy Schools is important to improve the relationships between pharmacists and patients, family members and other health professionals. It is important to highlight the need for further studies that can evaluate the curriculum in its real and hidden dimensions, identifying the teaching and assessment strategies used as well as the hours and practical experiences that contribute to this training.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest to disclose.

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Original Research

Prevalence of pain and treatment outcomes among cancer patients in a Malaysian palliative care unit

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Abstract

Background: Pain remains one of the most common and debilitating symptoms of advanced cancer. To date, there is a lack of studies on pain and its treatment among Malaysian palliative care patients.

Objective: This study aimed to explore the prevalence of pain and its treatment outcomes among adult cancer patients admitted to a palliative care unit in Sabah, Malaysia.

Methods: Of 327 patients screened (01/09/15-31/12/17), 151 patients with assessed self-reported pain scores based on the numerical rating scale of 0-10 (current, worst and least pain within the past 24 hours) upon admission (baseline), 24, 48 and 72 hours post-admission and discharge were included. Pain severity and pain score reductions were analysed among those who experienced pain upon admission or in the past 24 hours. Treatment adequacy was measured by the Pain Management Index (PMI) among discharged patients. The PMI was constructed upon worst scores categorised as 0 (no pain), 1 (1-4, mild pain), 2 (5-6, moderate pain), or 3 (7-10, severe pain) which is then subtracted from the most potent level of prescribed analgesic drug scored as 0 (no analgesia), 1 (non-opioid), 2 (weak opioid) or 3 (strong opioid). PMI≥0 indicated adequate treatment.

Results: Upon admission, 61.1% [95%CI 0.54:0.69] of 151 patients presented with pain. Of 123 patients who experienced pain upon admission or in the past 24 hours, 82.1% had moderate to severe worst pain. Throughout patients' ward stay until discharge, there was an increased prescribing of analgesics and adjuvants compared to baseline, excluding weak opioids, with strong opioids as the mainstay treatment. For all pain score types (current, worst and least pain within the past 24 hours), means decreased at each time point (24, 48 and 72 hours post-admission and discharge) from baseline, with a significant decrease at 24 hours post-admission ($p<0.001$). Upon discharge (n=100), treatment adequacy significantly improved (PMI≥0 100% versus 68% upon admission, $p<0.001$).

Conclusions: Accounting for pain's dynamic nature, there was a high prevalence of pain among cancer patients in the palliative care unit. Continuous efforts incorporating comprehensive pain assessments, evidence-based treatments and patient education are necessary to provide adequate pain relief and end-of-life comfort care.

Keywords

Pain; Pain Management; Pain Measurement; Prevalence; Palliative Care; Terminal Care; Treatment Outcome; Analgesics, Opioid; Analgesics, Non-Narcotic; Patient Reported Outcome Measures; Malaysia

INTRODUCTION

Pain remains one of the most common and debilitating symptoms of advanced cancer. In a recent systematic review and meta-analysis, the pooled prevalence of cancer pain was 50.7% in all cancer stages and 66.4% in with advanced, metastatic or terminal disease.[1] Among advanced (stage 4) cancer patients, 40% to 50% experienced moderate to severe pain and 25% to 30% experienced severe pain.[2]

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Despite being such a distressing symptom, cancer pain management remains a challenge. In an updated systematic review, the prevalence of undertreatment measured by the Pain Management Index (PMI) improved from 43.4% (1994-2006) to 31.8% (2007-2013). The systematic review also revealed that approximately one third of cancer patients were still inadequately managed for pain.[3] The PMI was first developed in 1994 by Cleeland *et al*. and is a well-validated method of assessing the adequacy of pain control for cancer patients based on the World Health Organization (WHO) guidelines.[4,5] Pain management is considered adequate if the prescribed analgesic therapy is appropriate for the patient's reported level of pain.[4]

Palliative care is an approach to provide optimal management of distressing symptoms and psychosocial support with the aim to reduce suffering and support the best quality of life for patients regardless of the disease stage or need for other therapies.[6] In Malaysia, palliative medicine is a developing discipline and has been a subspecialty in the Ministry of Health since 2005.[7] The first palliative care service was started in 1991 by a nongovernmental organization.[7] The palliative care unit, Queen Elizabeth Hospital, Sabah was the first inpatient unit in the country to be set up in 1995.[8] In 1998, the Palliative

Care Association (PCA) Kota Kinabalu, a nongovernmental organisation was established to provide home care services and to this day works closely with the palliative care unit.[8]

To date, as there is no published study of pain prevalence and its management among cancer patients in a Malaysian inpatient palliative care setting, it is unknown whether patients presenting with pain upon admission are treated adequately throughout their ward stay and upon discharge. Therefore, this study aimed to explore the prevalence of pain and its treatment outcomes among cancer patients in our setting. The findings of this study will serve to raise awareness among multidisciplinary healthcare professionals about pain and its treatment adequacy among palliative care cancer patients from the point of presentation to the point of discharge, and thus may provide greater insights on optimising pain relief and patient care.

METHODS

Study design and participants

This prospective observational cohort study was conducted from September 2015 to December 2017 in the palliative care unit, Queen Elizabeth Hospital, Sabah, Malaysia. Patients aged 18 years and above admitted to the ward with a diagnosis of cancer and able to communicate a pain score were included by convenience sampling. Exclusion criteria included non-cancer patients, patients that were unable to score, patients that developed pain during their ward stay and patients with brain cancer or brain metastases. Patients with brain cancer or brain metastases were excluded as some of these patients may have cognitive impairment or are unable to give reliable pain scores.

All clinical and demographic data were collected from the medical records. Patients' levels of functioning were measured by the Eastern Cooperative Oncology Group (ECOG) Scale of Performance Status.[9] The ECOG Performance status scales and criteria are used to assess patients' disease progression and how the disease affects their daily living abilities. Upon admission to the ward and throughout ward stay, a comprehensive pain assessment was carried out by a multidisciplinary team of clinicians, nurses and a clinical pharmacist using a pain assessment guide (Online appendix 1) incorporating the mnemonic PQRST (P = Provocation/Palliation; Q = Quality; R = Region/ Radiation; S = Severity; T = Timing) in both English and the local language (Sabah Malay).[10-12] To achieve consistency, both guides were written in a similar context and therefore allowed the clinicians to translate the patient's description of pain from Sabah Malay to English for the purpose of analysis. Self-reported pain severity was assessed using the numerical rating scale with a score of 0 being no pain and 10 being the worst pain experienced. Patients that experienced pain were defined as those who had scores of more than 0. Pain scores were then classified based on the approach described by Serlin *et al*. in which scores of 1-4, 5-6 and 7-10 corresponded to mild pain, moderate pain and severe pain, respectively.[13] At the point of admission, three types of pain scores (current pain, worst and least pain in the last 24 hours) were assessed as adapted from the Brief Pain Inventory.[14] The three types of pain scores were also documented at 24, 48 and 72 hours post-admission and upon discharge. The proposed clinical audit indicators for quality management in the national Management of Cancer Pain Clinical Practice Guidelines include the percentage of patients presenting with cancer pain whose pain is satisfactorily controlled within 72 hours.[12] To achieve optimal pain relief, dosage titration of a strong opioid is based on the total opioid dose (scheduled and as needed) taken in the previous 24 hours.[15] As our patients usually require a strong opioid, our study team decided that 72 hours was a reasonable time frame to evaluate the trend of patients' pain scores.

Baseline pain-related variables and treatment outcomes

Patients that fulfilled the inclusion criteria were included in the primary analysis of the prevalence of pain. Secondary analyses were performed among patients who experienced pain either upon admission or within the past 24 hours in which baseline pain-related variables and treatment outcomes were reported. Pain-related variables such as the cause of pain (cancer, treatment or unrelated to cancer/ treatment), number of pain locations, classifications such as acute or chronic (more than 3 months), continuous or intermittent pain and the inferred pathophysiology (nociceptive somatic, nociceptive visceral, neuropathic) were assessed by the clinicians.

Treatment outcomes included the usage of analgesic treatments, the reduction in pain scores means from admission (baseline) until discharge and the comparison of treatment adequacy between baseline and upon discharge. Data of analgesic treatments prior to admission, during ward stay and upon discharge were collected. All strong opioid doses were converted to the morphine equivalent daily dose (MEDD) based on the conversions in the Palliative Care Formulary.[16] The MEDD measures the relative potencies of opioids in comparison to morphine and is useful in determining the new opioid dosage during opioid rotation.[16] Treatment adequacy was defined by the PMI. The index was constructed upon the patient's level of worst pain in the last 24 hours categorized as 0 (no pain), 1 (1–4, mild pain), 2 (5–6, moderate pain), or 3 (7–10, severe pain). To compute the index, the pain level is then subtracted from the most potent level of prescribed analgesic treatment categorised as 0 (no analgesic drug), 1 (non-opioid), 2 (a weak opioid) or 3 (a strong opioid). Ranging from -3 (no analgesic drug prescribed for a patient with severe pain) to +3 (strong opioids prescribed for a patient with no pain), scores of 0 and higher indicated acceptable treatment.[17] Based on standard clinical practice, all patients were counselled on the indication, method of administration and possible side-effects of a strong opioid prior to its initiation by the clinicians and clinical pharmacist.

Ethics approval

This study was approved by the Malaysian Ministry of Health Medical Research and Ethics Committee (NMRR-15-615-25257).

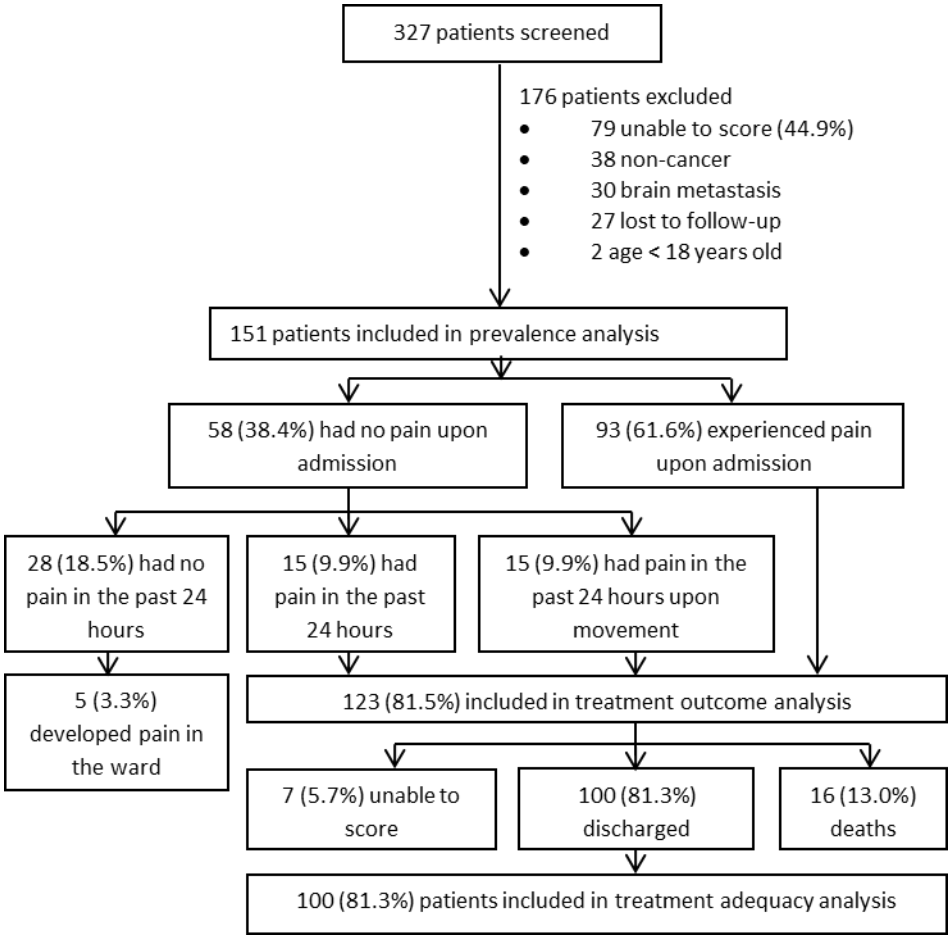

Figure 1. Overview of the study population from screening to discharge

Statistical Analysis

To determine the study's primary objective of pain prevalence, 151 patients were required to achieve 5% of precision in estimating prevalence which may be about 89% based on unpublished data.[14] Demographic data, clinical characteristics and pain-related variables were presented using frequencies with percentages for categorical variables and using means with standard deviation (SD) or median with interquartile range (IQR) for numerical variables. Pairwise comparisons of the proportion of patients who were adequately treated among patients who were discharged were performed using the McNemar test. For each type of pain score, the pain score means over time were compared using single-factor repeated-measures ANOVA with Box's conservative correction factor. The marginal pain score means at each time point were estimated with 95% confidence interval. Pairwise comparison of means pain score were made using Tukey's multiple comparison procedure and only those pairs with significant difference were presented. All statistical differences were two-tailed, with an alpha set at 0.05. Statistical analyses were carried out by using STATA 15.1 software (StataCorp 2017. Stata Statistical Software Release 15. College Station, TX: StataCorp LLC).

RESULTS

Of 327 patients screened, 151 patients were included in the prevalence analysis (Figure 1). Basic demographics are shown in Online appendix 2. Mean (SD) age was 57.1(13.5). The study population was well balanced in terms of gender and highly multi-ethnic, consisting predominantly of Chinese (31.8%), Kadazan-Dusun (28.5%) and other local ethnicities (29.8%). Local ethnicities include the Bajau, Sino (mixed heritage of Chinese and other local ethnicities), Brunei, Suluk, Murut, Rungus, Bugis, Kedayan, and Bisaya patients. A large proportion of patients (91.4%) did not obtain any tertiary education. Almost half of the admissions were new referrals and more than a third were already under PCA Home Care Program.

Most patients had a functional status of ECOG Performance Status 2 and 3, followed by ECOG 1 and 4 (Table 1). The most common cancers types were gastrointestinal consisting of colon-rectum, stomach and esophageal cancers (24.5%), followed by gynaecological consisting of uterus and cervical cancers (15.2%), breast (14.6%), lung (12.6%), head and neck (9.9%), genitourinary consisting of bladder and prostate cancers (7.3%) and liver (7.3%). A high percentage of patients (76.2%) were metastatic with liver, lung and bone being the most common sites. Pain was the most common reason of admission, followed by shortness of breath, family empowerment and others. Other clinical demographics are presented in Table 1. At discharge, median (IQR) of duration of ward stay was 86 (96.1) hours.

Table 1. Clinical Demographics of study participants

Clinical Characteristics	Overall n (%) (n=151)	No pain in the past 24 hours n (%) (n=28)	Pain in the past 24 hours n (%) (n=123)
ECOG[a] Performance Status			
1	20 (13.2)	5 (17.9)	15 (12.2)
2	62 (41.1)	54 (43.9)	8 (28.6)
3	58 (38.4)	44 (35.8)	14 (50.0)
4	11 (7.3)	1 (3.6)	10 (8.1)
Cancer type			
Gastrointestinal	37 (24.5)	6 (21.4)	31 (25.2)
Colon-rectum	19 (12.6)	2 (7.1)	17 (13.8)
Stomach	15 (9.9)	3 (10.7)	12 (9.8)
Esophageal	3 (2.0)	1 (3.6)	2 (1.6)
Gynaecological			
Uterus, cervical	23 (15.2)	2 (8.7)	21 (17.1)
Breast	22 (14.6)	7 (25.0)	15 (12.2)
Lung	19 (12.6)	3 (10.7)	16 (13.0)
Head and neck	15 (9.9)	1 (3.6)	14 (11.4)
Liver	11(7.3)	3 (10.7)	8 (6.5)
Genitourinary	11 (7.3)	2 (7.1)	9 (7.3)
Bladder	6 (4.0)	1 (3.6)	5 (4.1)
Prostate	5 (3.3)	1 (3.6)	4 (3.3)
Bone	5 (3.3)	1 (3.6)	4 (3.3)
Pancreas	4 (2.6)	1 (3.6)	3 (2.4)
Connective tissue (Sarcoma)	3 (2.0)	0 (0.0)	3 (2.4)
Skin (Melanoma)	2 (1.3)	1 (3.6)	1 (0.8)
Leukemia, lymphoma	2 (1.3)	1 (3.6)	1 (0.8)
Periampulary	1 (0.7)	1 (3.6)	0 (0.0)
Metastatic	115 (76.2)	17 (60.7)	98 (79.7)
Liver	52 (34.4)	10 (19.2)	42 (34.1)
Lung	44 (29.1)	7 (25.0)	37 (30.1)
Bone	35 (23.2)	5 (17.9)	30 (24.4)
Lymph node	28 (18.5)	4 (14.3)	24 (19.5)
Others	22 (14.6)	3 (10.7)	19 (15.4)
Spine	16 (10.6)	1 (3.6)	15 (12.2)
Peritoneum	10 (6.6)	0 (0.0)	10 (8.1)
Bladder	7 (4.6)	0 (0.0)	7 (5.7)
Pelvic Nodule	7 (4.6)	0 (0.0)	7 (5.7)
Reason for Admission			
Pain	64 (42.4)	0 (0.0)	64 (52.0)
Shortness of breath	18 (11.9)	6 (21.4)	12 (9.8)
Family empowerment	18 (11.9)	7 (25.0)	11 (8.9)
Procedure	15 (9.9)	6 (21.4)	9 (7.3)
Body weakness	11 (7.3)	2 (7.1)	9 (7.3)
Others	10 (6.6)	5 (17.9)	5 (4.1)
Poor oral intake	6 (4.0)	0 (0.0)	4 (4.9)
Respite care	3 (2.0)	0 (0.0)	3 (2.4)

[a] Eastern Cooperative Oncology Group

Prevalence of pain

Of 151 patients, 61.6%, [95%CI: 0.54,0.69] experienced pain upon admission. However, an additional 19.9% [95%CI: 0.13,0.26] who presented with no pain upon admission experienced pain in the past 24 hours, of which 9.9% experienced pain only upon movement. There were 5 (3.3%) patients who developed pain in the ward but were excluded from the secondary analyses.

Baseline pain-related variables

A total of 123 patients (81.5%, 95% CI: 0.75, 0.88) who experienced pain at some point in the last 24 hours were included in the secondary analyses (Table 2). Of these, 42.2% and 82.1% reported moderate to severe current pain upon admission and worst pain in the past 24 hours, respectively. Cancer was the most common cause of pain (85.4%), followed by pain unrelated to cancer or its treatment (16.3%) and cancer treatment (7.3%). Most patients presented with acute episodic pain. Approximately one third (30.1%) had pain in more than one location; 61.0%, 52.8% and 32.5% pains were visceral, somatic and neuropathic in nature, respectively. More than a third (39.8%) had pain of mixed pathophysiology.

Analgesic treatments

With regards to treatments prior to admission, less than a third were on a simple analgesic, non-steroidal anti-inflammatory drug (NSAID), anti-neuropathic agent or a weak opioid. Celecoxib was the most frequently prescribed NSAID. Drugs used for neuropathic pain were the tricyclic antidepressant amitriptyline and anticonvulsant gabapentin. More than half (54.5%) were already on a strong opioid with a median (IQR) MEDD of 10 (240) mg. During admission, there was an increase in the prescribing of paracetamol, NSAIDs, anti-neuropathic agents and strong opioids with the largest increase at 24 hours, but a decrease in weak opioids compared to those taken prior to admission (Table 3). Strong opioids were the mainstay treatment, followed by paracetamol, anti-neuropathic

Table 2. Baseline Pain-related variables of patients who experienced pain within the past 24 hours (n=123)

Pain Characteristics	n (%)
Pain cause	
Cancer	105 (85.4)
Cancer treatment	9 (7.3)
Unrelated to cancer or treatment	20 (16.3)
Number of pain location	
1	86 (69.9)
2	28 (22.8)
3	9 (7.3)
Duration of pain	
Acute pain (less than 3 months)	87 (70.7)
Chronic pain (more than 3 months)	31 (25.2)
Unknown	5 (4.1)
Episodic pain	99 (80.5)
Pain Pathophysiology	
Somatic only	19 (15.4)
Somatic and neuropathic	25 (20.3)
Visceral only	54 (43.9)
Somatic and visceral	8 (6.5)
Neuropathic only	0 (0.0)
Visceral and neuropathic	5 (4.1)
Somatic, visceral and neuropathic	11 (8.9)
Total somatic	65 (52.8)
Total visceral	75 (61.0)
Total neuropathic	40 (32.5)

agents, NSAIDs and weak opioids. Tramadol was the only weak opioid that was prescribed. Morphine (Injection morphine 10mg/ml, Tablet Morphine 10mg, 30mg, Aqueous morphine 10mg/5ml), was the most widely prescribed strong opioid, followed by oxycodone (Tablet OxyContin 10mg, 20mg, Capsule OxyNorm 5mg,10mg) and fentanyl (Injection fentanyl 100mcg/ml, Transdermal fentanyl 25mcg/hr). There was an increase in MEDD of regular opioids and a concurrent decrease in MEDD of breakthrough opioids prescribed from admission to discharge. The proportion of patients requiring breakthrough medications also decreased upon discharge. Four patients were non-adherent to the treatment prescribed and refused analgesia due to the fear of morphine. As the investigators explored further, these patients revealed their fears of addiction and morphine hastening death.

Pain score reduction and treatment adequacy

The study population sample varied throughout admission as some of the patients were eventually unable to give scores, discharged and passed away during their stay. For all types of pain score, means decreased from baseline at each time point with a significant decrease after 24 hours ($p<0.001$) (Online appendix 2, Figure 2). The largest decrease was seen in worst pain scores [95%CI: -4.1,-2.8] and the smallest decrease was seen in least pain scores [95%CI: -1.2,-0.3] (Online appendix 2). There was also a decreasing trend of patients experiencing moderate to severe pain from admission to discharge. At 72 hours, 1.5% and 14.7% patients had moderate to severe current and worst pain in the past 24 hours, respectively. Upon discharge, 2% and 25% patients had moderate to severe current and worst pain in the past 24 hours, respectively. Additionally, 38% and 39% still experienced mild current and worst pain in the past 24 hours, respectively (Table 3). The prevalence of under-treatment was 30.1% at the point of admission. Treatment adequacy significantly improved among the 100 discharged patients (PMI≥0 100% versus 68%, $p<0.001$).

DISCUSSION

This study is first in Malaysia to evaluate pain prevalence and its treatment outcomes among cancer patients in an inpatient palliative care unit. Our results revealed that there was a high prevalence of pain upon admission which reduced during ward stay (significantly after 24 hours) and was adequately treated upon discharge. Consistent with other studies that were conducted in outpatient palliative care settings, the prevalence of pain among cancer patients in our setting was high and almost half experienced moderate to severe pain upon admission.[1,18-21] A higher proportion of patients experienced pain 24 hours prior to admission, of which more than half reported severe pain. In a study by Caraceni *et al*., 66.7% reported that the worst pain intensity during the day prior to the survey was ≥7.[22]

The types of cancer pain were similar to previous published data, in which inferred pain mechanisms were greatly heterogeneous and mostly due to the cancer itself.[22] In the same survey by Caraceni *et al*., 71.6% of the patients' pains were nociceptive somatic, 34.7% nociceptive visceral, 39.7% neuropathic and more than a third of them had pain of mixed pathophysiology.[22] In this study, visceral pain was the most frequent type of inferred pain followed by somatic and neuropathic pain. This could be explained by the relatively higher proportion of patients with gastrointestinal, gynaecological cancer and liver metastasis which usually cause tumour-related visceral pain syndromes.[23] More than half of our patients experienced somatic pain which is caused by tumour involvement of bone, joints, muscle or connective tissue, and most commonly by bone metastases.[23] It was also observed that more patients had a combination of somatic and neuropathic pain than other combinations. This observation may be explained by a previous study which suggests the presence of a neuropathic component in cancers of somatic origin such as metastatic bone cancer and although only about 3% of patients in this study had bone cancer, almost a quarter had metastases of somatic origin such as bone metastases.[24] About one in three of our patients had neuropathic pain, comparable to that reported by a recent study whereby 32.3% of patients referred to a cancer pain clinic had a neuropathic pain component.[25]

The pharmacological management of cancer pain has been most widely based on the algorithm provided by WHO.[26,27] The WHO guidelines recommend a three-tiered cancer pain ladder in which patients can be started on paracetamol or NSAIDs and if these are inadequate, patients should be escalated to a "weak opioid" and subsequently to a "strong opioid," which should be administered 'round-the-clock'.[26,27] These guidelines therefore provide an excellent foundation for cancer pain management which has evolved to be significantly more complex in recent years. Our study patients were managed accordingly and there was an increased prescribing of every group of medications excluding the weak opioids throughout patients' ward stay and upon discharge. The use of adjuvants such as paracetamol, NSAIDs, tricyclic antidepressants and

Table 3. Patients' profile, treatment and pain severity from admission to discharge. n (%)

Variables	Baseline (n=123)	24-hour (n=111)	48-hour (n=90)	72-hour (n=67)	Discharge (n=100)
Patients profile over time					
Unable to score	-	5 (4.5)	8 (8.9)	8 (11.9)	7 (7.0)
Discharged	-	6 (5.4)	23 (25.6)	43 (64.2)	-
Death	-	1 (0.9)	2 (2.2)	5 (7.5)	16 (16.0)
Simple analgesic					
Paracetamol	33 (26.8)	55 (49.5)	48 (53.3)	36 (53.8)	56 (56.0)
Non-steroidal anti-inflammatory drugs	19 (15.4)	26 (23.4)	25 (27.8)	21 (31.3)	32 (32.0)
Diclofenac	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ibuprofen	2 (1.6)	1 (0.9)	1 (1.1)	0 (0.0)	0 (0.0)
Celecoxib	13 (10.6)	24 (21.6)	22 (24.4)	20 (29.9)	32 (32.0)
Etoricoxib	3 (2.4)	1 (0.9)	2 (2.2)	1 (1.5)	0 (0.0)
Anti-neuropathic agents	16 (13.1)	34 (30.6)	30 (33.3)	29 (43.3)	34 (34.0)
Amitriptyline	7 (5.7)	17 (15.3)	18 (20.0)	16 (23.9)	24 (24.0)
Gabapentin	7 (5.7)	10 (9.0)	9 (10.0)	7 (10.4)	7 (7.0)
Amitriptyline and Gabapentin	2 (1.6)	7 (6.3)	3 (3.3)	6 (9.0)	3 (3.0)
Weak Opioid	35 (28.5)	13 (11.7)	10 (11.1)	7 (10.4)	11 (11.0)
Tramadol	34 (27.6)	13 (11.7)	10 (11.1)	7 (10.4)	11 (11.0)
Dihydrocodeine	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Strong Opioid	66 (53.7)	85 (76.6)	72 (80.0)	52 (77.6)	78 (78.0)
Morphine	49 (39.8)	75 (67.6)	61 (67.7)	43 (64.2)	65 (65.0)
Oxycodone	12 (9.8)	8 (7.2)	10 (11.1)	7 (10.4)	8 (8.0)
Fentanyl	5 (4.1)	2 (1.8)	1 (1.1)	2 (3.0)	5 (5.0)
MEDD regular[a]: Median (IQR)	10 (240)	23 (325)	30 (300)	32.5 (280)	30 (400)
Breakthrough Medication	-	47 (42.3)	30 (33.3)	20 (29.9)	18 (18)
MEDD breakthrough[b]: Median (IQR)	-	0 (130)	0 (110)	6.3 (80)	0 (30)
Current pain score: Mean (SD)	3.8 (3.0)	1.5 (2.0)	1.3 (1.7)	1.2 (1.6)	0.9 (1.3)
0 (no pain)	30 (24.4)	57 (51.4)	44 (48.9)	35 (52.2)	60 (60.0)
1-4 (mild)	41 (33.3)	46 (41.4)	42 (46.7)	31 (46.3)	38 (38.0)
5-6 (moderate)	26 (21.1)	5 (4.5)	2 (2.2)	1 (1.5)	2 (2.0)
7-10 (severe)	26 (21.1)	3 (2.7)	2 (2.2)	0 (0.0)	0 (0.0)
Worst pain score: Mean (SD)	6.9 (2.4)	3.5 (2.5)	3.4 (2.7)	3.1 (2.8)	2.5 (2.5)
0 (no pain)	0 (0.0)	18 (16.2)	19 (21.1)	23 (34.3)	36 (36.0)
1-4 (mild)	22 (17.9)	52 (46.8)	38 (42.2)	22 (32.8)	39 (39.0)
5-6 (moderate)	29 (23.6)	27 (24.3)	21 (23.3)	13 (19.4)	20 (20.0)
7-10 (severe)	72 (58.5)	14 (12.6)	12 (13.3)	9 (13.4)	5 (5.0)
Least pain score: Mean (SD)	1.8 (2.1)	1.0 (1.7)	0.7 (1.2)	0.8 (1.3)	0.4 (0.9)
0 (no pain)	57 (46.3)	72 (64.9)	61 (67.8)	43 (64.2)	80 (80.0)
1-4 (mild)	47 (38.2)	33 (29.7)	28 (31.1)	24 (35.8)	20 (20.0)
5-6 (moderate)	18 (14.6)	4 (3.6)	1 (1.1)	0 (0.0)	0 (0.0)
7-10 (severe)	1 (0.8)	2 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Pain Management Index ≥0	86 (69.9)	110 (99.1)	89 (98.1)	65 (97.0)	100 (100)

[a] Morphine Equivalent Daily Dose of the regular dose of the weak or strong opioid
[b] Morphine Equivalent Daily Dose of the breakthrough dose of the weak or strong opioid

anticonvulsants more than doubled during the patients' ward stay to optimise pain relief. Adjuvant analgesics are known to have a therapeutic role in increasing the therapeutic index of opioids by a dose-sparing effect and adding a unique analgesic action in opioid-resistant pain.[28]

In our setting, morphine was the most extensively used strong opioid due to its wider availability and cheaper cost. Aqueous morphine is extemporaneously prepared from morphine powder by the pharmacy and extremely cheap.[7] Its additional benefits of relieving dyspnoea and cough also accounted for its higher usage as several patients were on morphine for these indications in addition to pain. Oxycodone was usually reserved as an alternative to morphine for opioid rotation especially in patients whose pains were uncontrolled despite being on high doses of morphine or who were unable to tolerate its side effects.[26] Fentanyl was used among patients with severe renal or hepatic impairment, who had difficulty swallowing or who refused either morphine or oxycodone.[16]

Upon admission, the prevalence of under-treatment was one third of the study population which was similar to previous findings in the recently updated systematic review and meta-analysis.[3,17] The large reduction in mean pain score after 24 hours and the significant improvement in the PMI may be attributed to the decrease in weak opioids usage and concurrent increase in strong opioids usage and its dosing as reflected by the increase in regular opioids MEDD. However, although treatment was adequate upon discharge, there were still more than a third of patients experiencing mild pain and about a quarter who had moderate to severe worst pain. Pain management in our setting can be further improved to provide better pain relief to patients, for example, by incorporating non-pharmacological treatments.

According to Lim, barriers to cancer pain management in Malaysia have been similar to those reported in studies conducted in other countries.[7] Those barriers include a) attitudes, knowledge and skills of healthcare professionals; (b) attitudes and perceptions of patients and the general

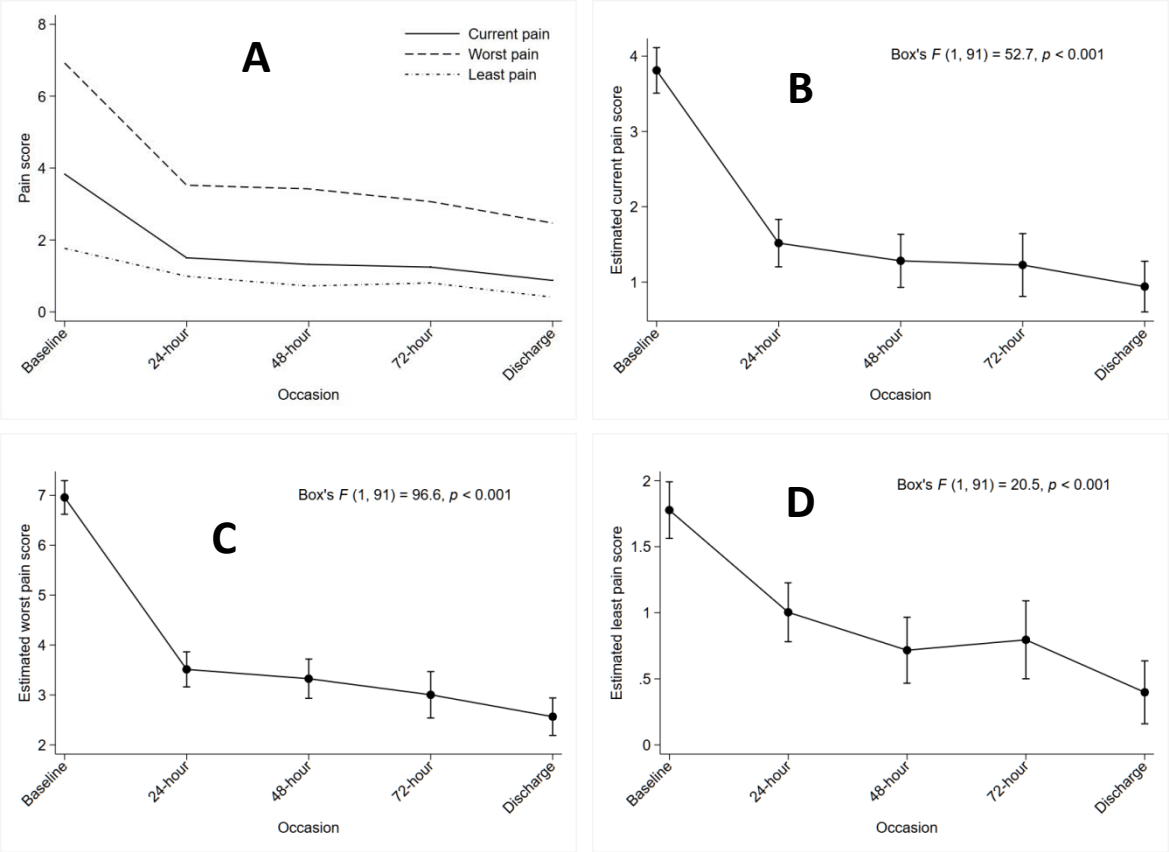

Figure 2. Observed and estimated pain scores over time (from the point of admission to discharge)
A: Observed pain scores over time
B: Estimated current pain score based on single-factor repeated-measures ANOVA model
C: Estimated worst pain score based on single-factor repeated-measures ANOVA model
D: Estimated least pain score based on single-factor repeated-measures ANOVA model

public, and (c) health care system issues and drug accessibility.[7] In the Malaysian public healthcare sector, medications are subsidised by the government and opioids are readily available in larger hospitals with pharmacists and specialists hence opioid availability was not an issue in our setting.[7] During the course of this study, several patients still had fears of morphine despite being counselled prior to its initiation. A recent study conducted in a Malaysian hospital reported that one of the most common misconceptions that 40% of the patients had was the fear of strong opioids damaging the immune system and causing addiction.[30] Patients' fears of morphine remain a worldwide phenomenon. A systematic review which synthesized qualitative and quantitative studies revealed that patients, carers, and clinicians still held deep-seated concerns regarding the symbolism of morphine, addiction, and tolerance.[31] Future qualitative studies that explore patients' fears of morphine in this local community of lower education levels would help us to better understand their perspectives and allow us to address those fears effectively through effective patient education. A recently published quasi-experimental study concluded that patient education significantly reduced overall pain intensity over 24 hours, encouraged the use of short-acting analgesics for breakthrough pain, improved quality of life and significantly reduced misconceptions regarding cancer pain management.[32]

There were several limitations to this study. This study was conducted among the Malaysian local population and may limit the generalizability of the data. Secondly, data on non-pharmacological interventions were not included in this study. Additionally, treatment adequacy defined by the PMI has some limitations related to its intrinsic characteristics. Only two variables (pain intensity and the most potent opioid prescribed) are taken into account to measure pharmacologic appropriateness. Other important characteristics such as the nature of pain, drug dosage, administration route, breakthrough doses, adjuvant drugs and the use of non-pharmacological therapies are excluded. Future studies incorporating non-pharmacological therapies with larger sample sizes would allow further analyses to better characterize the pain and the appropriateness of treatment for the various types of pain. There were, however, strengths of this study. Observing the trends of pain score reduction over 72 hours provides a better understanding of the significant role of strong opioids in pain relief among cancer patients. Additionally, a patient's self-report is the most valuable component of a comprehensive pain assessment which is the foundation of effective pain management.[33] The incorporation of a pain assessment guide which was culturally tailored in the local language was crucial for effective pain management.[33]

CONCLUSIONS

Accounting for pain's dynamic nature, there was a high prevalence of pain among Malaysian cancer patients in a palliative care setting. Continuous efforts incorporating comprehensive pain assessments and evidence-based treatments are necessary to provide adequate pain relief and end-of-life comfort care. In addition, patient education is imperative to improve patients' understanding of palliative care and their acceptance of treatments.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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Original Research

Anaemia in heart failure patients: the prevalence of haematinic deficiencies and the role of ACE inhibitors and aspirin doses as risk factors

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Abstract

Background: Patients with heart failure often have comorbidities that alter the progression of heart failure and impact on prognosis. One such comorbidity is anaemia, and clinicians have started to appreciate the full gravity of its impact on heart failure patients. Yet, the extent of the problem is not fully understood, particularly the role of heart failure therapy itself as a risk factor for developing anaemia.

Objective: This study aimed to investigate the prevalence of anaemia in a cohort of heart failure patients. The impact of using different ACEIs and different doses of aspirin was also explored, together with the prevalence of haematinic deficiencies.

Methods: Medication lists and pathology results were examined to establish the prevalence of ACEIs use, and the use of aspirin at its most common doses of 100mg and 150mg, together with haematinic deficiencies. Multinomial logistic regression and the Student's t-test were utilised for the analysis of data. Statistical significance was pre-set at $p<0.05$.

Results: Ninety-six patients were eligible for analysis, with 26% having anaemia. The use of ACEIs had a RR of 17.4 for the presence of anaemia. Perindopril was associated with a RR of 20.8, while the use of ramipril was not significantly associated with such a high RR. Haematinic anaemia occurred only at a rate of 3.3%, but borderline deficiencies were found in more than a third of all patients. An aspirin dose of 150mg was associated with a higher risk for anaemia, compared to a dose of 100mg.

Conclusions: ACEIs are associated with the presence of anaemia, with perindopril posing more risk than ramipril when used in heart failure patients. The dose of aspirin may also be a factor in the development of anaemia, with lower doses being safer. Despite the lack of high prevalence of haematinic anaemia among this cohort of patients, borderline haematinic deficiencies were common.

Keywords

Anemia; Angiotensin-Converting Enzyme Inhibitors; Aspirin; Drug-Related Side Effects and Adverse Reactions; Heart Failure; Risk Assessment; Multivariate Analysis; Clinical Audit; Australia

INTRODUCTION

Anaemia in heart failure is an under-recognised problem, but it has a great impact on the prognosis of patients.[1] Even mild anaemia increases the risk of mortality; in fact, for every 1% decrease in haematocrit (HCT) the risk of mortality increases by 6%.[1] Anaemia is associated with increased hospitalisation, worse cardiac function, need for high diuretic doses, and poor quality of life.[2] Its prevalence of about 15-55% makes it almost a public health hazard.[3] Indeed, it is an independent risk factor for mortality in heart failure patients.[1,4]

Causes for anaemia in this cohort of patients are not fully understood, but speculations have been made with regards to haemodilution, worsening renal function, and the use of aspirin and ACE inhibitors (ACEIs).[5] It is difficult to imagine that all patients on ACEIs would eventually develop anaemia, as this will certainly depend on their starting haemoglobin (Hb) level. However, ACEIs are widely used in patients with cardiovascular disease, particularly in those with heart failure, and the prevalence of anaemia may be high enough. Thus, the role of regular monitoring is important, as is a clear guideline of when to commence active treatment.

Heart failure patients who have anaemia tend to benefit from treating their anaemia, as demonstrated by improved functional capacity, quality of life and exercise tolerance.[6,7] However, there is some contradicting evidence that shows a lack of clinically significant improvement.[8] A meta-analysis concluded that using erythropoietin to correct anaemia is in fact associated with increased mortality if high levels of Hb are achieved, probably due to elevated BP or increased propensity to thrombosis.[9] Yet, as the authors of that meta-analysis have alluded, it is unclear whether it was the level of Hb achieved or the means by which this level was achieved is the true risk for higher mortality. Mounting evidence shows improvements in New York Heart Association classification, Quality of Life, ventricular function, and hospitalisation rate when anaemia of heart failure is corrected appropriately.[5,10]

The challenge, therefore, seems to be the under-detection of anaemia and the less proactive role clinicians currently play in correcting this risk factor. The current study aimed to explore the prevalence of anaemia in heart failure patients who received pharmacist interventions during their attendance at outpatient heart failure clinics. It also aimed to provide an insight into the role of ACEIs and aspirin, and the extent of monitoring for haematinic anaemia in the management of heart failure patients.

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METHODS

Design

This study is a retrospective audit of the data collected by pharmacists from patients who received pharmacist consultations while attending their heart failure outpatient appointments in an outpatient heart failure clinic at a major metropolitan hospital in Melbourne, Australia. The work described in this study was conducted according to institutional policies and guidelines, and in accordance with the Declaration of Helsinki.

Patients

Patients who attended their outpatient Heart Failure clinic were asked to be seen by the pharmacist, to review their medication regimens. This is a current practice, for pharmacists to see patients before they proceed with their cardiology appointments. The aim of this system is to optimise heart failure management, from a pharmacotherapeutic perspective and to ensure drug safety. Pathology results are always considered in conjunction with assessing patients' medications, so safety and efficacy of their pharmacotherapy is established and optimised. Advice and education are offered to patients, and liaison with their cardiologists occurs on an as-needed basis.

Intervention

Patients' medication lists were prepared, based on a review of their medical history, and an interview with the patient, after obtaining patient consent. Liaison with the patients' local pharmacies often occurred to confirm the medications or doses patients used, that may not be known to Heart Failure Clinic staff or the hospital. Pathology results were examined, e.g. renal function, full blood examination, etc. with the aim of monitoring the safety of the patients' therapy. Reference to the results of haematinic blood tests was made to investigate the prevalence and type of deficiencies among patients. Prepared medication lists were then consulted and the prevalence of ACEIs and aspirin use was tabulated for further analysis.

Outcome Measures were:

- Prevalence of anaemia among heart failure patients.
- Characterisation of the ACEIs used among the cohort of patients seen by pharmacists in the outpatient Heart Failure clinic.
- Relative Risk (RR) of ACEIs for the development of anaemia.
- RR of various aspirin doses for the development of anaemia.
- The prevalence of haematinic deficiencies and anaemia.

Statistical analysis

STATA/SE 10.1 was utilised to analyse the data. Multinomial logistic regression was used to establish the RR of independent variables known to cause anaemia including: age, gender, renal impairment, ACEIs use, and aspirin use. This statistical method was also used to establish the RR of two of the ACEIs most used in our cohort of patients, namely perindopril and ramipril. Student's t-test (two tailed) was used to compare the Hb levels between patients on ACEIs and those who were not on ACEIs. A 2x2 contingency table was made to compare the RR of different aspirin doses. Statistical significance was declared at a P value of less than 0.05.

Power analysis of this study indicates that patient numbers were sufficient for its objective. The multiple logistic regression had five independent variables, and thus a patient number of 10-20 times this number of variables should be used.[11] This study included 96 patients, which is 19 times the number of variables.

Table 1. Characterisation of angiotensin blockade in patients of the study.

Angiotensin inhibition	Number of patients (%)	
	Non anaemic	Anaemic
ACEI	15 (15.6)	24 (25)
Perindopril	8 (8.3)	12 (12.5)
Ramipril	4 (4.2)	6 (6.3)
Other ACEI	3 (3.1)	6 (6.3)
A2RB (instead of ACEI)	6 (6.3)	1 (1.0)
Candesartan	3 (3.1)	
Irbesartan	5 (5.2)	
Other A2RB	0 (0)	
Not on any ACEI or A2RB	50 (52.1)	0 (0)
ACEI/A2RB combination	2 (2.1)	4 (4.2)

Proportion of patients who are on angiotensin inhibitory drugs and whether they had anaemia or not.
ACEI: angiotensin-converting enzyme inhibitor; A2RB: angiotensin 2 receptor blocker.

RESULTS

Ninety-six patients were eligible for inclusion due to the availability of their data for analysis. The average age of patients was 65.3 years (95%CI 62.3-68.3). There were 68 males in the study, with 14 out of a total of 25 having a Hb level of less than 120g/L. ACEIs were used by all patients who had anaemia, while most patients in the non-anaemic group were not on any angiotensin blockade therapy, either ACEIs or angiotensin II receptor blockers (ARBs) (see Table 1).

The use of ACEIs for heart failure was associated with a RR of 17.4 for developing anaemia, compared to no ACEIs use (see Table 2). This is statistically significant (P=0.013). Multinomial logistic regression did not confirm that age older than 65 years, gender, renal impairment, or aspirin use were significant risk factors for the development of anaemia in the cohort of patients reported in this study. Furthermore, perindopril had a RR of 20.8, compared to ramipril which had a RR of 14.2 (see Table 2). However, statistical significance was achieved only for perindopril, not ramipril.

Patients who were using ACEIs had lower levels of Hb, almost 17g/L less than those who were not on ACEIs. This is a significant difference, with a P value of less than 0.0001 (see Table 3).

The prevalence of haematinic deficiencies was low, at only 3.3%. Only one folic acid test showed deficiency (see Table 4). However, when the lower limit of normal levels for these tests was raised, more patients were borderline

Table 2. Multinomial logistic regression analysis - the relative risk (RR) of various risk factors for the development of anaemia among patients with CHF.

	RR	Std Err.	Z	P value	95% Confidence Interval
Relative risk (RR) of various risk factors for the development of anaemia among patients with CHF.					
ACEI	17.38	20.00	2.48	0.01	1.82 - 165.9
Aspirin	2.65	1.97	1.32	0.19	0.62 - 11.33
Renal impairment	2.16	1.57	1.06	0.29	0.52 - 8.95
65 years or more	0.96	0.77	-0.05	1.0	0.20 - 4.66
Gender	0.78	0.55	-0.35	0.73	0.20 - 3.13
Risk factors including perindopril.					
Perindopril	20.78	27.53	2.29	0.02	1.55 - 279.06
Aspirin	2.74	2.98	0.93	0.35	0.33 - 23.11
Renal impairment	2.26	2.62	0.70	0.48	0.23 - 21.95
65 years of more	0.98	0.04	-0.40	0.69	0.91 - 1.06
Gender	0.22	0.22	-1.51	0.13	0.03 - 1.57
Risk factors including ramipril.					
Ramipril	14.18	19.41	1.94	0.05	0.97 - 207.13
Aspirin	2.10	2.85	0.55	0.58	0.15 - 29.90
Renal impairment	1.74	2.43	0.40	0.69	0.11 - 26.99
65 years of more	0.96	0.04	-0.83	0.41	0.88 - 1.05
Gender	0.71	1.03	-0.22	0.82	0.05 - 11.65

deficient. Almost 37% may have haematinic anaemia. It was also found that the majority of heart failure patients did not have a haematinic test during the year of being seen by the pharmacist in their outpatient clinic attendance. The rate of testing was only less than 15%, for iron deficiency, and slightly over 8% for vitamin B12 and folic acid deficiencies.

Despite logistic regression not establishing aspirin as a risk factor for anaemia, a 2x2 contingency table showed that aspirin may indeed be a risk factor for anaemia. Compared to being on no aspirin, those who were using aspirin 100mg had a RR of 4.7, while this RR increased to 7.3 for those taking 150mg of aspirin (see Table 5).

DISCUSSION

ACEIs use

The current study confirms that ACEIs are associated with an increased risk of developing anaemia. The RR of anaemia in patients who used an ACEI was 17.4 (see Table 1). This is in line with previous evidence that strongly suggested ACEIs to be a risk factor for anaemia in heart failure.[12] What this study adds, though, is that different ACEIs may pose different levels of risk for causing anaemia. The study demonstrated that perindopril was associated with a RR of 20.7 (see Table 2), while ramipril was not associated with such a large risk, and it was insignificant (see Table 2). Previous studies have shown that ACEIs are more potent at lowering Hb than ARBs.[13] It is only plausible to expect variability within ACEIs as a drug class.

Angiotensin blockade has been observed to reversibly decrease HCT, as early as within a month of starting ACEI or ARB therapy; HCT reaches its nadir within 3 months.[12] Losartan decreased Hb levels, with the largest decrease occurring after one year of treatment.[13,14] In the current study, users of ACEIs had significantly lower levels of Hb. The average difference between ACEIs users and non-users is about 17g/L, a Hb amount that may be the target of erythropoietin therapy in selected patients. This is congruent with previous studies that demonstrated the ability of ACEIs to reduce Hb, and their effective utilisation in treating erythrocytosis.[15,16] It is unclear from the current results, however, when Hb started to decrease after commencing angiotensin blockade therapy.

ACEIs have been found to not only inhibit the production of erythropoietin, and thus reduce its circulating level, but also to inhibit its action.[17] Other proposed mechanisms of action include the inhibition of Interleukin 12 (IL-12) and insulin-like growth factor-1 (IGF-1), with both having significant roles in erythropoietin production.[13,18] ACEIs can also inhibit the angiotensin II-induced stimulation of erythroid progenitor cell growth, and stimulate a stem cell regulator known as Ac-SDKP that inhibits erythroid growth.[19] Captopril was found to cause myelosuppression by inhibiting haematopoietic cell proliferation of progenitor and stem cells.[20] Enalapril had the same effect that explains its use in post-transplant erythrocytosis (PTE).[15,16] The detrimental actions of ACEIs are not unopposed, as this phenomenon is associated with higher doses of ACEIs. As such, they could be overcome by administering exogenous erythropoietin, or increasing its dose.[18] The current study did not investigate the impact of ACEI dosing on the development of anaemia.

The use of erythropoietin in anaemic patients adds another dimension to their management, and certainly would be the last resort after taking rather preventive measures to reduce the risk of anaemia. Whether there is a benefit in

Table 3. Significant difference in Hb levels between users and nonusers of ACEIs.

	ACEI users	95% Confidence Interval	Non ACEI users	95% Confidence Interval
Mean	122.69	116.87 - 128.52	139.23	135.51 - 142.94
Standard deviation	17.96		14.00	
Standard error of mean	2.88		1.85	
Number of patients	39		57	
The two-tailed P value is less than 0.0001, t=5.06, df=94				

Table 4. Results of haematinic tests and the observed Hb levels in the tested patients.

Anaemia Status	Ferritin (microg/L)		Vitamin B12 (pmol/L)		Folic acid (nmol/L)	
	< 15	<50*	<150	<200*	<7.6	<8.5*
Hb <120g/L (anaemia)	0	**6**	0	**2**	1	**2**
Hb > 120g/L	0	**3**	0	**6**	0	**5**
Total Tested	14		8		8	
Testing Rate in study ample (%)	14.6%		8.3%		8.3%	

* Arbitrarily chosen borderline lower levels to establish the prevalence of borderline deficiencies.

using ARBs instead of ACEIs, or substituting ACEIs, in heart failure patients who are at risk of developing anaemia is a question still unanswered. Further studies are needed to understand whether ARBs should replace ACEIs as the first line therapy for heart failure, or whether ramipril should be used in place of perindopril in those at risk of anaemia.

Haematinic anaemia

Haematinic deficiencies do not seem to be the main cause of anaemia observed in patients with heart failure. In one study, vitamin B12 deficiency was encountered in only 6% of patients, while folate deficiency was found in 8% of them.[3] Iron deficiency anaemia was seen in 13% of patients of that study. This low prevalence of haematinic anaemia is consistent with the results of the current study. The underlying cause of these deficiencies is of some interest, because cytokines were found to inhibit the absorption of iron and its release from iron stores.[2] This may explain why this study demonstrated a relatively high prevalence of borderline haematinic anaemia, including iron deficiency anaemia.

In the population of this study, there was a total of 30 haematinic tests requested, 14 for ferritin, and 8 for each of vitamin B12 and folic acid (see Table 2). Only one test showed frank haematinic deficiency, a folic acid test. The rate of detecting a deficiency on haematinic tests was only 3.3%. However, when higher borderline cut-off points were considered for these tests, this rate increased to 37%. The cut off points were only borderline, i.e. ferritin <50 microg/L (normal range: 30-300 microg/L), vitamin B12 <200 pmol/L (normal range: 148-590 pmol/L) and folate <8.5 nmol/L (normal range: 5.7-45.3 nmol/L).[21] This demonstrates that many heart failure patients with anaemia may have a haematinic predisposition, and are indeed borderline haematinic deficient.

Furthermore, haematinic abnormalities could, after all, be responsible, at least partially, for their anaemia. Should such abnormalities be treated? Further research is required to answer this question. However, given the multifaceted nature of anaemia in CHF, different causes of anaemia may be present in different patients. It seems only plausible that treating haematinic anaemia, or deficiency, should be sought in those who are known to be at risk. It might be a safer clinical practice to treat a deficiency suspected of causing the anaemia, rather than risk a poorer heart failure prognosis if left untreated.

Aspirin dose

Aspirin has been shown to contribute to anaemia in heart failure, which the results of this study support. Compared to non-aspirin-users, patients who used aspirin have a relatively higher risk of developing anaemia. An interesting finding of this study, however, is that aspirin dose may have a role in the development of anaemia. A 2x2 contingency table demonstrated that the use of aspirin 100mg had a relative risk of 4.7, while using aspirin 150mg had a RR of 7.3 (see Table 3). Compared to aspirin 100mg, the use of aspirin 150mg had a relative risk of 1.55. This poses the question of whether it is safer to use a lower dose of aspirin in heart failure patients. The antiplatelet action is still maintained, but there would be a reduced RR with a lower dose of aspirin. The study was not large enough to detect the relative risk of even lower antiplatelet doses of aspirin, i.e. 50-75mg.

This dose-related effect is a phenomenon consistent with that reported in previous studies that looked at various doses of the ACEIs. It seems that anaemia in heart failure is related to the doses of the medications used, i.e. ACEIs and aspirin, not only their class. Although reducing the aspirin dose from 150mg to 100mg may not be a problem, reducing the dose of an ACEI may pose a challenging clinical dilemma. Down-titration of ACEI doses is not the current trend in heart failure management, and may be related to worse outcomes. However, since anaemia is also related to worse outcomes, further studies are required to well define the doses that are considered safer in those at risk of anaemia. The use of the maximum tolerated doses of ACEIs may not be safest option in this cohort of patients.

Drug utilisation and pathology monitoring

This study demonstrates that among all patients considered for data analysis, only 48% of them had been on either an ACEI or an ARB. The reason for this relatively low uptake of angiotensin inhibition among this cohort is beyond the scope of the current study. However, it demonstrates that should more patients have been on angiotensin blockade, many more may have been diagnosed with anaemia, and the results providing a clearer picture of the role of ACEIs and aspirin dosing in the development of anaemia.

Another observation from this study is the low rate of screening for haematinic deficiencies. Only 14.6% of patients had haematinic anaemia assessed, during the year when the pharmacist saw them, while 43% of those

Table 5. Contingency table showing the use of aspirin to be associated with a higher risk of anaemia, which seems to be aspirin-dose dependent.

	Anaemia present	Anaemia absent	Relative risk	95% Confidence Interval
Aspirin 100mg	11	9	4.7	2.24 - 9.76
Aspirin 150mg	6	1	7.3	3.21 - 16.54
No aspirin	8	60	RR compared to "no aspirin"	
Compared to aspirin 100mg, aspirin 150mg confers a RR of 1.56.				

suspected of haematinic anaemia had only one type of haematinic test, i.e. vitamin B12, folic acid or iron study, but not all three tests. More than half of all tested patients had only one test. The rate of haematinic deficiencies may have been higher, and thus the prevalence of haematinic anaemia higher, if the levels of folate, B12 and ferritin were all tested for all patients. The reason for this low level of screening could be that clinicians tested patients some years earlier and decided there were no anaemias or deficiencies to be concerned about. They may have determined that further screening was unwarranted. This study, however, shows that there is some merit in frequent regular screening to actively detect and monitor haematinic deficiencies and anaemia of heart failure.

CONCLUSIONS

The current study demonstrates that anaemia is common among patients who have heart failure. One possible cause is the use of ACEIs, but it seems that some ACEIs are less likely to cause anaemia than others. The level of Hb among ACEIs users is significantly lower than that observed in non-ACEIs users. Moreover, the dose of aspirin may have a role in the development of anaemia, as has been previously established with the dose of ACEIs. Furthermore, haematinic deficiencies are common in heart failure patients and should be monitored regularly. Although patients may not be "diagnosed" with haematinic anaemia, many would have deficiencies that could compromise their heart failure management, and worsen their prognosis.

CONFLICT OF INTEREST

There are no potential conflicts of interest.

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